THE IMPACT OF HOSPITAL SURVEILLANCE PROGRAMMES ON THE INCIDENCE OF ADVERSE DRUG REACTION REPORTING IN A SOUTH AFRICAN TEACHING HOSPITAL

by

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COVER PAGE

The freeway sign, illustrated by two syringes and a bridge, illustrates the free use of medicine in clinical practice. The question mark illustrates the question of whether sufficient information or knowledge is available regarding the safety of medicine used in clinical practice. The yield sign illustrates a watchful eye on drug effects after drug registration. Medical, nursing and pharmacy staff collaborated in this study.

CONTENTS

ABSTRACT

Post-marketing surveillance refers to any non-experimental or observational study, method, or monitoring strategy that is applied to obtain information on drug experience (primarily adverse) after a drug has been approved for clinical use (1).

One of the major problems in post-marketing surveillance studies is the lack or under-reporting of drug experiences by health care professionals. This study was developed to describe the impact of three different prescription event monitoring programmes on the reporting of adverse drug reactions (ADR's) in the hospital situation. The intensive ADR monitoring programme and two voluntary ADR monitoring programmes which followed were conducted in the medical wards of an urban teaching and referral hospital. All patients admitted to the designated wards were monitored by a dedicated pharmacist in the intensive programme, ward pharmacists in the first voluntary programme and by medical and nursing staff in the second voluntary programme.

The pharmacist monitored a cohort of patients prospectively in two medical wards for a period of three months. The patient's record was linked with any suspected ADR. All details, i.e. patient drug orders, characteristics and ADR description, were recorded and then reported. From 228 patients monitored, 25 cases have been reported. The impact of the intensive ADR monitoring programme was a reporting rate of 11 percent. Reports were received on ADR's of a particularly mild, common and pharmacologically predictable (type A) nature.

The first voluntary ADR monitoring programme comprised the reporting of suspected ADR's and the recording of drug orders for the patients and the patient characteristics. The ward pharmacists monitored for suspected ADR's in all patients during their regular ward rounds. Six cases were reported in a population of 1506 patients monitored during the three months. The reports were mainly on moderate to severe suspected ADR's of pharmacologically unpredictable (type B) nature. The rate of reports received by the surveillance unit in this study was 4 reports per ward pharmacist per annum.

The second voluntary ADR monitoring programme comprised the prospective monitoring of 1555 patients by medical and nursing staff during their stay at the designated medical wards during the three month period. Patients were monitored for any ADR and when an ADR was suspected, the patient characteristics and drug orders were recorded and reported to the surveillance unit. Ten cases were reported represented by six reports from doctors and four by sisters. The reporting rate was 2 reports per doctor in four years and 3 reports for each member of the nursing team in 5 years. Reports were mainly received on moderate to severe suspected ADR's of a pharmacologically unpredictable (type B) nature.

LIST OF DEFINITIONS AND ABBREVIATIONS USED IN THE STUDY

Post-Marketing Surveillance (PMS):

Any non-experimental or observational study, method, or monitoring strategy that is applied to obtain information on drug experience (primarily adverse) after a drug is approved for clinical use.

Surveillance unit:

A non-profit company funded by a university and pharmaceutical companies. Its aim is to promote the safe use of medicines, to give advice on clinical aspects of pharmacology, and to monitor and collect reports on drug events. It is an independent body responsible only to the university.

The surveillance unit in the study was the Ciba-Geigy: Medicines Safety Centre (MSC), Department of Pharmacology, University of Cape Town, Observatory, 7925, Republic of South Africa.

Adverse drug reaction (ADR):

Any effect due to a drug which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis or therapy (2).

Adverse Drug Reaction Monitoring Pharmacist (ADRMP):

A clinical pharmacist, committed to a surveillance unit, responsible to conduct studies to promote the safe use of medicines. The pharmacist needs to give advice on clinical aspects of pharmacology.

Also the monitoring for adverse drug reactions and evaluation of suspected adverse drug reactions are part of the pharmacist's responsibility.

Clinical Pharmacology Ward Round (CPWR):

The clinical ward round is a regular weekly consulting teaching service to the teaching hospital. It is attended by clinical pharmacologists, medical and pharmacy staff, and medical and pharmacy students. One of its aims is to give advice on clinical aspects of pharmacology.

Ward Pharmacist Clinical Meeting (WPCM):

The meeting is held at weekly intervals. Clinical pharmacologists and "ward" pharmacists attend. Discussions on drug use and drug related problems in patients are held.

ADR'S: Adverse drug reactions

CM: Clinical manifestation

BCDSP: Boston Collaborative Drug Surveillance Program

SAMCC: South African Medicines Control Council

GSH: Groote Schuur Hospital

TYPE A reactions: The known pharmacology ADR's which are predictable, relative frequent, and seldom fatal.

TYPE B reactions: The unpredictable, idiosyncratic reactions including those that are mediated by immunological mechanisms. They are usually infrequent but can be very serious or fatal.

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1 INTRODUCTION

After World War Two, a phenomenal increase in the development of new drugs took place. Some of the drugs showed unanticipated therapeutic effects while others were not effective when taken by patients. The price paid for these remarkable therapeutic advances has been a high incidence of unwanted adverse effects.

In 1937 seventy six persons died after they had received a sulphonamide preparation which contained seventy two percent diethylene glycol. The preparation was put on the market without adequate animal toxicology studies (4).

In the 1950's, a relationship between aplastic anemia and chloramphenicol was suspected and a Registry of Blood Dyscrasias was initiated which established the danger and its likelihood (5,6).

The experiences with thalidomide (7) and practolol (8) during the sixties and seventies respectively focused attention upon, and raised serious questions about, the drug approval and monitoring process.

Recently, tienilic acid, benoxaprofen and zomepirac were withdrawn from several countries, due to the recognition of serious ADR's.

These emergencies indicated that a spontaneous reporting system on blood dyscrasias alone was inadequate and that a more comprehensive approach to the overall problem of recognizing ADR's was required. It also reinforced the search for new methods that would speed detection without adding appreciably to the burden of paperwork imposed on the health care professions.

While doctors take the responsibility for prescribing medicines for patients, it is the patient who takes the risk when taking the medicine. Therefore drug regulatory authorities were established to help combat the development of unsafe and ineffective drugs in an effort to reduce the risk for the patient.

The main objective of the regulatory authority is to ensure safe and effective drug provision to patients on a national level by means of legislation (9). These and other ADR's have prompted careful review of the drug approval process and stimulated efforts to develop post-marketing surveillance systems capable of early detection of ADR's.

In certain countries, committees and/or surveillance centres were established complementary to the regulatory authority to monitor drugs for safety and efficacy in the clinical setting. In 1963 the United Kingdom commenced with the gathering of information on rare ADR's and problems with new products when the Adverse Reactions Sub-Committee of the Committee on Safety of Medicines (CSM) established the Adverse Reactions Reporting System (10). The Swedish ADR Committee was established in October 1965. Furthermore a branch of the U.S.A. Food and Drug Administration (FDA), a branch of the World Health Organization (WHO), and many other countries and organizations established similar detection services (10).

On the South African scene, the South African Medicines Control Council (SAMCC) was established in the early sixties as the drug regulatory agency. The Ciba-Geigy Medicines Safety Centre was established in 1980 as an independent, university situated information centre with interests in drug safety surveillance (11).

Thus, in understanding the baseline risk of drugs for all recipients, it should be understood that the safety in drug development, as understood in regulatory and scientifically acceptable terms, must reflect safety under normal medical practice conditions. Because of the way new drugs are developed, the tendency is to exclude from clinical study those patients with unusual risk factors (children, pregnancy, old age) beyond the specific disease condition for which the clinical indication for regulatory approval is being sought (12). It has been widely accepted that pre-marketing studies on drugs are inadequate and therefore it became important to gain information on the adverse effects of drugs in clinical practice (9).

One of the major problems experienced with post-marketing surveillance studies is the under-reporting of suspected ADR's experienced in patients under normal daily practice. In the United Kingdom the reporting rate recorded by the Drug Surveillance Research Unit (DSRU) for prescription event monitoring programmes averaged 3 reports per doctor per year on drug events while the Committee on the Safety of Medicines experienced 1 report per doctor in four years with their voluntary surveillance ADR monitoring programme (13). The under-reporting of ADR's has been a major problem facing the effectiveness of post-marketing surveillance studies and many discussions were held to help combat this problem.

The literature was reviewed to unveil this problem in post-marketing surveillance and also to look for reasons why the reporting of ADR's is neglected. Incentive measures were also identified. The classification of ADR's, definitions in the literature and evaluation thereof were reviewed. The literature was reviewed to look at post-marketing surveillance in the development of drugs in man. Prescription event monitoring and other programmes were reviewed focusing on hospital drug surveillance methods.

In this study three different methods of prescription event monitoring have been implemented to promote the reporting of ADR's to a surveillance unit. The impact of these programmes on the reporting rate of ADR's in the hospital situation were described. These studies took place in the medical wards of an urban referral and teaching hospital. The hospital situation was seen to be incentive since the different health care professionals serve under one roof, often in the same ward. Ward pharmacy was also newly introduced at the hospital.

The intensive ADR monitoring programme comprised the monitoring of 228 patients by a dedicated pharmacist for all suspected ADR's to any drug prescribed during the patient's stay in hospital. Numerator data, i.e. drug orders and ADR's experienced as well as denominator information, i.e. total number of patients and patient characteristics were available. The impact of the intensive ADR monitoring programme was demonstrated by the relatively large number of mild, common and pharmacologically predictable ADR's recorded.

The voluntary ADR monitoring programme comprised ward pharmacists to monitor the 1506 patients admitted to these designated medical wards. The programme showed an impact on the reporting of moderate to severe often not pharmacologically predictable suspected ADR's. The ward pharmacist programme showed a report rate of 4 reports per pharmacist per annum.

The third method comprised the monitoring of 1555 patients admitted to the designated wards. The medical and nursing staff were requested to monitor these patients for any suspected ADR to any drug prescribed. Ten cases were reported which represented 2 reports per doctor in four years and 3 reports per member of the nursing staff in five years.

Thus, these observational studies described their impact on the reporting rate of information on drug experiences (primarily adverse) in hospital patients.

2 LITERATURE REVIEW

2.1 Introduction

The literature was reviewed for information concerning (ADR's). Different definitions of ADR's were described and the classification of ADR's, concerning the type, probability, and severity was looked at.

The monitoring of drugs for their adverse reactions is an important aspect of post-marketing surveillance. The knowledge accrued in pre-marketing studies is limited and was found inadequate to provide full information on drug effects (14). It was then decided to review the literature for aspects of post-marketing surveillance studies. The focus was on the position of post-marketing surveillance in drug development. The need for these studies was examined because a lack of information on rare effects, latent effects, drug interactions and effects occurring in special populations exists (12,15). The components of these studies might consist of a source of signals, resource to strengthen these signals, a resource to verify the hypotheses, and a resource to disseminate information. The objectives might be to identify ADR's at the earliest possible time, identify the factors relating to the ADR, and reduce the information gaps on rare and serious ADR's. Finally the limitations of these studies are the monitoring of very rare effects, latent effects and not readily detectable ADR's.

Various methods of post-marketing surveillance studies are applied to monitor drugs for ADR's in the clinical setting. Prescription event monitoring, a method of post-marketing surveillance and the method of choice for this thesis, and other post-marketing surveillance methods applicable to the hospital setting were reviewed.

Finally the problem of under-reporting of ADR's in post-marketing surveillance studies was reviewed. The response rate of ADR's reported is estimated at 1 to 10% and many reasons are found why the reporting of ADR's is neglected (16). The focus was on problems in the identification of ADR's, confidentiality, the report format, and incentive measures. Special attention was given to the reporting of ADR's in the clinical setting.

2.2 Adverse effects of drugs

One of the objectives of post-marketing surveillance studies is to keep vigilance on drugs in the clinical setting to enable man to get to know and understand the action of a drug, not known off at the time of registration. Very often unforeseen ADR's fall part of this action. The economic cost of ADR's is estimated as close to $5 billion per year in the United States. The direct costs includes the cost of treatment, cost of hospitalization, cost of efforts taken to prevent and diagnose ADR's (17).

2.2.1 Definition

The literature showed a variety of definitions for ADR's. An ADR was defined as " one which is noxious and unintended and which occurs at doses used in man for prophylaxis, diagnosis or therapy" (18,2,19) This definition was applied in this study. Other definitions which are used in the literature describe an ADR's as "any undesirable clinical manifestation (CM) that is consequent to and caused by the administration of a particular drug. The CM may be an abnormal sign, symptom, or laboratory test, or it may be a cluster of abnormal signs, symptoms and tests" (20). The Food and Drug Administration in the USA defines an ADR as "any experience associated with the use of a drug, whether or not considered drug related and includes any side effect, injury, toxicity, or sensitivity reaction, or significant failure of expected pharmacological action" (1).

2.2.2 Classification

Information retrieved from the literature classifies ADR's primarily into two general groups. The known pharmacology type A ADR's are usually predictable, relatively frequent, and seldom fatal. The unpredictable, idiosyncratic reactions including those that are mediated by immunological mechanisms are defined as type B. Type B reactions are usually infrequent but can be very serious or fatal (3).

The determination of the causality in the development of an adverse reaction has been a problem since man started with ADR monitoring. Medical judgement was based on knowledge and experience, and disagreement among experts exists. This was demonstrated in the literature (1). Attempts have been made to resolve this situation. Various drug monitoring systems have selected lists of terms and indicated conditions that should be met in order to assign a case to a given causality level. The causality scale retrieved from a study by Naranjo has been accepted for the purpose of this thesis (21). It consists of a short questionnaire (10 questions) and the probability index is given from a total score of -3 to 12. The method has been shown to be reliable and quick. It was compared with the detailed algorithm imposed by Kramer (20,22) and the result of this comparison indicated that both algorithms are equally reliable in the determination of causality (23). Similar conclusions were reached, but Naranjo's algorithm is the shorter and easier algorithm to use.

ADR's are classified to be:

i) not drug-related

ii) doubtful: some other cause of ADR's is judged more likely.

iii) possible: ADR's known to occur. The temporal relationship is less clear and other aetiologies are also possible.

iv) probable: ADR's commonly known to occur with clear cut temporal association and improvement on withdrawal of medicine.

v) definite: ADR's that were known to occur with clear cut temporal association, positive rechallenge test, or laboratory confirmation.

In this study the severity of ADR's was classified as follows (24):

- mild: no antidotes, therapy or prolongation of hospital stay required
- moderate: antidote or therapy required and/or hospital stay prolonged by at least one day.
- severe: potentially life threatening.
- contributed to death

Fortunately ADR's are rare events. It is often impossible to detect detrimental ADR's during the pre-clinical evaluation studies of new drugs. It has become necessary to conduct post-marketing surveillance studies complementary to pre-marketing studies. In the next section the literature was reviewed for post-marketing surveillance as a model to disclose more information on adverse effects of drugs after registration.

2.3 The Principle of post-marketing surveillance

2.3.1 The position in drug development

Since the main objective of the regulatory authorities is to ensure safe and effective drug utilization, drug development has become a costly and time-consuming process. The period of development of a new drug average about ten to fifteen years from initial invention of the chemical structure to approval by FDA for general use in the United States of America. The period of development depends on the benefit of the entity and the side effects or risks of the entity. Millions of dollars are spent in the development of a new drug (25).

A similar situation obtains in South Africa. The South African Medicines Control Council (SAMCC), the regulatory authority, has as its objective the assessment of drugs for safe and effective use (11).
The regulation of drugs is to protect the public and patients from unsafe drugs. The

SAMCC has to consider information on safety and efficacy of drugs in terms of registration, evaluation, manufacturing and promotion (11).

A series of tests is necessary to ensure maximum safety, though complete safety can never be achieved. The tests are, in order of succession, toxicity studies in animals, pharmacological studies in human volunteers, clinical trials, and finally, determination of any adverse effects after the drug is marketed and used on a large scale. Post-marketing surveillance studies form part of the latter phase.

The period of development of a new drug can be divided into two main stages (25).
(See table 1)

Table 1 The different stages of drug development

STAGE ONE → STAGE TWO

PRECLINICAL STUDIES

CHEMISTRY → PHARMACOLOGY

CLINICAL TRIALS

PHASE 1 → PHASE II → PHASE III → PHASE IV

The pre-clinical studies (first stage) comprise chemistry (synthesis, purification, patenting), pharmacology, pharmacokinetics and toxicity studies in animals and pharmaceutical development of dosage forms. The second stage, the clinical stage, includes four phases which embrace all the studies done in man.

Phase I studies can be defined as dose tolerance studies to determine an approximate dose for use in patients. This phase comprises studies done on 20 to 50 healthy volunteers.

Phase II studies aim to give information about the appropriate dose range, drug effects on disease processes and side effects. Patients suffering from the specific diseases, for which the drug is in development, are exposed to the drug. A limited number (50 to 100) of patients are included.

Phase III studies are undertaken by most of the pharmaceutical companies after they have gained information on the safety and efficacy of the drug in the appropriate dose range. This phase is aimed at the confirmation of efficacy, appropriate dose range and safety. Comparative studies on a number (500 to 2 000) of persons are conducted.

If the new drug shows good efficacy, better than placebo and better or at least as good as the comparative drug, and if the new drug causes no more or less ADR's than the comparative drug, a new drug application is submitted to the council. If the new drug application is approved, the entity is considered to be a drug and is marketed.

The three pre-marketing phases need to be distinguished from the phase IV studies. During phase IV clinical studies, the pharmaceutical industry plays a major role in providing information about newly introduced drugs and their effects, and in educating medical practitioners.

Phase IV studies could be experimental studies which include clinical trials or non-experimental studies. Non-experimental studies include spontaneous reports, cohorts and case-control studies (26).

In South Africa, any adverse reaction to the newly marketed drug, must be reported to the SAMCC by the pharmaceutical company responsible for the drug. No extensive surveillance system exists currently and the updating of the risk-benefit status of drugs is dependent on spontaneous reports from medical practitioners and pharmacists to pharmaceutical representatives. Because of the vagaries and inconsistencies of this ADR reporting system, post-marketing surveillance as an organised phase IV study on national and international level might emphasise problems with drugs not recognised by individual companies or national regulatory authorities.

While pre-marketing clinical trials are concerned with the efficacy of the entity, relative to existing alternatives (other drugs, placebos, surgical treatment, etc.) and with the detection of any high frequency of particular ADR's, post-marketing surveillance studies are seen to be complementary to pre-marketing clinical trials and are envisaged to ensure that observations on reactions of a large number of persons who receive a new drug are collated and used effectively (27).

In pre-marketing studies five hundred to three thousand patients are included. Such numbers lack the potential to detect rare events (in the 1 in 10 000 bracket, or rarer).

The probability of observing an ADR could be mathematically expressed as:

$$Pr = 1 - e^{-xy}$$

where Pr = Probability of observing the ADR's
e = Natural log
x = Probability of the ADR's
y = Number of patients needed

From the expression the number of patients needed to observe an adverse drug effect (with a probability of 1 : 10 000) once with 95% probability requires approximately 30 000 patients. An example of a drug effect with an probability of occurrence of 1 : 10 000 is penicillin anaphylaxis.

In assessing the feasibility of detecting ADR's by different approaches, information on the distribution of actual incidence among different important reactions is obviously critical. The literature regards an incidence of 1 in 200 or greater as high and of 1 in 10 000 or less as low, with others as intermediate (28). ADR's with an incidence of 1 in 200 or greater could be identified at the clinical trial stage. The ADR's with an intermediate frequency of < 1 in 200 or > 1 in 10 000 might be identified in post-marketing surveillance schemes, whereas those of low frequency may be verified by other methods, e.g. cohort studies (29).

While on average 3000 subjects are recruited for pre-marketing studies (Table 2) approximately 6000 patients are needed to detect an ADR's of intermediate incidence (1:2000) (Table 3).

Table 2: Numbers of patients usually recruited in pre-marketing studies

Phase I	Volunteer or very early patient studies	25-50
Phase IIa	Clinical pharmacology in patients	50-100
Phase IIb	Dose-finding studies and early efficacy studies	100-250
Phase III	Extended clinical studies leading to marketing	250-1000
		rarely > 2000
Total		Usually < 3000

Table 3: Numbers of patients required to detect 1, 2, or 3 cases of an ADR

Expected incidence of adverse reaction	Numbers of patients required		
	1	2	3
1 in 100	300	480	650
1 in 200	600	960	1 300
1 in 1000	3 000	4 800	6 500
1 in 2000	6 000	9 600	13 000
1 in 10 000	30 000	48 000	65 000

The numbers of patients in table 3 are based on the following assumptions:

(a) that there is no background incidence of the adverse effect;

(b) that the number of adverse events follows a Poisson distribution.

2.3.2 The need for post-marketing surveillance

At the time of approval and marketing of a drug, a need exists for information on rare effects, latent effects, drug interactions and effects occurring in special populations such as paediatric and geriatric groups, drugs during gestation and the perinatal period (15,12).

Drugs are prescribed to patients in clinical practice where poly-pharmacy is a reality. Patients often suffer from pre-existing diseases like impaired kidney function and chronic liver disease (12). An important need is information on the safety and efficacy of drugs in the broader perspective of population exposure to effect optimal drug therapy. Post-marketing surveillance, if used systematically could accomplish this need (30).

2.3.3 Limitations of pre-marketing studies

It has been appreciated that the knowledge accrued in pre-marketing studies is limited and therefore pre-marketing studies are inadequate to provide full information in the following areas (14).

These studies often do not permit the identification of side effects that might occur in certain subgroups of patients. They often do not permit for the identification of modified drug action when drug-drug or drug-food interactions develop.

In these often efficacy-directed studies, small numbers of carefully selected patients are included and this could result in uncommon ADR's (less than 1 per 10 000 drug users) not being detected (31).

Many types of patients who will ultimately use the drug in clinical practice are excluded from phase III studies. This includes the elderly, pregnant women, patients with diseases different to the one being studied, and patients on concurrent drug use (32). The risk-benefit ratios in clinical trials are rightfully considered by the ethical committees, and so limit, by various stipulations, these persons to be drug-exposed (33).

The duration of phase III studies are often short and therefore do not permit the identification of toxicity manifestations after long term use (25).

Pre-marketing testing does not provide absolute assurance of safety on drugs. In order to quantify the need for post-marketing surveillance studies on efficacy of drugs, 100 drug uses were reviewed in 1978 in the United States of America. From this study specific examples were provided of important modifiers of the efficacy of drugs that were not investigated prior to marketing. This indicated the gaps remaining in the information needed for optimal clinical use of drugs (34). The limitations are summarised in Table 4.

Table 4 Summary of limitations of pre-marketing studies

- often efficacy-directed studies
- small numbers of patients exposed to tested drug (500-3000)
- carefully controlled conditions
- tests are of a limited time duration
- a selected physician population conducts clinical studies
- indications for use are restricted
- specific exclusion criteria are followed.

2.3.4 Advantages of post-marketing surveillance studies

Post-marketing surveillance studies have certain advantages compared to pre-marketing studies. When post-marketing surveillance studies are conducted complementarily to pre-marketing studies the gaps remaining in the information needed for optimal clinical use of drugs might be limited.

Once a drug is registered, it can be used in any dosage for any indication, despite the restrictions implied by the package insert (30). The literature indicated that adverse effects of detrimental impact could manifest during this phase. Some of the reasons for this phenomenon could be that the drug is now used in larger numbers and in a greater variety of patients.

Large numbers of patients participate in post-marketing surveillance studies e.g., the U.S.A. Medicaid drug event method linked data on 1.4 million patients in the states of Michigan and Minnesota (14).

A multitude of patients of diverse age, sex, culture, ethnicity, geographical setting, nutrition, personal and social habits (smoking), and pathologies are treated by health care professionals in clinical practice (33).

Post-marketing surveillance supports and interacts with drug epidemiological studies (study of how drugs are used in patient care), clinical pharmacology (study of how drugs act in patients) and drug information (knowledge derived from these studies can be utilized in making the prescribing of drugs optimal, safer and cost effective) (35).

Different post-marketing surveillance methods could be developed and applied in a multiple complementarily system to satisfy the requirements of post-marketing drug evaluation (36).

Table 5 Summary of advantages of post-marketing surveillance studies

- large numbers and a heterogeneous patient population
- unrestricted use of the drug
- heterogeneous physician population
- drugs are prescribed/used for a longer period of time
- new information on drugs not determined in pre-marketing studies
- indication to patterns of drug use
- complementary to pre-marketing studies

2.3.5 South Africa's need for post-marketing surveillance

The majority of developed countries of the world keep an watchful eye on the drugs prescribed for and consumed by patients. These countries have learnt from previous experience to minimize the risk of drugs in clinical practice and initiated post-marketing surveillance studies (37,38).

South Africa has established the SAMCC to regulate her medicines, but lack a national network of post-marketing surveillance studies. The lack of a national post-marketing surveillance system might hamper the work of the regulatory unit in assessing national drug utilization. In this country, the medical practitioner voluntarily reports suspected ADR's to the pharmaceutical industry. The pharmaceutical industry is required by legislation to report any ADR's, previously not listed in the registration literature on their individual products, to the SAMCC. The channels from the practitioner to the industry are usually long and the industry is sceptical that their drug might be causally involved in ADR's; therefore serious shortcomings exist.

In the Western Cape, invited voluntary reporting of ADR's by the health care professions to the University of Cape Town's Ciba-Geigy: Medicines Safety Centre, is encouraged (39).

South Africa has a different climate from many other monitoring countries. Within the first three months of release of benoxaprofen in South Africa, 16 reports of significant skin reactions (photo sensitivity) were received by the UCT: Ciba-Geigy Medicines Safety Centre (33). In a country like Scotland with less sunshine, this drug toxicity passed unnoticed and resulted in more severe reactions (40).

South Africa has a variety of ethnic groups. People from different ethnic backgrounds often react differently to drugs. Surveillance should be done to investigate the genetic peculiarities of the different groups in the metabolism of drugs (41).

Many patients in the country still consult non-scientific healers and this different background drug utilization might have an influence on drug actions and interactions.

In Southern Africa malaria, bilharzia and other endemic diseases exist and drug treatment differs from other monitoring countries.

New drugs are often introduced to the South African market while not readily available in other countries.

Table 6 Summary of reasons for post-marketing surveillance in South Africa

- No formal national surveillance system available
- Difference in climate
- Variety of ethnic groups
- Different background drug utilization
- Different disease patterns
- Introduction of new drugs not readily available in foreign countries

2.3.6 Components of post-marketing surveillance

Post-marketing surveillance studies might differ in method, design and approach, but when used complementarily to other methods, they could serve as a system to meet the need for information on drug effects after marketing. The post-marketing system could consist of surveillance studies performed both nationally and internationally.

For proper surveillance of drugs after marketing, the system should comprise the following components:

- a source of signals of possible problems related to drug use.
- a resource to independently corroborate the existence of or strengthen signals or hypotheses in drug use.;
- a resource to verify or test the hypotheses and ideally quantify the magnitude of drug effects.
- dissemination of information to health care professions and patients

2.3.7 Objectives for post-marketing surveillance

The primary objective of drug surveillance is to identify at the earliest possible time the liability of a drug to produce unwanted effects which have not been established during pre-marketing studies (42).

Secondly, factors relating to the adverse reaction need to be identified from accumulated epidemiological, clinical and pharmacological data and if done comprehensively, this could lead to the assessment of risks of drugs in man (42).

Ideally, effective post-marketing surveillance would attain most information as soon as possible after marketing to reduce the information gaps (26). An emphasis was put on the earlier recognition of rare and serious ADR's and that provision should be made to estimate their incidence in a recorded population (43).

Post-marketing surveillance might complement pre-marketing studies in the identification of adverse reactions to drugs at the earliest possible time if it could be used to replace certain elements of phase III testing. This could possibly enable reduction in cost and shorter and less expensive drug development procedures (30).

With the three objectives in mind, post-marketing surveillance could be seen to protect the patient from serious drug problems, empower the physician to use the drug better and enable pharmaceutical companies to develop and market more effective drugs (18).

2.3.8 Limitations of post-marketing surveillance studies

Several practical limits to the goals of post-marketing surveillance exists.

Many ADR's of legitimate concern are rare, e.g. less than one per 50 000 to 100 000 and simply won't appear until an adequate population is exposed. Some adverse effects are latent e.g. interstitial nephrites and endometrial cancer and particularly if somewhat unpredictable, they can only be found after this latent period. Some adverse effects are not readily detectable, e.g. low sperm count in cimetidine users; thus, even if common, they may not be discovered unless otherwise signalled (26).

The logistical problem in performing adequate post marketing surveillance is to conduct the study at a reasonable cost, yet with a sufficient number of subjects exposed to the drug to detect drug effects that were not detected prior to marketing.

2.4 Post-marketing surveillance - The Methods

An urgent need exists to report ADR's. Various methods and systems have been designed through the years to enable researchers to file reports of ADR's into useful resources to determine drug safety and efficacy.

No single method of data collection will meet all the needs for post-marketing surveillance studies. A need remains for a large, relatively inexpensive, yet comprehensive system of collecting data on drug effects after marketing (44).

2.4.1 Prescription event monitoring

One of the methods of this modern post-marketing surveillance system applied in private practice comprised the identification of target prescriptions filled by pharmacists when submitted to the pharmaceutical pricing agency. The prescriber of the drug under surveillance was firstly identified and then requested to complete a questionnaire on any events encountered in patients taking the drug under investigation. The prescriber was requested to write any comment concerning the patient's clinical response or outcome on the patient record and the practice's nurse or secretary completed the questionnaire, subsequently signed by the prescriber (45).

In the hospital situation the pharmacist/nurse could identify the target inpatient prescriptions during a ward round. The prescriber could write any comment concerning the patient's clinical response or outcome on the patient record and the ward sister or pharmacist could complete the questionnaire, subsequently signed by the prescriber.

Prescription event monitoring could be seen as a combination of record linkage (an effort to link the patient's prescription with the patient's record) and cohort studies (an effort to monitor patients on selected drug treatment for ADR's) (45).

Advantages of the prescription event monitoring system are that no interference with normal prescribing practice takes place, no medical opinion about causality is needed, the information could be copied by the pharmacist, practice nurse or secretary, and it is relatively inexpensive and not time consuming. Information about the pattern of drug use and drug efficacy can be derived from these systems and the incidence of ADR's can be estimated in selected studies (46).

Disadvantages exist in the prescription event monitoring system. It can only be applied when substantial sales or prescribing of the drug has been effected. In general practice the number of selected drugs will be limited to the number of drugs a pharmaceutical pricing agency could manage to identify at a time. Physician cooperation could be a limitation to this system and non-prescribed drugs and drugs used in hospital practice are excluded. There is a potential for confusion in practices with many Botha's and Jones's. An increase in new drug registrations could start a bottleneck effect with the pharmaceutical pricing agency (27,30). The ward pharmacist, with one of his functions to monitor target drugs prescribed for inpatients, could partially meet the need for information on drugs used in hospitals.

A special drug survey research unit was initiated at the University of Southampton in 1980 (45). The objective was to detect with 95% certainty ADR's that occur in more than 0.1% of the first 10 000 patients who receive a new product. All prescriptions written by general practitioners, were selected and followed up through contact with the general practitioners. This was the extension of the recorded-release method and the development of prescription event monitoring in the United Kingdom.

During its first two years, prescription event monitoring provided data on nearly 120 000 patients, an average of about three reports per general practitioner per year. The great majority of reports described events which were not drug-related. The voluntary reporting method, the Yellow Card System runned by the Committee for Safety of Medicines (CSM), reported suspicions that drugs may have been responsible for ADR's at a rate of one per doctor every four years (13). While the voluntary reporting method dealt with reports on suspected ADR's, prescription event monitoring reflected a very good response rate of reports on events. Subsequently, statistical screening for drug-event associations might lead to special studies.

In eight prescription event monitoring studies done by the Drug Surveillance Research Unit between February 1982 and February 1984, an average of 63 three percent green forms were returned to the unit. Invaluable information about beneficial as well as harmful effects of the drugs were received and the method allowed for measure for their incidence (47).

2.4.2 Voluntary reporting

Voluntary reporting of ADR's is a relatively inexpensive method of collecting data but lacks comprehensive information on drug effects. Anecdotal reports, spontaneous reports, manufacturer (mandatory) reports and the published literature form an important source of information from voluntary reporting (48). These reports, whether reported on official report cards or in writing, form the backbone of a post-marketing surveillance system (18). The voluntary reporting system could generate signals on drug related problems in clinical practice, informs on well known reactions, incorporates all drugs, and could uncover rare, serious or fatal reactions. Its size is limited by the population sample, and allows for the generation of hypotheses for further studies (48,30,26).

The voluntary reporting system is often characterised by under-reporting of ADR's. It a lacks of denominator data, e.g. number of patients, drug exposures. It is often difficult to obtain follow-up information and the success often relies on individual vigilance and astuteness (48). The setting of priorities to reports and the effect of inflation on printing costs might cause serious long delays between the suspicion and publication of an ADR's (49).

Anecdotal reports might unjustly damage the reputation of a drug and its manufacturer and deprive ill patients of valuable treatment if not reviewed before publishing (50). Anecdotal reports need to be reviewed or otherwise published under the heading "unreviewed reports" to prevent unjust damage.

The Yellow Card System currently used in the United Kingdom and managed by the Committee on Safety of Medicines is an example of a voluntary reporting system (51). Its credits include identifying thromboembolism due to oral contraceptives (52).

The current blue card system developed in Australia accommodates the pharmacist as a voluntary monitor of ADR's. Hospital pharmacists are encouraged to report all suspected ADR's they encountered in patients during ward rounds to the surveillance institute (53).

The FDA's voluntary reporting system receives more than 20 000 reports annually on suspected ADR's from physicians and the pharmaceutical industry (54).

2.4.3 Intensive Monitoring

Intensive drug monitoring studies consist of systematic and detailed collection of data from well-defined groups of hospital inpatients (48). The surveillance is usually done by specially trained health professionals who devote their full-time efforts towards recording all drugs administered and all events which might conceivably be drug-induced (55). These monitors collect relevant information including diagnosis, therapy, and smoking habits of patients.

There are mainly three approaches of study applied to intensive monitoring of ADR's (89):

- <u>the patient-orientated</u> approach where all adverse drug reactions, in all patients and in relation to all drugs are monitored. The possibility exists that susceptible patient populations can be detected and predicted.

- <u>adverse-reaction-orientated</u> (case) approach where adverse drug reactions in patients in relation to all drugs are monitored. The use of this type of study approach is important in those patients whose admission to hospital is fully or partly due to an ADR's.

- <u>drug-orientated</u> approach where all adverse reactions in all patients but only in relation to some drugs are monitored. In this type of surveillance an individual drug or group of drugs is monitored for known, suspected or previously unsuspected adverse reactions.

Intensive drug monitoring systems, in general, are advantageous in that they could provide quantitative and qualitative data about the incidence of ADR's, identify certain groups of patients at high risk or predisposed to ADR's and analyse factors which might contribute towards reactions. These systems might determine whether ADR's are related to the dosage, source or quality of certain drugs (56).

Intensive drug monitoring studies are impaired by several factors. Mainly inpatients at hospitals are monitored and usually only during their stay in hospital. Often drugs on hospital code only could be studied. Relatively small population sizes observed for relatively short periods in these studies often result in the non-identification of rare and delayed ADR's. These studies call for a great demand on resources in the hospital setting (56).

The "Comprehensive Hospital Drug Monitoring Berne" determined the mathematic-statistical frequency of a maculopapular rash at 11.0% for aminopenicillins, 3.7% for other penicillins, and 3.4% for co-trimoxazole and sulphonamides compared to 1.2% in patients treated with other than the especially mentioned drug groups. Two new ADR's were detected by this intensive system: arterial hypotension due to novaminesulfon-dipyrone and drug fever to the antidepressive-drug nomifensin (57).

The "Boston Collaborative Drug Surveillance Program" (BCDSP) is the most successful scheme of this type of monitoring (58). Trained nurse monitors on hospital wards survey patients for ADR's and collect relevant information including diagnoses, therapy, and smoking habits. Many results have been published by this unit and the observation that postmenopausal oestrogen therapy and the contraceptive pill can increase the incidence of gallstones, has been acknowledged (37,38).

Apart from the BCDSP, mention should be made of a drug information system operating in hospitals in Aberdeen and Dundee (59). This system has been used to investigate a number of problems including the relationship between methyldopa and haemolytic anaemia, between tricyclic antidepressants and sudden death, and between furosemide and thrombocytopaenia (60).

2.4.4 Other methods

2.4.4.1 Cohort methods

Cohort studies comprise the identification of a cohort of patients started on treatment with a particular drug(s). The cohort study is a very powerful method, where feasible, and was used for example in the Royal College of General Practitioners' study on oral contraception (56).

The identification of a cohort of patients could be done by the pharmacist (53), doctors (61) or an interviewer (88). ADR's could be identified from the patient's record (53) or during interviews (62). Interviews with patients must be designed and conducted to prevent biased recording. The SAFTEE modification used in a study represents reduced biased interviewing (62). Leading questions on suspected ADR's were not asked, but information was clustered by asking questions on drug effects on the body region.

Four traditional types of cohort studies are used in the pre-clinical and clinical stage of drug development. The types of studies are registered release, recorded release and monitored release (43).

The registered release of a drug comprised the filling of registers on the new drug. Between 5 000 and 10 000 registers had to be filled before normal marketing or promotion of a drug was permitted. Questionnaires on symptoms in patients, for whom the drug were prescribed, had to be completed by the prescriber (63).

Monitored release permitted the approval of a new drug to be marketed, but at the time a normal prescription is dispensed, the pharmacist must transcribe all information on to a simple form and forward it to a central monitoring agency. Follow up was done by filling out a questionnaire by the prescribing doctor on ADR's (64).

Recorded release of a new drug comprised the normal marketing and promotion of the drug but the prescribing doctor was requested to complete a special prescription form, a copy of which had to be sent for registration to a central agency. Follow up information included the completion of a questionnaire by the doctor to identify ADR's (65).

In a cohort study, 8291 patients were monitored for ADR's with the drug ketotifen. For one year the drug was tested for efficacy and adverse effects, and applicable information was also communicated to the prescribers (66).

The cohort study method is about the most scientific, logical way to answer the question of cause and effect and is often used to study newly marketed drugs. It demonstrates time relationships between the presence of variables and the subsequent disease. It is also an ideal study method to answer a question on single exposure experienced by a relatively small population and multiple possible outcomes (67). The numerator (e.g. number of ADR's) and denominator (e.g. number of patients) can be monitored and it is useful for in-depth information for several measures on drug safety and efficacy. Cohort study allows to study the effects of known demographic variables and the production of follow-up information which is complete and comprehensive. It also generates hypotheses, tests them and enable researchers to test hypotheses derived from other studies.

The cohort study method is logistically difficult to perform because of relative high costs and long-term commitment by staff. Biased reporting could happen and compliance and adherence to the programme must be enforced to prevent this. Doctors might prescribe alternative drugs rather to go to trouble of completing the documents.

2.4.4.2 Record linkage

This ADR's monitoring method links patient records with drug treatment and any clinical event after treatment. It consists of the recording of medicines given to a large patient population and the studying of their morbidity and mortality rates over a long period. Opportunities for this type of research method are greatest in countries with highly organised health services, such as the Scandinavian countries and the United Kingdom. The patient records might consist of general practice records or hospital records of illness events or prescriptions.

The BCDSP collects data for patients admitted to selected hospitals. Success with this program includes incidence rate determination and population-at-risk information for susceptible drug use. The database permits dozens of studies on a variety of disease states in all ages of patients (10).

In England, the Oxford Record Linkage Group used population based data to monitor major ADR's to drugs prescribed in general practice (68). A total of about 43 000 people were included.

Retrospective linkage of drugs prescribed in general practice with illness events noted, confirmed the association between practolol prescribing and peritonitis (29).

Record linkage is expensive when started, but once developed it serves as an excellent and relatively inexpensive method to detect delayed effects, sudden deaths outside hospitals and effects on the fetus, all of which are difficult to study by other means. This method enables opportunities for research on prescribing patterns.

This method is limited by incomplete or inaccurate records. The studies are usually retrospective and there is omission of any record of self-medication.

2.4.4.3 Special epidemiological studies

This method consists of a modification of the classical case-control study (69). In these studies one starts with the effect and looks for the associated drug(s). It is not a method for detecting new ADR's but rather to test a hypothesis.

Investigators start by assembling a group of people (cases) who are known to have experienced a particular effect that is suspected of being an adverse reaction to a drug. The number of cases are then determined from the group of patients who had previously taken the suspected drug and for comparison the previous usage of the drug is then determined in a control group of people selected for not having had the ADR's.

A case-control study was done on the safety of cimetidine in 9928 cases and 9351 controls (70).

2.4.4.4 Vital and mortality statistics in outomated data bases

Vital and mortality statistics are the basic research data issued by a bureau. The data (information) is usually computerised and easy screening of essential data can be done (71). The data includes registries of blood dyscracia, birth defects, teratogenicity and mortality rates of a population. Information from the data base could also include the identification of the patient characteristics (confidential), prescriptions filled and the medicine dispensed, the prescriber and demographic data. Medications can also be linked to diagnoses and outcomes in patients.

These data bases could be utilised to analyse cohorts of patients who have been exposed to a drug or have specific diseases and to compare them with matched or unmatched control groups (44).

Such a data base could also be screened for important ADR's to assist clinical reviewers in finding associations between drugs and important adverse reactions which have enough potential credibility to warrant subsequent in-depth evaluation by other means e.g., cohort or case-control studies (71).

Examples of studies where automated data bases were used extensively included the BCDSP (72) on hospital inpatients, the experimental Kaiser-Permanente Surveillance System (73) on hospital outpatients and Prescription Event Monitoring (45) in clinical practice.

2.5 THE PROBLEM

2.5.1 Under-reporting of ADR's.

One of the major problems in post-marketing surveillance and ADR's monitoring is the lack of or under-reporting of ADR's to surveillance units. International literature estimates the response rate of ADR's reported at 1 to 10 percent (16,74). The South African response to the reporting of ADR's is not much different to international figures. In a report published 149 report forms were completed and returned to the surveillance centre from a total of 24 369 sent out (39).

This worldwide phenomenon happens to be a major defect in individual reporting systems. It decreases the quantity of data and makes statistical evaluations more difficult. Reports received might not be representative or typical of the reactions that are actually occurring. Conferences are held regularly to address the problem.

Knowledge about a drug and the experience with a drug are two vital elements in well-considered drug therapy. It is only with regular use in clinical practice that experience is gained. Reporting of ADR's means the sharing of drug experiences which could lead to the growth of scientific objective information. It could assist the practitioner in decision making, and so optimises drug therapy in the patient. Reporting is not a one way process, since findings are ploughed back into clinical practice by means of information bulletins and consulting services to healthcare professionals.

For many reasons, health care professionals fail to report drug experiences. Studies unveiled some of the reasons why health care professionals hesitate to report ADR's (51,75).

2.5.1.1 Reasons why reporting is neglected

Inman described the "seven deadly sins" which result in non-reporting (51):

- complacency, the mistaken belief that only safe drugs are allowed on the market
- fear of involvement in litigation.
- guilt because harm to the patient has been caused by the treatment the doctor has prescribed
- ambition to collect and publish a personal series of cases, a common human failing that may lead to serious delays in recognition of a hazard.
- ignorance of the requirements for reporting
- diffidence about reporting mere suspicions which might perhaps lead to ridicule
- lethargy : an amalgam of procrastination, lack of interest or time, inability to find a report card and other excuses.

In a survey the decision not to report an ADR's was found be one of the following (76):

- the event is an established side effect mentioned in the package insert
- the event is not of a serious nature - therefore no need to report
- difficulty in assessing which drug is responsible for the reaction
- do not have enough time to fill out the formal reporting form

2.5.1.2 Identification of ADR's

The recognition or identification of ADR's is often difficult for health care professionals because the effects cannot always be viewed as clear-cut cause-effect events and this could contribute to the under-reporting of ADR's (77).

Drugs that accumulate in certain tissues could cause damage long after they have been discontinued (78). Difficulty in proving a cause-and-effect relation in drug toxicity is compounded with variable compliance with medical orders (79). Another obstacle to recognition of drug reactions is the physicians' low index of suspicion of a drug to cause ADR's. A final obstacle to the identification of ADR's is the use of combinations of drugs which might increase the difficulty to identify ADR's (80).

2.5.1.3 Confidentiality

Some professionals might resist the reporting of suspected ADR's due to fear for the general identification of patients. Much controversy exists on what needs to be made available to surveillance officials regarding the content of patient records.

It is essential to obtain the correct identification of patients to avoid duplication of reports on the same patient by different observers. In this case a suggestion was made that a protocol has to be cleared through hospital research committees to protect the patient, prescriber and researcher (81).

The general view was that certain criteria need to be reached. Permission needs to be obtained from the patient before the interview, the patient's surname needs to be secured in computer files and the prevention of decoding must be rendered by internal security systems (81).

In ADR's monitoring the emphasis is on patient characteristics and not the identification of the patient. In order to simplify the complexity of confidentiality, the coding of patients under surveillance was a logical step. For the purpose of this study, numeric codes were allocated to the patients to ensure confidentiality..

2.5.1.4 Report format

Too little information on a report card might result in a useless report, while comprehensive report formats might antagonise the professionals to report ADR's. Researchers might differ on the minimum information needed on a report form, but they all agree that poor documentation of ADR's is a major obstacle in the evaluation of ADR's (18). Special care needs to be taken when documenting a report.

The basic or minimum information needed on a report form could be summarised as follow:

- patient: essential demographic and nosological information
- drug: formulation, route of administration, duration of treatment and indications for use.
- reaction: description (including timing, severity, de or re challenge) treatment and outcome
- other factors: concurrent diseases, concomitant drugs and environmental factors

The more information available in a report the better, and when a voluntary drug monitoring method is followed, the following summarised minimum information is required (82):

- correct identification of patient (confidential)
- age
- sex
- name and formulation of drug(s) given (all concomitant medication should be listed)
- dosage
- duration of treatment
- interval between starting treatment and appearance of adverse drug reaction
- outcome of ADR's.

2.5.1.5 Incentive measures

The following suggestions were made to maintain a high level of reporting (9):

- keep the professions regularly informed about the work and data collected
- it is important for reporters to have feedback on information.
- give reply to reporters of ADR's
- encourage manufacturers to inform the press or profession on newly reported unexpected reactions

3 AIMS AND OBJECTIVES

3.1 Introduction

From the literature reviewed it was seen that ADR's are an every day problem in clinical practice. ADR's caused major disasters in history. The incidence of ADR's occurring in clinical practice is not always reflected by the reporting rate. Dozens of methods have been developed to assist the surveillance centres and drug regulatory agencies in determining the safety of medicines in clinical practice. Response varied from low rates found with the cheaper voluntary monitoring systems (11) to high rates found with the very expensive intensive surveillance studies. These studies were not the complete answer to the prevailing problems facing the industry and government controlling bodies in putting a new and promising compounds onto the market. Soon it became clear that no single method of post-marketing surveillance could answer the need of ADR monitoring.

A large number of reasons were found in the literature why the professions hesitate to report ADR's. Some of the concerns of the professions were met by new systems complementing both pre-marketing and post-marketing systems. Such a new and promising post-marketing surveillance system developed recently to monitor for drug events, is the prescription event monitoring system (46). The advantages of this method were described in the literature review. The importance of the saving of both time and cost led to the design of this study.

3.2 Aims

This descriptive study aimed to observe the impact of three different methods of prescription event monitoring on the reporting of ADR's in a teaching hospital. The first method, the intensive adverse drug reaction monitoring method, monitored for any adverse drug reaction in all patients exposed to any drugs in the designated wards. The monitoring was done by a dedicated pharmacist in collaboration with the ward staff. The second method comprised the monitoring of any adverse drug reaction in all patients in the designated wards on a voluntary basis by the ward pharmacist. The third method aimed at the monitoring and reporting of any adverse drug reactions in all patients from the designated wards on a voluntary basis by medical and nursing staff.

Incentive measures taken in the voluntary programmes aimed to promote the reporting of ADR's. Reply was given to reporters. Information concerning ADR's, the monitoring and reporting thereof, was provided. Incentive letters were sent to the staff concerned to encourage the reporting of suspected ADR's.

The general aim was to monitor for common ADR's to all drugs in every patient admitted to the designated wards. This study was designed to monitor for ADR's with an incidence of 1 in 20 to 1 in 200. A population of 60 to 600 was needed to find an adverse drug reaction with 95% certainty once. It was hoped that a total population of 3 000 medical hospital patients monitored over the nine months would result in 30 to 330 reports. This figure was based on the statistics found in the literature estimating the incidence of ADR's in acute medical hospital patients at between 1% and 11% (57).

The reports received by the surveillance centre were analysed and classified according to type, severity and probability.

3.3 Objectives

The main objective for this study was to describe the impact of three different prescription event monitoring methods on the incidence of ADR reporting in a South African teaching hospital.

3.4 Hypothesis

Hospital surveillance programmes have an impact on the incidence of ADR reporting in a South African teaching hospital.

4 METHODS

4.1 Introduction

There seems to be no best method of drug monitoring, but only methods better suited for answering particular questions (83). In this study an epidemiological approach was followed and the prescription event monitoring programme was applied in three different methods of ADR monitoring.

A trial study was designed to enable the researcher to become familiar with the clinical environment of the teaching hospital and to stimulate a "feel" for the study designs best suited to answer the needs of the hospital situation. The trial study was followed by the intensive ADR monitoring programme. This was conducted by a specially designated pharmacist who monitored prospectively, all patients for suspected adverse reactions associated with any drugs prescribed for the patients in the assigned medical wards. This method was followed by a voluntary ADR monitoring programme in which the regular ward pharmacists were encouraged to monitor all patients for suspected adverse reactions due to any of the drugs prescribed in their assigned wards. The third method was a voluntary ADR monitoring programme and doctors and sisters were requested to report any suspected adverse reactions due to any of the drugs prescribed for all patients in the assigned medical wards.

The definition of an ADR described by the WHO was applied in all programmes (2). The same ADR report card was used in the voluntary monitoring programmes and the reports were evaluated by the same surveillance unit. A specially designed ADR report form was used in the intensive monitoring method to enable suitable space to document all drugs prescribed.

The "Draft of proposed scheme for ADR monitoring programme at Groote Schuur Hospital" in Annexure 1 need to be consulted when the following information is read:

When an ADR is suspected by a doctor, sister, nurse or pharmacist, the necessary basic information needs to be gathered and an ADR report card completed. It was made clear that it was preferred that the staff member who suspected the ADR or another suitable person instructed by that staff member, should complete the report card. The report card was to be secured by folding and stapling it and posted into the box (labelled ADR REPORTS) in the ward sister's office. The patient's doctor, if not involved already, had to be informed about the suspected drug effect.

The regular ward pharmacist was asked to collect the secured report cards and to hand them to the secretary at the main dispensary, and the secretary then to send the reports to the surveillance unit.

The report was unsealed at the surveillance unit by the ADR monitoring pharmacist (ADRMP). These measures were designed to help ensure confidentiality as well as efficiency.

The patient's doctor was officially informed (Annexure 2) that the case would be evaluated.

The following ADR criteria were followed to generate official notification: If the effect was not to be found in the official package insert of any drug received by the patient; if the effect was of major significance and if the effect provided new or additional dimensions to the established ADR knowledge of the drug concerned.

If the suspected effect did not match with these criteria, an abbreviated adverse drug report form was completed and filed in the data base at the surveillance unit.

If immediate attention was required, the case was referred to the surveillance unit for literature evaluation. If additional assistance was required, the appropriate service was contacted by the ADRMP. Such a service is the Clinical Pharmacology Ward Round (WCPR), or specialists or departments with expert knowledge of the drug and the use thereof.

Information from the ADR report card was subjected to evaluation. An algorithm (Annexure 3) was used to determine the liability of the suspected drug(s) to have caused the adverse effect.

If the information on the ADR report card was insufficient, the report was followed up to completion.

Feedback was provided for every report received: every report was acknowledged to encourage and motivate the hospital staff to report ADR's. The feedback report was mailed directly to the reporter and/or the doctor. Furthermore, if deemed advisable, supporting educational literature and documentation accompanied the report.

Should the need for publication of the case exist, the doctor in charge of the patient involved was contacted, and consulted on the manuscript.

Confidentiality was maintained throughout and only the reporter, the ADRMP and the surveillance unit personnel had access to the ADR report.

4.2 TRIAL STUDY

The study was based upon a cohort of patients from the six medical wards with a total of 244 beds and one dermatology ward with 15 beds. The study commenced in October 1985 and lasted four weeks.

The method applied was voluntary reporting. The ward medical staff, nursing staff and ward pharmacy staff were personally "orientated" by the ADRMP and requested to report to the surveillance unit any suspected ADR's they encountered in patients from these seven wards at Groote Schuur Hospital. All the patients in these wards over the four week period were included in the study. Any ailment suspected to have been caused by a drug and which led to the admittance of a patient to these wards, was to be sought and reported. Any suspected adverse reactions to any drug prescribed and taken by any patient in these wards during the patients' stay in the ward, was to be reported. The patients were excluded from the study once discharged from the ward or when transferred to another ward that did not form part of the study.

Incentive measures taken to promote the reporting of ADR's included the following: Information provided to staff on a definition of an ADR, objectives of the study and the method of reporting and mechanism for monitoring. The information was given verbally and in print to the nursing and pharmacy staff during the regular ward pharmacist-sister monthly meetings (Annexure 4). These meetings served as a forum where pharmacists and nursing staff discussed provisionary problems as well as new incentive ideas.

At this hospital, the medical, nursing and in some cases the pharmacy staff met once a week to discuss ward activities. Information (Annexure 4) was given verbally at these meetings. Personnel are invited on a weekly basis to present ideas and findings to the nursing staff of the hospital. Attendance to such meetings is voluntary. The hour per week meeting was used as a regular reminder and to provide more information on the study to the nursing staff (Annexure 4).

A letter, in both official languages (Annexure 5), was sent to all Groote Schuur medical staff to inform them about the proposed trial study. An ADR report card (Annexure 6) was included. Information on this proposed study was published in the Pharmacy News Bulletin and distributed to the wards.

The ADR report card was handed out to the staff during meetings, mailed to medical staff and put in special containers, labelled "ADR REPORTS". A container was put in each ward sister's office. Additional report cards were put in the container and the container also served as a mail box for completed ADR report cards. The report card was designed to fit the pocket of the hospital white coat to encourage ready availability of the report card.

When the ADR had been reported, the report was re-coded, evaluated and classified at the surveillance unit. The liability of a drug to have caused the suspected ADR was evaluated according to a probability scale.(Annexure 3) When follow-up was needed for completion of a case report, the reporter was contacted for more information. All ADR reports were acknowledged and when deemed necessary, feedback of an educational nature was provided on the case. After the evaluation, the ADR was classified according to the categories of the WHO Collaborating Centre for International Drug Monitoring in Adverse Reaction Terminology (84). The codes were used to classify suspected ADR's according to international drug monitoring system-organ classes. The ADR was also classified according to type and severity. Finally the ADR was entered into the unit's data base.

If additional assistance was needed on the suspected adverse reaction, the case was referred to the Ward Pharmacist Clinical Meeting for discussion and also to the weekly clinical pharmacology grand round.

4.3 Intensive ADR monitoring programme: Ward pharmacist

This study was based upon a cohort of patients during their stay in two medical wards with a total of 40 beds. The programme was conducted over a period of three months, November and December 1985 and January 1986.

All patients treated in these wards over the three month period were included in the study. Any ailment suspected to have been caused by a drug and which led to the admittance of a patient to the wards was identified and reported. Any suspected adverse reaction to any drug prescribed and taken by any patient while in the wards was to be reported. The patients were excluded from the study once discharged from the ward or when transferred to another ward which didn't form part of the study.

A pharmacist was assigned to act as ADR monitor to these wards. The pharmacist engaged in a specific ADR-orientated ward round three times per week. On this ward round, every patient's medical history was studied and the medical staff were interviewed to gain further information on suspected ADR's. All patient characteristics and a complete drug profile of every patient was taken and documented (Annexure 7). This was necessary since computer facilities at the hospital were not developed to accommodate medication history and patient characteristics. Patient medication histories, reports of night staff, medicine orders and dosages, reasons for change of drug orders and treatment regimes were screened and the relevant information was documented. The pharmacist also interviewed individual patients whenever possible, and sought from them any unusual symptoms/problems they had noticed. A general and broad inquiry was first done, and when possible this was followed by a systematic inquiry covering specific organs or systems relevant to the drugs prescribed and taken. The inquiry was done by using a modification of SAFTEE, The National Institute of Mental Health's "Systematic Assessment For Treatment of Emergent Events" (84). The method was designed to avoid leading questions; leading questions might well encourage over-reporting through suggestion.

The ward staff were actively encouraged to inform the pharmacist of any suspected adverse reactions in patients that they encountered in these wards.

The pharmacist attended the weekly clinical consultations held by ward staff. In general, case studies were presented and experts were asked for their advice in the treatment of patients.

These ADR ward rounds of the pharmacist took, on average, two hours to complete. The three ward rounds and attendance of the clinical consultations took seven hours per week all together.

When the ADR had been reported, the report was re-coded, evaluated and classified at the surveillance unit. Information was relatively easy to obtain as ward staff members became well known and were easily accessible. If additional assistance was needed on the suspected adverse reaction, the case was referred to the Ward Pharmacist Clinical Meeting for discussion and also to the weekly clinical pharmacology grand round. The ADR was then entered into the unit's data base. A program Dbase III, run on MS Dos, was used to file the data for the purpose of this study.

Feedback on the monitoring was given to the ward personnel on a monthly basis and problems encountered were discussed. Prescribing patterns were analysed and recommendations were made.

4.4 Voluntary ADR monitoring programme: Ward pharmacists

The study was based upon a cohort of patients in six medical wards. The six wards involved were all medical wards and involved 244 beds in total. The study took place from March 3, 1986 until the end of May 1986.

The ward pharmacist was asked to collaborate in this programme and to report any suspected ADR's to the surveillance unit. Six ward pharmacists were involved at any one time. All patients treated in the wards were included in the study. Any ailment suspected to have been caused by a drug and which led to the admittance of a patient to the wards was to be reported. Any suspected adverse reactions to any drugs prescribed and taken by any patient in the wards during the patient's stay in the ward, were to be reported. The patients were excluded from the study once discharged from the ward or when transferred to another ward which did not form part of the study.

On their daily ward round, the pharmacists were encouraged to check the prescription orders of the patients, to interview the patients where possible and to discuss drug related problems of the patients with the medical and nursing staff. The pharmacists were requested to assist in the identification of drug safety problems. To accomplish this, the pharmacists had to interview patients on admittance to the ward to gain familiarity with the medication history of patients; to screen the prescription cards for possible drug interactions, to check on dosages, and to enquire into reasons for changes in drug orders for the patients. The pharmacists were also encouraged to attend weekly clinical meetings of the ward staff (if such meetings took place in the particular wards involved).

Incentive measures taken included a formal orientating oral presentation made to the ward pharmacists on the proposed study a week before the study started.(Annexure 8) A questionnaire was handed out to those who attended the Ward Pharmacist Clinical Meeting. The questionnaire (Annexure 9) was designed to probe the awareness-threshold of the pharmacists for ADR report-worthiness; this questionnaire was completed by nine out of twelve pharmacists who attended the meeting. During the study, letters

(Annexures 10, 11, 12 and 13) were sent to the ward pharmacists on a monthly basis to encourage, remind and motivate them to report any suspected ADR they could discover in the patients from these medical wards. ADR cards were enclosed.

If an ADR was suspected, the ward pharmacist gathered all the basic information, filled out a report card and handed it over to the secretary at the main dispensary. The pharmacists were also encouraged to report cases by telephone, or to phone the "on call service" to contact the ADRMP should attention to the case be needed. If additional assistance was needed on the suspected adverse reaction, the case was referred to the Ward Pharmacist Clinical Meeting for discussion and also to the weekly clinical pharmacology grand round.

When the ADR had been reported, the report was re-coded, evaluated and classified at the surveillance unit. When follow-up was needed for completion of a case report, the ward pharmacist was contacted for more information. All ADR reports were acknowledged and when deemed necessary, feedback of an educational nature was provided on the case. The ADR was then entered into the unit's data base.

4.5 Voluntary ADR monitoring programme: Medical and nursing staff

The study was based upon a cohort of patients in six medical wards with 244 beds in total. It was conducted over a period of three months and started April 1, 1986 until the end of June 1986.

The medical and nursing staff were requested to voluntarily report to a surveillance unit any suspected ADR's they encountered in patients from the six wards at Groote Schuur Hospital. All patients treated in the wards during the three month period were included in the study. Any ailment suspected to have been caused by a drug and which led to the admittance of a patient to the wards was to be identified and reported. Any suspected adverse reactions to any drug prescribed and taken by any patient in the wards during the patient's stay in the ward, was to be reported. The patients were excluded from the study once discharged from the ward or when transferred to another ward which did not form part of the study.

When an ADR was suspected, the doctor or sister gathered the basic information on the case, completed an ADR report card and deposited it into the box provided at the doctor's office. The ward pharmacist collected the report cards and gave them to the secretary at the main dispensary. If additional assistance was needed on the suspected adverse reaction, the case was referred to the Ward Pharmacist Clinical Meeting for discussion and also to the weekly clinical pharmacology grand round.

During the two months (April and May) overlapping of this programme with that of the ward pharmacist programme took place. The medical and nursing staff were not informed that pharmacists were also requested to report any suspected ADR's to the surveillance unit. This overlap was designed to check on any difference in report incidence and information, submitted by doctors, sisters and pharmacists.

Incentive measures taken in this method included letters and information leaflets (Annexures 14, 15 and 16) sent to the doctors and sisters during the study period. ADR report cards were also included. This was done on a monthly basis to encourage, remind and motivate the staff to report any suspected ADR's they encountered in any patient in these medical wards.

When the ADR had been reported, the report was re-coded, evaluated and classified at the surveillance unit. When follow-up was needed for completion of a case report, the reporter was contacted for more information. All ADR reports were acknowledged and when deemed necessary, feedback of an educational nature was provided on the case. The ADR was then entered into the unit's data base.

5 RESULTS

5.1 Trial study

In all 848 (Table 7) patients were treated in the seven wards during the trial study. The number of 848 patients was calculated when the number of patient days were divided by the average length of stay. The statistics were disseminated by the Department of Statistics, Groote Schuur Hospital (GSH). Figure 1 illustrates the population distribution in this study.

Figure 1: Population distribution in wards.

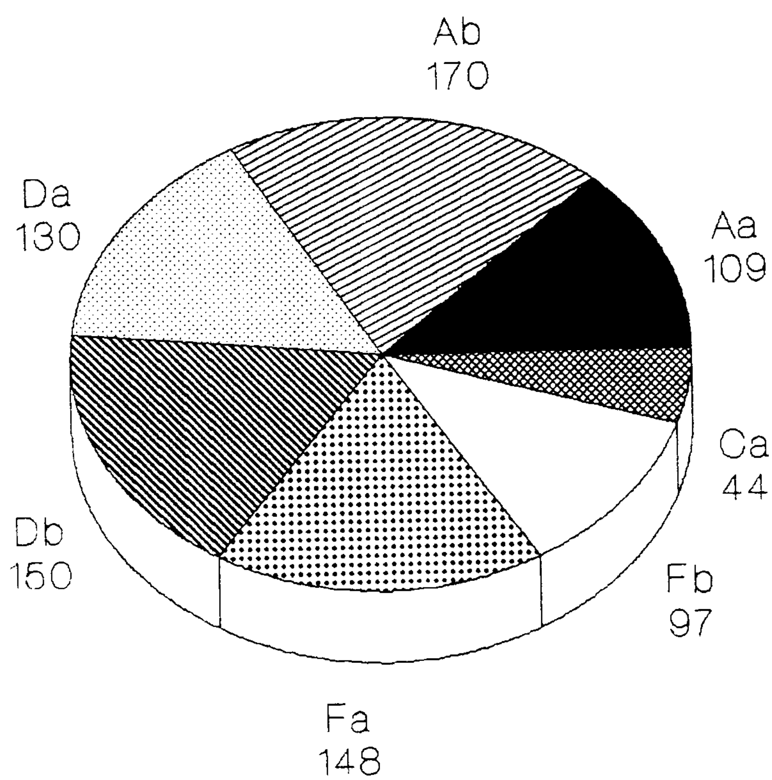


Table 7: Patient numbers included in the trial study

WARD	PATIENT DAYS	AVERAGE LENGTH OF STAY (DAYS)	NUMBER OF PATIENTS
Aa	808	7.41	109
Ab	796	4.68	170
Da	925	7.12	130
Db	936	6.20	150
Fa	961	6.49	148
Fb	647	6.67	97
Ca	356	8.09	44
TOTAL NUMBER OF PATIENTS			848

(Statistics from GSH Department of Statistics)

In this population, only 4 (four) reports were received by the surveillance unit and are summarised in table 8.

Table 8: Alphabetical summary of ADR's reported and drug liability in the trial study

SUSPECTED ADR	DRUG	LIABILITY OF DRUG			
		DO	PO	PR	DE*
tinnitus	chloroquine	1			
skin allergy	dipyrone			1	
photosensitivity	hydrochlorothiazide			1	
skin disorder	phenobarb	1			

* DO = Doubtful PO = Possible

PR = Probable DE = Definite

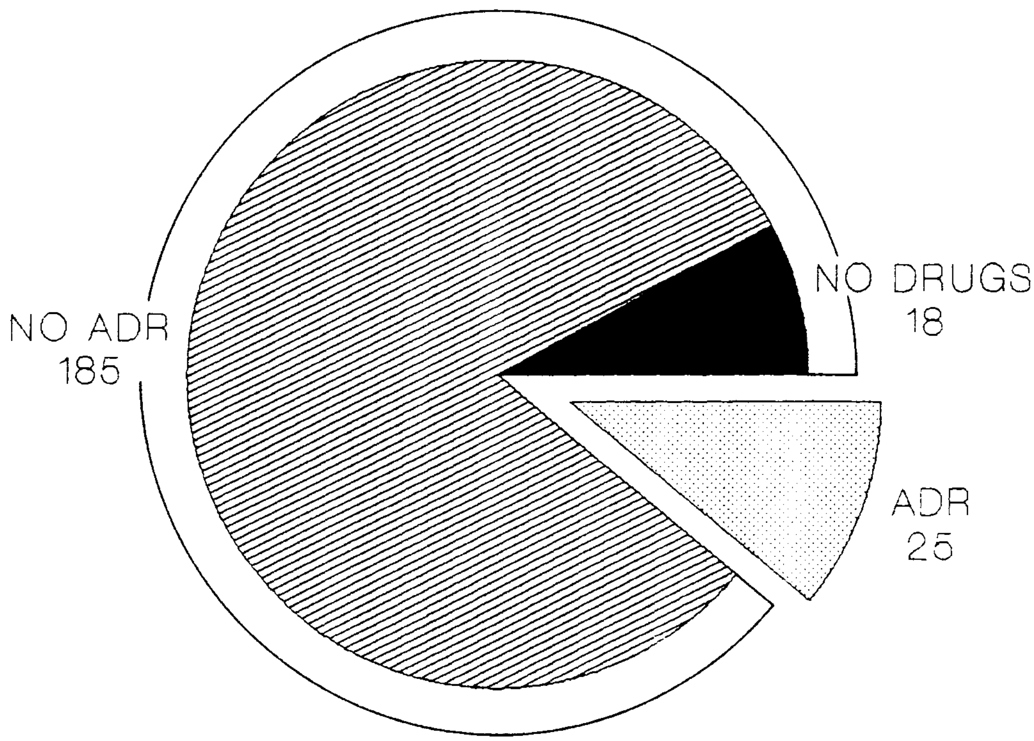
The information contained in the reports were incomplete and when followed up for completion, one case was found to be reported three weeks after it was identified. Little success was achieved with the follow up of reports. The incomplete nature of the reports resulted in difficulties being experienced during the evaluation of the reports.

Two ADR's were classified as type B reactions and one as type A. It was not possible to classify one case due to insufficient information. The suspected ADR's occurred in two white males, a black female and a coloured female. Two patients were from the adult and middle age group each. Two reports were received by the same doctor and he classified the reactions as severe. The other two reactions were classified as moderate and were identified by doctors. The ward pharmacist reported one case and it was signed by the doctor. No reports were received by nursing staff.

5.2 Intensive ADR monitoring: Ward Pharmacist.

In all, 228 patients were monitored for suspected ADR's. From this total population, 18 patients didn't receive any drugs and were admitted to the wards for observation purposes. No ADR's could be found in 203 patients while 25 patients experienced suspected ADR's. These findings are illustrated in figure 2.

Figure 2: Total population monitored.



Some patients experienced more than one suspected ADR and this resulted in 33 ADR's experienced by the 25 patients. In only one case did the suspected ADR result in prolongation of hospital stay. This suspected ADR was severe and the case was referred to the Ward Pharmacist Clinical Meeting (WPCM) and the Clinical Pharmacology Ward Round (CPWR) for discussion. Seven cases were admitted to the wards with reactions related to drugs. One case was a drug-induced ailment, two cases suffered from suspected ADR's when admitted and four cases were caused by overdose. Nineteen potential drug interactions took place in 15 cases but no adverse effects were suspected.

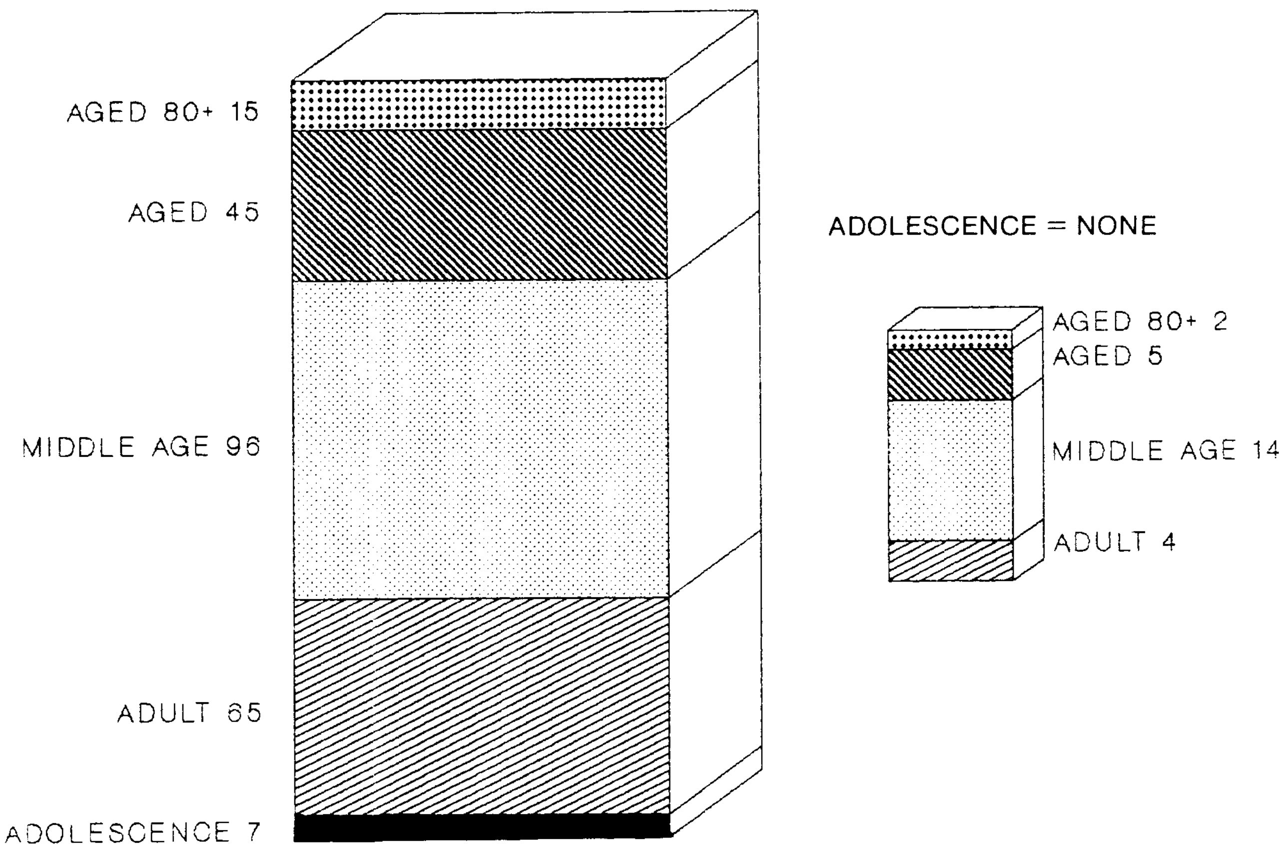
Of the 33 ADR's experienced by patients, 28 were reported to the ADRMP by patients and 5 were reported by doctors. The patients reported 19 mild reactions and 9 moderate ADR's. Doctors reported 3 mild reactions, 1 moderate reaction and 1 severe reaction.

At the end of the period 139 males and 89 females were monitored. From 25 patients who experienced suspected ADR's, eleven were males. A comparison between the distribution of sexes and the number of ADR's suspected with the sexes is found in figure 3. Five patients, four males (Annexure 17, cases 4, 9, 13 and 15) and one female (case 2) experienced more than one ADR during their stay in hospital. The one male experienced four suspected ADR's caused by 1 drug.(Case 15) From 33 ADR's suspected, 17 occurred in males and 16 in females.

Figure 3: Comparison of sexes and ADR's suspected in both sexes.

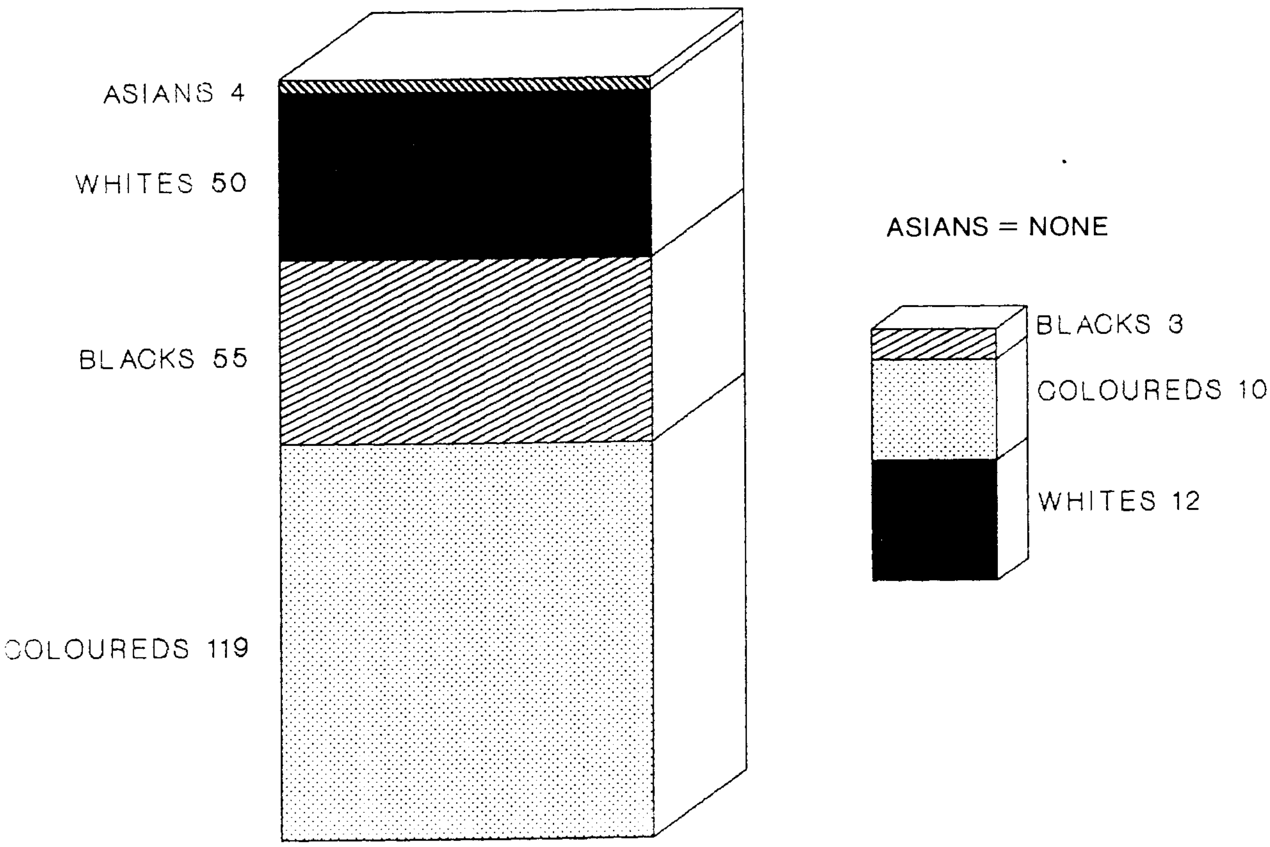
The population was divided into five age groups. Seven patients were adolescents (13-18 years), 65 were adults (19-44 years), 96 were patients in their middle years (45-64 years), 45 were from the aged group (65-79 years) and 15 were from the aged 80+ group (80 years and older). No ADR's were suspected in the adolescents, while 4 adults, 14 patients from the middle age group, 5 patients from the aged group and 2 patients from the aged 80+ group experienced an ADR. Figure 4 reflects these results. From a total of 33 ADR's suspected, no ADR's were suspected in the adolescence group. Four ADR's were suspected in the adult group, 21 in the middle age group, 6 in the aged group and 2 in the aged 80+ group.

Figure 4: Comparison of age distribution and ADR's suspected in the age groups



Fifty whites, 55 blacks, 119 coloureds and 4 asians were monitored in this study. Twelve white patients experienced ADR's while three blacks and 10 coloureds experienced ADR's. No ADR's were suspected in Asian patients. Figure 5 illustrates the comparison between the different race groups and ADR's suspected in these groups. Sixteen ADR's were suspected in whites, 4 in blacks, 13 in coloureds and none in asians.

Figure 5: Comparison of race distribution and ADR's suspected in the race groups.



From a total of 33 ADR's suspected, 23 were classified as Type A reactions. Figure 6 illustrates the ratio between Type A and Type B reactions.

The severity of these reactions ranged from mild, moderate, severe to contributed to death. No ADR was classified as contributed to death. Twenty reactions were mild, 12 were moderate and only one reaction was severe. The ratio in severity of suspected ADR's is illustrated in figure 7.

Figure 6: ADR types

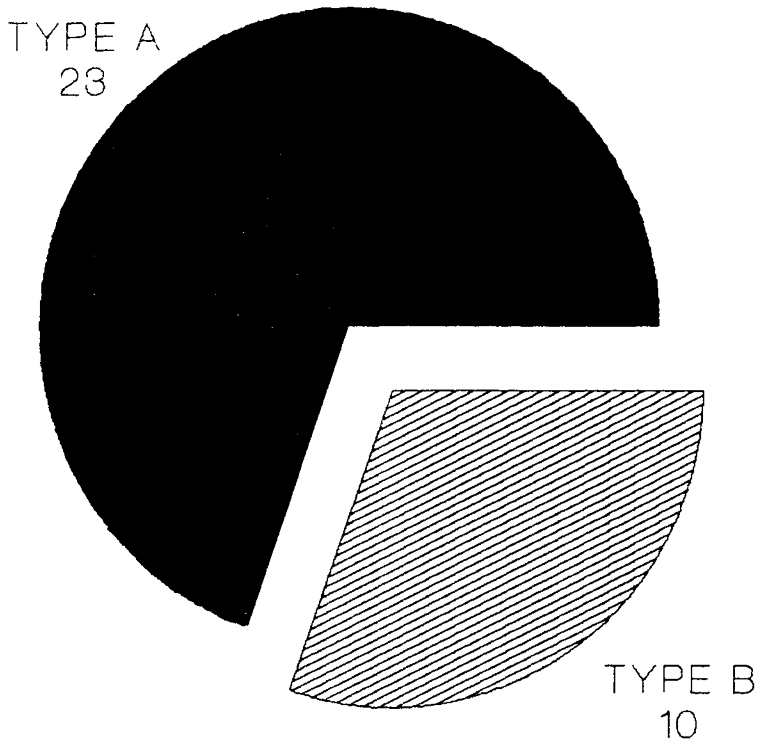
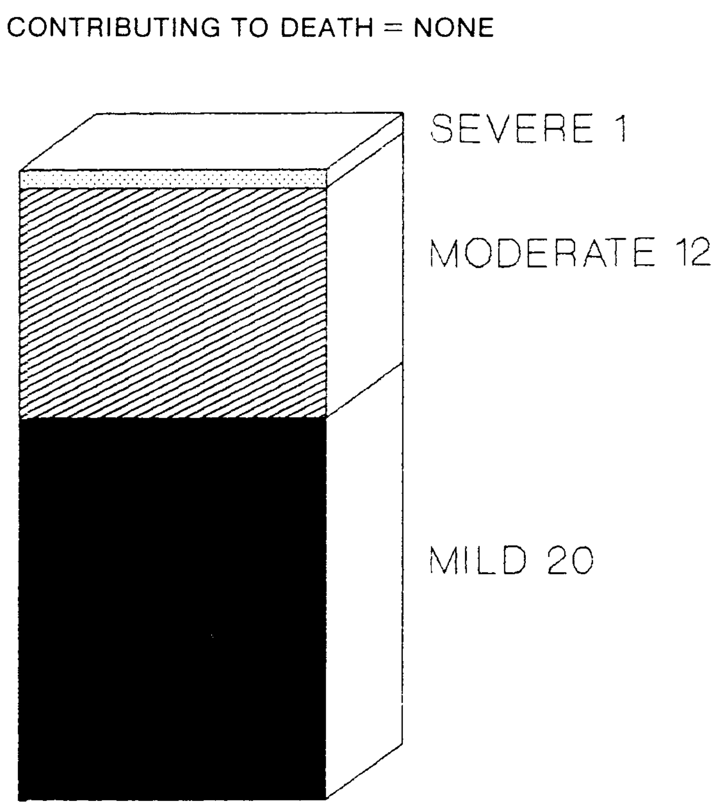


Figure 7: ADR severity ratio



The liability of a drug to be responsible for an ADR was determined by means of a questionnaire. The probability was indicated by the total score derived from the questionnaire. The probability of ADR's was classified to be doubtful, possible, probable or definite. In this study 4 ADR's were classified as doubtful, 15 were possible, 13 were probable and one was definite. Figure 8 illustrates the ratio between the different classes of ADR's.

Figure 8: ADR probability ratio

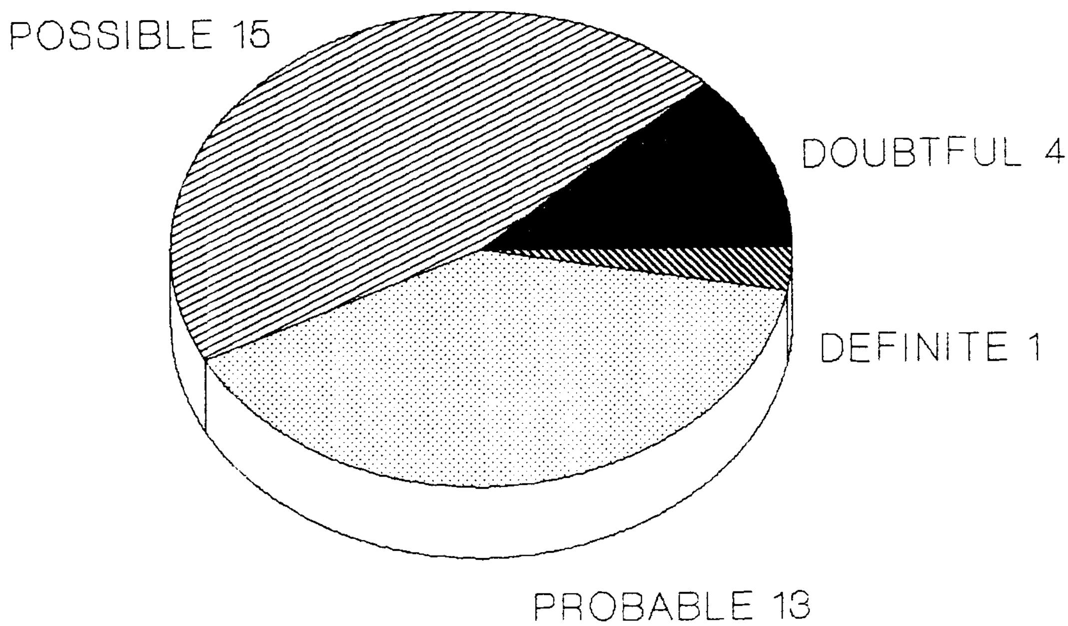


Table 9 gives a summary of suspected ADR's reported in the intensive ADR monitoring programme. The drugs and the liability of the drugs suspected to have caused the ADR is expressed in this table. From this table it could be followed that furosemide was possibly responsible for dizziness at one occasion.

Table 9: Alphabetical summary of ADR's suspected with drugs and drug liability

SUSPECTED ADR	DRUG	LIABILITY OF DRUG			
		DO	PO	PR	DE*
anorexia	rifampicin		1		
bitter taste	carbamazepine		1		
clammy hands	isosorbide dinitrate		1		
constipation	codeine			1	
	lorazepam		1		
	propoxyphene		1	1	
	ranitidine		1		
convulsion	aminophylline		1		
cramps	furosemide	2			
diarrhoea	amoxycillin			1	
	prazosin		1		
dizziness	diltiazem		1		
	furosemide		1		
	isosorbide dinitrate		2		
	nifedipine		1		
dry mouth	mianserin	1			
headache	isosorbide dinitrate			2	1
hot flushes	isosorbide dinitrate			2	
hyperkalaemia	amiloride co			1	
hypotension	atenolol		1		
	isosorbide dinitrate		1		
hypothrombinaemia	warfarin sodium			1	
itching	furosemide		1		
	spironolactone		1		
mouth ulcers	isoniazid	1			
	methyldopa		1		
	rifampicin		1		
nausea	digoxin		1		
	isosorbide dinitrate		1	2	
	nifedipine		1		
paraesthesia	furosemide	1			
purpura	atenolol		1		
pyrexia	oxybutinin			1	
TEN	isoniazid			1	
	rifampicin			1	
tinnitus	furosemide		1		

DO = Doubtful
PO = Possible
PR = Probable
DE = Definite

Three common ADR's made up for a total of 15 out of 33 suspected ADR'S. Dizziness, constipation and nausea each were suspected 5 times in the patients. Table 10 reflects the five commonly suspected ADR's.

Table 10: Five ADR's suspected commonly

Suspected ADR	DO	PO	PR	DE	Total
dizziness		5			5
constipation		3	2		5
nausea		3	2		5
headache		2	1		3
diarrhoea		1	1		2

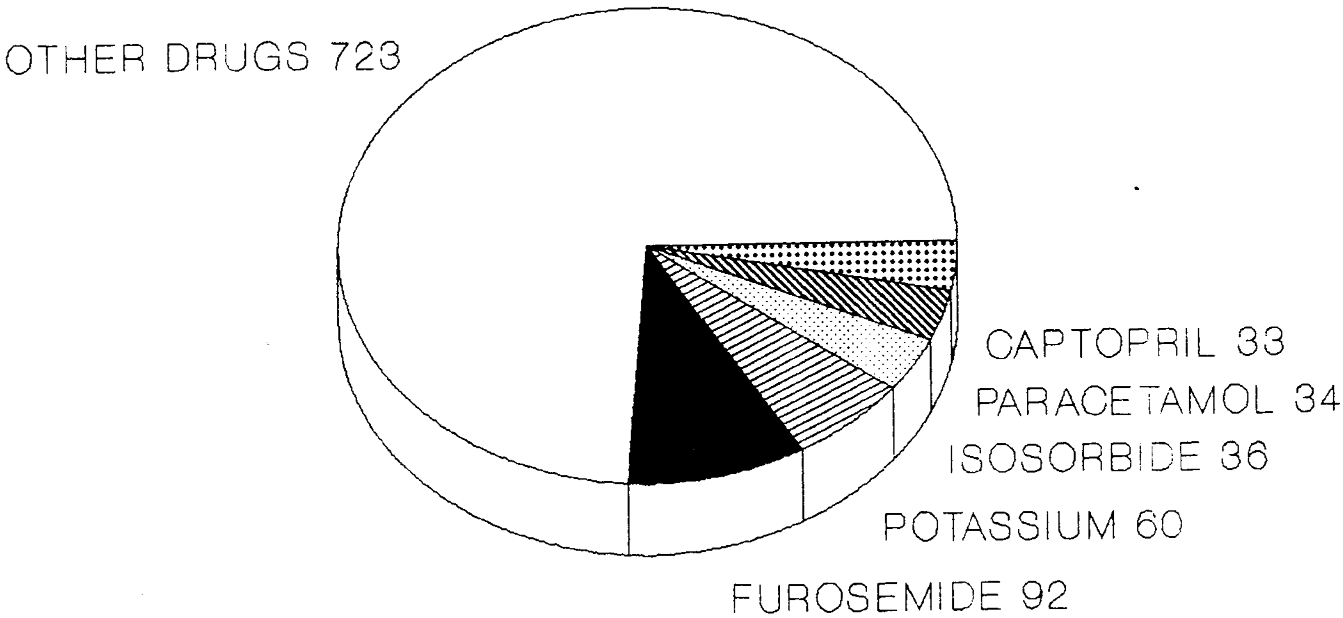
Nine hundred and seventy eight drug orders were written out for these patients. Each patient received on average 4,70 drug orders during the hospital stay. Table 11 summarises the top ten drugs ordered for patients in this study. From this table it can be followed, for example, that furosemide was ordered 92 times for 67 patients.

Table 11: Drugs commonly ordered for patients

DRUGNAME	NUMBER OF ORDERS	NUMBER OF PATIENTS
furosemide	92	67
potassium	60	54
isosorbide dinitrate	36	29
paracetamol	34	34
captopril	33	18
penicillin	30	29
tobramycin	29	24
digoxin	26	25
co-trimoxazole	26	25
amoxycillin	24	24

Figure 9 illustrates the top five drugs ordered in relation to the total number of drug orders (n = 978).

Figure 9: Drug order distribution.

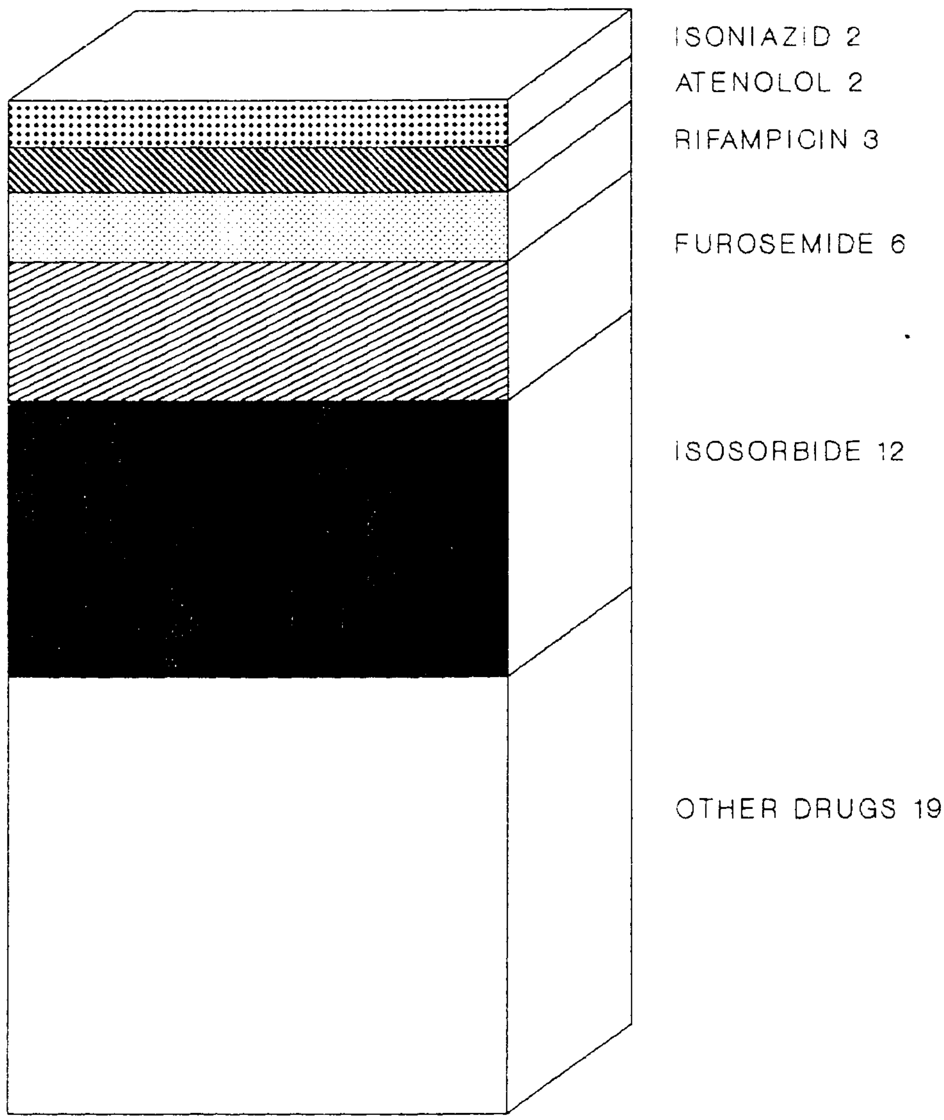


In table 12 the top six drugs suspected to have caused an ADR is summarised. From this table isosorbide dinitrate was suspected to have caused 12 ADR's. The drug was ordered 36 times in the study for 29 patients. Figure 10 illustrates the top three drugs in relation to the total number of drugs suspected to have caused ADR's (n = 44).

Table 12: Drugs commonly suspected with ADR's

DRUGNAME	NUMBER OF ADR'S SUSPECTED	NUMBER ORDERED	NUMBER PATIENTS
isosorbide dinitrate	12	36	29
furosemide	6	92	67
rifampicin	3	10	9
atenolol	2	13	9
isoniazid	2	10	9
nifedipine	2	8	7

Figure 10: Drugs commonly suspected in ADR's



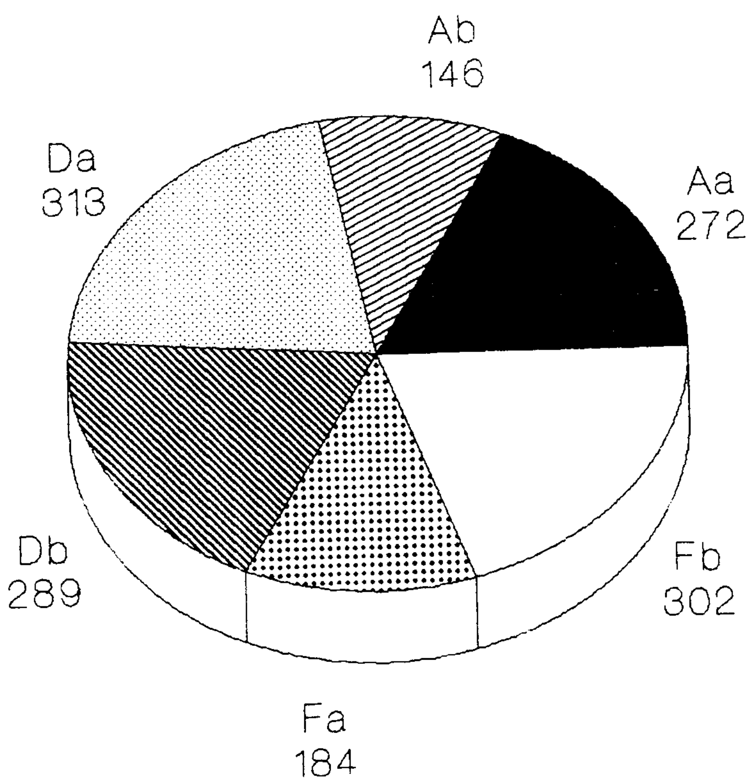
5.3 Voluntary ADR monitoring: Ward pharmacists

In all, 1506 patients were treated in the wards. Figure 11 illustrates the distribution of patients in the different wards.

Table 13: Patient numbers

WARD	PATIENT DAYS	AVERAGE LENGTH OF STAY (DAYS)	NUMBER OF PATIENTS
Aa	2715	9.97	272
Ab	3276	22.43	146
Da	2915	9.30	313
Db	2994	10.35	289
Fa	3557	19.30	184
Fb	3153	10.43	302
TOTAL NUMBER OF PATIENTS			1506

Figure 11: Population distribution in wards (n = 1506)



Eight ADR's were reported in six cases. Two reports were received from a newly qualified pharmacist, while three other reports were received by a ward pharmacist who had completed a drug information course prior to the study. In two cases the doctor informed the ward pharmacist on the suspected ADR.

No denominator information e.g. total drug orders, patient characteristics and patient medical history, was documented, except for the total number of patients. The ADR's reported, were suspected in three males and five females. In the different race groups involved, ADR's were suspected in 4 whites, 2 blacks, and 2 coloureds. No ADR's were suspected in the asian race group. ADR's were suspected in 1 adult, 3 from the middle age group, 2 in the aged group and 1 in the aged 80+ group. In one case report the patient's age was not recorded. The ADR's were classified as four type A reactions and 4 type B reactions. Six ADR's were possible and 2 probable while none were classified as doubtful or definite. Three ADR's were moderate, 5 severe and none were mild or contributed to death.

Table 14 summarises the suspected ADR's and drugs and the probability of ADR's received by the surveillance unit.

Table 14: Alphabetical summary of ADR's suspected with drugs and drug liability

SUSPECTED ADR	DRUG	LIABILITY OF DRUGS			
		DO	PO	PR	DE*
ataxia	phenytoin			1	
drowsiness	phenytoin			1	
erythema multiforme	phenobarbitone		1		
haematemesis	indomethacin		1		
hallucination	morphine		1		
nausea	digoxin		1		
skin rash	azathioprine		1		
tongue pain	metronidazole		1		

DO = DOUBTFUL
PO = POSSIBLE
PR = PROBABLE
DE = DEFINITE

Table 15 summarises the results of the questionnaire (Annexure 9) completed by the ward pharmacists.

Table 15: Results of ward pharmacist questionnaire

QUESTION	TYPE OF REACTION	YES	NO
1	Serious drug interaction	0	9
2	Common serious toxicity	4	5
3	Common drug interaction	0	9
4	Common side effect	0	9
5	Possible drug interaction	0	9
6	Serious allergic reaction	7	1
7	Common ADR	2	6
8	ADR	7	2
9	Serious uncommon reaction	9	0
10	Low patient compliance	0	9
11	Drug induced ailment	0	9
12	Beneficial combination	2	7
13	Serious drug-induced ailment	7	2
14	Serious uncommon toxicity	5	4
15	Fatal drug induced reaction	9	0

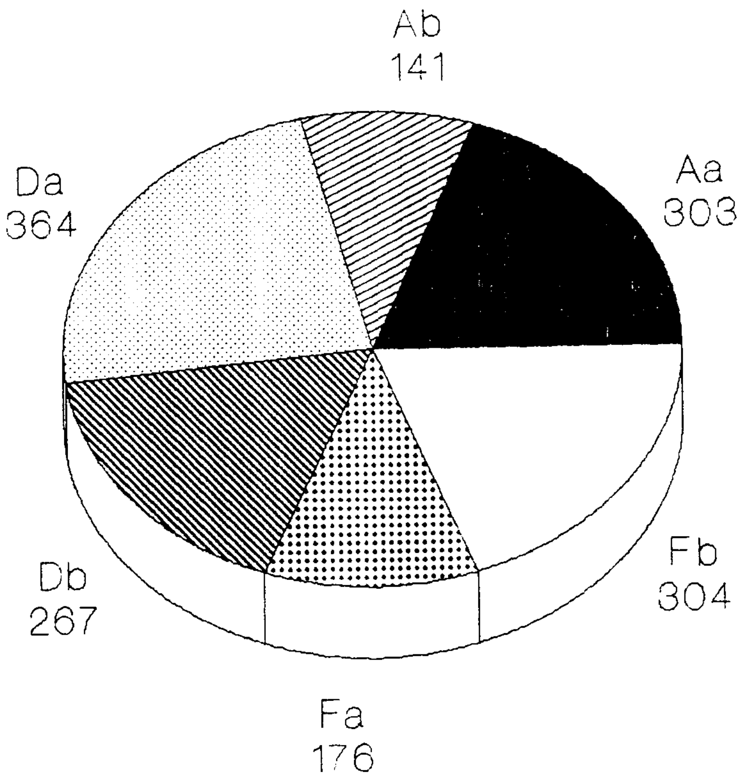
5.4 Voluntary ADR monitoring: Ward pharmacists

In all, 1555 patients were treated in the wards. Figure 12 illustrates the distribution of patients in the different wards.

Table 16: Patient numbers

WARD	PATIENT DAYS	AVERAGE LENGTH OF STAY (DAYS)	NUMBER OF PATIENTS
Aa	2975	9.80	303
Ab	3606	25.49	141
Da	2684	7.36	364
Db	3072	11.49	267
Fa	3720	21.06	176
Fb	2952	9.70	304
TOTAL NUMBER OF PATIENTS			1555

Figure 12: Population distribution in wards (n = 1555)



Twelve ADR's were reported in ten cases. Six cases were reported by doctors. The nursing staff reported 4 cases.

No denominator information was available except for the total number of patients. The ADR's were suspected in three males and nine females. In the different race groups ADR's were suspected in 5 whites, 4 blacks, 2 coloureds and 1 asian. ADR's were suspected in 1 adolescent, 3 adults, 2 from the middle age group, 3 in the aged group and none in the aged 80+ group. In one case report was the patient's age not recorded. Two ADR's were classified as type A reactions and 10 as type B reactions. The twelve ADR's were all classified as possible. None were classified as doubtful, probable or definite. Six ADR's were mild and 6 were moderate. No suspected ADR was severe or contributed to death.

Table 17 summarises the suspected ADR's and drugs and the probability of ADR's received by the surveillance unit.

Table 17: Alphabetical summary of ADR's suspected with drugs and drug liability

SUSPECTED ADR	DRUG	LIABILITY OF DRUGS DO	PO	PR	DE*
eosinophils rise	captopril		1		
erythema	propoxyphene		1		
erythema	ranitidine		1		
fever	captopril		1		
fever	indomethacin		1		
hypotension	vancomycin		1		
pain	vancomycin		1		
psychotic state	phenytoin		1		
urticaria	cephamandole		1		
urticaria	clindamycin		1		
urticaria	erythromycin		1		
urticaria	propoxyphene		1		

6 DISCUSSION

6.1 Introduction

The literature indicated that the knowledge accrued in pre-marketing studies is limited and was found inadequate to provide full information on drug effects. Post-marketing surveillance studies, the observational non-experimental studies of drugs in clinical practice, were developed to complement pre-marketing studies to assist the industry and government controlling bodies to overcome problems experienced in putting a new and promising compound onto the market. Despite the development of post-marketing surveillance studies, some limitations still exist. It has been postulated that ADR's with an intermediate frequency of < 1 in 200 or > 1 in 10 000 might be identified by post-marketing surveillance studies (29). Many ADR's are rare, e.g. less than one per 50 000, while some are not readily detectable, e.g. low sperm count in cimetidine users and others are latent, e.g. interstitial nephritis or endometrial cancer (26).

Various methods of post-marketing surveillance were developed. These methods vary from the inexpensive voluntary monitoring methods, e.g. Yellow Card System of the Committee on Safety of Medicines in the United Kingdom which usually lack denominator information, to the often expensive intensive monitoring methods, e.g. Comprehensive Hospital Drug Monitoring Berne (51, 57). Denominator information regards information on patient characteristics, drug orders and the patients' medical history. The intensive monitoring methods contain comprehensive numerator (suspected ADR's, population size) and denominator information. A new generation of post-marketing surveillance studies focus on comprehensive information at a cost-effective management level. Prescription event monitoring is an example of this new generation. Prescription event monitoring comprises the identification of target inpatient prescriptions by a monitor during a ward round. The prescriber is requested to write any comment concerning the patient's clinical response or outcome on the patient record and the monitor completes a questionnaire, subsequently signed by the prescriber (45).

The simultaneous application of different monitoring methods in a community could serve as a surveillance system to meet the important objectives set for such a system: to facilitate and promote safe and effective drug use in clinical practice. Current post-marketing surveillance programmes focus largely on regulation, overlooking other important methods of public health intervention, namely education and service. In the hospital ward situation, patients could be counselled on their medication before being discharged from hospital in order to enhance patient compliance and to encourage them to report suspected ADR's to health care personnel.

The decision to use prescription event monitoring and variations thereof in this study was taken to promote the saving of time and money, yet to obtain a comprehensive perspective of numerator and denominator information. At the time of the design of this thesis, the computerisation at ward level in GSH was very limited. Patient characteristics were available but the system lacked information on drug orders and patient medical history. For the purpose of the intensive ADR monitoring study, the pharmacist had to document the patient characteristics, drug orders and patient medical history to ensure comprehensive denominator information. The information was punched into a personal computer at the surveillance unit. The documentation of the information took at least half the time spent at the wards in this study. The voluntary ADR monitoring comprised the identification of the suspected ADR and the documentation of patient characteristics and drugs ordered prior or at the time of the ADR. In both the voluntary and intensive study computerisation could possibly save on time and also served as a resource for denominator information.

The lack or under-reporting of ADR's to surveillance units is one of the major problems of post-marketing surveillance. The response rate of ADR's reported averages between 0.6 and 10 percent (16, 39). Reports were received by the CSM at a rate of 1 report per doctor in four years (13). Various reasons were mentioned by authors concerning this problem.

In this study many incentive measures were taken to help combat the problem. Annexures 2, 4, 5, 8, 10, 11, 12, 13, 14, 15 and 16 reflects the incentive measures taken to promote an increase in the response of ADR reporting. These measures were taken to promote the reporting of ADR's to the surveillance unit. Feedback was provided to reporters, all reports were acknowledged, and when requested a case summary was provided to the reporter of the specific case. In the intensive ADR monitoring programme staff members of the ward were informed at monthly intervals about the work and data collected. Confidentiality was ensured at all times. The patient's folder number was recoded and the names of reporters were not computerised. The emphases for information needed were patient characteristics, avoidance of duplication, the suspected ADR and drugs ordered. The report card used in the voluntary ADR monitoring programmes was designed to ensure a quick, time saving yet comprehensive format for information on a suspected ADR. The basic information needed on the report form was included should the fifteen questions be answered by the reporters.

A few assumptions were made in this study. It was assumed that doctors have the best experience and knowledge of the overall clinical aspects of the disorders of the patients and that nurses spend more of their time at the patient's bed, than do doctors. It is also assumed that the pharmacist is the logical professional for studies of drug usage and ADR's. This study was designed to enable the pharmacist to function more directly as part of the medical service and to serve as a drug consultant. GSH, a South African teaching and referral hospital was assumed to be the ideal setting to conduct this study. Continuing education and in-practice training is part of the hospital activity. No official ADR surveillance system existed at GSH at the time of the design of this protocol. In general the structure and operation of a hospital provides incentive to perform surveillance studies. Educational meetings, where cases are discussed, take place regularly. All health care professionals serve under one roof, and are often represented in the ward situation too. In the hospital, detail on patterns of drug use may easily be determined because of its self-contained nature. Details on the frequency of ADR's, possible drug interactions, and the emergence of totally unexpected ADR's could be studied. Teaching hospitals operate in close contact with the universities and academia. The staff at these hospitals are encouraged to render a service using the most up-to-date techniques and medicine to treat very ill patients. In these hospitals patients are often treated with medicines not regularly found in other situations. Interaction and communication among the professions, especially medical and nursing, is active.

6.2 Trial study

The results found in this study were very limited. Only moderate and severe reactions were reported and they were type B reactions. Type B reactions are usually unpredictable, idiosyncratic reactions including those that are mediated by immunological mechanisms. Three of 4 reactions could be identified visually. Collaboration between the doctor and pharmacist resulted in the submission of one report by the pharmacist. This collaboration was encouraging since collaboration between the different health professions was seen to be of importance in the monitoring of ADR's. The experience gained from this trial study indicated a need for a dedicated monitor to be present at the ward. The limited results didn't allow for conclusions to be made on which profession would be best to fill the monitoring role.

6.3 Intensive ADR monitoring programme: Ward pharmacist

Patients treated in these wards suffered from coronary heart diseases or diabetes to a large extent. In the group relationship cardiovascular drugs and diuretics were implicated most often, and accounted for two thirds of the reactions suspected. The majority of the 33 suspected ADR's were mild (20/33) and of the type A (23/33). Type A reactions are pharmacologically known and are usually predictable, relatively frequent, and seldom fatal (3).) It was interesting to note that patients reported the mild (19) and moderate (9) ADR's to the ADRMP. The doctors reported 3 mild reactions, 1 moderate and the only severe reaction to the ADRMP. No additional ADR's were identified at the weekly clinical consultation session. More males received treatment in the wards, while females experienced more suspected ADR's than men. The majority (156/228) of patients admitted to these wards were older than 45 years of age. The majority (21/25) of ADR's suspected were also from this group. More than half the patients admitted were coloureds (119), followed by blacks (55) and whites (50). It was noticed that most suspected ADR's (16/33) were reported in whites. In this study cases could be followed up for completion much more easily. The staff was well known to the ADRMP and patients who experienced an ADR could be contacted easily. Despite the good communications, only one ADR could be classified as definite, while 13 were probable, 15 were possible and 4 were doubtful. Difficulty was experienced by the ADRMP to distinguish between the drug(s) and disease or other factors being responsible for the ADR.

Twenty five patients experienced 33 ADR's in this study. Forty-four drugs were suspected of being responsible for these ADR's. From the summary in table 9 it can be seen that four different drugs were suspected of being responsible for constipation in 5 patients. It is interesting to note that the top 5 drugs ordered for patients were not necessarily commonly suspected to give rise to ADR's.

6.4 Voluntary ADR monitoring: Ward pharmacists

The development of ward pharmacy in this hospital was in its infancy at the time of the design of this protocol. Pharmacists were mainly involved with dispensing, both for inpatients and outpatients. Pharmacists were allocated to wards where stock control was their main activity. The development of ward pharmacy in hospital practice could introduce a new dimension to better medical care for hospital patients.

The development of a staffing standard for hospital pharmacists was looked at (85). The authors found that dispensing of outpatient prescriptions occupied 22.05 percent of the pharmacist's time. Non-productive time accounted for 22.68 percent of the pharmacist's time while "other activities" occupied 54.21 percent of the pharmacist's time. The 54.21 percent of time listed as "other activities" embraces such activities as TPN compounding, reading of journals, telephonic and verbal communication with other health professionals and general stockkeeping/administrative work.

The South African Pharmacy Council resolved that the profession of the pharmacist, without neglecting its remedial role, should gradually assume a bigger role in preventative health services (86). A very low percentage (1.06%) of the pharmacist's time is occupied in checking inpatient prescriptions (85). This figure indicates that in such a dispensation the pharmacist neglects to play an important role in preventative health services in the hospital setting. Too little time is spent on checking inpatient prescriptions for drug-drug interactions, doses, and ADR's. The advisory and therapeutic functions that the pharmacist should play are underestimated and as yet, under-developed.

It is important for the pharmacist to be in the ward and to communicate with the patient and the rest of the health care team to gradually assume a more meaningful role in preventative and remedial health services in the hospital situation.

Table 15 reflects the results of the questionnaire completed by the ward pharmacists. The results of this questionnaire were very limited due to the fact that only 9 of the 12 pharmacists completed the questionnaire. The discussion and conclusions drawn from these results will be limited to the extend of the results. The ward pharmacists preferred reporting type B to type A reactions. Five out of five type B reactions (questions 6, 8, 13, 14, 15) were found reportable by the ward pharmacists. The severity of the reaction also played an important role. Severe reactions and reactions contributing to death were found reportable. Common serious reactions would be reported by less than half of these pharmacists. According to the questionnaire the pharmacists decided not to report drug related problems other than ADR's or drug toxicities to a surveillance unit. Common ADR's and non-serious ADR's might not be reported to a surveillance unit.

Six cases from the 1506 patients were reported by 6 pharmacists. The 6 reports reflected a report rate of 4 reports per pharmacist per annum when extrapolated. This report rate is good when compared with a report rate of 3 per doctor in four years found with the voluntary monitoring method in the United Kingdom (45). Percentage wise, the report rate of 0.4% reflects a very poor response and corresponds with the 0.6% rate experienced by the surveillance unit on a national base (39). The ward pharmacists' common complaint was a heavy work load at the out patient department that prevented them from spending enough time at the ward. No analysis was made on the time spent at different departments. The lack of time often complained about by pharmacists might be reflected by the 1.06% of time spent with inpatient prescriptions (85). If the ward pharmacist was kept busy at the out patient department the greater part of each day, leaving them with limited time to screen through inpatient records, how did they manage to report the six cases to the surveillance unit? Two cases were reported by doctors to the ward pharmacist in the first month of the study. The ward pharmacist completed the report card and submitted it to the surveillance unit. One case was identified at the clinical discussion group session of the ward. The ward pharmacist submitted the report. It is unknown by what means the other 3 reports were identified. No remarkable distinction could be made between the type of reactions reported. Equal numbers of type A and type B reactions were reported. Five ADR's were classified as severe and three were moderate. A newly qualified pharmacist (2) and a drug information pharmacist (3) reported 5 of the 6 cases.

6.5 Voluntary ADR monitoring: Medical and Nursing staff

During this study 1555 patients were treated in the wards. Letters were sent to 48 doctors and 28 members of the nursing staff monthly for three months. Only ten cases of suspected ADR's were reported by the medical and nursing staff to the surveillance unit. Six cases were reported by doctors and 4 by the nursing staff. The extrapolation of the results reflects a report rate of 0,5 reports per doctor per annum or 2 reports per doctor in four years and 0,6 reports per sister/nurse per annum or 3 reports per member of the nursing staff in five years. The 7 suspected ADR's reported by the doctors were classified as follow: 3 were mild type B and moderate type B reactions each, while 1 ADR was moderate and of type A. Three out of 5 suspected ADR's reported by the nursing staff were classified as mild reactions. Two reactions were moderate type B reactions. Ten of the 12 suspected ADR's were type B reactions. No information could be obtained on how many suspected ADR's were identified at the weekly clinical consultations. No overlapping of reports took place between those submitted in the ward pharmacist voluntary ADR monitoring programme and this programme.

The total number of patients treated during the voluntary ADR monitoring programmes was 3061. Only 16 cases were reported in this population. Twenty ADR's were suspected in this population. The suspected ADR's voluntarily reported by ward pharmacists, doctors and nursing staff were mainly classified as moderate or severe. Moderate and severe suspected ADR's counted 14 while mild ADR's were 6 in total. Fourteen type B reactions were reported as apposed to 6 type A reactions. The intensive ADR monitoring programme recorded 25 type A ADR's in a population of 228 patients. Twenty-two reactions were classified as mild reactions and 10 were moderate.

7 CONCLUSIONS

The results of the different monitoring programmes applied in this study, characterise the problems the industry and regulatory bodies have to face when putting a new drug on the market. The intensive ADR monitoring programme had a good impact on the reporting rate of ADR's to a surveillance unit, but failed to unveil new information on ADR's reported. The voluntary ADR monitoring programmes had little impact on the report rate of ADR's to the surveillance unit. The type and severity of ADR's recorded was of greater magnitude than what was experienced in the intensive programme.

The intensive ADR monitoring programme showed a report rate of approximately 11 percent. Reports were mainly documented on mild, common, and pharmacologically well known ADR's. These reports were clusters of patient complaints of drug adverse and side effects experienced during their hospital stay. ADR's with a frequency of < 1 in 20 could have been identified in the intensive ADR monitoring programme. This incidence is reflected by the maximum number of drug orders prescribed, i.e. furosemide 92 times ordered to 67 patients. Approximately 60 patients are needed to detect an ADR with a frequency of 1 in 20 with a 95% certainty. These common ADR's are usually detected in the pre-marketing studies. The reporting of these types of ADR's could have contributed to the high report rate compared to the report rate found with the voluntary ADR monitoring programmes. A major limitation of intensive ADR monitoring programmes in general is the high cost of conducting the programme. The larger the population the greater the expenses for full time monitors and resources. The prescription event monitoring intensive programme conducted in this study has the advantage over general intensive monitoring programmes in that it was a relatively cheap programme. Seven hours per week were spent on monitoring for ADR's and a maximum of two hours per week were spent on data-processing. If the information on patient characteristics and the drugs ordered for patients were computerised at ward level, monitoring could have occupied half the time it did. The patients were found to complain of symptoms they were familiar with. This could be the reason why the patients reported the common, well-known side effects to the ADRMP. It could also be possible that a well educated population reflects an even higher incidence of ADR's reported. The difference between white patients admitted to the wards and the greater number of whites who experienced suspected ADR's in the study compared with their counterparts might be due to a better education and knowledge of drugs by whites. Better communications between the ADRMP and the white patients could have contributed to the higher rate of reported ADR's in white patients.

Identification of ADR's in clinical practice depends mainly upon the clinical experience of the health care professional. Background knowledge and professional interests might consequently influence the reporter in his decision as to whether a drug or the disease was responsible for the reaction. Professionals with a predominantly pharmaceutical or pharmacological background might rather suspect the drug to be responsible for an adverse reaction. Professionals with more clinical or medical background might be of the understanding that the underlying disease might have changed the patient's response to the drug, or indeed that the disease itself may be responsible. This statement follows the experience gained from the intensive ADR monitoring programme. The monitoring pharmacist experienced difficulty in distinguishing between an event as the course of the disease or the result of drugs taken by the patient. This might be one of the reasons why the pharmacist, who is familiar with the drug, reported the large number of common type A reactions.

It is evident that a specific person has to take the responsibility for reporting, co-ordinating and monitoring of ADR's in an intensive ADR monitoring programme. The pharmacist-monitor in the intensive ADR monitoring programme was dedicated to the ward and was committed for the three months. The intensive ADR monitoring programme yielded a 20 fold better ADR reporting response than the voluntary ADR monitoring programmes. The pharmacist's primarily task was to monitor patients for ADR's. In the voluntary ADR monitoring programmes, doctors and nursing staff was committed to treat the ill patients. The monitoring for ADR's could have been seen as a negligible task compared to therapy.

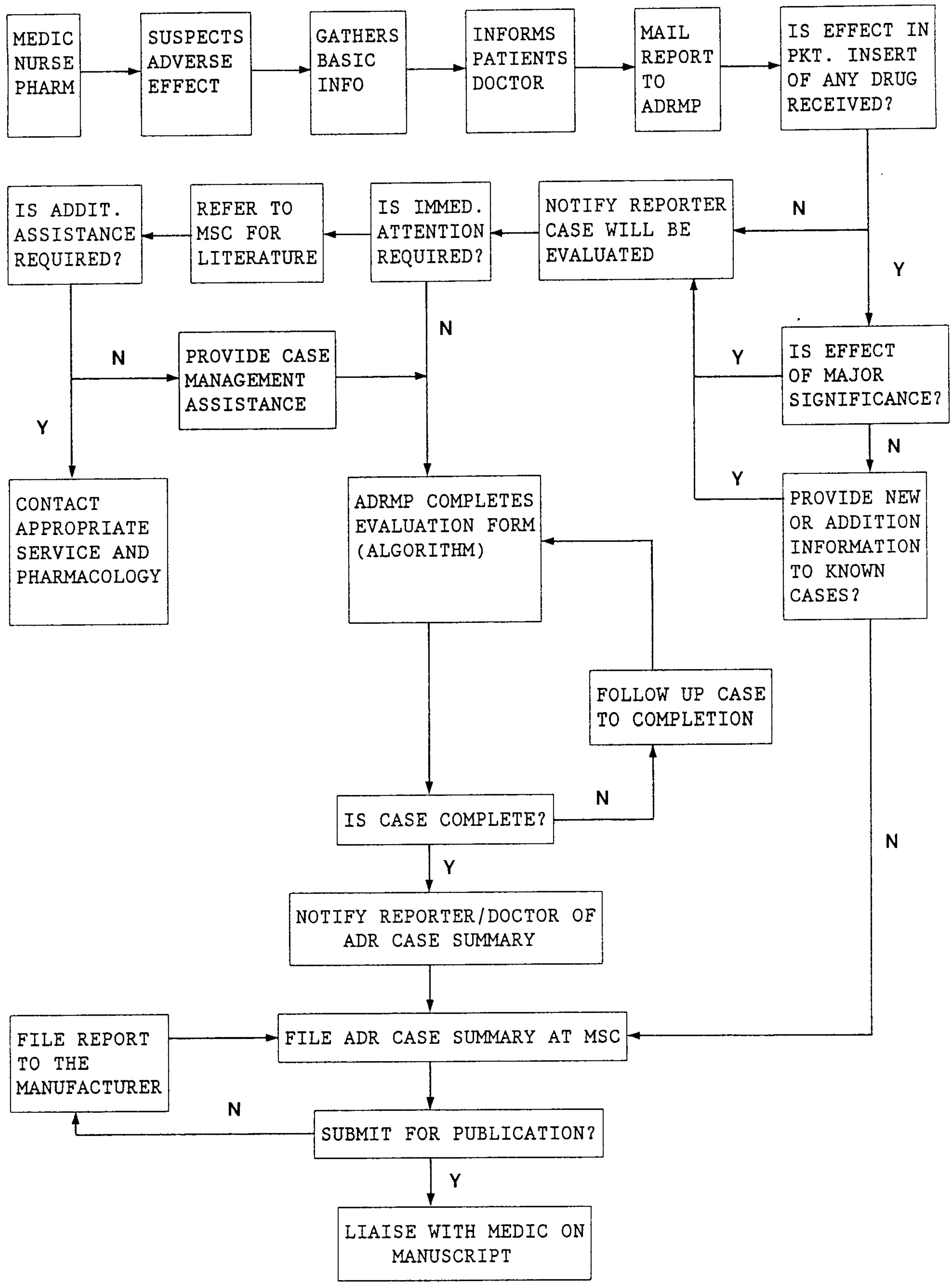
The ward pharmacist voluntary ADR monitoring programme showed a report rate of 4 reports per ward pharmacist per annum. This reflected a report rate comparable to prescription event monitoring on the reporting of ADR's (13). The collaboration between the doctor and pharmacist was positively identified in two cases reported to the surveillance unit. This relationship was seen to be beneficial as the doctor is seen to have the best experience and knowledge of the clinical aspects of patient disorders and the pharmacist the logical professional for studies of drug usage and ADR's. The questionnaire completed by the ward pharmacists showed that pharmacologically unpredictable ADR's with greater severity and uncommon side effects were the types more likely to be reported by ward pharmacists to surveillance units. From the results newly qualified pharmacists and pharmacists with special interest in drug information might have the need to report ADR's

The impact of the voluntary ADR monitoring by medical and nursing staff on the report rate of ADR's was limited when compared to the intensive ADR monitoring programme and the voluntary ADR monitoring by ward pharmacists. The report rate of 0,5 and 0,6 reports per annum per doctor and nursing staff member respectively, is comparable with other voluntary ADR monitoring methods found internationally (13). The recorded reports in this study were severe and the greater number was of the type B.

Finally, the intensive ADR monitoring programme did have a good positive impact on the reporting of common, mild, pharmacologically predictable (type A) ADR's. The voluntary monitoring of ADR's by ward pharmacists showed an impact, comparable to Prescription Event Monitoring, on the report rate of ADR's. The voluntary reporting of ADR's by medical and nursing staff showed a low impact of 2 reports per doctor in four years. The reports received from the voluntary ADR monitoring programmes were moderate to severe ADR's and often from the pharmacologically unpredictable type B.

ANNEXURE 1

Draft of proposed scheme for adverse drug reaction monitoring programme at Groote Schuur Hospital.



ANNEXURE 2

ADVERSE DRUG REACTION MONITORING - GROOTE SCHUUR HOSPITAL

Dear

Thank you for the suspected adverse drug reaction report on the patient .
The case is currently being evaluated and feedback will be provided in the shortest possible time.
Please note that if a case needs urgent attention, dial tie line 7 - 291.

Best wishes

S.A.Gouws
Du Pont Fellow: Post-Marketing Surveillance.

Geagte

Dankie vir die geneesmiddel ervaring wat u met ons gedeel het in die pasiënt .
Die geval word geëvalueer en terugvoer sal aan u verleen word so spoedig moontlik. Ek wil u aandag daarop vestig dat indien spoedige aandag verleen moet word aan 'n geval, u kan skakel per koppellyn 7 - 291.

Beste wense.

S.A.Gouws
Du Pont beurshouer: Nabemarkingswaarneming.

ANNEXURE 3

The algorithm used to determine the probability/causality of a drug to have caused an adverse drug reaction was designed by Naranjo (21).

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent scores.

SCORE	YES	NO	DO NOT KNOW
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse reaction appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was re administered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction reappear when a placebo was given?	-1	+2	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

TOTAL SCORE ________________

Definite - >/= 9
Probable - 5 - 8
Possible - 1 - 4
Doubtful - </= 0

ANNEXURE 4

A voluntary adverse drug reaction monitoring programme for Groote Schuur Hospital.

INTRODUCTION

For the objective of safe and effective drug use in clinical practice, thorough knowledge of drugs and their effects need to be accomplished. The promotion of drug effect surveillance must be seen as an approach to accomplish optimal information for the evaluation of drugs used in clinical practice.

No official adverse drug reaction monitoring programme exists at Groote Schuur Hospital. The objective of this trial study is to test the feasibility for a voluntary prescription event monitoring programme on adverse drug reactions.

Ward staff, e.g., doctors, sisters and pharmacists are requested to report any suspected adverse drug reactions encountered in patients to the surveillance unit

DEFINITION OF AN ADVERSE DRUG REACTION

The definition for an adverse drug reaction from the World Health Organisation (WHO) will be applied (87). Do not hesitate to report when you suspect the following:

"any noxious and unintended effect of a drug, which occurs at doses used in man for prophylaxis, diagnosis or therapy."

GENERAL STRATEGY

Seven wards are included in this study. Patients in the designated medical wards as well as those in the designated dermatology ward will be monitored.

The monitoring period starts October 7, 1985 until November 8, 1985.

This epidemiological-orientated study monitors for suspected adverse drug reactions in all patients exposed to any drug during their stay in the wards.

Please use the adverse drug reaction report card, enclosed. Extra adverse drug reaction report cards are available in the container labelled "ADR REPORTS" at the ward sister's office. If folded in half, the card will fit the top pocket of your white coat.

If you suspect an adverse drug reaction, complete the adverse drug reaction card, secure it and put it into the ADR report container.

The ward pharmacist will collect the report.

At the surveillance unit, the UCT/Ciba Geigy: Medicines Safety Centre, the adverse drug reaction report will be subjected to an algorithm for evaluation of the likelihood of a causal relationship with the drug.

The reporter of the suspected adverse drug reaction might be contacted for follow-up information.

If feedback is required on the case, please indicate. All reports will be acknowledged.

Strict measures to ensure confidentiality are followed in the reporting of suspected adverse drug reactions. The reporter and the adverse drug reaction monitoring pharmacist at the surveillance unit are the only parties to have sight of the adverse drug reaction report card.

Case summaries however will be filed to the database at the surveillance unit.

It is every health care professional's responsibility to report adverse drug reactions.

Thank you.

S.A.Gouws
Du Pont Fellow - Post-Marketing Surveillance

ANNEXURE 5

The following letter was addressed to the medical staff at Groote Schuur Hospital

Dear Doctor

ADR - REPORTS

Side effects occur in hospitals on a daily base!

It is the Medicines Safety Centre's (MSC) concern to estimate to what extent this happens.

Being a doctor and member of a firm puts you in the best position for the monitoring of suspected adverse drug reactions in patients. Once teamed up with sisters, nurses and pharmacists in the ward situation, adverse drug reaction monitoring might be successful.

BENEFITS TO YOU!

The MSC consists of a database, sufficient to give information for your benefit. You don't have time to trace answers to questions that might arise in practice. Consult the MSC and get support in getting the answers.

AN EXAMPLE

A patient takes a drug and during the course of therapy suffers from various bone fractures. Are these fractures because of a possibility of hypotension, CNS effects or a change in bone metabolism?

THE DISCOVERY - WHAT NEXT?

The ADR-report card which will fit in your white coat's pocket must be completed. Hand the completed card to your ward sister or put it into the box at the ward sister's office. The ward pharmacist will collect the report card. If so requested, an adverse drug reaction case summary will be sent to you. All reports will be acknowledged.

Additional adverse drug reaction report cards are available in the ADR report container at the ward sister's office.

THE PROJECT

A trial study will start October 7, 1985 until November 8, 1985. The wards involved are the six designated medical wards and the designated dermatology ward.

Best wishes.

S.A.Gouws
Du Pont Fellow - Post-Marketing Surveillance

ANNEXURE 6

The adverse drug reaction report card

An example of the adverse drug reaction report form. The report card was printed in black on white and measured 12cmX16cm.

WARD NO. PATIENT'S NAME AGE SEX HOSP. FOLD NO.

LIST ALL EVENTS (INCLUDING SIGNS OR SYMPTOMS) DATE:

DRUG	DAILY DOSE	ROUTE	DRUG	DAILY DOSE	ROUTE
1.			1.		
2.			2.		
3.			3.		
4.			4.		

LIST ALL DRUGS STARTED AFTER THE EVENT(S)

1.	1.
2.	2.

COMMENTS: MAY LIST MOST SUSPECT DRUG(S)

CIRCLE THE INITIAL SEVERITY OF THE EVENT(S)

FATAL SEVERE MODERATE MILD LABORATORY ONLY

EXPERIENCE SUBMITTED BY (CONFIDENTIAL) DATE:

STATE: DR/MR/MRS/MISS

CIRCLE NEED:
1. ORIGINAL REPORT
2. FEED BACK REQUIRED Y N
3. FOLLOW-UP REPORT

PLEASE FOLD, SECURE AND POST TO MAIN DISPENSARY. THANK YOU.

At the back of the adverse drug reaction report card:

MEDICATION EXPERIENCE MONITORING

DEFINITION OF AN EVENT: ANY adverse or beneficial effect which MAY EVEN REMOTELY be related to drug therapy or UNEXPLAINED by the underlying disease. Expected and unexpected EVENTS may be reported.

EXAMPLES

1. An increase in creatinine unrelated to the disease is an EVENT.
2. A change in a dose of warfarin which was well controlled is an EVENT.
3. All allergic, dose related or idiosyncratic toxicities and birth defects are EVENTS.

PLEASE DELIVER TO THE FOLLOWING

MEDICATION EXPERIENCE REPORT COORDINATOR

MAIN DISPENSARY

GROOTE SCHUUR HOSPITAL

OBSERVATORY

7925

ANNEXURE 7

Questionnaire used in the intensive surveillance programme.

PATIENT CHARACTERISTICS

(1) Ward Number () __________
(2) Hospital Folder Number (Patient) __________
(3) Date of Birth __________
(4) Age (Years) __________
(5) Sex (M/F) __________
(6) Race: White Black Asian Coloured __________
(7) Allergies(if any) __________
____

(8) Weight (kg) __________
(9) Date Admitted YYMMDD __________
(10) Admission attributed to: Suspected drug induced illness __________
Non-drug induced illness __________

DRUG PROFILE

(1) Date started __________
(2) Name of drug (Generic) __________
(3) Dose __________
(4) Regimen of administration __________
(5) Route of administration: 0 Gyno/Rectal
1 Parenteral
2 Local
3 Oral __________

(6) Reason for stopping drug: 0 not effective
1 effective, no longer necessary
2 prefer other drug
3 change of route
4 pre-op medication
5 patient refused drug
6 according to protocol
7 patient discharged/transferred
8 suspected adverse effect
9 other __________

(7) Suspected adverse drug reaction classification __________
(8) Probability of suspicion of adverse drug reaction __________
(9) Date stopped. YYMMDD __________

ANNEXURE 8

A lecture presented to the ward pharmacists of Groote Schuur Hospital

Title

The impact of a ward pharmacist surveillance programme on the incidence of adverse drug reaction reporting.

Objectives

To achieve its objective of safe and effective drug utilization in this country, the South African Medicines Control Council (MCC) has to make ongoing risk - benefit assessments.

The reporting of adverse drug reactions is a major contribution made to enable the assessment of drug effects. As ward pharmacists, the monitoring of adverse drug reactions in the ward situation is essential to promote the safe and effective use of drugs in hospital practice.

The study is calculated to establish the ability of the ward pharmacist, under current conditions, to be a monitor and reporter of adverse drug reactions in the ward.

The magnitude of the problem

An adverse reaction occurring with a frequency of 1 in 1 000 requires a trial of 3 000 subjects to have a 95% chance of observing it once. As no extensive government supported system currently exists, the medical practitioner, pharmacist, academic and pharmaceutical industry have a responsibility to report adverse drug reactions to a surveillance unit which evaluates the reports and provides feedback and information to the health care professions. The unit must also report alerting drug effects to the industry and the Medicines Control Council

The evaluation of a drug

Before a drug can be registered for clinical use, it must go through different phases of development.

The pre-marketing trials have proven to be inadequate for the purpose of giving a complete profile on the effects and side effects of a drug.

Disasters like those of thalidomide, practolol and diethylstilboestrol in patients, forced drug regulating authorities to look at the drug in its natural setting - Clinical Practice. The ward in which the ward pharmacist has a major role to play, obliges the pharmacist to participate in activities other than just dispensing and stock control.

Definition of an adverse drug reaction

The WHO definition will be applied for this study, describing an adverse drug reaction as " one which is noxious or unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or the modification of physiological function".

The definition includes dose-related side effects, drug-induced illness, paradoxical effects and idiosyncratic effects in patients.

Method of monitoring.

Pharmacists are requested to participate in the following activities when at the ward.

Interview the patients admitted to the ward and screen the medication history of the patient.

Screen through the patient blue prescription card and look for possible drug interactions, drug overdosages, antidotes prescribed, and for drugs stopped. Examine the age and weight of the patient in relation to the dosages prescribed.

Try to communicate with the patient to uncover any suspected adverse drug effects.

It is essential for the pharmacist to communicate with the sister-in-charge, medical registrar and the housemen on drug effects and suspected adverse effects in patients.

When an adverse drug reaction is suspected, gather all basic information and complete an adverse drug reaction report card (enclosed report card) and give it to the secretary at the main dispensary.

If more information is needed to complete the case, contact will be made with the ward pharmacist.

All suspected adverse drug reaction reports will be acknowledged, and if feed back is required, a summary of the case will be mailed to the reporter.

Additional report cards are available at the ward sister's office. Should a case need urgent attention, contact me, the adverse drug reaction monitoring pharmacist at tie-line 7-291 or simply bleep 151.

Thank you.

S.A.Gouws
Du Pont Fellow - Post-Marketing Surveillance

ANNEXURE 9

Estimating the threshold of adverse drug reaction reporting

Please state your profession: ....

Evaluate the following case summaries, and decide what action should be taken.

For the purpose of this study an adverse drug reaction is defined as "one which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function".

Ask yourself the following when you evaluate the case summaries: Do I need to report this suspected adverse reaction to a surveillance unit?

If you think it is reportable to a surveillance unit tick the Y and if any other plan of action is needed like consulting the doctor or patient counselling, tick off the N

....

1) A male, age 46 received Phenelzine 15mg tid as treatment for depression. He developed a cold and preparation containing phenylephrine was prescribed to him.

Y N

2) A sixty four year old manic - depressive female on lithium carbonate treatment was stabilized on 800mg daily. During a visit to the Transvaal, she developed a gastric infection. Due to dehydration, her lithium bloodlevel elevated and reached 2.5 mmol/l. The normal range is 0.4 to 1.5 mmol/l.

Y N

3) A girl, suffering from acne was prescribed oxytetracycline. She also suffered from heart burn and she took aluminium hydroxide gel to get symptomatic relief.

Y N

4) Mr X, was diagnosed as suffering from angina pectoris. Isosorbide dinitrate was prescribed to him and after taking the first tablet sublingually, he complained of a severe headache.

Y N

5) A lady in her early twenties suffered from a sore throat. A broad spectrum penicillin was prescribed for her. She took an oral contraceptive, but despite this, she found herself pregnant and wondered whether the oral contraceptive was ineffective.

Y N

6) Mrs Y, aged 61, received nomifensine for a few months. The dose was increased from 50mg daily to 150mg daily over this period. She became acutely ill, with severe pain between the shoulders, dyspnea at rest and low blood pressure. Her liver function tests were abnormal and her cell count was elevated.

Y N

7) P, a twenty five year old male, received indomethacin for a sport injury. He developed stomach cramps, nausea and vomiting. He claimed that he had not eaten a bite for days.

Y N

8) A patient was given imi penicillin by a general practitioner. Four hours later, the patient became breathless and a diffuse macular rash was noticed on her chest and to a lesser extent on her legs. She was started on erythromycin at this time, and after four days the rash became more erythematous. After the erythromycin was stopped, the rash cleared totally.

Y N

9) A team of workers used insecticides, containing organophosphates. One of them became poisoned and he was admitted to hospital with organophosphate poisoning and a significant crystaluria. The pronounced crystaluria supports the potential for renal involvement in an organophosphate poisoning.

Y N

10) A diabetic was admitted to hospital in a comatose state. She had a history of alcohol abuse and due to this fact, her compliance with medication was shown to be very poor. Hyperglycaemia was reported.

Y N

11) A lady, who relied on her 84 year old spouse for reminding her to take her medicine, was admitted to hospital for a check-up. She was found to be nauseous and vomited. A blood sample indicated a Digoxin level of 5.2 ug/ml. The maximum safe level is 2.6 ug/ml.

Y N

12) A female, edematous and suffering from cardiac failure, was put on furosemide. She didn't respond well and the dose was increased to maximum range. Still no satisfying response was achieved. The registrar, known to read international publications, added 5mg of metolazone daily to the furosemide. Potassium chloride was prescribed and the lady responded well.

Y N

13) A male, aged 36, developed porphyria cutanea tarda and disturbed liver functions following treatment with rifampicin and isoniazid. Challenge-testing with both drugs incriminated rifampicin as the agent precipitating porphyria cutanea tarda.

Y N

14) Mr Z, aged 55, received anti-tuberculosis treatment, e.g., rifampicin, isoniazid, streptomycin and pyrazinamide. He showed side effects like yellowing of the eyes and skin and he complained of pain and swelling in his joints. He was later diagnosed as suffering from toxic epidermal necrolysis (TEN).

Y N

15) A 78 year old male was started on 300mg allopurinol daily for asymptomatic hyperuricemia. The drug was discontinued after one week when he complained of sore eyes and an ulcerated mouth. On admission to hospital, a diagnosis of Stevens-Johnson syndrome was made and he was treated with antibiotics and topical steroids. Despite intensive therapy, pseudomonas aeruginosa was cultured from his blood. He died six days after admission to hospital.

Y N

Thank you.

S.A.Gouws
Du Pont Fellow: Post-Marketing Surveillance.

ANNEXURE 10

February 27, 1986

Dear Ward Pharmacist

Study: Adverse drug reaction reporting - The ward pharmacist approach

To achieve the goal where the pharmacist is identified with the information and knowledge, and not with the product, the time has come that we as pharmacists must prove that we are rightful members of the health care team.

It is important to communicate with medical, nursing and other ward staff on clinical aspects of patient care. Communication with the patient is important to encounter drug-related problems. Communication links must be developed - your time and work load taken in account, to ensure that the other ward health care professionals can familiarise themselves with the challenging new role the pharmacist has to play.

Reporting of adverse drug reactions

Whenever you have time to communicate with the sister-in-charge, registrar or housemen in a ward, ask them about suspected drug related problems in patients in the ward.

When on the ward round, and at the patient's bed, screen the patient's blue board for abnormal combinations of medicine, antidotes prescribed, and drugs stopped. Compare dosages with weight and age in patients.

Speak to the doctors and patients to get a better picture of the patient's health. Do not hesitate to give advice where applicable. Be careful not to give advice in such a manner that it conflicts with the advice and decisions taken by the medical staff. Consult the medical staff once you suspect an adverse reaction to any of the drugs prescribed to a patient.

Gather the basic information on the suspected case, and complete an adverse drug reaction report card. Secure the report card and give it to the secretary at the main dispensary.

If urgent attention need to be given to a case, don't hesitate to call me at tie-line 7-291, or bleep me at Groote Schuur Hospital 151.

The study starts on March 3, 1986 and the ward pharmacists at the designated wards are thanked for their support in this project.

S.A.Gouws
Du Pont Fellow - Post-Marketing Surveillance.

ANNEXURE 11

March 7, 1986

Dear Ward Pharmacist

Adverse drug reaction reporting - ward pharmacists

Many thanks to the ward pharmacists who tried their very best to put together reports on suspected adverse drug reactions. I have heard that circumstances are not easy and time is very limited when on the ward rounds.

Keep up with the good work.

Adverse Drug Reactions - What to report

The Medicines Safety Centre encourages the reporting of all suspected adverse reactions to drugs. The reporting of seemingly insignificant or common adverse reactions may highlight a widespread prescribing problem.

The Centre particularly requests reports of:

- All suspected reactions to new drugs.
- All suspected drug interactions.
- Reactions to other drugs which are suspected of significantly affecting the course of a patient's management, including reactions suspected of causing: death; danger to life; admission to hospital; prolongation of hospitalisation; absence from productive activity; increase investigation or treatment costs; birth defects.

Medicines Safety Centre, Dept of Pharmacology, Anatomy Building, UCT Medical School, Observatory, 7925. Tel: 417-3202 (021)

Thank you.

S.A.Gouws
Du Pont Fellow - Post-Marketing Surveillance.

ANNEXURE 12

March 27. 1986

Dear Ward Pharmacist

I would like to thank all pharmacists who took part in the post-marketing surveillance study: Adverse drug reaction monitoring, ward pharmacists.

The past month brought us closer to the goal and served as a useful introduction for our work together.

Clinical ward pharmacy is a new concept to hospital pharmacy in South Africa. We have to convince the sceptical that clinical ward pharmacy is essential and an inexpendible service to patient care. One way to accomplish this goal is to develop the role of the pharmacist as a drug data manager.

The role of a data manager comprises functioning as an adverse drug reaction monitor for drug safety, drug utilization reviewer and pharmacokinetic drug monitor. The pharmacist need to be identified with information on products and not with the product.

We need to communicate our expertise to medical, nursing and other health care professions to assist and promote optimal health care.

Medical, therapeutic experiences need to be discussed amongst pharmacists and other health care professions.

Let us begin this month with new courage and work our way through to success. To be a clinical ward pharmacist will need definite extra effort from each one of us.

Best wishes.

S.A.Gouws
Du Pont Fellow - Post-Marketing Surveillance

P.S. All adverse drug reaction report cards must be handed over to the designated person at the main dispensary.

ANNEXURE 13

April 28, 1986

Dear Ward Pharmacist

I wish to thank the ward pharmacists for their reports on suspected adverse drug reactions. The reporting of such effects is a perfect tool in the sharing of information on medicines, their effects and safety.

I write this letter to remind you all to report any suspected adverse drug reactions you encounter in any of the patients in the ward you serve. Also to assist the ward pharmacist with information to stimulate you in the detection of suspected adverse drug reactions when you look through the patient's blue boards.

When you observe the following, an adverse drug reaction might be suspected:

* When antibiotics are discontinued within 5 days of initiating therapy.
* A change from Penicillin-like antibiotics to erythromycin or tetracycline.
* When 2 pharmacologically similar drugs are combined. (e.g. 2 benzodiazepines)
* When 2 pharmacologically antagonistic drugs are combined (e.g. morphine and naloxone).
* When drugs which should be, but are not given with meals.
* When the dosage is decreased by more or less 25% or one dosage unit
* When the following types of drugs are prescribed for example:

Vitamin K IVI, IM	Activated charcoal
Naloxone	Parvolex
Antihistamines	Atropine IVI
Antinauseants	Akineton
Steroids - topical/oral	Calamine lotion
Nystatin oral	Ipecac
Chelators - Desferal/EDTA/BAC etc	

* Any rashes or bruisings.

I trust such information will be useful in the monitoring of adverse drug reactions.

Best wishes.

S.A.Gouws
Du Pont Fellow - Post-Marketing Surveillance

ANNEXURE 14

April 1, 1986

Dear Doctor and Sister

Adverse drug reaction monitoring: Voluntary reporting.

The spontaneous or voluntary reporting of adverse drug reactions has been shown to be a very important alerting source for adverse reactions to drugs not identified prior to marketing.

The medical staff, registrars and housemen as well as the nursing staff, ward sister in charge from the designated wards are requested to report any suspected adverse drug reactions to the surveillance unit.

When an adverse effect is suspected, gather the basic information and complete an adverse drug reaction report card. Secure the card and send it off to the secretary at the main dispensary.

Confidentiality is considered a high priority. Should feedback be needed, contact will be made with you.

Do not hesitate to call tie-line 7-291 or bleep GSH 151 if a case needs urgent attention.

Feedback will be provided if so requested. All reports will be acknowledged.

Yours sincerely

S.A.Gouws
Du Pont Fellow - Post-Marketing Surveillance

ANNEXURE 15

April 28, 1986

Dear Doctor/Sister

I wish to thank the members of the health care team for their reports on suspected adverse drug reactions; by doing so, you have shared important information on medicines in hospital practice.

This letter is written to remind all medical and nursing staff to continue with the reporting of suspected adverse drug reactions which occurred in the wards.

The following information in question form might assist the reporter in the completion of reports on suspected adverse drug reactions.

* Did the adverse drug reaction appear after the suspected drug was received or administered? How soon after? What quantity was given to the patient?
* Did the adverse drug reaction improve when the suspected drug was discontinued or a specific antagonist administered?
* Was the patient rechallenged with the same or similar kind of drug?
* Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?
* Was there any change in the severity of the reaction when the dose was increased or decreased?
* Did the patient have a similar reaction to the same or similar drugs in any previous exposure?
* Was the effect confirmed by any objective evidence?

Please note that additional report cards are available from the blue/green containers in the doctor's office.

Thank you

S.A.Gouws
Du Pont Fellow - Post-Marketing Surveillance

ANNEXURE 16

May 21, 1986

Dear Doctor/Sister

The following information is thought to be of assistance in the monitoring for suspected adverse drug reactions.

What to report:

The Medicines Safety Centre encourages the reporting of all suspected adverse reactions to drugs. The reporting of seemingly insignificant or common adverse reactions may highlight a widespread prescribing problem.

The Centre particularly requests reports of:

* All suspected reactions to new drugs.
* All suspected drug interactions.
* Reactions to other drugs which are suspected of significantly affecting the course of a patient's management, including reactions suspected of causing:

  death; danger to life; admission to hospital; prolongation of hospitalisation; absence from productive activity; increase investigation or treatment costs; birth defects.

Medicines Safety Centre, Dept of Pharmacology, Anatomy Building, UCT Medical School, Observatory, 7925. Tel: 417-3202 (021)

Thank you.

S.A.Gouws
Du Pont Fellow - Post-Marketing Surveillance

ANNEXURE 17

Reports received on suspected adverse drug reactions.

In this section, the adverse drug reaction report cards on suspected adverse drug reactions are evaluated. The package inserts of the respective medicine were used as information source. Suspected adverse drugs reactions were given record numbers which were developed for international adverse drug reaction monitoring by the World Health Organisation (84). A case summary was compiled from the information found on the report card. The report was subjected to an algorithm developed by Naranjo (21). The case summary was indexed and filed into the surveillance unit's data base for use by the surveillance unit.

i) Voluntary adverse drug reaction monitoring programme: The trial study

Four reports were received. Three adverse drug reaction report cards were completed by medical staff and the fourth by a pharmacist.

Case 1

A thirty nine year old white male, developed tinnitus, blurred vision and a hint of photophobia.

He received chloroquine, 250mg q12h orally; paracetamol, 500mg q4h orally; quinine sulphate, 600mg q8h orally and metoclopramide 10mg tds orally during his stay in the medical ward.

The reaction was described as moderate. The reaction was identified by the doctor and reported by the ward pharmacist. Chloroquine was suspected to be responsible for the reaction.

No information was available on drugs started after the reaction and no comments were made.

In follow up of the case, the patient was found to be discharged from the ward and no further information could be obtained.

Index Terms: tinnitus (0264), vision blurred (0257), photophobia (0250) , chloroquine, paracetamol, quinine sulphate, metoclopramide.

Summary:

Reports of double vision, photosensitivity and ototoxicity caused by chloroquine are found in the literature.

According to the literature insert of quinine sulphate, both tinnitus and disturbed vision could be caused by the drug.

The patient took quinine and metoclopramide on a regular basis before he was admitted to hospital.

Probability:

According to the algorithm it is doubtful that chloroquine was responsible for tinnitus (type A), blurred vision (type A) and photophobia (type B).

Case 2

The 25 year old coloured female suffered from severe conjuctivitis and haemorrhagic stomatitis at the time of admittance to the ward. During the course of her stay in the ward, she developed target lesions of the skin.

She received oxytetracycline 250mg orally, propan gel orally and phenobarbitone orally.

The doctor suspected the phenobarbitone to be responsible for this lesions of the skin. No full description of the type of lesions could be obtained.

The lack of information didn't allow for useful evaluation of the report. The effect was reported to be severe.

Index Terms: skin disorder (0037), oxytetracycline, phenobarbitone, propan gel.

Summary:

The prolonged ingestion of barbiturates such as phenobarbitone on a regular daily basis gives rise to enzyme induction. This might be one of the reasons why phenobarbitone is contra- indicated in porphyric patients.

Probability:

Because of the insufficient information available on the report card, phenobarbitone was classified doubtful to be responsible for the reaction.

Case 3

A black female aged fifty one was admitted to the dermatology ward after she developed morbilliform eruptus (miliaria), associated with fever and purpura.

Before the severe reaction developed, she received one ampoulle of hyoscine-n-butylbromide and dipyrone intramuscularly.

Hydroxyzine was given after the reaction. The reporter suspected hyoscine-n-butylbromide and dipyrone to be responsible for the reaction.

The reaction was ranked severe and was submitted by a doctor.

It was an original report and no feed back was required.

Index Terms: morbilliform eruptus (0030), miliaria (1166), fever (0725) , purpura (0459), hyoscine-n-butylbromide and dipyrone.

Summary:

According to the literature insert of hyoscine-n-butylbromide and dipyrone, all pyrazole derivatives may cause very rare cases of anaphylactic reactions or other allergic symptoms which can effect the skin.

The reporter confirmed that no other drugs were given to the patient prior to the reaction.

Probability:

The allergic skin reaction (type B) was probably caused by the dipyrone in this case.

Case 4

A sixty nine year old professional white male was admitted to the dermatology ward. The man suffered from annular erythematous photosensitivity and a subacute rash of lupus erythematosus.

It was found on admittance that he took amiloride co 1 tablet daily orally; atenolol 100mg mane orally and isosorbide dinitrate 40mg tds orally.

No information was made available on any drugs started after the reaction.

The reporter suspected amiloride co of being responsible for the reaction which was classified as moderate in the patient.

The reporter was a specialist doctor and this was a follow up report. The original report was not found. No feed back was required.

Index Terms: erythema photosensitivity (0028), lupus erythematosus rash (0080), amiloride co atenolol, isosorbide dinitrate.

Summary:

Reports of photosensitivity were recorded with hydrochlorothiazide, the one constituent of amiloride co. The reaction appeared after amiloride co was taken. No other causes were mentioned to have caused the reaction and the patient used the drug on previous occasions.

The reporter, a dermatologist strongly suspected amiloride co to be responsible for the reaction.

Probability:

The thiazide in amiloride co could probably be responsible for this sensitivity reaction (type B) reactions suspected.

Method 1: Intensive adverse drug reaction monitoring programme: Ward pharmacist.

In this section all suspected adverse drug reactions were identified and reported by the adverse drug reaction monitoring pharmacist, unless stated in the contrary.

Case 1

Patient number 8, a white female aged twenty eight complained of constipation after she was put on lorazepam. She took 1 mg twice daily. After the complaint a bulk forming laxative was prescribed for her.

Index Terms: constipation (0204), lorazepam.

Summary:

No reports were received on constipation in patients on lorazepam according to the literature insert published in November 1971.

The patient continued to take lorazepam, but a laxative was also prescribed for her. The constipation could also be due to lack of mobility.

Probability:

According to the algorithm, lorazepam could possibly be responsible for the moderate constipation (mild Type A) in this case.

Case 2

Patient number 9, a coloured female was born in 1930. During her stay in hospital, she received metoclopramide 10mg orally; isosorbide 5mg sublingually; furosemide 80mg orally; MERASYN 15ml when needed.

She complained about a feeling of pins and needles which was followed by hot flushes of the face after she put the isosorbide under her tongue. She did have night cramps.

Index Terms: hot flushes (0207), cramps (0939), paraesthesia (0148), metoclopramide, isosorbide dinitrate, furosemide.

Summary:

Isosorbide dinitrate commonly causes cutaneous vasodilation with flushing. Furosemide may cause electrolyte disturbances due to the natriuretic effects of the drug and the electrolyte depletion may provoke cramps in the legs, weakness, loss of appetite etc.

Furosemide was also reported to cause paraesthesia (feeling of pins and needles) in sensitive patients.

The patient complained of the side effects but she was kept on the medicine since the side effects were not so troublesome as to require withdrawal of the medicine.

No electrolyte levels were taken to give objective evidence of electrolyte disturbances in the patient.

Probability:

It was probable that isosorbide dinitrate caused the hot flushes (mild, type A). The night cramps (moderate, type A) and paraesthesia (mild, type B) were doubtfully caused by furosemide in this case.

Case 3

The patient, a fifty two year old black male, was put on isosorbide dinitrate 5mg sublingually, and paracetamol 1g q6h orally.

He claimed to have suffered from head aches for short periods. He asked the doctor to prescribe a pain killer for the head ache. The pain killing tablets didn't help much.

Index Terms: headache (0109), isosorbide dinitrate, paracetamol.

Summary:

Isosorbide dinitrate is known to be a common cause of headache in patients, and the headache may be severe and persistent. The patient only took isosorbide and was monitored in the ward for attacks of angina . The pain killer, paracetamol, prescribed to the patient showed not to be very effective in this case.

Probability:

According to the probability scale, isosorbide dinitrate had definitely caused the headaches (moderate, type A) in this case.

Case 4

This fifty five year old coloured male patient, was started on isosorbide dinitrate 5mg sublingually and oxazepam 1mg bd orally. The next day metoclopramide 10mg tds orally and paracetamol 1g q6h orally was prescribed. On the third day, isosorbide dinitrate was discontinued, since it was found not to be effective, and atenolol 50mg mane orally was prescribed.

On day two the patient complained of headache and nausea. This occurred every time when he took the little white tablet sublingually.

The headaches and nausea improved when the isosorbide dinitrate was discontinued on day three.

Index Terms: headache (0109), nausea (0308), isosorbide dinitrate, oxazepam , metoclopramide, paracetamol, atenolol.

Summary:

Headache is common side effect and may be severe and persistent in patients taking isosorbide dinitrate. The severity usually decreases and the patient often suffers less and less of these side effects. Nausea could occasionally be exhibited in patients who are sensitive to the hypotensive effects of nitrate and severe responses could appear even within the usual therapeutic dose range.

The metoclopramide and paracetamol was prescribed to the patient to treat the side effects suspected to be caused by isosorbide dinitrate.

Probability:

The isosorbide dinitrate probably caused both the headaches (moderate, type A) and nausea (moderate, type A).

Case 5

A coloured female, aged sixty two was admitted to the ward for a regular check up. She was started on furosemide 80mg mane orally and propoxyphene 130mg prn orally for her pain.

She developed constipation after two days, and after she had mentioned her complaint, ispaghula husk was prescribed to her. Lorazepam 1mg nocte orally was also prescribed, but only two days after she received the ispaghula husk.

Index Terms: constipation (0204), furosemide, propoxyphene, erythromycin, ispaghula husk, lorazepam.

Summary:

Constipation has been reported to be caused by propoxyphene, whereas gastrointestinal disturbances were reported from erythromycin and furosemide. No reports were received on lorazepam.

The treatment continued despite the constipation, since the side effect did not outrank the pain-killing effects of propoxyphene.

Probability:

Constipation (moderate, type A) was probably caused by propoxyphene in this case.

Case 6

This sixty year old white female was referred to hospital because of asthma attacks.

She was started on aminophylline 250mg q8h parenteral; amoxycillin 250mg q8h orally and furosemide 40mg mane orally.

She complained of cramps in her legs, and two days after admittance theophylline and ethylenediamine dihydrochloride 350mg bd orally and potassium 1g bd was prescribed.

On the fourth day dothiepin 75mg nocte orally was prescribed for her and she was discharged a day later. No further information could be obtained concerning the night cramps..

Index Terms: cramps (0939), aminophylline, amoxycillin, furosemide, theophylline and ethylenediamine dihydrochloride, potassium, dothiepin.

Summary:

No reports were found on any other drug except furosemide, to have caused night cramps in patients.

No potassium levels were taken to give objective evidence of electrolyte disturbances in the patient.

Probability:

The night cramps (moderate, type B) were doubtfully caused by furosemide in this case.

Case 7

This sixty three year old coloured female was put on diltiazem 60mg q6h orally; isosorbide dinitrate 40mg bd orally and furosemide 160mg mane orally on admittance.

She complained of feeling dizzy and potassium 1g tds orally was prescribed and the furosemide was cut down to 120mg mane orally three days later.

Metoclopramide 10mg tds orally was then prescribed and amiloride Co mane orally instead of furosemide.

Index Terms: dizziness (0101), diltiazem, isosorbide, furosemide, metoclopramide, amiloride co.

Summary:

Dizziness has been associated with diltiazem, isosorbide dinitrate and furosemide.

It was postulated that the combination of the three drugs, in relative high doses, were likely to have caused the dizziness of the patient. The rapid reduction in her blood pressure caused by isosorbide dinitrate and furosemide could be responsible for the dizziness.

Probability:

It was possible that any one of the three or the combination of diltiazem, isosorbide dinitrate and furosemide caused the dizziness (moderate, type A) in this case.

Case 8

This seventy year old coloured female received prazosin 1mg bd orally; orciprenaline nebulizer and amoxycillin 250mg suspension q8h orally on admittance.

The registrar described loose stools which developed in this patient. On investigation it was found that the amoxycillin was stopped two days prior to commencing treatment with co-trimoxazole 960mg bd orally.

Index Terms: diarrhoea (0205), prazosin, orciprenaline, amoxycillin, co-trimoxazole.

Summary:

Both diarrhoea and constipation have been reported with prazosin. As with other broad spectrum penicillins, gastrointestinal tract disturbances might occur.

The amoxycillin was discontinued and co-trimoxazole was started in this patient. Diarrhoea caused by amoxycillin is very rare according to the literature insert.

The patient was kept on prazosin treatment.

Probability:

The diarrhoea (mild, type B) in this case was possibly caused by prazosin. It was however, more likely that amoxycillin caused the reaction in this case (probable).

Case 9

This very ill black male patient was born in 1925. He was started on theophylline and ethylenediamine dihydrochloride 350mg bd orally and methyldopa 250mg bd orally.

A day later streptomycin 1g mane parenteral; rifampicin 450mg mane orally and isoniazid 400mg mane orally and pza 1.5g mane orally was started.

The patient developed mouth ulcers and loss of appetite over the next day or two.

The patient was discharged from the ward after six days of treatment in this ward.

Index Terms: appetite lost (0165), mouth ulceration (0328), theophylline and ethylenediamine dihydrochloride, methyldopa, streptomycin, rifampicin, isoniazid, pza.

Summary:

Rifampicin has been reported to cause anorexia (loss of appetite) whereas reports have been received on mouth ulcers with rifampicin, isoniazid and methyldopa. Methyldopa has been shown to be responsible for sore or "black" tongue.

The patient was very ill on admittance and the lack of appetite as well as the mouth ulcers could have been due to the course of the disease.

Probability:

It was possible that methyldopa or rifampicin caused the mouth ulceration (mild, type B) in this case, but doubtfully the isoniazid. It could have been caused by the combination of methyldopa and rifampicin.

It was possible that rifampicin caused the anorexia (mild, type A) in this case.

Case 10

This white, sixty three year old male, hypertensive patient, was admitted. On admittance, lorazepam 1mg nocte orally; iron sulphate 200mg tds orally and atenolol 100mg mane orally was prescribed.

It was noticed that the patient developed purpuric spots on his legs and atenolol was suspected to have caused this reaction. The reaction was mentioned by the patient.

Index Terms: purpura (0459), lorazepam, atenolol, iron sulphate.

Summary:

There have been reports of skin rashes and/or dry eyes associated with the use of beta-blocking agents. The patient mentioned that he has been on atenolol for a number of months and it was only recently that he saw this pupuric rash on his legs.

Probability:

It was possible that the purpuric rash (mild, type B) was caused by atenolol in this case.

Case 11

This fourty one year old coloured female received furosemide 40mg mane orally; digoxin .25mg mane orally; paracetamol/codeine phosphate q6h orally; diazepam 10mg q8h orally and ispaghula husk mane orally on admittance.

She complained of constipation and paracetamol/codeine phosphate was suspected to be responsible for this adverse reaction.

The patient was also put on warfarin 5mg mane orally and delayed and/or decreased absorption of warfarin was suspected as an interaction with the ispaghula husk. No objective proof could be found of this during treatment.

Index Terms: constipation (0204), furosemide, digoxin, paracetamol/codeine phosphate, diazepam, ispaghula husk.

Summary:

Constipation is commonly known to be caused by morphine derivatives, such as codeine phosphate. The patient's constipation was overcome by ispaghula husk.

Probability:

It was probable that codeine phosphate caused the constipation (mild, type A) in this case.

Case 12

The patient, a seventy nine year old white male, received treatment in the intensive care department of the ward.

He received metformin 500mg tds orally; amantadine 100mg bd orally; phenytoin 100mg tds orally and furosemide 80mg mane orally on admittance.

Three days later amoxycillin 250mg q8h orally was prescribed and the next day oxybutynin 5mg mane orally was prescribed. The registrar to this ward reported pyrexia in this patient to the monitoring pharmacist and he suspected oxybutynin to have caused the reaction.

The patient's temperature was raised and the drug was discontinued after the third dose. The patient's temperature returned to normal.

Index Terms: pyrexia (0725), metformin, amantadine, phenytoin, furosemide, amoxycillin, oxybutynin.

Summary:

The amoxycillin is presumed to have been prescribed for an infection in this patient. The registrar however mentioned that the patient's temperature was normal until oxybutynin was taken by the patient.

Oxybutynin, when administered in the presence of high environmental temperature, can cause heat prostration due to decreased perspiration.

Probability:

The pyrexia (mild, type A) was probably caused by oxybutynin in this case.

Case 13

This sixty four year old white male received aspirin 100mg mane orally; dipyridamole 100mg tds orally; nifedipine 10mg tds orally; furosemide 250mg tds orally and isosorbide dinitrate 40mg bd orally on admittance.

He complained of severe dizziness and nausea when he got out of bed.

The furosemide dose was increased to 1g mane orally the following day and diltiazem 60mg q6h orally was also prescribed.

The nifedipine and isosorbide dinitrate were suspected to have caused the reactions.

Index Terms: dizziness (0101), nausea (0308), aspirin, dipyridamole, nifedipine, furosemide, isosorbide dinitrate.

Summary:

Both nifedipine and isosorbide dinitrate have been reported to provoke dizziness, due to postural hypotension in patients.

Nausea is commonly found in patients sensitive to nitrite and severe responses can occur in therapeutic doses.

Both nifedipine and isosorbide dinitrate could be responsible for the nausea in this patient.

Probability:

It is possible that nifedipine caused the nausea (mild, type A) and dizziness (mild, type A) in this case. Isosorbide dinitrate possibly caused the dizziness (mild, type A) and was probably responsible for the nausea (mild, type A) in this case.

Case 14

This eighty one year old white male patient was admitted to hospital because of a prolonged prothrombin time.

He was put on folic acid 5mg mane orally; allopurinol 100mg mane orally; sucralfate 1g bd orally and furosemide 200mg mane orally.

On admittance he it was found that he took warfarin 5mg mane orally. The patient suffered from intestinal bleeding and only the third day after admittance did the doctor again prescribe warfarin 2.5mg mane orally to the patient.

This case was suspected to be admitted to hospital because of a
drug-induced ailment.

Index Terms: hypoprothrombinaemia (0590), allopurinol, warfarin, furosemide, sucralfate.

Summary:

It was suspected that allopurinol reduced the metabolism of warfarin sodium and therefore raised the prothrombin time in the patient.

Prolonged prothrombin time is found when the dose of warfarin is increased. This is the therapeutic effect of warfarin sodium, but if prothrombin time is prolonged above therapeutic levels, bleeding might occur as was suspected in this case.

Probability:

Prolonged prothrombin time (mild, type A) was probably caused by warfarin sodium in this case.

Case 15

The patient, a fifty one year old white male received isosorbide 10mg q4h orally; atenolol 100mg mane orally; chlormethiazole 384mg tds orally on admittance.

The patient complained of clammy hands, hot flushes, head ache and orthopaedic hypotention.

The dose of isosorbide dinitrate was reduced to 10mg q6h orally and paracetamol 1g q6h orally was then prescribed to the patient.

Index Terms: clammy hands (0043), flushing face (0207), headache (0109), hypotension orthopaedic (0213), isosorbide dinitrate, atenolol, chlormethiazole

Summary:

An occasional individual exhibits a marked sensitivity to the hypotensive effects of the nitrite in isosorbide dinitrate, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration) can occur even with the usual therapeutic dose.

Cutaneous vasodilation with flushing occurs in isosorbide dinitrate and headache is common and may be severe and persistent in some cases.

Atenolol is indicated for hypertension and patients responding well to these drugs might initially suffer from hypotension but will normalise.

Probability:

It is possible that isosorbide dinitrate caused the clammy hands and hypotension in this case. The flushing and headache were probably caused by isosorbide dinitrate, while atenolol possibly contributed to the hypotensive reaction in this case.

Case 16

A forty two year old coloured male received paracetamol 1g q6h orally and propoxyphene 130mg q6h orally on admittance.

He was in pain and he also complained of constipation. After three days, tilidene 100mg q6h orally; indomethacin 25mg tds orally; penicillin V 500mg q6h orally and senna 15mg mane orally was prescribed.

Index Terms: constipation (0204), paracetamol, propoxyphene.

Summary:

Constipation has been reported in patients treated with propoxyphene.

Probability:

Constipation (mild, type A) was possibly caused by propoxyphene in this case.

Case 17

This fifty two year old white male received spironolactone 100mg tds orally; furosemide 40mg mane orally and lorazepam 1mg nocte orally.

On the next day, he complained of itching all over his body. No rush was visible but his skin was somewhat dry. He claimed that it was the first time that he received furosemide.

Index Terms: itching (0024), spironolactone, furosemide, lorazepam.

Summary:

A maculopapular or erythematous cutaneous eruption has been reported with spironolactone. Various forms of dermatitis including urticaria, exfoliative dermatitis and pruritis, as well as paraesthesia may occur with furosemide.

Probability:

The pruritis (mild, type B) was possibly caused by furosemide and/or spironolactone.

Case 18

This sixty year old coloured female is a cardiac patient admitted to the ward for observation.

Digoxin 0.125mg mane orally; potassium 1g tds orally; furosemide 120mg mane orally; isosorbide dinitrate 10mg q6h orally were prescribed for her on admittance.

The patient complained of nausea. The next day, lorazepam 1mg nocte orally and paracetamol 1g q6h orally was also prescribed to her. She still complained from nausea from time to time.

Index Terms: nausea (0308), digoxin, potassium, furosemide, isosorbide dinitrate, lorazepam, paracetamol.

Summary:

Nausea is listed as one of the most frequently encountered symptoms, especially following overdosage from digoxin.

An occasional individual exhibits a marked sensitivity to the hypotensive effects of the nitrite in isosorbide dinitrate, and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration) can occur even with the usual therapeutic dose.

Probability:

It was possible that both or either one of the two drugs caused the nausea (moderate, type A) reaction in this case. Isosorbide dinitrate, was more likely than digoxin to have caused the nausea (moderate, type A).

Case 19

This ninety one year old white female, developed a fit while she was on furosemide 40mg mane orally; ampicillin 500mg qid parenteral; aminophylline 200mg; and potassium 1g tds orally.

It was suspected that the aminophylline caused the convulsion in this patient. The drug was discontinued.

The lady did not develop another fit and was discharged eleven days later on potassium 1g tds orally and furosemide 40mg mane orally.

Index Terms: convulsion (0093), furosemide, aminophylline, potassium.

Summary:

Aminophylline has been shown in overdose or idiosyncrasy to have led to repeated vomiting with extreme thirst, delirium, hyperthermia and convulsions.

Probability:

It was possible that the aminophylline caused the convulsion (mild, type B) in this patient. It could have been a idiosyncratic reaction and the possibility of an overdose in this ninety one year old female wasn't confirmed.

Case 20

This fifty three year old coloured female received furosemide 120mg mane orally; potassium 1g tds orally; glibenclamide 5mg bd orally and captopril 6.25mg tds orally on admittance.

Her captopril dose was increased to 25mg tds orally and the furosemide to 160mg mane orally.

She complained of buzzer sound in her ears and earache.

The furosemide dose was maintained and metolazone 5mg mane orally was also prescribed.

The patient responded well to the treatment and was discharged twelve days later.

Index Terms: tinnitus (0264), furosemide, potassium, glibenclamide, captopril, metolazone.

Summary:

With the parenteral use of furosemide in high doses, reversible deafness and tinnitus have been reported when the infusion is faster than 4mg per minute. The patient received oral treatment in this case.

Captopril in combination with diuretics may occasionally provoke dizziness or light-headedness, indicative of hypotension.

Probability:

Tinnitus (mild, type A) could possibly be caused by furosemide. It was postulated that the combination of captopril and furosemide could have led to tinnitus in this case.

Case 21

The patient, a seventy three year old white female took triclofos 500mg nocte orally; metoclopramide 10mg q8h orally and folic acid 5mg mane orally on admittance.

A few days later carbamazepine 300mg tds orally was prescribed for her. She then complained of a very bad bitter taste in her mouth.

Index Terms: taste bitter (0267), triclofos, metoclopramide, folic acid, carbamazepine.

Summary:

It was noticed that loss of appetite, dryness of the mouth and other gastrointestinal effects frequently occur in patients, irrespective of their medications.

Probability:

Carbamazepine was possibly responsible for the bitter taste (mild, type A) in this case.

Case 22

This seventy year old white female was put on chlorpropamide 250mg mane orally; ranitidine 150mg bd orally and oxethazaine co 10ml q4h orally.

She complained of constipation and sterculia/frangula 10ml bd orally was prescribed after two days.

Index Terms: constipation (0204), chlorpropamide, ranitidine, oxethazaine, sterculia/frangula.

Summary:

Dizziness, constipation, diarrhoea and nausea have been reported in ranitidine use. It is not apparent whether chlorpropamide or oxethazaine might cause constipation in patients.

Probability:

Ranitidine possibly caused constipation (moderate, type A) in this case.

Case 23

The patient, a fifty seven year old white female received lorazepam 1mg nocte orally; metoclopramide 10mg tds orally and tilidine 100mg nocte when needed for pain, orally.

Lactulose 20ml bd orally was prescribed for her two days later as well as mianserin 10mg nocte orally.

She complained of a very dry mouth on day three and it was suspected that the mianserin could be responsible.

Index Terms: mouth dry (0218), lorazepam, metoclopramide, tilidine, lactulose, mianserin.

Summary:

Mianserin belongs to the piperazino-azepines, which are not chemically related to the commonly used tricyclic antidepressants. Its structure lacks the basic side-chain which is considered to be responsible for the anti-cholinergic activity of the tricyclics.

None of the other medicines prescribed for this patient showed anti-cholinergic activities and a dry mouth is also not suspected to have been caused by them.

Probability:

It is doubtful that mianserin caused the dry mouth (mild, type B) suspected reaction in this patient.

Case 24

Mr V was referred to this hospital by a chest clinic. He was a thirty seven year old coloured male with a mass of 37kg and suffering from tuberculosis.

On admittance, he received propoxyphene 130mg Q6H when needed orally; rifampicin 450mg mane orally and isoniazid 300mg mane orally.

He developed a very high temperature and toxic epidermal necrolysis. The skin peeled off his hands, lips and upper parts of his chest and chloromycetin applicaps was prescribed for the severe eye reaction.

The rifampicin and isoniazid and other medication was discontinued. He made good progress.

On follow-up, it was found that he suffered from a viral infection as well.

The patient was then rechallenged with rifampicin 450mg mane orally and isoniazid 300mg mane orally because of the severe tuberculosis.

The same reaction occurred. His temperature raised. New skin eruptions occurred and his liver enzymes raised.

The patient was transferred to another ward three days later.

Index Terms: toxic epidermal necrolysis (0013), viral infection propoxyphene, rifampicin, isoniazid, chloromycin.

Summary:

The patient was referred to the clinical ward meeting for discussion.

The case was also referred to the clinical pharmacology ward round. At this meeting, the decision was made to determine the patient's acetylator status. The patient was found to be a slow acetylator.

Probability:

Both isoniazid and rifampicin were probably responsible for the TEN (severe, type B) this case.

The slow acetylator status of the patient however made isoniazid more likely to be responsible for the reactions with the associated viral infection; the patient was fortunate to recover from this episode.

Case 25

This sixty nine year old black female received furosemide 40mg mane orally; glibenclamide 10mg bd orally and metformin 1g tds orally on admittance.

The furosemide was discontinued the following day and amiloride co 5mg mane orally was prescribed. The patient also received isosorbide dinitrate 10mg q6h orally.

The registrar reported a hyperkalaemia in this patient after five days and discontinued the amiloride co. The patient also received protophane 35iu mane subcutaneously.

Index Terms: hyperkalaemia (0383), furosemide, glibenclamide, metformin.

Summary:

Hyperkalaemia may occur during therapy with amiloride in diabetic patients if chronic renal disease is present. The hydrochlorothiazide component may increase the requirements of insulin in these patients.

Hyperkalaemia was confirmed by laboratory tests in the patient and the drug was discontinued after the result.

Probability:

Amiloride co probably caused the hyperkalaemia (moderate, type A) in this case.

Method 2: Voluntary adverse drug reaction monitoring programme: Ward pharmacists.

In this study six case reports were received by the surveillance unit.

Case 1

The patient, a thirty year old female received phenobarbitone 15mg tds orally to control convulsions.

The patient developed erythema multiforme two days after she took the first dose of phenobarbitone.

The patient didn't take any other medicine at the stage that this reaction developed.

The reaction was classified to be severe and no feedback was required on this original report by the ward pharmacist.

Index Terms: erythema multiforme (0912), phenobarbitone, convulsions.

Summary:

Because of slow excretion of phenobarbitone, chronic poisoning could be due to cumulative action. Skin reactions are the most common form of allergic reaction. Exfoliative dermatitis has occasionally been reported, as has erythema multiforme.

Probability:

Phenobarbitone possibly caused the suspected erythema (severe, type B) in this case.

Case 2

This patient, a male developed a very dry mouth and sensitive tongue while being treated with metronidazole 800mg tds orally and tobramycin 120mg q8h parenteral.

The pharmacist listed metronidazole as the suspected drug and classified the reaction as moderate.

Index Terms: mouth dry (0218), tongue pain (0295), metronidazole, tobramycin.

Summary:

There have been occasional reports of a peculiar taste in the mouth, furred tongue, nausea and vomiting caused by metronidazole.

Probability:

No evidence could be found in prove that metronidazole caused the painful tongue (moderate, type B) in this case. The causality factor was rated at possible.

Case 3

This forty nine year old white female developed a rash all over body and a swinging temperature.

The lady took azathioprine 100mg daily orally; 6-alpha-methyl-delta-1 hydrocortisone 32mg daily orally; cefoxitin 1g q6h orally and acyclovir 200mg five times daily orally.

She received hydroxyzine and promethazine for two days after the reaction.

The ward pharmacist suspected cefoxitin to be responsible for the rash.

The reaction was classified to be severe.

Index Terms: rash (0028), pyrexia (0725), 6-alpha-methyl-delta 1 hydrocortisone, azathioprine, cefoxitin, acyclovir, hydroxyzine, promethazine.

Summary:

Cefoxitin is a cephamycin antibiotic reported to resist degradation by beta-lactamase. It has similar allergic reactions to the cephalosporins including skin reactions.

Azathioprine, because of its immunosuppressant activity, has been reported to have caused severe skin infections and reactions in patients. Other toxic reactions were nausea, vomiting and pyrexia.

Probability:

Very little information was provided concerning time intervals and other distinctive evidence.

Azathioprine was possibly responsible for the skin rash (severe, type B) in this case. Cefoxitin possibly caused the skin rash in this case.

Case 4

The patient, a fifty six year old black female was presented to casualty with a non-ketotic coma. She was given 10 iu Actrapid, after which she had a convulsion. She was then given 500mg phenytoin parenteral. At the ward she remained on phenytoin 300mg nocte orally.

She did not respond to actrapid, glibenclamide and metformin. She remained very drowsy. She was on phenytoin for 11 days after which it was stopped and she started to improve.

The ward pharmacist spoke to the houseman who said that the patient was obviously phenytoin-toxic ataxic and drowsy.

Unfortunately no phenytoin level was done. The case was classified as severe.

Drugs taken prior to the reaction were phenytoin 300mg nocte orally; glibenclamide orally; metformin orally; actrapid subcutaneous; monotard subcutaneously; tobramycin parenteral and co-trimoxazole.

Index Terms: drowsiness (0197), ataxia (0088), insulin, phenytoin.

Summary:

Side effects of phenytoin sodium are fairly common, and include nausea, vomiting, constipation, ataxia, slurred speech, blurred vision, mental confusion, and hallucinations together with headache and dizziness.

Probability:

Phenytoin was probably responsible for the ataxia (severe, type A) and drowsiness (severe, type B) in this case.

Case 5

This eighty one year old coloured female was admitted to the ward because of nausea and vomiting. Her digoxin level was 5 ug/ml and it was thought that the reason for toxicity was due to altered renal function due to her age.

After she was admitted tests taken showed that her urea was 17.4 mmol/l and creatinine 176 mmol/l, normal for a female of her age.

It was then suspected that she took a whole tablet daily instead of a half tablet. Her digoxin level was then done every day.

Drug taken prior to the reaction were digoxin 0.125mg daily (?); amiloride co one daily; prazosin 5mg bd orally; furosemide 120mg daily orally and paracetamol 1g daily orally.

She took the furosemide, prazosin and her digoxin blood level was monitored daily.

No feedback was required on this reaction, classified to be severe.

Index Terms: nausea (0308), vomiting (0228), digoxin, amiloride co, prazosin, furosemide, paracetamol.

Summary:

Nausea is common to digoxin overdose. It is important to note that she was on furosemide as well. It would have been interesting to have the laboratory results on both potassium and digoxin blood level.

The registrar changed the treatment to amiloride co.

Probability:

Digoxin possibly caused nausea (severe, type A) in this case.

Case 6

This seventy-eight year old male received morphine mixture 60mg nocte; tilidine 200mg four to six hourly and indomethacin.

Hallucinations and haematemesis were identified in the patient..

Ranitidine, aluminium hydroxide and magnesium trisilicate were then prescribed for him.

The ward pharmacist suspected morphine to be responsible for the hallucinations and the indomethacin responsible for haematemesis.

The severity of the reactions was classified to be moderate.

No feedback was required.

Index Terms: hallucination (0179), haematemesis (0297), indomethacin, morphine, tilidine, ranitidine, aluminium hydroxide, magnesium trisilicate.

Summary:

Reactions to indomethacin reported include mental confusion, anxiety, involuntary muscle movements and psychic disturbances such as depersonalization. These might be transient and may disappear with continued treatment.

Gastro intestinal ulceration, including perforation and haemorrhage have been reported with indomethacin.

Probability:

It is possible that indomethacin caused the haematemesis (moderate, type A) in the patient. Morphine was assessed to be possibly responsible for the hallucinations (moderate, type A) in the patient. The combined action of these medications may well have compounded the reaction.

Method 3: Voluntary adverse drug reaction monitoring programme: Medical and Nursing staff.

In this study, the medical staff and ward sisters were encouraged to report any suspected adverse drug reactions to the surveillance unit.

Eleven reports on suspected adverse reactions to drugs were received by the surveillance unit.

Case 1

The patient, a sixty six year old male was admitted to the dermatology ward after he developed a mild urticarial rash. The rash developed two days after he was started on erythromycin 250mg orally.

The reporter, a doctor, described it of mild severity and he suspected the erythromycin to have caused the adverse effect.

He required feed back on the case.

Index Terms: urticaria (0044), erythromycin.

Summary:

Mild allergic reactions such as urticaria and other skin rashes have occurred rarely with erythromycin.

Probability:

It is possible that erythromycin caused the urticaria (mild, type B) in this case.

Case 2

This forty year old black female developed an acute psychotic reaction after she was put on phenytoin 250mg as a loading dose.

After the loading dose she received 100mg of phenytoin nocte orally and the psychotic reaction occurred for six days.

She was given chlorpromazine and clothiapine 40mg parenterally after the reaction.

The reporter, a doctor, suspected phenytoin to be responsible for this reaction. The reaction was classified as moderate.

Index Terms: psychotic state (0193), phenytoin, chlorpromazine, clothiapine.

Summary:

Side effects of phenytoin are of fairly common occurrence, and include ataxia, slurred speech, blurred vision, mental confusion, and hallucinations together with headache, dizziness, tremor and insomnia.

Probability:

It is possible that phenytoin caused the psychotic state (moderate, type A) in this case.

Case 3

A seventy three year old black female developed an urticarial rash on her arms and trunk during her stay in the medical ward.

At the time of the reaction, penicillin 8 mu parenterally; tobramycin 240mg parenterally; cephamandole 4g parenteral; furosemide 40mg daily orally and potassium 2g orally were prescribed for her.

After the reaction, promethazine 25mg parenterally was given to her as a stat dose.

The reporter, a medical doctor, suspected the cephamandole to be responsible for the reaction.

The reaction was classified as moderate in severity.

Feed back was required.

Index Terms: urticaria (0044), penicillin, tobramycin, cephamandole, furosemide, potassium.

Summary:

Cephamandole, a cephalosporin antibiotic, showed allergic reactions in patients. Skin reactions occur in about 1% of patients and rises in serum transaminases have been noted.

Penicillin and furosemide also showed skin reactions in patients. Urticaria, maculopapular rash, abnormal liver-functions occurs in tobramycin.

Probability:

The urticaria (moderate, type B) was possibly caused by cephamandole in this case; however the penicillin was the more likely cause.

Case 4

A sixteen year old white female, developed an urticarial rash on her head, neck and both legs.

At the time of the reaction two propoxyphene capsules orally; paracetamol 1g orally; heparin 6250 units parenterally; probucol 250mg daily; diltiazem 60mg orally; dipyridamole 100mg orally and aspirin 1 tablet daily was prescribed for her.

After the reaction occurred, promethazine 25mg was given to her parenterally as a stat dose.

The reporter, a professional nurse, suspected propoxyphene to be responsible for the reaction.

The reaction was classified as mild in severity.

Index Terms: urticaria (0044), propoxyphene, paracetamol, heparin, probucol, diltiazem, dipyridamole, aspirin, promethazine.

Summary:

Adverse reactions observed with propoxyphene include constipation, abdominal pain, skin rashes and minor visual disorders among other.

Probability:

Urticaria (mild, type B) was possibly caused by propoxyphene in this case, although the probucol, diltiazem and dipyridamole and aspirin are also possible causes.

Case 5

The patient, a sixty seven year old white female took digoxin 0.0625mg daily orally; furosemide 250mg daily orally and captopril 25mg daily orally.

She developed a postural hypotension and the effect continued for three days.

The reporter, a professional nurse, suspected the captopril to be responsible for the reaction.

The postural hypotension was classified as mild.

Index Terms: hypotension postural (0213), digoxin, furosemide, captopril.

Summary:

In patients who are receiving aggressive diuretic and antihypertensive therapy, exaggerated hypotensive responses have occurred.

Probability:

It is possible that captopril caused the postural hypotension (mild, type A) and the reaction might have been potentiated by the diuretic.

Case 6

This seventy eight year old white male developed pain over the kidney region which radiated to his neck and legs. He perspired and his blood pressure dropped to 90/60.

He had been prescribed vancomycin 1g parenterally; pilocarpine eye drops 1 drop bd; paracetamol q4h orally and co-trimoxazole 960mg orally which was stopped on the day when the reaction occurred.

After the reaction promethazine 25mg as a stat dose and cloxacillin 1g parenterally was given to him.

The reaction was classified as moderate and vancomycin was suspected to be responsible.

The report was submitted by a professional nurse.

Index Terms: pain (0730), hypotension (0213), vancomycin, pilocarpine, paracetamol, co-trimoxazole, promethazine.

Summary:

Eosinophilia, anaphylactic reactions and alterations in kidney function have been reported with vancomycin. Very little information was given in this case. Follow up didn't provide more information.

Probability:

The pain (moderate, type B) and hypotension (moderate, type B) were possibly caused by vancomycin.

Case 7

A coloured female developed erythematous papules on her trunk and knee. The papules scaled in the middle. She took ranitidine 150mg bd orally and two propoxyphene capsules bd prior to the reaction.

No drugs were prescribed after the reaction.

The reporter, a ward sister, suspected ranitidine to be responsible for this reaction which she classified as mild.

Feed back was required.

Index Terms: erythema (0028), ranitidine, propoxyphene.

Summary:

Anaphylactoid reactions (anaphylaxis, urticaria) might follow oral administration of ranitidine.

Skin rashes have followed the administration of propoxyphene.

Probability:

It is possible that both ranitidine and propoxyphene or either of them alone, could have caused the erythema (mild, type B) in this case.

Case 8

A twenty eight year old coloured male received indomethacin 50mg tds orally and paracetamol.

The patient suffered from a back ache which radiated anteriorly. He developed fever.

He received hyoscine-N-butylbromide and lactulose after the reaction occurred.

The reporter, a doctor, suspected indomethacin to be responsible for the pyrexia.

The reaction was classified as moderate.

Index Terms: fever (0725), indomethacin, paracetamol, hyoscine N-butylbromide, lactulose.

Summary:

No reports have been found of indomethacin-induced fever. It was thought that normal development of the disease could have been responsible for this reaction.

Probability:

Indomethacin was possibly responsible for the fever (moderate, type B) in this case.

Case 9

This forty nine year old black female received vitamin E 500iu orally; colchicine orally; penicillin v 1g orally; captopril 12.5mg daily orally; tilidine and propoxyphene when needed, prior to the reaction.

The patient developed fever two days after she was given captopril. Her eosinophils rased (42) and a rise in her liver enzymes was noticed.

She received nifedipine 10mg bd orally and aspirin tds after the reaction.

The reporter, a registrar, suspected the captopril to be responsible for the reaction, which was classified as mild.

Feed back was required.

Index Terms: fever (0725), eosinophils rased (0571), vitamin E, colchicine, penicillin V, captopril, tilidine, propoxyphene.

Summary:

Elevation of liver enzymes has been noted in patients receiving the drug although no causal relationship has been found.

No information was found on pyrexia reactions after administration of captopril.

Probability:

Both the fever (mild, type B) and the rise in eosinophils (mild, type B) were possibly caused by captopril in this case.

Case 10

The patient, a forty two year old asian male, developed an urticarial rash.

The following drugs were prescribed for him prior to the reaction: clindamycin 300mg orally (1 dose); Insulin slow scale parenterally; erythromycin 300mg q6h parenterally and tobramycin 80mg q12h parenterally.

Promethazine 25mg parenteral as a stat dose, hydroxyzine 10mg qid increased to 20mg qid orally; diamicron 40mg nocte and 80mg mane and calamine lotion were prescribed after the reaction occurred.

The reporter suspected clindamycin to be responsible, since the reaction was noticed five hours after the first and only dose of the agent.

It was a moderate reaction and a doctor reported the case.

Index Terms: urticaria (0044), clindamycin, erythromycin, tobramycin, promethazine, hydroxyzine.

Summary:

Skin rashes and urticaria have been reported with clindamycin in patients.

Probability:

The urticaria (moderate, type B) was possibly caused by clindamycin in this case.

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