THE PHARMACOKINETICS OF RANITIDINE IN PATIENTS WITH CHRONIC DUODENAL ULCERATION AND IN PATIENTS WITH CHRONIC RENAL FAILURE.

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SUMMARY

The pharmacokinetics of orally administered ranitidine were studied in 10 patients with endoscopically proved duodenal ulceration after a single 150 mg dose and after 4 weeks' ranitidine treatment (150 mg twice daily), at which time there was endoscopic evidence of complete ulcer healing. After a single dose, the median elimination half-life was 135 minutes and the median area under the curve (AUC) was 1 844 ng/ml.hr. Although the maximum concentration after a single dose (Cmax = 365 ng/ml) was significantly different from that after continuous treatment (Cmax = 562 ng/ml) ($p < 0,05$) there was no significant difference between the minimum concentrations at 12 hours post-dosing (Cmin = 35 ng/ml and 30 ng/ml respectively) and the median half-lives were identical. No accumulation of ranitidine occurred in these patients after 4 weeks' chronic ranitidine treatment.

Five patients received 20 mg ranitidine intravenously. The apparent volume of distribution of the central compartment ranged from 10,5 to 28,4 l while the elimination rate constant β range drom 0,34 to 0,78 h^{-1} with the $t_{\frac{1}{2}}$ ranging from 53 to 122 minutes. The mean oral bioavailability was 51%.

The pharmacokinetics of ranitidine were studied in a further 7 patients with chronic duodenal ulceration who showed endoscopic evidence of unhealed ulcers after at least 8 weeks' treatment with ranitidine. There were no significant differences in any of the pharmacokinetic parameters when these patients were compared with the 10 responders above after multiple-dosage except that the disposition rate constant was smaller in non-responders (0,24 h^{-1} compared with 0,31 h^{-1}, $p < 0,002$). Two patients did, however, have very low plasma concentrations with above average basal

and maximal acid output which may have contributed to the lack of response to ranitidine treatment.

Single- and multiple-dose pharmacokinetic studies of oral ranitidine were carried out in 6 patients with chronic renal failure (RF) (creatinine clearance <25 ml/min) and compared with those obtained for the 10 patients with chronic duodenal ulceration with normal renal function (creatinine clearance >65 ml/min). There appeared to be no significant differences in absorption rate or amount absorbed but the median elimination rate constant was significantly reduced from 0,31 h^{-1} in controls to 0,14 h^{-1} in RF ($p < 0,002$) resulting in a two-fold increase in $t_{\frac{1}{2}}$ (312 minutes) after a single dose. Cmax did not differ significantly although Cmin and AUC were significantly larger in RF patients (both $p < 0,002$). It is suggested that the dosage of ranitidine be reduced from 150 mg to 75 mg twice daily in severe renal failure although it was not possible to relate half-life, elimination rate constant or AUC directly to creatinine clearance.

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CHAPTER 1

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INTRODUCTION AND LITERATURE REVIEW

1. INTRODUCTION AND LITERATURE REVIEW

1.1. INTRODUCTION

The discovery by Black and co-workers in 1972 of a specific antagonist to the effects of histamine at the histamine H_2-receptor heralded a new era in the research into mechanisms of gastric secretion and added a new dimension to the treatment of peptic ulceration. Cimetidine, the only H_2-antagonist to become generally available, has been used to treat millions of patients suffering from peptic ulceration. The evidence attesting to the efficacy of cimetidine treatment for duodenal ulceration is overwhelming (Bardhan 1980, Domschke et al 1980, Grossman 1980). Cimetidine has in fact become the yardstick against which other anti-ulcer drugs are measured (Marks et al 1980, Vantrappen et al 1980). However, as with all pharmacologically effective compounds, unwanted effects do occur although the incidence is relatively low in short-term treatment (Domschke et al 1980, Kruss et al 1979). Patients with renal failure or hepatic failure and the aged are at particular risk of developing more serious side-effects such as mental status changes (Bleumink 1980, Fastner 1980) probably due to reduced clearance of the drug.

At present there are new H_2-receptor antagonists which are more potent than cimetidine undergoing investigation (Domschke et al 1980). Ranitidine is an H_2-antagonist which differs from cimetidine in that the imidazole ring has been replaced by a furan ring (Peden et al 1979). Ranitidine is claimed to be more potent than cimetidine, and a simplified dosage schedule has been proposed. It may cause fewer side-effects.

Limited pharmacokinetic studies of ranitidine have been carried out in healthy volunteers (McNeil et al 1980, Woodings et al 1980). No pharmacokinetic studies have as yet been published on a patient population. The pharmacokinetic behaviour of a drug in healthy man is not necessarily a true reflection of the situation in patients as the disease state may alter

absorption, distribution, metabolism or elimination, thereby reducing efficacy or increasing toxicity.

I have therefore conducted the following studies into the pharmacokinetics of ranitidine following oral administration in patients suffering from chronic duodenal ulceration and in patients with severe renal failure and also a limited study of intravenous ranitidine in patients with chronic duodenal ulceration.

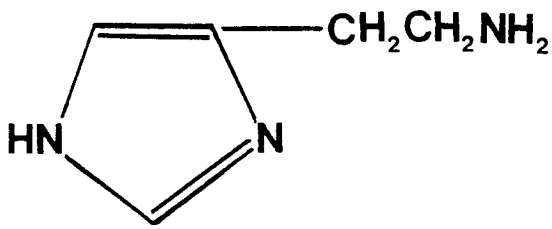
1.2. THE HISTORY OF THE H_2-RECEPTOR ANTAGONISTS

The histamine H_1-receptor antagonised by the conventional antihistaminic drugs such as mepyramine was defined by Ash and Schild in 1966. It was recognized that there was another class of histamine receptors which was not antagonised by the conventional or H_1-receptor antihistaminics. Black and co-workers commenced a search for antagonists to the effects of histamine on gastric secretion, heart rate and contractions of the rat uterus, using the analogy with catecholamine receptors and working from the structure of histamine. In 1972 Black et al published a report defining the histamine H_2-receptor and announcing the discovery of burimamide, a specific antagonist at the H_2-receptor (Figure 1.1.) (Black et al 1972).

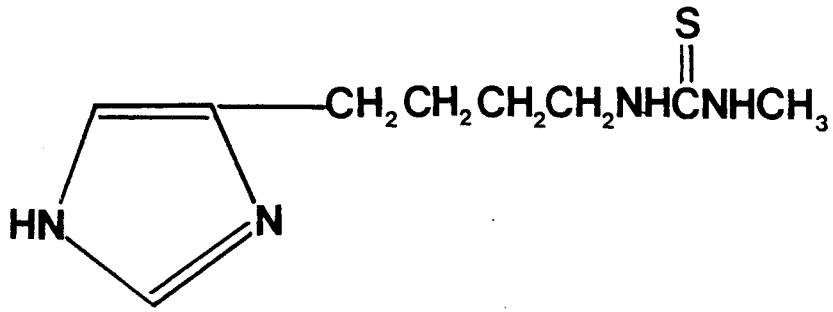
The structure of burimamide was then modified slightly to give the more potent orally active compound metiamide (Black et al 1973). Metiamide, although of therapeutic value in duodenal ulcer disease (Multicentre Trial 1975) was not marketed as it caused agranulocytosis (Burland et al 1975). The toxicity was thought to be related to the thiourea moeity in the side chain (Figure 1.1.) and this was changed to a cyanoguanidine to give cimetidine (Brimblecombe et al 1975) which was found to be an effective inhibitor of gastric acid secretion in animals in response to various stimuli including histamine and pentagastrin (Parsons 1977). Studies carried out in man confirmed these results both in healthy volunteers (Aadland et al 1977, Misiewicz 1976, Pounder et al 1976a, Pounder et al 1976b) and in duodenal ulcer patients (Longstreth 1976, Richardson et al 1975a, Richardson 1975b).

Many placebo-controlled trials of cimetidine have confirmed its efficacy in promoting the healing of duodenal ulcers when administered over a period of 4 to 6 weeks (Bank et al 1976, Bodemar and Walan 1976, Burland and Simkins 1977, Brogden et al 1978, Torsoli et al 1979, Winship 1978).

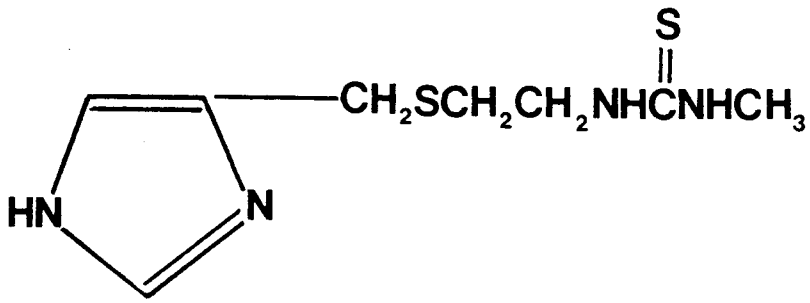
Histamine



Burimamide



Metiamide



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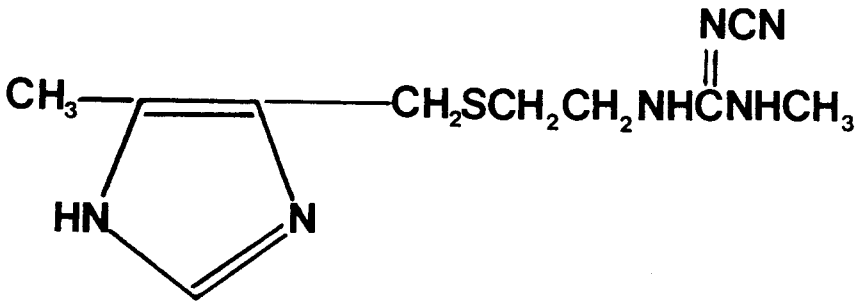

Ranitidine

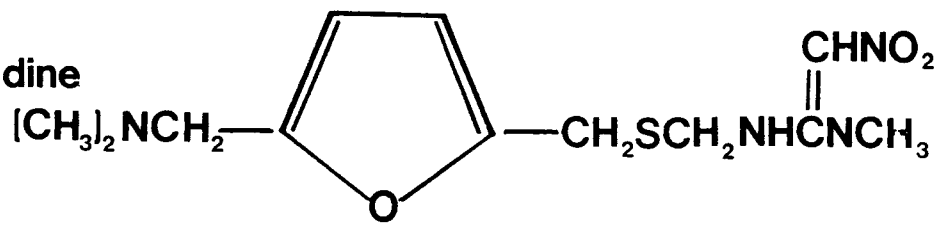

Figure 1.1. The structures of histamine and some H_2-receptor antagonists.

The percentage healing rate with cimetidine varied in these reports from 67 to 97%.

The position of cimetidine in the treatment of gastric ulcer is controversial as some trials show cimetidine to be more effective than placebo (Dyck et al 1978, Frost et al 1977) and as effective as carbenoxolone with fewer side-effects (La Brooy et al 1979) while others have shown little difference between the effects of cimetidine and placebo (Finkelstein and Isselbacher 1978, Grossman 1980). There have been recent suggestions that cimetidine may mask or even promote malignant changes in the gastric mucosa (Elder et al 1979a, Reed et al 1979, Taylor et al 1979) possibly through the formation of nitrosocimetidine (Elder et al 1979b). Cimetidine has proved useful in the control of peptic ulceration associated with the Zollinger-Ellison syndrome although in most cases a larger than normal dosage was necessary (Brogden et al 1978, McCarthy et al 1978).

Clinical experience has shown cimetidine to be relatively free of side-effects in the short-term with minor side-effects such as headache, dizziness, fatigue, skin rash, diarrhoea, constipation and muscular pain occurring with the same incidence as in placebo-treated groups (Brogden et al 1978, Finkelstein and Isselbacher 1978). Since H_2-receptors are distributed throughout the body including the brain and the heart, theoretically the potential for side-effects involving these systems exists. Cimetidine has been linked with changes in mental status such as depression, lethargy, coma, restlessness, agitation, disorientation, confusion, delirium, unsteadiness, visual impairment, hallucinations and somnolence (Russell and Langley 1980). Breast pain, galactorrhoea and more frequently gynaecomastia with or without raised prolactin levels, have been mainly reported in patients on long-term therapy (Bleumink 1980). Impotence in a number of duodenal ulcer patients on cimetidine has been reported (Bleumink 1980) and is thought to be due to anti-androgenic properties of the drug (Sawyer et al 1981).

Haematological abnormalities such as agranulocytosis and pancytopenia have occurred in a small number of patients taking cimetidine although the role played by cimetidine is uncertain (Bleumink 1980, Fastner 1980). Drug-drug interactions between cimetidine and the oral anticoagulants are of clinical importance (Flind 1978, Serlin et al 1979, Silver and Bell 1979). A potentiation of the effects of coumarin anticoagulants is due to inhibition of their metabolism by cimetidine inhibition of microsomal drug metabolism (Park and Breckenridge 1981, Puurunen et al 1980). Cimetidine similarly prolongs the half-life of other drugs metabolised by cytochrome P-450 such as chlordiazepoxide (Desmond et al 1980) and diazepam (Klotz et al 1979).

New H_2-antagonists with increased potency in relation to cimetidine are at present undergoing investigation (Domschke and Domschke 1980). Ranitidine is an H_2-antagonist which differs from histamine and cimetidine in that the imidazole ring which was thought at one stage to be essential for H_2-receptor blockade (Ganellin et al 1976) has been replaced with a furan ring (Figure 1.1.) (Bradshaw et al 1979).

Experiments on the guinea pig atrium and rat uterus in-vitro have demonstrated competitive antagonism by ranitidine to the effects of histamine without altering responses to isoprenaline (Daly et al 1980a, Daly et al 1981). Ranitidine inhibited pentagastrin- and histamine-induced gastric acid secretion in the perfused stomach preparation of the anaesthetized rat where it was 7 times more potent than cimetidine on a molar basis (Daly et al 1981). The effects of oral ranitidine in inhibiting gastric acid secretion stimulated by histamine, pentagastrin and bethanechol in Heidenhain-pouch dogs were 4,3, 5,0, 9,2 times more potent than those of cimetidine respectively (Daly et al 1980b). In chronic gastric fistula rats and Heidenhain-pouch dogs the comparative potency in inhibition of gastric acid output of 4 H_2-antagonists was cimetidine < BL-5641 < Ranitidine < ICI 125211 (Cavanagh et al 1980). In the dog with a gastric fistula,

food- and 2-deoxy-D-glucose-induced acid secretion was inhibited by ranitidine (Daly et al 1979).

Ranitidine is a selective H_2-antagonist in-vitro and in-vivo it is active after oral administration in animals in inhibiting histamine-induced gastric acid secretion as well as the effects of other secretagogues (pentagastrin, bethanechol, food and 2-deoxy-D-glucose).

Other H_2-antagonists at present under investigation include SK&F 92994, ICI 125211 (Domschke and Domschke 1980) and BL-5641 (Cavanagh et al 1980).

1.3. CLINICAL PHARMACOLOGY OF RANITIDINE.

Studies carried out in healthy volunteers have shown ranitidine to inhibit pentagastrin-stimulated gastric acid secretion when administered intravenously (Domschke et al 1979, Kett et al 1980, Sewing et al 1980, Woodings et al 1980) and orally (Simon and Kather 1979). Intravenous ranitidine significantly reduced histamine-stimulated gastric acid and volume output in normal subjects (Bohman et al 1980). When administered intravenously to volunteers, ranitidine was found to be 6-times more effective than cimetidine in raising gastric transmural electrical potential (Von Kleist et al 1979). Cimetidine and ranitidine inhibit gastric acid secretion induced in volunteers by amino acid infusion (Weingart et al 1980).

A comparative study of ranitidine and cimetidine in patients with duodenal ulcer in clinical remission showed ranitidine to be 8-times more potent than cimetidine in inhibiting histamine-induced secretion and 4- to 5-times more potent as an inhibitor of sham- and real-feeding-induced secretion without affecting serum gastrin levels (Konturek et al 1980).

Ranitidine given orally (100 mg) to 6 patients caused a clear increase of intra-gastric pH for over 9 hours (Damman et al 1980). In patients with clinically active duodenal ulceration, ranitidine was a powerful inhibitor of nocturnal and pentagastrin-stimulated gastric acid secretion (Peden et al 1979a). In 5 of these patients 50% inhibition of pentagastrin-stimulated acid secretion was achieved at a mean plasma ranitidine concentration (IC_{50}) of 93,6 ng/ml after intraduodenal administration (Peden et al 1979b).

After 6 weeks of ranitidine treatment, 94% of patients with gastric ulceration and 83% of patients with duodenal ulceration showed endoscopic evidence of healing in an open study (Barbier et al 1979).

In a double-blind placebo-controlled trial of patients with duodenal ulceration, ranitidine given in a dose of 100 mg twice daily for 4 weeks healed 92% compared to 46% healing in the placebo group (Berstad et al 1980).

In another double-blind placebo-controlled trial with 150 mg ranitidine administered twice daily, 80% of ulcers were healed compared with 33% in the placebo group (Chatterji 1980). Cimetidine 1000 mg daily and ranitidine 200 mg daily were proved equivalent in promoting ulcer healing (94% and 89% healing respectively after 8 weeks' treatment) (Langman et al 1980).
It is hoped that the side-effects of cimetidine which are unrelated to H_2-receptor blockade may be avoided with more potent drugs such as ranitidine where the imidazole ring has been replaced. Thus far ranitidine does seem to have an advantage over cimetidine with respect to some of the side-effects. Ranitidine does not appear to influence cardiac function (Barbat and Warrington 1980). When administered intravenously, ranitidine had no effect on prolactin levels (Barbat and Warrington 1980). Cimetidine, but not ranitidine, tends to raise blood teststerone levels in peptic ulcer patients (Walt et al 1981). One patient with Zollinger-Ellison syndrome was successfully treated for duodenal ulceration with ranitidine after having to discontinue cimetidine treatment because of painful gynaecomastia (Mignon et al 1980). In a clinical trial in which ranitidine (200 mg daily) and cimetidine (1 g daily) were compared, cimetidine caused significant increases in serum urea and creatinine concentrations although still within the normal range, whereas ranitidine had no effect (Langman et al 1980).

The inhibition of the metabolism of a number of drugs including warfarin (Serlin et al 1979), chlordiazepoxid (Desmond et al 1980), antipyrine (Puurunen et al 1980), diazepam (Klotz et al 1979) by cimetidine has been attributed to the imidazole ring structure (Wilkinson et al 1973).
These interactions might be expected to be absent when using ranitidine.
In a paired study of hepatic microsomal function in 8 subjects, ranitidine (200 mg daily) did not affect the metabolism of aminopyrine or antipyrine whereas cimetidine (1 g daily) did so (Henry et al 1980). Another study of ranitidine (150 mg daily for one week) showed no effect of the drug on antipyrine half-life, clearance or volume of distribution (Staiger et al

1980). In patients being treated with drugs metabolised by cytochrome P-450, ranitidine would seem to be a suitable alternative to cimetidine.

1.4. PHARMACOKINETICS AND BIOAVAILABILITY OF H_2-RECEPTOR ANTAGONISTS.

The H_2-antagonist metiamide was developed when the original H_2-antagonist burimamide was found to be inactive orally (Black et al 1973). The bone-marrow toxicity of metiamide limited its clinical usefulness and led to the development of cimetidine.

Several studies of cimetidine blood levels after intravenous and oral administration have been carried out in healthy humans (Burland et al 1975b, Grahnen et al 1979, Griffiths et al 1977, Tayler et al 1978, Walkenstein et al 1978). Following oral administration, cimetidine is rapidly absorbed with the peak occurring from 0,5 to 2 hours after dosing (Griffiths et al 1977, Walkenstein et al 1978) and a marked secondary peak 2 to 5 hours after dosing when administered on a fasting stomach (Griffiths et al 1977, Grahnen et al 1979, Walkenstein et al 1978). Bioavailability after oral dosage has been reported variously as 62% (Walkenstein et al 1978), 72% (Griffiths et al 1977) and over 100% in most subjects in a third study (Grahnen et al 1979). Grahnen has proposed that bioavailability of greater than 100% may be explained by entero-hepatic recycling (Grahnen et al 1979). A pharmacokinetic model taking into account the discontinuous absorption following recycling has been constructed and has shown good agreement with oral, intravenous and intramuscular data (Veng Pedersen and Miller 1980). In healthy humans, antacids administered with cimetidine after a meal did not interfere with cimetidine absorption (Burland et al 1976) but in peptic ulcer patients antacids taken with cimetidine on a fasting stomach caused a reduction in blood concentrations of cimetidine (Bodemar et al 1979b).

After intravenous administration cimetidine blood concentration data fit a two-compartment open model (Grahnen et al 1979, Griffiths et al 1977) with the initial distribution phase having a short half-life of approximately 7 minutes (Griffiths et al 1977). The terminal elimination phase half-life is usually between 1,8 and 2 hours (Burland et al 1975b, Grahnen et al 1979, Griffiths et al 1977, Walkenstein et al 1978) and does

not differ with different routes of administration. In most studies 70 to 80% of the parent drug is excreted in the unchanged form in the urine when cimetidine is administered intravenously (Griffiths et al 1977, Taylor et al 1978, Walkenstein et al 1978) but only 40 to 50% is recovered in the urine after oral dosage (Grahnen et al 1979, Walkenstein et al 1978). Approximately 10% is found as the sulphoxide metabolite in urine (Burland et al 1975b, Griffiths et al 1977) independent of dose or route of administration. A four-fold bile to blood concentration gradient has been recorded although the total amount of drug secreted was insignificant when compared to the dose (Spence et al 1977). There is some evidence that cimetidine is excreted in human breast milk (Wilson et al 1980).

In-depth pharmacokinetic studies of cimetidine in peptic ulcer patients are few and have only recently been published. Henn showed a direct relationship between inhibition of meal-stimulated gastric acid secretion and peak blood cimetidine concentration in ulcer patients on oral treatment (Henn et al 1975). A study in 28 patients with peptic ulcer treated with oral cimetidine showed no change in bioavailability over 12 weeks of treatment as assessed by area under the curve (AUC). The AUC was dose-related and there was no difference in bioavailability when the drug was taken on a fasting stomach or together with a meal (Bodemar et al 1979a). This study also demonstrated a secondary peak when cimetidine was given on an empty stomach which was not seen when the drug was given with food (Bodemar et al 1979a). Somogyi et al compared the pharmacokinetics and bioavailability of 200 mg cimetidine given intravenously and orally in 6 gastric and 6 duodenal ulcer patients (Somogyi et al 1980a). There were no pharmacokinetic differences between the two ulcer groups although a considerable age-related variation in pharmacokinetic parameters was noted (Somogyi et al 1980a).

Rune et al (1979) measured acid secretion and its inhibition by cimetidine

in 40 duodenal ulcer patients. They also measured cimetidine blood concentrations in order to examine why some patients were resistant to standard cimetidine therapy. They demonstrated a wide inter-individual variation in sensitivity to cimetidine and a low correlation of acid inhibition with AUC. There was no correlation of effectiveness with gastric secretory capacity or individual sensitivity to cimetidine (Rune et al 1979). In a report on one patient, cimetidine was found to have no effect on acid secretion despite apparently adequate plasma levels and the author suggests that gastric secretory studies in non-responders are necessary to identify patients of this type (Kisloff 1980).

There is as yet very little human pharmacokinetic information available on the newer H_2-antagonists. SK&F 92994, a compound with an isocytosine ring in its side-chain, is more potent than cimetidine and a dosage schedule of 400 mg twice daily has been suggested (Gotthard et al 1980). In patients with duodenal ulceration the half-life of SK&F 92994 was about 3,3 hours and the bioavailability 36% (Somogyi and Gugler 1980b).

Ranitidine is reported to have an elimination half-life of approximately two hours (McNeil et al 1980, Woodings et al 1980). Bioavailability is about 50% and peak levels occur 0,5 to 1,5 hours after dosage; secondary peaks were observed when administered on a fasting stomach (Woodings et al 1980). The total apparent volume of distribution is 115 litres and the total plasma clearance is estimated at 709 ml/min (McNeil et al 1980). Ranitidine is excreted chiefly in unchanged form in the urine with small amounts of N-oxide, S-oxide and desmethyl metabolites (Bell et al 1980). All these studies involved healthy volunteers and to date no ranitidine pharmacokinetic data in duodenal ulcer patients have been published.

1.5. H_2-ANTAGONISTS AND RENAL IMPAIRMENT.

There is an incidence of peptic ulceration and gastrointestinal bleeding in patients with chronic renal failure and this incidence further increases (up to 50%) when patients are managed with chronic haemodialysis (Doherty et al 1977, Shepherd et al 1973, Wormsley 1980). Gastric output is high in uraemic patients, particularly in those on regular haemodialysis (Doherty et al 1977, Shepherd et al 1973) and hypergastrinaemia is often observed as well (Doherty et al 1977, Doherty et al 1978a). After renal transplantation the occurrence of peptic ulceration varies from 4,4 to 18% and a high proportion of these patients experience complications (Editorial 1979, Perrott et al 1981). H_2-antagonists might therefore be expected to be of benefit in the prevention or treatment of upper gastrointestinal problems in chronic renal impairment.

Two reports confirm the therapeutic efficacy of cimetidine in patients with renal impairment (Doherty et al 1977, Jones et al 1979) although there are conflicting reports on its prevention of upper gastrointestinal complications after kidney transplantation (Doherty et al 1978b, Hussey and Belzer 1979). Cimetidine is mainly eliminated unchanged by the kidneys (Burland et al 1975) and tends to accumulate in patients with renal disease or age-related reduction in renal function. There is some evidence to suggest that side-effects such as mental confusion may be related to relatively high cimetidine concentrations, particularly in patients with renal or hepatic dysfunction or in the elderly (Russell and Lopez 1980, Schentag et al 1979). A study in healthy subjects showed a significant correlation between AUC and age although the correlation of AUC with creatinine clearance was poor (Redolfi et al 1979). Another study showed total plasma clearance and volume of distribution of cimetidine to be inversely related to age (Somogyi et al 1980a). Elderly, healthy individuals have slower metabolic and renal removal of drugs in general (Crooks et al 1976) and dosages may have to be adjusted for this

group of patients as well as those patients in renal failure.

A number of studies of cimetidine blood levels in patients with impaired renal function (Bjaeldager et al 1980, Canavan and Briggs 1977, Larsson et al 1979, Luk et al 1979) and hepatic dysfunction (Schentag et al 1979) have appeared in the literature. After intravenous administration, the elimination half-life of cimetidine was significantly longer (2,56 h) than in normals (1,52 h) although in anephric patients the half-life was shorter than expected (3,66 h) indicating greater use of alternative pathways (Ma et al 1978). Similar results were obtained in two other studies where oral cimetidine was administered (Bjaeldager et al 1980, Larsson et al 1979) showing slower elimination and higher blood levels in uraemic patients. Various methods of calculation of dosage adjustments have been advocated including one based on AUC (Bjaeldager et al 1980) a nomogram relating dosage to creatinine clearance (Luk et al 1979), and another based on the length of time blood cimetidine concentrations remained above 0,5 µg/ml (Larsson et al 1979).

The above studies all gave similar results and Bennett et al (1980) recommend the following dosage guidelines to patients with:

i) glomerular filtration rate (GFR) exceeding 50 ml/min, dose and dosage interval remain unaltered at 200 mg 6-hourly;

ii) GFR of 10 to 50 ml/min, 150 mg 6-hourly or 200 mg 8-hourly;

iii) GFR below 10 ml/min, 100 mg cimetidine 6-hourly or 200 mg 12-hourly.

The efficacy of 200 mg cimetidine when given 12-hourly for 6 weeks in the treatment of various upper gastrointestinal peptic disturbances (including duodenal ulcer, oesophagitis, and erosions) in 8 patients undergoing haemodialysis without undesirable side-effects, has been confirmed by Jones et al (1979).

Cimetidine is dialysable (Bjaeldager et al 1980, Canavan and Briggs 1977, Ma et al 1978) although the amount varies in the different reports. Ma et al recommend an extra dose at the end of dialysis but Bjaeldager et

al consider this unnecessary (Ma et al 1978, Bjaeldager et al 1980).

There is no information available on the blood levels of any of the new H_2-antagonists in patients with renal failure. Ranitidine, which like cimetidine, undergoes elimination in the unchanged form in the urine to a large extent (Bell et al 1980), can be expected to have a similar pharmacokinetic profile in renal failure to that of cimetidine.

CHAPTER 2

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METHODS

2.1. PATIENT STUDY DESIGN.

Separate protocols were drawn up for each aspect of the trial and submitted to the South African Medicines Control Council and to the Ethical Committee of the University of Cape Town Medical School for approval prior to initiation of the study.

2.1.1. Patients with chronic duodenal ulceration (Responders)

2.1.1.1. Study Location

The study was conducted in conjunction with the staff of the Gastrointestinal Unit of Groote Schuur Hospital. All blood sampling was carried out either in the Gastrointestinal Unit itself or in the wards of the hospital.

2.1.1.2. Patient selection

Ten patients were studied in this group. They all presented to the Gastrointestinal Unit with signs and symptoms of peptic ulceration. The following exclusions were applied:

i) patients who were considered likely to be uncooperative or unable to attend the clinic regularly;
ii) patients with concurrent systemic disease;
iii) patients with a history of previous lower oesophageal or gastric surgery;
iv) patients with a history of pyloric stenosis;
v) pregnant or lactating women;
vi) people who had received therapy with H_2-receptor blocking agents in the month prior to the trial;
vii) patients with a history of recent ulcer perforation.

The diagnosis of duodenal ulceration was established by endoscopy. The ulcer size was required to be equal to or larger than 3 mm for inclusion in the study.

The purpose and nature of the study was explained to the patients and they were asked to sign a consent form.

The age, sex, race, weight, smoking and drinking habits and concurrent illnesses and medication of the patients included in the study are recorded in Table 2.1. Detailed case histories are to be found in Appendix I. (Duodenal ulcer patients-No. 1-10).

2.1.1.3. Schedule of visits and investigations.

Each patient was seen on three occasions over a 4 week period, and four returned subsequently for a fourth visit. (Figure 2.1.).

VISIT ONE. SINGLE-DOSE STUDY

The diagnosis was made on endoscopic examination.

A pentagastrin stimulated gastric secretion study was carried out in the Gastrointestinal Clinic. After an overnight fast a Rüsch nasogastric tube was passed and the subject was screened by X-ray to confirm the position of the tube. The stomach was emptied of residual contents under constant pressure (3 mm/H_2O). Basal secretions were collected at half-hourly intervals for 1 hour. An intramuscular injection of pentagastrin (6 µg/kg) was administered and gastric juice collected at 15 minute intervals for 1 hour. Volumes of gastric aspirates were recorded and the acidity was measured by titrating 1 ml samples of gastric juice in 10 ml distilled water with 0,1N NaOH (Automatic Titration System TTT60, Radiometer, Copenhagen, Denmark).

The patients were then hospitalised for the duration of the pharmacokinetic study. After an overnight fast an indwelling intravenous catheter was inserted into a forearm vein. The catheter was kept patent throughout the sampling period by flushing with heparin in normal saline (100 units/ml). A 150 mg tablet of ranitidine was administered immediately prior to a standard hospital breakfast (porridge, egg, bread and jam, coffee).

Blood samples were drawn at the following times after dosing:

0, ¼, ½, ¾, 1, 1½, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours. The samples

TABLE 2.1.

DUODENAL ULCER PATIENTS - RESPONDERS

Initials	Age (years)	Weight (kg)	Sex	Race	Smoking habits (number of cigarettes)	Alcohol intake	Other illnesses	Concurrent Medication	Duration of ulcer disease (years)
J.H.	25	70	male	Coloured	20/day	occasional	sinusitis	tetracyclines	5
T.W.	42	47,5	male	Coloured	Discontinued 1 year previously	none	nil	nil	16
A.d.S.	26	69	male	Coloured	nil	occasional	nil	nil	10
M.S.	26	50	male	Coloured	20/day	none	bronchitis	tetracyclines	3
S.M.	31	57	male	African	nil	none	nil	nil	6
D.F.	23	48	male	Coloured	6-8/day	occasional	nil	nil	2
P.d.J.	24	50	male	Coloured	30/day	occasional	nil	nil	1,5
W.M.	34	65	male	Coloured	20/day	750 ml wine per day	nil	nil	0,1
A.O.	42	73	male	Coloured	25/day	none	nil	nil	1
D.S.	36	94	male	Coloured	nil	Discontinued 2 months previously	nil	nil	16
mean	30,9	62,4							6,1
range	23-42	47,5-94							0,1-16

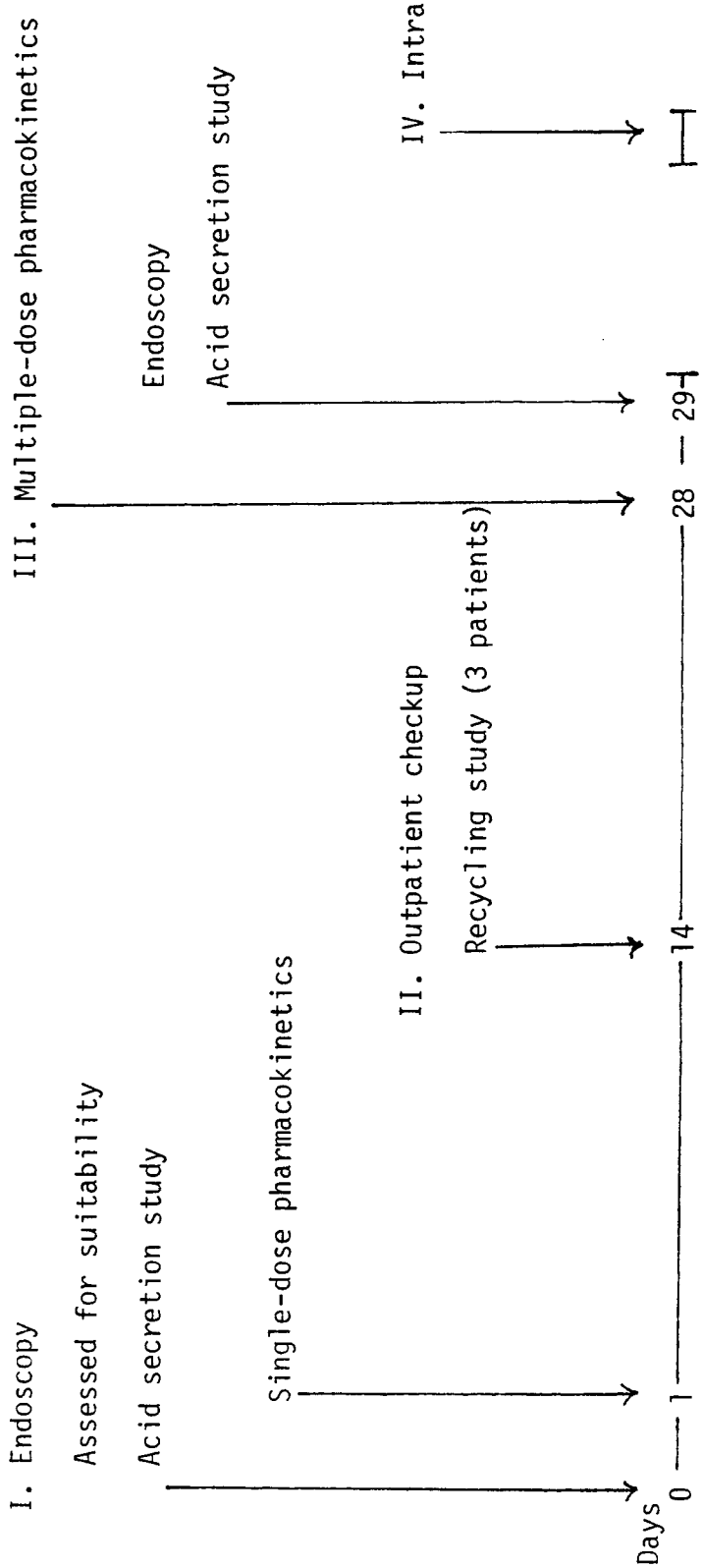

Figure 2.1. Study design for duodenal ulcer patients.

were centrifuged as soon as possible and the separated plasma stored at -20°C until assayed. No further restrictions on food or fluid intake were made during the study period. The timing of meals was noted.

A twenty-four hour urine collection was commenced at the time of dosing.

At the end of the study therapy commenced with 150 mg ranitidine twice daily.

VISIT TWO. CHECK-UP AND RECYCLING STUDY.

All the patients were seen at the Gastrointestinal Clinic 14 days after the initiation of therapy. Careful note was taken of symptoms, response to therapy and compliance.

Three of the patients were requested to omit their morning dose on this occasion. A basal blood sample was taken and the patients were then given breakfast after which blood samples were taken every 10 minutes for 1 hour. This was done in an attempt to see if a rise in the levels of ranitidine could be detected which would suggest release of the drug from bile secreted as a result of the meal, followed by reabsorption of the ranitidine from the intestine (Veng Pedersen and Miller 1980).

VISIT THREE. MULTIPLE-DOSE STUDY.

Twenty-eight days after commencing therapy each patient was again admitted to hospital for a further 24-hour period. Again, 150 mg ranitidine was taken orally after an overnight fast immediately before breakfast. Samples were taken through an indwelling intravenous cannula at the following times:

0, ¼, ½, ¾, 1, 1½, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours after the dose.

A 24-hour urine collection was made.

On the day following the study the drug was withheld and a repeat endoscopy and acid study were done to evaluate response to therapy.

NOTE: Prior to treatment, at the 14-day visit and at 28 days blood samples were taken from all the patients for the determination of routine haemotological and biochemical parameters. The samples

were analysed by the Chemical Pathology Department of Groote Schuur Hospital.

The results are given in Appendix II (TABLES A1 and A2).

2.1.2. Patients with chronic duodenal ulceration who did not respond to ranitidine therapy (Non-responders)

The 7 patients in this group were selected from two large-scale clinical trial investigations. Patients who showed endoscopic evidence of unhealed ulcers after at least eight weeks of treatment with the standard dose of ranitidine (150 mg taken twice daily), where compliance was satisfactory, were regarded as being non-responders.

2.1.2.1. Study location.

Two patients were drawn from the clinical trial of ranitidine undertaken during 1979 and 1980 by the Gastrointestinal Unit of Groote Schuur Hospital.

The remaining five patients were drawn from the clinical trial of ranitidine conducted in 1979 and 1980 at the Gastrointestinal Unit, Department of Medicine, University of Natal.

2.1.2.2. Patient selection.

The patients were selected on the grounds of their failed response to ranitidine as indicated above. Patients were excluded from further investigations on suspicion of malignant ulcer change, or if the failure of response was considered to be due to lack of compliance in taking the medicine.

Details of these patients are given in Table 2.2. Case histories are presented in Appendix I.(Duodenal ulcer patients - No. 11-17).

2.1.2.3. Schedule of visits and investigations.

The 2 patients from Groote Schuur were seen on more than one

TABLE 2.2.

DUODENAL ULCER PATIENTS - NON-RESPONDERS.

Initials	Age (years)	Weight (kg)	Sex	Race	Smoking habits (number of cigarettes)	Alcohol intake	Other illnesses	Concurrent Medication	Duration of ulcer disease (years)
J.S.	52	66	male	Coloured	20/day	heavy (750 ml wine/day)	nil	nil	5
R.L.	50	66	male	Coloured	20/day	none	nil	nil	5
D.M.	20	54	male	Asian	12/day	occasional	nil	nil	4,5
S.S.	50	72	male	Asian	10/day	discontinued	diabetes mellitus	chlorpropamide	10
P.M.	47	62	male	Asian	10/day	beer	nil	nil	6
D.S.	56	72	male	Asian	10-12/day	weekends	diabetes mellitus	chlorpropamide	5
P.P.	24	57	male	Asian	10/day	none?	nil	nil	8
mean	42,7	64,3							6,2
range	20-56	54-72							4,5-10

occasion. R.L. underwent single- and multiple-dose pharmacokinetic studies as he was originally included in the group described in 2.1.1. above. J.S. was studied after multiple-dosing with 150 mg twice daily and after multiple-dosing with 300 mg daily. Acid secretion studies were carried out in both patients.

The remaining patients were studied on one occasion only 1 week after they had been re-started on ranitidine therapy 150 mg twice daily. The blood samples were taken as described in 2.1.1.3 (multiple-dose). Fasting serum gastrin levels were determined in all cases in order to exclude the possibility of hypergastrinaemia being the cause of the failed response to ranitidine. The gastrin levels were measured by the Endocrine Laboratory of the Department of Medicine, University of Cape Town, using a CIS CEA-SORIN radioimmunoassy kit (Sorin Biomedica, Italy).

2.1.3. Patients with chronic renal failure.

2.1.3.1. Study location

These patients all presented to the Renal Unit, Somerset Hospital, Green Point, Cape Town.

2.1.3.2. Patient selection.

All patients suffered from chronic renal failure of varying aetiology. A summary of patient details is given in Table 2.3. and detailed case histories are given in Appendix I. (Patients with renal failure - No. 1-6) Two groups were identified:

Group I: Six patients with severe renal failure (creatinine clearance 0-25 ml/min), not undergoing haemodialysis;

Group II: Three patients with endstage renal failure (creatinine clearance 0-5 ml/min) treated with chronic haemodialysis.

The duodenal ulcer patients described in section 2.1.1. with normal

TABLE 2.3.

DETAILS OF PATIENTS WITH RENAL FAILURE

Initials	Age (years)	Weight (kg)	Sex	Race	Smoking habits (number of cigarettes)	Alcohol intake	Other illnesses	Concurrent Medication
B.S.	35	64,5	male	Coloured	non-smoker	occasional	hypertension	hydrallazine, atenolol, furosemide, aluminium hydroxide gel, sodium bicarbonate
J.Se.	39	73	male	Coloured	2/day	occasional	hypertension	hydrallazine, furosemide, atenolol, aluminium hydrozide gel.
L.A.	75	57,5	male	Coloured	non-smoker	nil	diabetes mellitus hypertension	digoxin, lente insulin, dipyridamole, dyclopenthiazide.
H.D.	34	55	male	African	non-smoker	nil	hypertension	hydrallazine, furosemide, labetalol
T.C.	40	68,5	male	Coloured	non-smoker	nil	hypertension	hydrallazine, atenolol, furosemide, aluminium hydroxide gel, dihydralazine.
R.W.	21	60,0	male	Coloured	2/day	nil	hypertension	aluminium hydroxide gel, prazosin, paracetamol.
mean	40,7	63,1						
range	21-75	55-75						
R.D. *	42	53,5	female	Coloured	non-smoker	nil	hypertension	atenolol, hydrallazine, ferrous sulphate, prazosin, folic acid.
O.P. *	49	60	male	Coloured	10-15/day	occasional	hypertension diabetes mellitus	aluminium hydroxide gel, multi-vitamins, ferrous sulphate, metoprolol.
F.P. *	38	58,5	female	Coloured	15/day	nil	systemic lupus erythematosus	atenolol, cyclophosphamide aluminium hydroxide

* on haemodialysis

renal function (creatinine clearance greater than 70 ml/min) served as the group for comparison with this renal failure group.
Patients were not admitted to this study if they had a history of drug allergy or intolerance, or of liver disease.

2.1.3.3. Schedule of visits and investigations.

The details of the study were explained to the patients and they were required to sign consent forms before starting the drug administration.

The Group I patients were seen on two occasions one week apart. Haematological and biochemical investigations were carried out prior to ranitidine being given, and again at the end of the week's treatment. The results are detailed in Appendix II (TABLES A3 and A4) These assays were done by the Chemical Pathology and Haematology Laboratories at Somerset Hospital.

The single-dose pharmacokinetic sampling was carried out after administration of 150 mg ranitidine before a standard hospital breakfast. Blood samples were drawn through an indwelling intravenous catheter at the following times after dosage:

0, $\frac{1}{4}$, $\frac{1}{2}$,$\frac{3}{4}$, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24 hours.

A 24-hour urine collection was made for the determination of total ranitidine excreted over that time, and for determining creatinine clearance. The patients were then given 75 mg ranitidine twice daily for 1 week (except B.S. who received 150 mg twice daily). Four of the patients remained in hospital for the duration of the study period. All patients were on a number of other drugs which were not altered except in the case of antacids, which were omitted when they were due to be taken at the same time as ranitidine on the day of a pharmacokinetic study. Sampling for the multiple-dose study was done in an identical manner to that of the single-dose (in each case a 75 mg dose was given, with the exception of B.S.).

The dialysis patients were given a single 150 mg dose of ranitidine 3 hours prior to commencing dialysis with a Travenol dialyser (Baxter). Two blood samples were taken simultaneously, from the line leading into the dialyser and from the line leading out of the dialyser respectively. In two patients this was done at two different flow rates. Flow rate was measured by running saline through the dialyser and measuring the volume pumped through the machine per unit time at a particular setting.

Dialysance (which is the volume of blood cleared of ranitidine each minute) was calculated from the following formula

$$Q_D = \frac{Q_B\ (B_i - B_o)}{(B_i - D)}$$

where Q_D = dialysance (ml/min)

B_i and B_o = drug concentration going into (B_i) and coming out of (B_o) the dialyser

D = drug concentration in the dialysate

Q_B = blood flow (ml/min)

(Bjaeldager et al 1980, Ma et al 1978).

2.2. ANALYTICAL TECHNIQUE.

Ranitidine hydrochloride is a potent H_2- antagonist (Bradshaw et al 1980). A sensitive analytical method for measuring the drug in plasma and urine was necessary as the peak plasma concentrations were expected to be in the nanogram range after administration of oral therapeutically active doses in man. A high pressure liquid chromatographic (hplc) method using an untraviolet detector was developed (Carey and Martin 1979). This method involves extraction of the drug and an internal standard, AH.20480 into octanol and then a back extraction into an aqueous phase prior to separation by reversed phase high pressure liquid chromatography.

Described below is the modified version of this method which was used for analysis of all samples in our pharmacokinetic studies.

2.2.1. Materials.

Ranitidine hydrochloride (batch no. C.314/152) and AH 20480 (batch no. C.331/52/2) were obtained from Glaxo Group Research Ltd., Ware, England.

Ranitidine hydrochloride tablets (150 mg base equivalent) (batch no. MR/0314, MR6241W), and the intravenous form containing 10 mg/ml (batch no. MR5090W) were also supplied by Glaxo Group Research Ltd., Ware, England.

The following laboratory reagents with the grade and manufacturer as indicated were used:

octan-1-ol, extra pure (E. Merck, Darmstadt);

disodium hydrogen phosphate, analytical grade (E. Merck, Darmstadt);

potassium dihydrogen phosphate, analytical grade (E. Merck, Darmstadt);

trisodium orthophosphate, analytical grade (E. Merck, Darmstadt);

methanol, analytical grade (BDH Chemicals (Ltd.), Poole, England);

phosphoric acid, 88 - 93% pure (BDH Chemicals (Ltd.), Poole, England).

2.2.2. Instrumentation

The liquid chromatograph was made up of separate units. The eluent was delivered by a single piston, reciprocating pump (LC3 Chromatograph, Pye Unicam Ltd., Cambridge). Two different injection valves were used in the course of the study. The original fixed loop injection valve (Pye Unicam, Cambridge) was replaced by another fixed loop injection valve (Rheodyne Model 70-10, California, U.S.A.) as the former did not wear well with leakage being the major problem. A 100 µl loop was used for plasma samples and a 20 µl loop was used for urine assays.

The pre-packed reversed phase columns (µBondapak C18, Waters Associates Inc.) were 30 cm in length with an internal diameter of 3,9 mm. The packing material was octadecylsilane chemically bonded to 10 µm silica particles. The drug and internal standard were detected by a reference compensated variable wavelength, single beam ultraviolet absorbance monitor (LC3 UV Detector, Pye Unicam, Cambridge). The signal from the detector was fed through an integrator (Minigrator, Spectra Physics, California) to a linear recorder (AR 55, Pye Unicam, Cambridge).

2.2.3. Extraction Procedure.

Ranitidine hydrochloride and the internal standard, AH 20480, were weighed out on a digital analytical balance (Sartorius 2400, Göttingen, Germany). Aqueous solutions of 200 µg/ml of ranitidine and AH 20480 respectively were made up and stored for periods not exceeding one month prior to use.

Fresh dilutions of the above stock standards were made for each sample batch assayed. The internal standard, AH 20480 was diluted to 10 µg/ml and an S.M.I. Micropettor (Scientific Manufacturing Industries, California) was used to add 25 µl of this solution to clean dry 10 ml Quickfit glass test tubes. The standard solutions of ranitidine appropriately diluted to cover the range 0 - 1000 ng/ml were prepared using constriction pipettes (Goldbrand, Brand, West Germany). Ten standards were run with each batch of 20 patient samples.

One millilitre volumes of either ranitidine-free plasma in the case of standards or patient plasma were added to the tubes containing internal standard with an Oxford sampler (Oxford Laboratories). One millilitre of buffer (0,2M trisodium orthophosphate brought to pH 10,5 with phosphoric acid) was added to each tube. The tubes were agitated prior to the addition of 5 ml octanol with an adjustable sampler (Macroset, Oxford Laboratories).

The tubes were stoppered and clamped onto a tipping table (Scientific Manufacturing Company, Milnerton, South Africa) and mixed at a rate of 100 tips/min for 20 minutes and at an angle which ensured complete mixing. They were then centrifuged at 2000 r.p.m. (Sorvall RC 3B Centrifuge, Du Pont, Connecticut).

Approximately 4,5 ml of the octanol layer were transferred to glass tubes containing 0,5 ml of 0,1M phosphate buffer (pH 6,0) for back extraction. The tubes were again mixed on the tipping table for 20 minutes and then centrifuged for a further 10-minute period. The buffer layer was carefully removed using a pasteur pipette and placed in clean glass tubes. The samples were normally left at room temperature overnight.

Urine samples were extracted in a similar manner except that a dilution of 1:5 or 1:10 with distilled water was made before extraction and the calibration curve was set up over the range 0 - 7 µg/ml.

2.2.4. Chromatography.

The eluent consisted of 58% methanol and 42% 0,1M phosphate buffer, pH 7,0. In order to eliminate particulate matter and to de-gas the eluent it was filtered through a 0,5 µm millipore filter (Millipore Corporation, Massachusetts) under vacuum. The eluent was delivered to the column at a flow rate of 1,5 ml/min. The column was maintained at room temperature. Absorbance was measured at a wavelength of 318 nm with the integrator set at maximum sensitivity. In the case of plasma 100 µl samples were injected and for urine 20 µl samples were injected onto the column. The retention times for ranitidine and AH 20480 were approximately 300 and 400 seconds respectively. Figure 2.2 shows a chromatogram of a plasma standard containing 104 ng/ml of ranitidine and internal standard. and Figure 2.3. shows the chromatogram of a patient plasma sample with an estimated ranitidine concentration of 204 ng/ml. It is clear that the peaks of interest are adequately separated and that the peak heights can easily be measured. Figure 2.4 is the chromatogram of a plasma sample from a patient with renal failure. In addition to ranitidine (peak A) and AH 20480 (peak B) there is a peak (peak C) with a retention time shorter than ranitidine. This was identified as a metabolite but could not be quantitated.

The chromatogram of a urine extract from a patient with renal failure is shown in Figure 2.5. The metabolite peak C, is again apparent. The ranitidine peak (A) and AH 20480 (B) were well resolved and there was no interference from other drugs or endogenous material in the urine. Prior to the analysis of patients' samples validation of the methods for urine and for plasma were carried out to determine sensitivity linearity and precision.

In the case of the plasma validation, 5 spiked samples at 5 different concentrations were assayed (Table 2.1.). It can be seen from Figure 2.6 that the relationship between the peak height ratio of ranitidine and internal standard to the concentration is linear. The best straight line through the points was obtained by linear regression on a

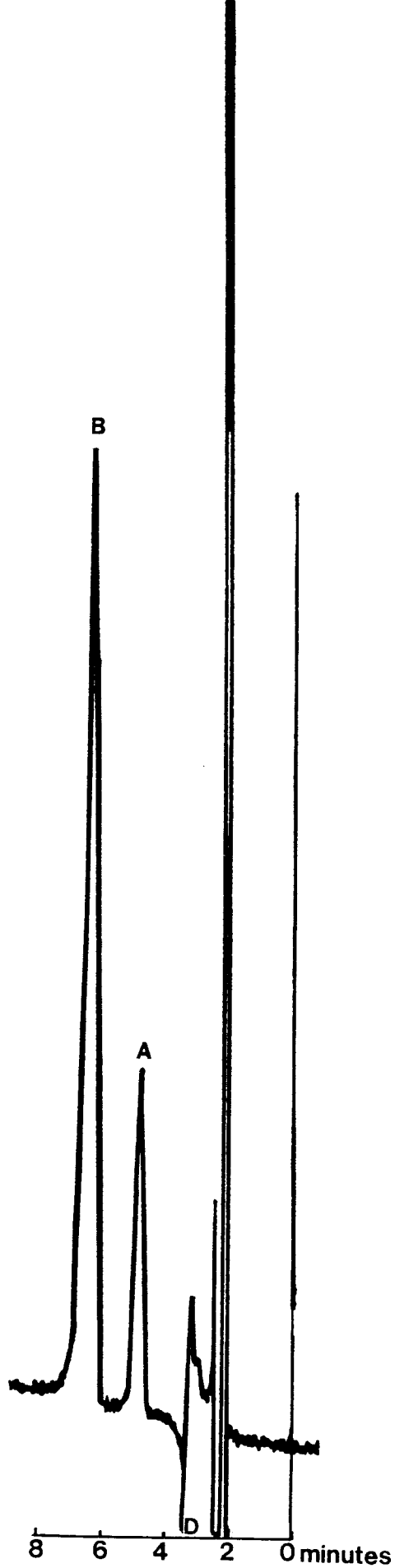

Figure 2.2. Chromatogram of a standard plasma sample spiked with 104 ng/ml ranitidine [peak A] and internal standard [peak B].Wavelength 318 nm and sensitivity 0,01[aufs]

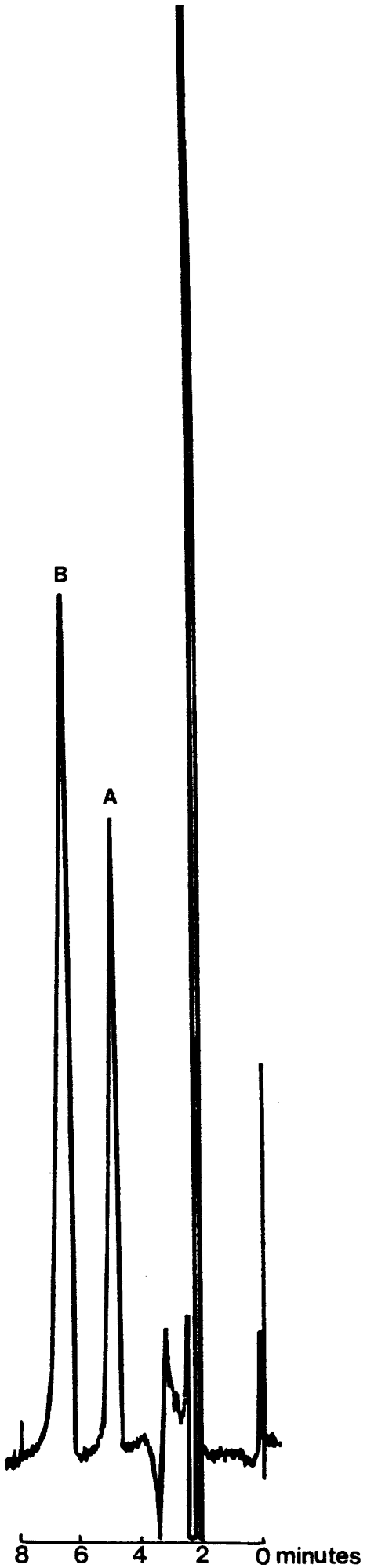

Figure 2.3 Chromatogram of plasma extract containing 204ng/ml ranitidine from patient with duodenal ulceration taken 25 minutes after intravenous administration of 20 mg ranitidine. Peak A ranitidine and Peak B AH 20480.

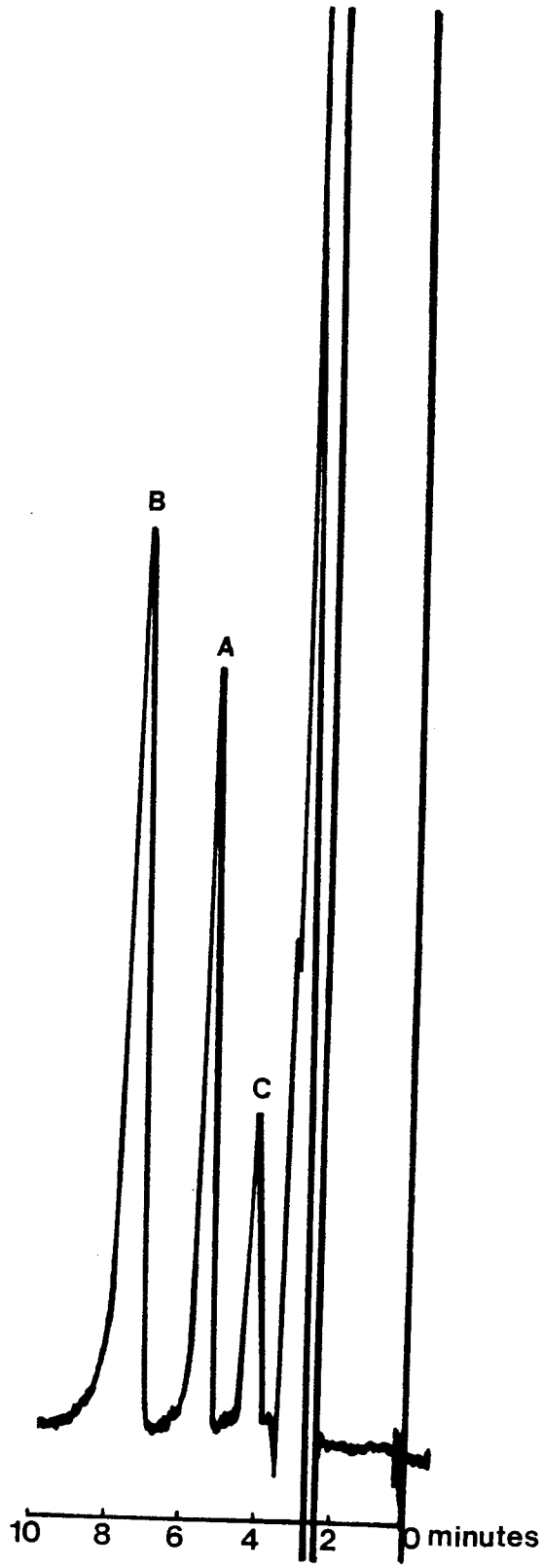

Figure 2.4. Chromatogram of a plasma extract from a patient with renal failure containing ranitidine 221 ng/ml 6 hours after oral administration. Peak A ranitidine, peak B AH 20480, peak C ranitidine metabolite.

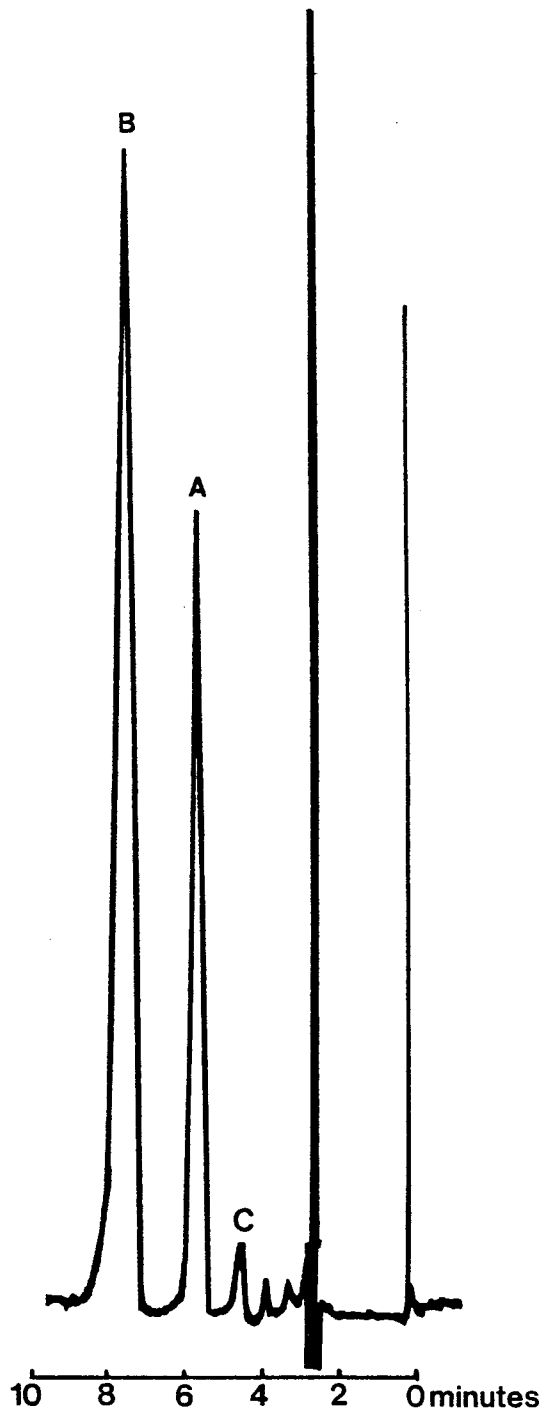

Figure 2.5. Chromatogram of a urine extract from a patient with renal failure. The sample contained 2.5 μg/ml of ranitidine after a 5-fold dilution. Peak A ranitidine, peak B AH 20480, peak C ranitidine metabolite.

Expected concentration (ng/ml)	Number of determinations	Mean peak height ratio	Standard deviation	Coefficient of variation (%)	Observed concentration (ng/ml)
0,0	5	0,000	0,000	0,0	0,4
21,4	5	0,091	0,006	6,7	24,2
107,1	5	0,396	0,018	4,4	103,6
535,5	5	2,044	0,034	1,6	533,1
749,7	5	2,889	0,041	1,4	753,4
1071,0	5	4,104	0,062	1,5	1070,0

TABLE 2.1. Validation results for the extraction of ranitidine from plasma. The linear regression equation had a slope of 0,0038 with an axis intercept of -0,0019 and a correlation coefficient, r=0,9998

Expected concentration (g/ml)	Number of determinations	Mean peak height ratio	Standard deviation	Coefficient of variation (%)	Observed concentration (g/ml
0,00	4	0,000	0,000	0,0	0,02
1,08	4	0,249	0,007	2,9	1,08
2,15	4	0,498	0,005	1,0	2,14
5,39	4	1,259	0,023	1,8	5,37
7,54	4	1,774	0,013	0,7	7,56

TABLE 2.2. Validation results for the extraction of ranitidine from urine. Linear regression analysis gave a slope of 0,235 with an axis intercept of -0,0045 and a correlation coefficient, r=0,9998.

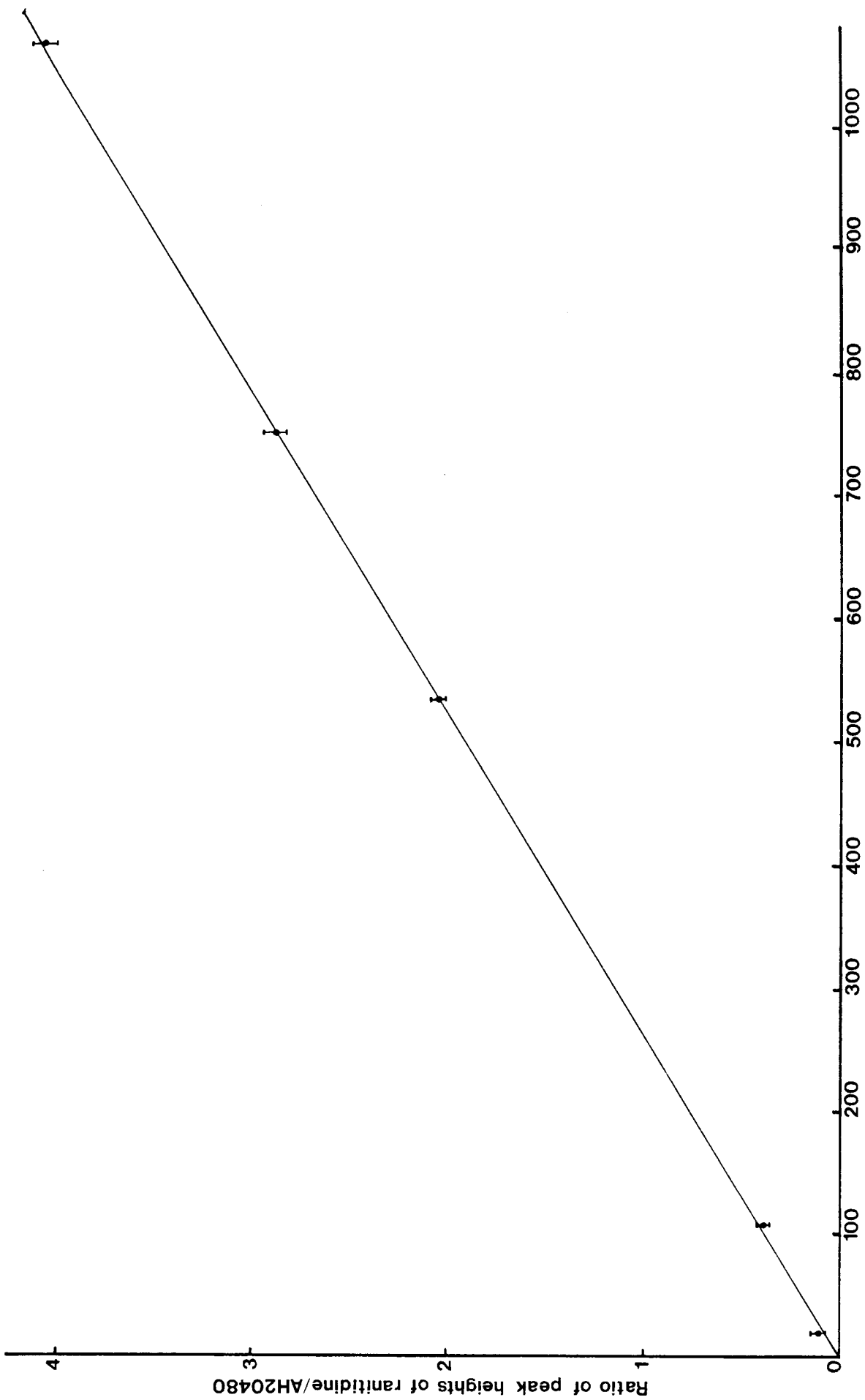

Figure 2.6 Validation curve for ranitidine extracted from plasma from 6 sets of 5 standards. (Regression coefficient r = 0,9998)

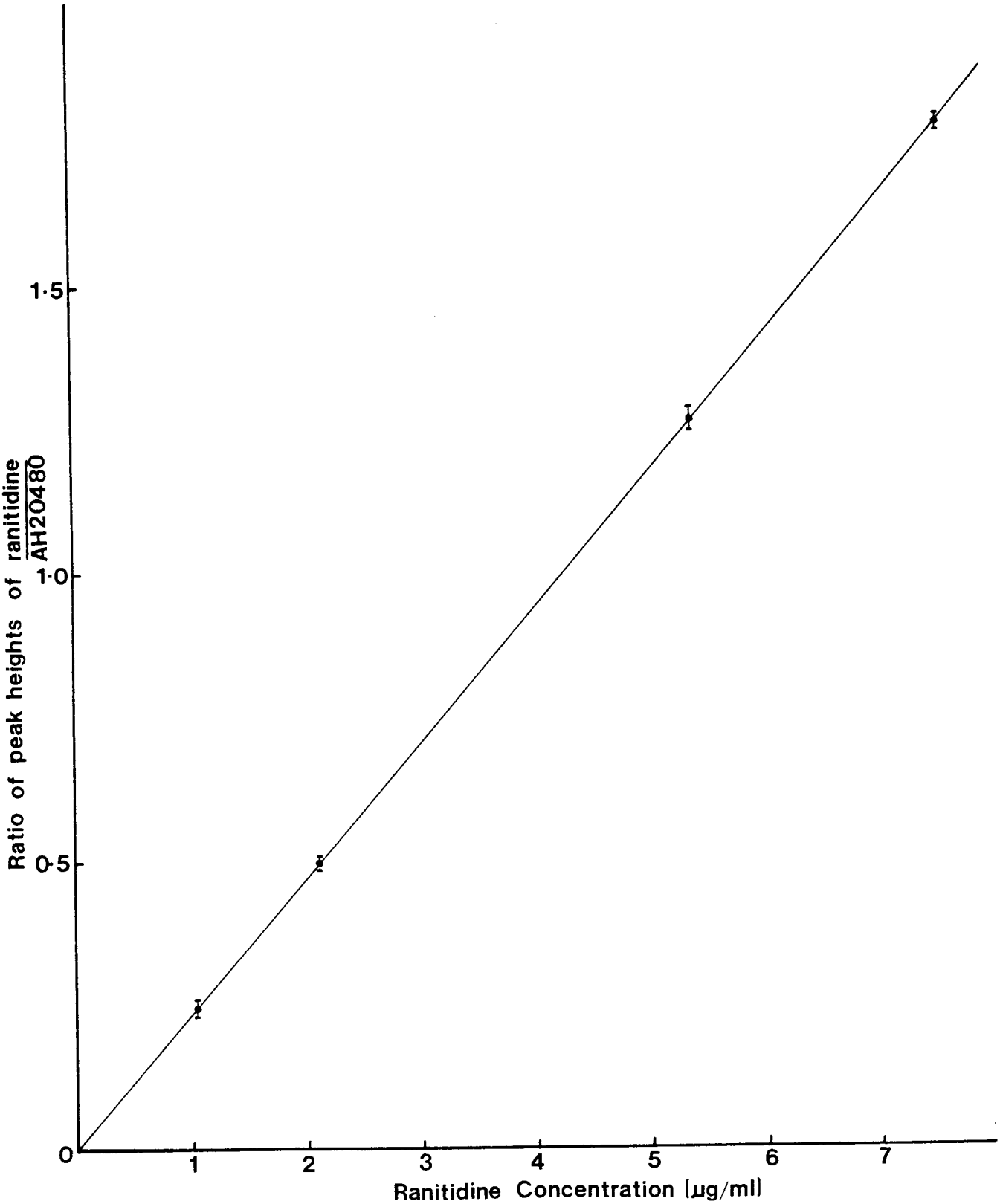

Figure 2.7 Validation curve for ranitidine extracted from urine from 5 sets of 4 standards. [Regression coefficient r = 0,9998]

Texas Instruments 59 calculator giving the equation

$y = 0,0038\ x - 0,0019$ with a regression coefficient $r = 0,9998$.

The lower limit of detection was taken as 20 ng/ml as the coefficient of variation for concentrations lower than this exceeded 10% due to difficulty in measuring small peak heights.

The results for the validation of the method for urine are given in Table 2.2. The regression equation was $y = 0,2350\ x - 0,0045$ with a regression coefficient, $r = 0,9998$ showing the linearity of this ratio of peak heights of ranitidine and internal standard to concentration over the range 1 - 7.5 µg/ml. The coefficient of variation ranged from 2,9% at a concentration of 1 µg/ml to 0,7% at a concentration of 7,5 µg/ml.

At least 50% of patients' plasma samples were re-assayed on a separate occasion. If the two assays did not agree to within 10% the samples were assayed a third time.

2.2.5. Discussion.

The differences between the published method (Carey and Martin 1979) and the one described above are that our system was not automated, the column was at room temperature instead of 40°C and the buffer used in the initial extraction was of pH 10,5 and not pH 9,0.

Peak height ratios were used instead of peak areas. The reason for this was that without regulating column temperature there was no control over the separation of the ranitidine peak (A) and the negative peak (D) (Figure 2.2) which made setting up of the integrator difficult.

The negative peak was caused by solvent mismatching.

It was impossible to quantitate metabolites simultaneously with ranitidine as the desmethyl and S-oxide metabolites could not be resolved from each other while the N-oxide of ranitidine had a retention time coinciding with the solvent front under our chromatographic conditions.

2.3. PHARMACOKINETIC ANALYSIS

2.3.1. Computer fitting of data

The nonlinear least squares regression programme NONLIN (Metzler, C.M., Upjohn Company, Kalamazoo, Michigan 49000l) was used for the fitting of plasma concentration-time data and for the estimation of pharmacokinetic parameters.

Rough estimates for the computer fitting of the data were obtained by the method of residuals (Gibaldi and Perrier 1975).

The oral data were fitted to both a one-and two-compartment model. No weighting functions were used. Akaike's Information Criterion (AIC) was used to determine the least number of exponential terms which best described the data. (Yamaoka et al 1978). The equation with the lowest AIC was taken as the simplest representation of the data. The following formula was used to calculate AIC:

$$AIC = N \ln R_e + 2p \qquad (2)$$

where N = number of experimental points

R_e = residual sum of squares

p = number of parameters in the estimated model

ln = natural logarithm

The notations used in the regression equations are

C_p = concentration in plasma at time t

FD/V = availability term made up of

F = fraction of the dose absorbed

D = dose

V = apparent volume of distribution

k_a = absorption rate constant

t_{lag} = lag time to start of absorption

k_{21} and k_{12} = rate constants for transfer of drug into and out of the peripheral compartment

k_{el} = apparent first order elimination rate constant

k_{10} = apparent first order elimination rate constant from central compartment

C_0 = residual concentration present at time zero of multiple dosing

β = disposition rate constant (for a one compartment model $k_{el}=k_{10}=\beta$)

α = distribution rate constant

The regression equations for the single dose situation are as follows:

$$C_p=(FD/V)\left(\frac{k_a}{k_a - k_{el}}\right)\left(e^{-k_{el}t^*} - e^{-k_a t^*}\right) \qquad (3)$$

where $t^* = t-t_{lag}$

for an oral one-compartment open model and

$$C_p=(FD/V)k_a\left[\frac{(k_{21}-k_a)}{(\alpha-k_a)(\beta-k_a)}e^{-k_a t^*} + \frac{(k_{21}-\beta)}{(k_a-\alpha)(\beta-\alpha)}e^{-\alpha t^*} + \frac{(k_{21}-\beta)}{(k_a-\beta)(\alpha-\beta)}e^{-\beta t^*}\right] \qquad (4)$$

where $= \frac{1}{2}(k_{12}+k_{21}+k_{10}) + \sqrt{(k_{12}+k_{21}+k_{10})^2-4k_{21}k_{10}}$

$= \frac{1}{2}(k_{12}+k_{21}+k_{10}) - \sqrt{(k_{12}+k_{21}+k_{10})^2-4k_{21}k_{10}}$

for an oral first order input two-compartment model.

In the multiple-dose situation the models used do not assume that the patient is in steady state but the residual concentration (C_0) due to previous dose present in plasma compartment at the time of the dose administration was taken into account by using the principle of superposition, assuming linear kinetics.

The regression equations for multiple oral doses are

$$C_p=(FD/V)\left(\frac{k_a}{k_a-k_{el}}\right)\left(e^{-k_{el}t^*} - e^{-k_a t^*}\right) + C_0 e^{-k_{el}t} \qquad (5)$$

for a one-compartment model and

$$C_p=(FD/V)k_a\left[\frac{(k_{21}-k_a)}{(\alpha-k_a)(\beta-k_a)}e^{-k_a t^*}+\frac{(k_{21}-\alpha)}{(k_a-\alpha)(\beta-\alpha)}e^{-\alpha t^*}+\frac{(k_{21}-\beta)}{(k_a-\beta)(\alpha-\beta)}e^{-\beta t^*}\right.$$
$$+C_0\left[\frac{(k_{21}-\alpha)}{(\beta-\alpha)}e^{-\alpha t}+\frac{(k_{21}-\beta)}{(\alpha-\beta)}e^{-\beta t}\right]$$
$$\left.+C_0k_{21}(1-\beta)\left[\frac{1}{(\beta-\alpha)}e^{-\alpha t}+\frac{1}{(\alpha-\beta)}e^{-\beta t}\right]\right. \qquad (6)$$

for the first order absorption two-compartment model.

The plasma concentration-time data obtained after intravenous dosing were fitted to the standard two-compartment model without weighting. The equation describing the model is

$$C_p=D/V_c\left[\frac{(\alpha-k_{21})}{(\alpha-\beta)}e^{-\alpha t}+\frac{(k_{21}-\beta)}{(\alpha-\beta)}e^{-\beta t}\right] \qquad (7)$$

where V_c = apparent volume of distribution of the central compartment

These equations were all derived by standard means (Veng Pedersen 1978).

2.3.2. Theoretical plasma concentration-time curves

The pharmacokinetic parameters estimated by computer fitting were used to construct the theoretical plasma concentration-time curves. These figures were plotted on a Hewlett-Packard 9872A plotter connected to a Hewlett-Packard 9825A calculator.

2.3.3. Biological half-life($t_{\frac{1}{2}}$)

The half-time of a drug which is eliminated by first-order processes is a constant which is independent of initial concentration and dose. The overall elimination rate constantβ (or k_{el} = β in a one-compartment model) was used to calculate the half-life:

$$t_{\frac{1}{2}} = \frac{0,693}{\beta} \qquad (8)$$

2.3.4. Area under the plasma level-time curve (AUC).

The trapezoidal rule, an approximate integration formula, was used to determine the area under the plasma level-time curves in the oral

single and multiple-dose studies from time 0 to 12 hours.

Since sampling intervals were not constant the following general formula was used

$$\int_{t_0}^{t_n} \phi\,(t)dt = \sum_{i=0}^{n-1} \frac{t_{i+1}-t_i}{2} \left(C_i + C_{i+1} \right) \qquad (9)$$

(Gibaldi and Perrier 1975)

This method was chosen because of its simplicity but at the same time it was recognised that it is not the most accurate means of measuring AUC. (Chiou 1978, Yen and Kwan 1978).

In the case of the ranitidine study the underestimation in the relatively short absorption phase is balanced to a certain extent by the overestimation in the post-absorption phase. The error in the post-absorption phase is approximately 4% since in our case the ratio of the longest sampling interval (2 hours) to the half-life is approximately 1 (Chiou 1978). This was considered acceptable as AUC is the end point measurement and all data have similar sampling times and shapes.

The AUC for single-dose studies was calcuated in two parts. The trapezoidal rule as described above was used to calculate AUC from 0 to 12 hours. The AUC from 12 hours to infinity was calculated using the formula

$$AUC_{12-\infty} = \frac{C_{12}}{\beta} \qquad (10)$$

where C_{12} = concentration at 12 hours

β = disposition rate constant

The total AUC for the intravenous data was calculated using the formula

$$\int_0^{\infty} C(t)dt = AUC_{0-\infty} = \frac{D}{V_c} \left[\frac{(\alpha - k_{21})}{(\alpha-\beta)\alpha} + \frac{(k_{21}-\beta)}{(\alpha-\beta)\beta} \right] \qquad (11)$$

(Wagner 1975)

2.3.5. Apparent volume of distribution

The apparent volume of distribution of a drug in a given compartment of a

model is the constant (expressed as a volume) which relates the concentration in that compartment to the total amount of drug in the compartment.

In the two-compartment intravenous model the volume of distribution of the central compartment (V_c) was estimated from the least squares regression analysis. V_c relates the plasma concentration (C) to the total amount of drug in the central compartment (X_c). Hence

$$X_c = V_c C \tag{12}$$

The apparent volume of distribution of a drug in the whole body (V_B) can be related to the plasma concentration (C) in the post-distributive phase since

$$V_B = X/C \tag{13}$$

where X = total amount of drug in the body.

But $$X = \frac{V_c C}{\beta / k_{10}}$$

therefore $$V_B = \frac{V_c \, k_{10}}{\beta} \tag{14}$$

V_B was therefore calculated from the computer estimates of V_c, k_{10}, and β. (Gibaldi and Perrier 1975).

This volume of distribution (V_B) has also been called the volume of distribution area (V_{darea}) as it can be calculated from

$$V_B = \frac{X_0}{\beta \int_0^\infty C dt} \tag{15}$$

where X_0 = dose administered

and $\int_0^\infty C dt$ = total area under the plasma concentration-time curve from zero to infinity

The volume of distribution normally quoted in the literature is the volume of distribution (V_{dext}). By definition

$$V_{dext} = \frac{(\alpha - \beta)}{(k_{21} - \beta)} V_c \tag{16}$$

This was calculated from the computer derived parameters α, β, K_{21} and V_c

The fourth volume of distribution commonly used is the volume of distribution steady state (V_{dss}). This was calculated by

$$V_{dss} = V_c(1+\frac{K_{12}}{K_{21}}) \quad (17)$$

These volumes of distribution were calculated using the intravenous study data.

The relative magnitudes of the volumes of distribution are

$$V_{dext} > V_{darea} > V_{dss} > V_c$$

(wagner 1975)

2.3.6. Clearance

The total clearance of a drug (C) from the body is a constant since it is the product of two constants in any given patient

$$C = V_B \beta \quad (18)$$

It is also equal to the clearance from the central compartment

$$C = V_c\, k_{10} \quad \text{and thus} \quad (19)$$

$$C = \frac{X_0}{\int_0^\infty Cdt} \quad (20)$$

(Gibaldi and Perrier 1975)

Clearance values were calculated from the above equations for intravenous data.

From equation (20) it is clear that C is inversely proportional to the area under the curve (AUC). AUC was used as an index of clearance in the oral dosage situation where C cannot be calculated, to compare clearance in patients with normal renal function with those with impaired renal function.

2.3.7. Bioavailability.

The efficiency of absorption (F) assuming no significant first-pass effect was assessed for oral single-dose administration using the

following formula

$$F = \frac{Dose_{iv} \; AUC_{oral}}{Dose_{oral} \; AUC_{iv}} \tag{21}$$

where the AUC was measured as described above.

2.4. STATISTICAL ANALYSIS

The Wilcoxon matched-pairs signed-ranks test was used to test for differences between pharmacokinetic parameters obtained in the same patient after single and multiple dosage (Siegel 1956). $\alpha < 0,05$ was taken as the level of significance for a two-tailed test.

The Mann-Whitney U test was used to test the differences between responders and non-responders and between patients with normal renal function and with renal failure. $\alpha < 0,05$ for a two-tailed test was decided on as being significant (Siegel 1956).

Correlations were determined by linear regression analysis.

CHAPTER 3

3. RESULTS.

3.1. CHRONIC DUODENAL ULCER PATIENTS - RESPONDERS.

The ten patients in this group responded to a 28 days' course of ranitidine, at the end of which they had endoscopic evidence of ulcer healing. The endoscopy reports are summarized in Table 3.1. The results of the acid studies prior to treatment and at the end of the 28 days' treatment are given in Table 3.2.

The mean basal acid output (BAO) pre-treatment was 4,4 meq/h (range 0,0-9,1) and pentagastrin stimulated maximum acid output (MAO) pre-treatment was 27,2 meq/h (range 16,2-39,1). After 28 days' treatment, the mean BAO was 5,7 meq/h (range 2,0-11,7) and the MAO was 24,0 meq/h (range 14,6-36,5).

The post-treatment levels did not differ significantly from pre-treatment values.

3.1.1. Oral single- and multiple-dose studies.

Plasma ranitidine concentrations after administration of a single 150 mg tablet and the concentrations after multiple dosing are shown in Tables 3.3 and 3.4 respectively.

The maximum and minimum concentrations which are discussed below are taken directly from the concentration-time data.

The median maximum plasma concentration (Cmax) after a single-dose was 365 ng/ml which was achieved at a median time of 2 hours (Table 3.5).

In the case of multiple dosing the time taken to reach Cmax was shorter in most patients but the median value of 1 hour did not differ significantly from the median value after single dosing ($p > 0,05$). The median Cmax after multiple dosing was 562 ng/ml and this was significantly greater than Cmax after single-dosing ($p < 0,05$). Even after the multiple dosing Cmax was corrected for the residual concentration present at time zero (Cmin(0)) the difference from single-dose Cmax remained significant ($p < 0,05$).

Table 3.1. Summary of endoscopy reports of responders.

Initials	Pre-treatment	Post-treatment
J.H.	Oesophagus and stomach normal. Deformed duodenal cap. Single duodenal ulcer, superior superficial 0,8 cm diameter.	Duodenitis of anterior aspect of greater curve of duodenum. Linear scar in duodenum.
T.W.	Normal oesophagus. Gastritis. Pylorus deformed, wide. Small shallow ulcer on superior aspect of duodenal cap.	Duodenal diverticulum noted. Small linear scar on anterior wall of duodenum.
A.d.S.	Oesophagus and stomach normal. Erosive duodenitis. Single ulcer in duodenum, 1 x 0,6 cm in size.	Erosions, duodenitis and scar.
M.S.	Fundal erosions with mild gastritis. Posterior-inferior ulcer, 0,5 cm in diameter in duodenum.	Scar just inside cap on floor of duodenum.
S.M.	Oesophagus and stomach normal. 0,4 cm duodenal ulcer on base of anterior wall at beginning of second part.	Duodenitis and erosions at site of old ulcer.
D.F.	Pyloric narrowing. 0,4 x 0,8 cm oral duodenal ulcer on anterior aspect of lesser curve.	Duodenal erosions.
P.d.J.	Blood stained fluid ++. Small blood clot in fundus. Multiple ulcers in duodenum. Ulcer 1,0 cm diameter on greater curve of duodenum.	Complete healing of target duodenal ulcer with two peripheral erosions. Anterior ulcer with large central erosion.
W.M.	Deformed antrum. 0,8 cm diameter duodenal ulcer.	Gastric erosions, due to nasogastric tube. Duodenitis, swollen mucosal folds and scarring.
A.O.	Deformed duodenal cap. Circumferential swollen fold with duodenal ulcer 0,6 x 0,4 cm.	Duodenum: pit and erosions. Healed duodenal ulcer.
D.S.	Duodenitis. Single duodenal, 0,3 cm diameter ulcer.	Healed duodenal ulcer with a deformed duodenal cap.

Table 3.2. Basal acid output (BAO) and pentagastrin-stimulated maximum acid output (MAO) pre- and post-treatment (28 days) in duodenal ulcer patients who responded to ranitidine.

Initials	PRE-TREATMENT		POST-TREATMENT (28 DAYS)	
	BAO meq/h	MAO meq/h	BAO meq/h	MAO meq/h
J.H.	2,6	16,2	7,2	16,4
T.W.	2,4	26,4	6,7	14,6
A.d.S.	6,7	27,9	11,7	26,7
M.S.	3,2	25,5	8,0	23,5
S.M.	9,1	39,1	4,2	36,5
D.F.	5,8	25,6	3,1	21,6
P.d.J.	7,2	27,6	2,4	27,2
W.M.	0,0	22,9	2,0	25,4
A.O.	2,7	24,2	-	-
D.S.	4,7	36,4	-	-
mean	4,4	27,2	5,7	24,0
range	0,0-9,1	16,2-39,1	2,0-11,7	14,6-36,5

TABLE 3.3

ORAL SINGLE DOSE DATA IN RESPONDERS. PLASMA RANITIDINE CONCENTRATIONS (ng/ml) AFTER A 150mg TABLET ADMINISTRATION IN PATIENTS WITH DUODENAL ULCERATION.

Patient	Time (hrs) 0	.25	.50	.75	1.0	1.5	2.0	3.0	4.0	4.5	5.0	5.5	6.0	8.0	10.0	12.0	24.0
J.H.	0	-	39 (.67)	-	83	187	207	252	180	191	182	175	157	110	60	36	7
T.W.	0	-	25	-	187	283	354 (2.25)	302	239	214	192	178	134	95 (7.75)	-	27 (14.0)	6
M.S.	0	-	400	-	408	410	451	322	249	228	202	-	140	81 (8.1)	51	48 (11.75)	16
A.d.S	0	-	147	-	226	347	332	240 (3.2)	178	136	121	-	95	52	43 (9.75)	33 (11.6)	12 (23.6)
S.M.	0	-	165	-	237	292	382	288 (3.5)	242 (3.8)	234 (4.5)	187 (5.0)	153 (6.1)	125	73	31	24 (11.8)	2
D.F.	0	12	236	302	327	358	336	245	207 (3.7)	187 (4.0)	152	-	89	58	37	23	0
P.d.J	0	8	50	305	306	430	444	387	370	-	289	-	173	114	74	37	8
W.M.	0	4	88	328	494	540	396	333	235	-	132	-	77	46	19	12	0
A.O.	0	5	114	171	207	203	181	116	95	-	90	-	88	74	49	38	7
D.S.	0	5	69	173	249	299	340	302	235	-	170 (5.1)	-	135	84	60	40	9

Figures in brackets are the times of sampling when these differ from the column headings.

TABLE 3.4

ORAL MULTIPLE DOSE DATA IN RESPONDERS. PLASMA RANITIDINE CONCENTRATIONS (ng/ml) AFTER FOUR WEEKS OF CONTINUOUS TREATMENT WITH 150mg RANITIDINE TWICE DAILY.

Patient	Time (hrs) 0	.25	.50	.75	1.0	1.5	2.0	3.0	4.0	4.5	5.0	5.5	6.0	8.0	10.0	12.0	24.0
J.H.	35	-	579	-	506	442	394	267	229	178	157	126	99	81 (7.75)	45	32	0
T.W.	48	-	186	-	545	380	369	321	239	198	166	-	133 (5.75)	79 (7.75)	48	36	14
M.S.	8	173	-	807	819	660	660	453	358 (3.5)	310 (4.0)	235	-	169	100 (7.9)	54 (9.8)	38	8 (23.7)
A.d.S	15	339 (.4)	-	458 (.7)	640	803	683	352	288 (3.5)	235 (4.0)	156	-	89	50	24 (9.9)	16	0 (23.8)
S.M.	31	171	366	419	489	526	498	348	262 (3.5)	207 (4.0)	160 (4.5)	148 (4.75)	101	49 (8.25)	30	20 (11.9)	7
D.F.	34	35	175	271	326	274	326	222 (3.1)	197 (3.5)	167 (4.0)	117	-	77 (6.7)	45 (8.7)	32	17 (11.9)	0
P.d.J.	110	108	292	705	824	741	636	382	315	-	230	-	168	106	58	35	6
W.M.	16	39	181	221	270	250	313	243	182	-	125	-	102	52	29 (10.1)	18	0
A.O.	30	41	124	225 (.8)	398	389	422	250	177	-	97	-	92	76	49	28	5
D.S.	146	176	544	578	692	613	498	348	259	-	177	-	128	89 (7.9)	63	42	0

Figures in brackets are the times of sampling when these differ from the column headings.

Table 3.5. The maximum concentration (Cmax) and the time taken to reach Cmax (tmax) after single- and multiple dosing; and the Cmax corrected for residual concentrations at zero time (Cmin(0)) after multiple dosing.

Initials	SINGLE DOSE Cmax (ng/ml)	tmax (h)	MULTIPLE DOSE Cmax (ng/ml)	tmax (h)	Cmax-Cmin(0) (ng/ml)
J.H.	252	3,0	579	0,5	544
T.W.	354	2,25	545	1,0	497
A.d.S.	347	1,5	803	1,5	788
M.S.	451	2,0	819	1,0	811
S.M.	382	2,0	526	1,5	495
D.F.	358	1,5	326	1,0	292
P.d.J.	444	2,0	824	1,0	714
W.M.	540	1,5	313	2,0	297
A.O.	207	1,0	422	2,0	392
D.S.	340	2,0	692	1,0	546
mean	368	1,9	585	1,25	538
median	356	2,0	562*	1,0	521*
range	207-540	1,0-3,0	313-824	0,5-2,0	292-811

* $p < 0,05$

The median minimum concentrations (Cmin(12)) at 12 hours post-dosing in the single- and multiple-dose studies were 35 and 30 ng/ml respectively (Table 3.6). These values were not significantly different ($p > 0,05$). When the Cmin values for multiple dosing at zero time (Cmin(0)) and 12 hours post-dosing (Cmin(12)) were compared there was no significant difference ($p > 0,05$).

Table 3.6. The minimum concentrations (Cmin) at 12 hours post-dosing after single dosing and at zero time and 12 hours post-dosing after multiple-dosing.

Initials	SINGLE DOSE Cmin(12) (ng/ml)	MULTIPLE DOSE Cmin(0) (ng/ml)	Cmin(12) (ng/ml)
J.H.	36	35	32
T.W.	30	48	36
A.d.S.	33	15	16
M.S.	48	8	38
S.M.	24	31	20
D.F.	23	34	17
P.d.J.	37	110	35
W.M.	12	16	18
A.O.	38	30	28
D.S.	40	146	42
mean	32	47	28
median	35	33	30
range	12-48	8-146	16-42

The concentration-time data for single- and multiple-dosing for each patient were fitted to both a one-compartment and a two-compartment model. Akaike's Information Criterion (AIC) was calculated in order to choose the simplest model fitting the data (Table 3.7.). One patient exhibited two-compartment model characteristics after single dosing, and two patients did so after multiple dosing. After multiple-dose model fitting, two patients (S.M. and D.S.) had the same AIC value for both models, therefore the one-compartment model was chosen.

Table 3.7. Akaike's Information Criterion calculated for single and multiple dosing.

	SINGLE-DOSE		MULTIPLE-DOSE	
	1 Compartment	2 Compartments	1 Compartment	2 Compartments
J.H.	117*	121	162	114*
T.W.	106*	117	132*	135
A.d.S.	110*	112	152*	166
M.S.	122*	126	130*	146
S.M.	120*	124	143*	143
D.F.	134	110*	121*	131
P.d.J.	131*	141	129	118*
W.M.	122*	126	122*	137
A.O.	111*	123	141*	156
D.S.	96*	125	133*	133

* The model chosen

The pharmacokinetic parameters generated from the computer fitting of the concentration-time data were: the absorption rate constant (k_a); the bioavailability term (FD/V); lag time to start of absorption (t_{lag}); the disposition rate constant (k_{el} or β) and where a two-compartment model was chosen, the distribution rate constant (α).

Tables 3.8. and 3.9. show these parameters for single- and multiple-doses respectively.

Table 3.8. Computer generated pharmacokinetic parameters after single dosing in duodenal ulcer patients (responders).

Initials	k_a (h^{-1})	t_{lag} (min)	FD/V (ng/ml)	k_{el} or β (h^{-1})	α (h^{-1})
J.H.	0,78	33,8	378,3	0,22	-
T.W.	0,92	27,9	567,4	0,32	-
A.d.S.	1,38	15,9	531,8	0,36	-
M.S.	2,41	0,0	576,0	0,23	-
S.M.	0,37	7,8	1 381,4	0,82	-
D.F.	2,01	10,9	492,9	0,01+	0,30
P.d.J.	0,89	22,6	855,9	0,32	-
W.M.	2,46	27,1	731,4	0,40	-
A.O.	3,26	14,9	229,0	0,19	-
D.S.	1,24	22,8	499,8	0,27	-
mean	1,57	18,4	624,4	0,34	-
median	1,31	19,3	549,5	0,31	-
range	0,37-3,26	0,0-33,8	229,0-1 381,4	0,19-0,82	-

+ α value used in mean and median calculations

Table 3.9. Computer generated pharmacokinetic parameters after multiple dosing in duodenal ulcer patients (responders).

Initials	k_a (h^{-1})	t_{lag} (min)	FD/V (ng/ml)	k_{el} or β (h^{-1})	α (h^{-1})
J.H.	2,39	0,0	3 381,1	0,30	13,07
T.W.	11,05	28,2	523,3	0,27	-
A.d.S.	1,01	6,4	1 568,1	0,67	-
M.S.	4,54	12,5	989,0	0,32	-
S.M.	0,70	5,1	1 504,9	0,80	-
D.F.	2,38	18,2	416,2	0,30	-
P.d.J.	2,78	25,9	1 226,3	0,26	1,30
W.M.	1,33	11,0	438,9	0,30	-
A.O.	1,65	24,7	615,9	0,42	-
D.S.	3,26	13,8	712,7	0,34	-
mean	3,11	14,6	1 137,5	0,40	-
median	2,39	13,2	850,9*	0,31	-
range	0,70-11,05	0,0-28,2	416,2-3 381,1	0,26-0,80	-

*$p < 0,05$

Absorption was rapid with median k_a values of 1,31 h^{-1} and 2,39 h^{-1} for for single and multiple dosing respectively. These values were not significantly different. The respective median lag times to start of absorption were 19,3 min and 13,2 min. Again there was no significant difference between single and multiple dosing. The FD/V values were on the margin of being significantly larger after multiple dosing ($p = 0,05$) than after single dosing, with median values of 850,9 and 549,5 ng/ml respectively. There was no significant difference in the disposition rate constants and the median values were identical (0,31 h^{-1}). The value of α(0,30 h^{-1}) for patient D.F. after single dosing was used in the calculation of the median disposition rate constant as this value correlated better with the elimination rates in other patients than the β value of 0,01 h^{-1}. This small β value appears to be due to slow release of ranitidine from a deep body compartment.

The median half-lives after both single and multiple dosing were 135 minutes (Table 3.10). There is thus no significant difference in the disappearance of the drug from plasma after single or multiple dosage. The half-lives were calculated from k_{el} or β values generated by the computer.

The theoretical plasma concentration-time curves derived from the computer fits of data are shown in Figures 3.1 - 3.10. Each figure, showing the theoretical curves for single- and multiple-dosing with their respective regression coefficients as well as the observed concentrations after single and multiple doses, represents a single patient. The data for one patient (A.O.) fitted poorly to one- and two-compartment models for both single- and multiple-doses (Figure 3.9.). Another model such as a recycling model may fit the data better.

TABLE 3.10. Plasma ranitidine half-lives ($t_{\frac{1}{2}}$) after single and multiple doses in responders.

Initials	Single dose $t_{\frac{1}{2}}$ (min)	Multiple dose $t_{\frac{1}{2}}$ (min)
J.H.	189	139
T.W.	130	154
A.d.S.	116	62
M.S.	181	130
S.M.	51	52
D.F.	139	139
P.d.J.	130	160
W.M.	104	139
A.O.	219	99
D.S.	154	122
mean	141	120
median	135	135
range	51-219	52-160

TABLE 3.11. The areas under the plasma ranitidine concentration-time curves (AUC) for single- and multiple-dose studies in responders.

Initials	Single dose AUC (ng/ml.hr)	Multiple dose AUC (ng/ml.hr)
J.H.	1 700	2 138
T.W.	1 983	2 036
A.d.S.	1 616	2 486
M.S.	2 444	3 074
S.M.	1 738	2 078
D.F.	1 700	1 467
P.d.J.	2 688	2 989
W.M.	1 845	1 458
A.O.	1 304	1 695
D.S.	1 950	2 601
mean	1 897	2 202
median	1 844	2 108*
range	1 304-2 688	1 458-3 074

* $p < 0,05$ vs single-dose

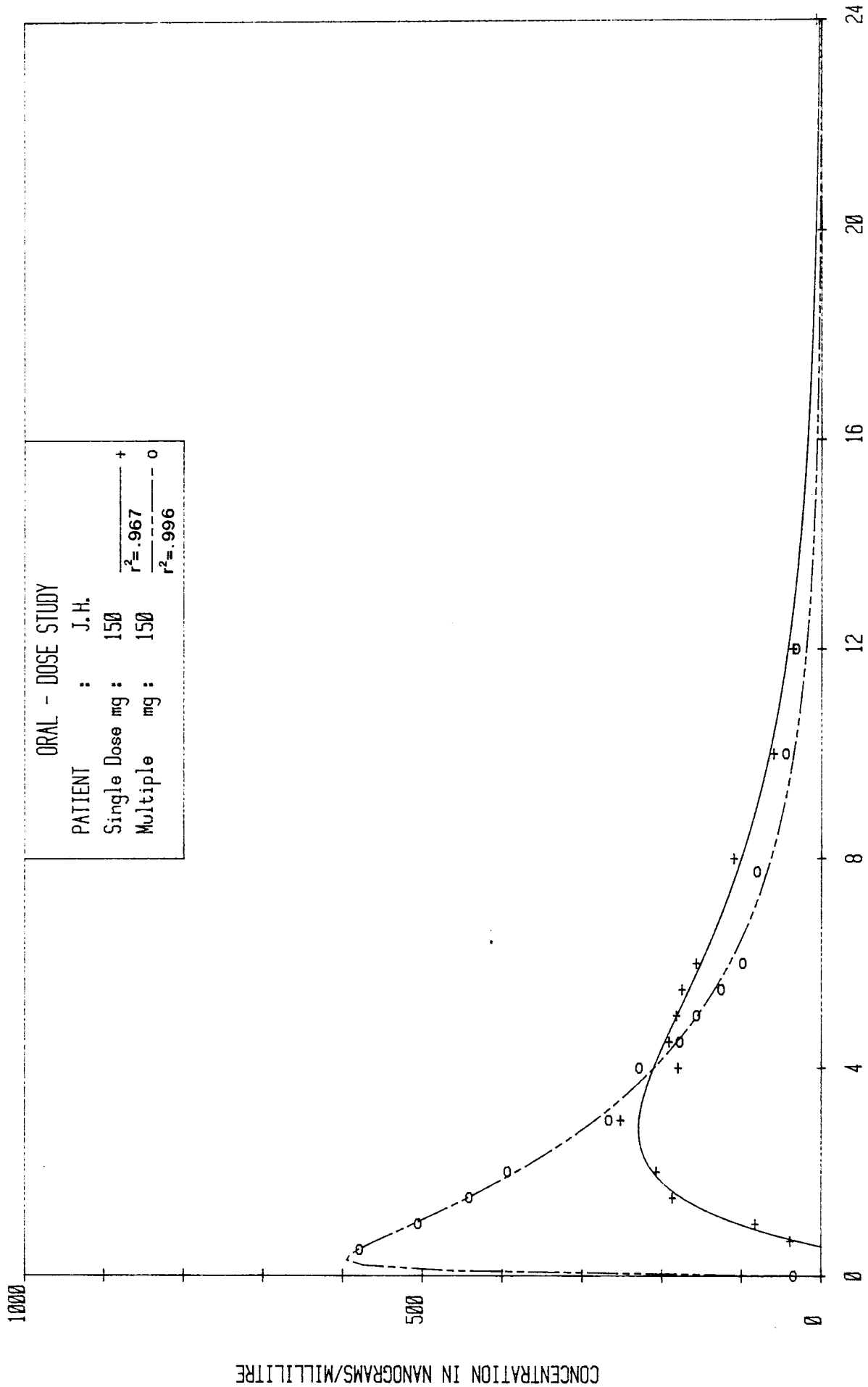
ORAL - DOSE STUDY
PATIENT : J.H.
Single Dose mg : 150 r²=.967
Multiple mg : 150 r²=.996
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.1.

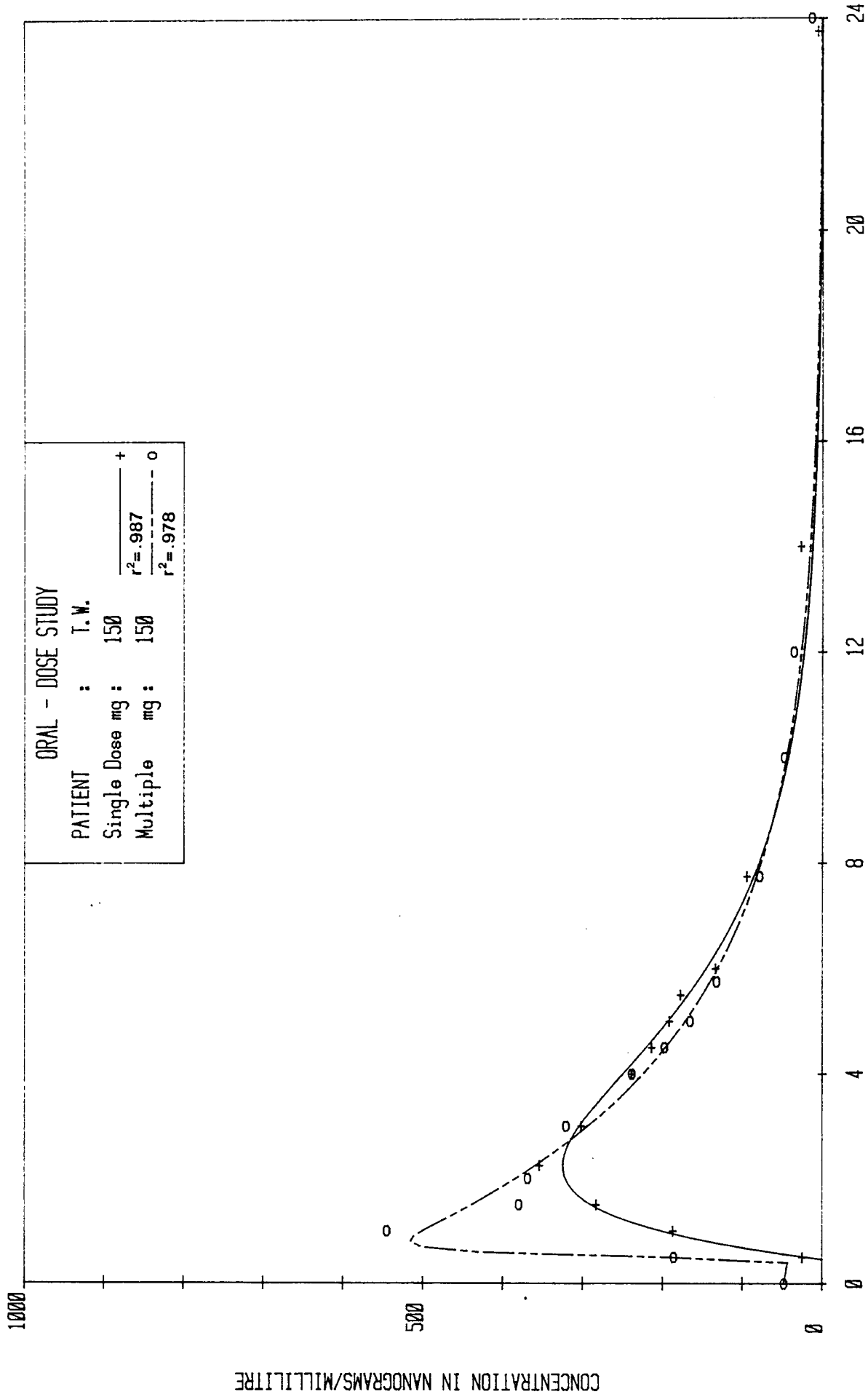
ORAL - DOSE STUDY
PATIENT : T.W.
Single Dose mg : 150
Multiple mg : 150
r²=.987
r²=.978
CONCENTRATION IN NANOGRAMS/MILLILITRE
TIME IN HOURS
1000
500
0
0
4
8
12
16
20
24

Figure 3.2.

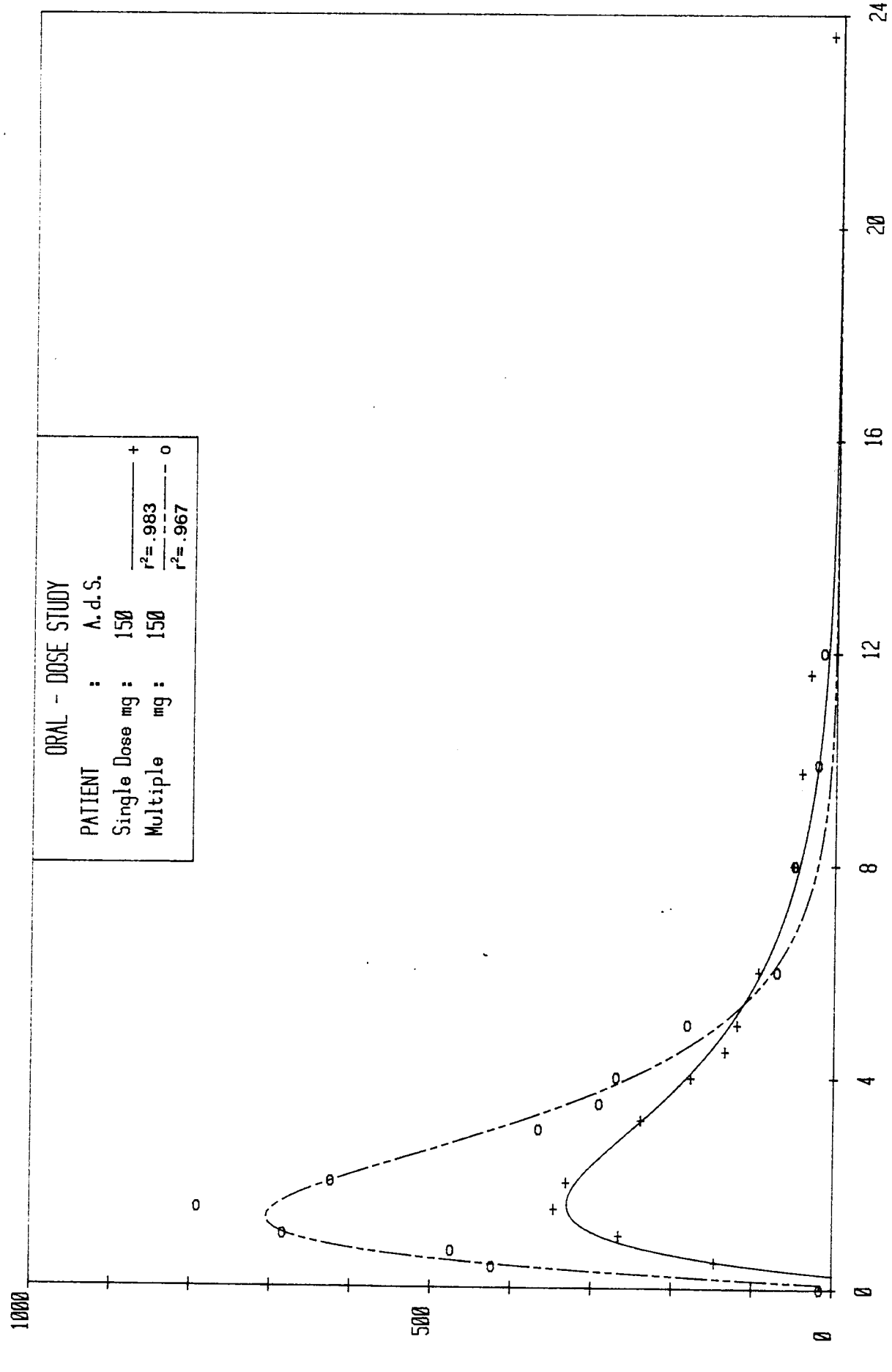
ORAL - DOSE STUDY
PATIENT : A.d.S.
Single Dose mg : 150
Multiple mg : 150
r²=.983
r²=.967
CONCENTRATION IN NANOGRAMS/MILLILITRE
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS

Figure 3.3.

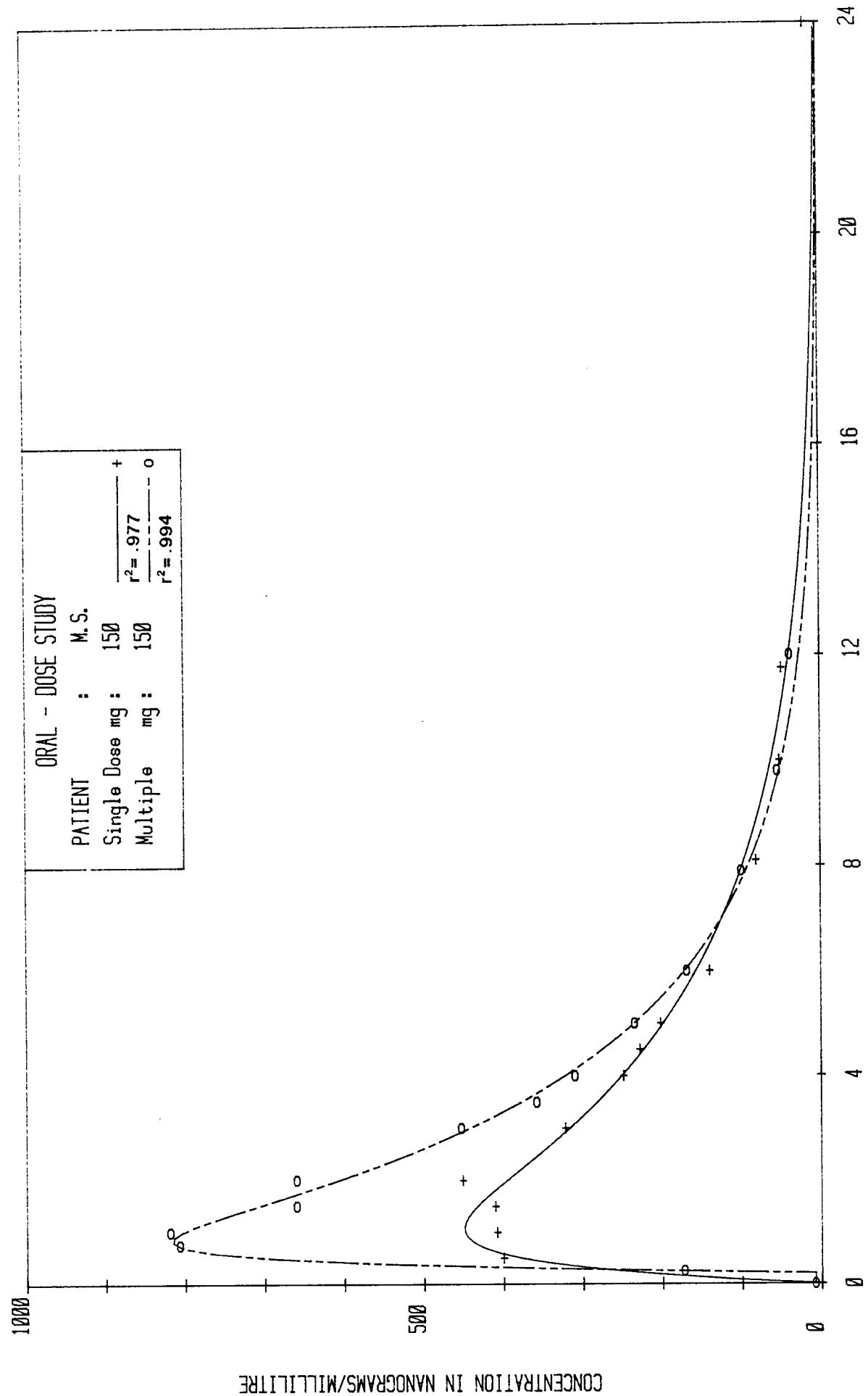
ORAL - DOSE STUDY
PATIENT : M.S.
Single Dose mg : 150
Multiple mg : 150
r²= .977
r²= .994
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.4.

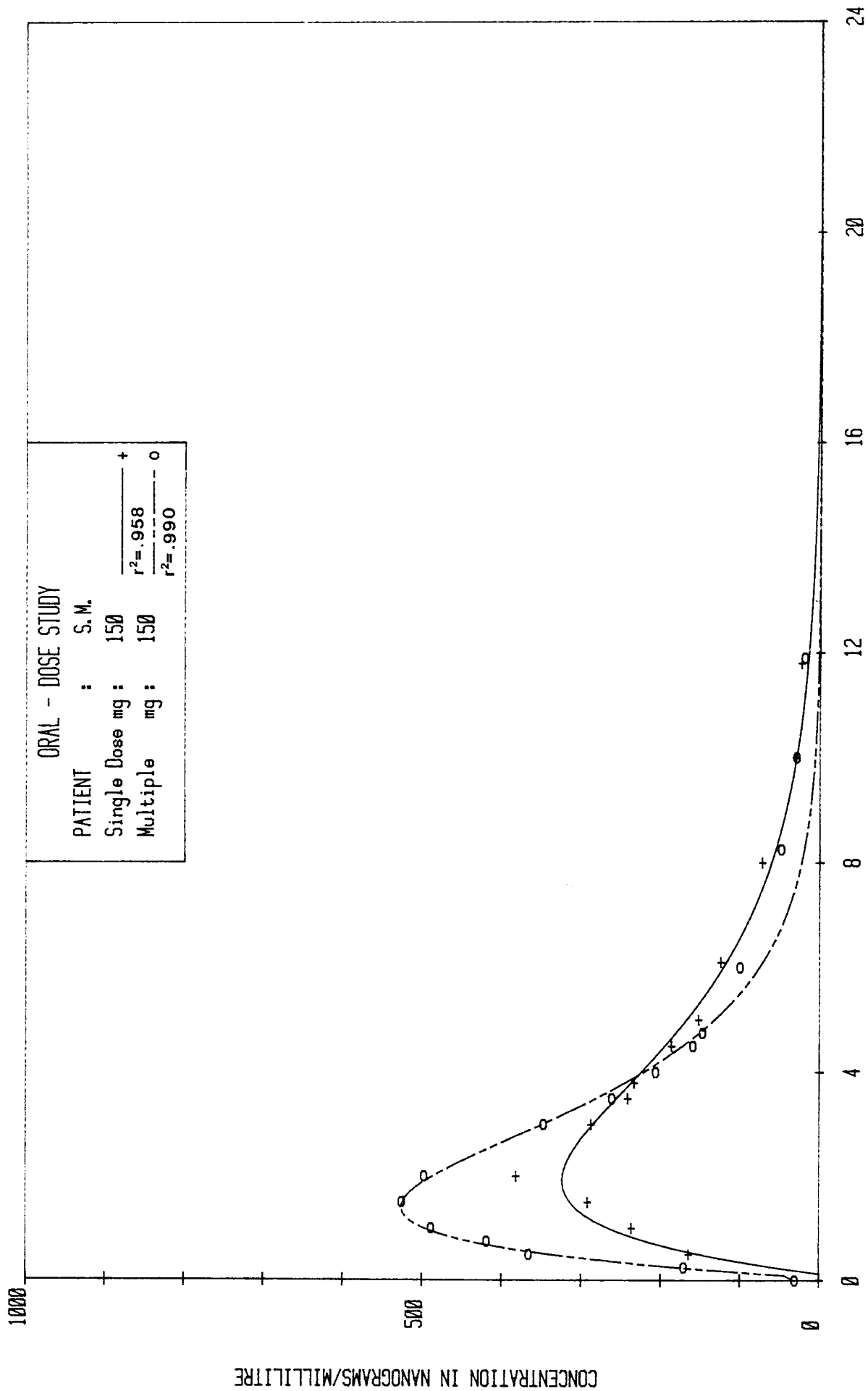
ORAL - DOSE STUDY
PATIENT : S.M.
Single Dose mg : 150
Multiple mg : 150
r²=.958
r²=.990
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.5.

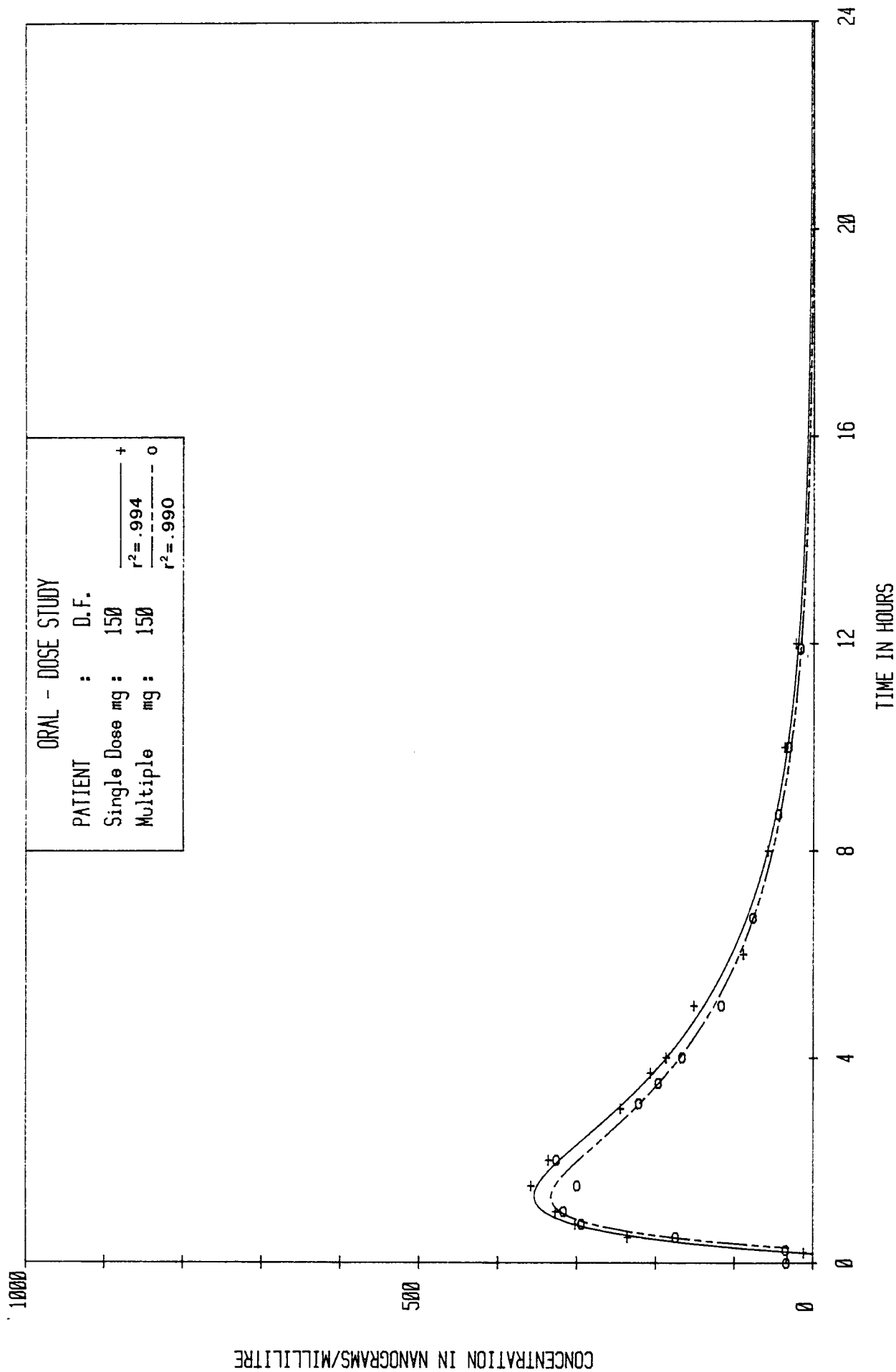
ORAL - DOSE STUDY
PATIENT : D.F.
Single Dose mg : 150
Multiple mg : 150
r² = .994
r² = .990
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.6.

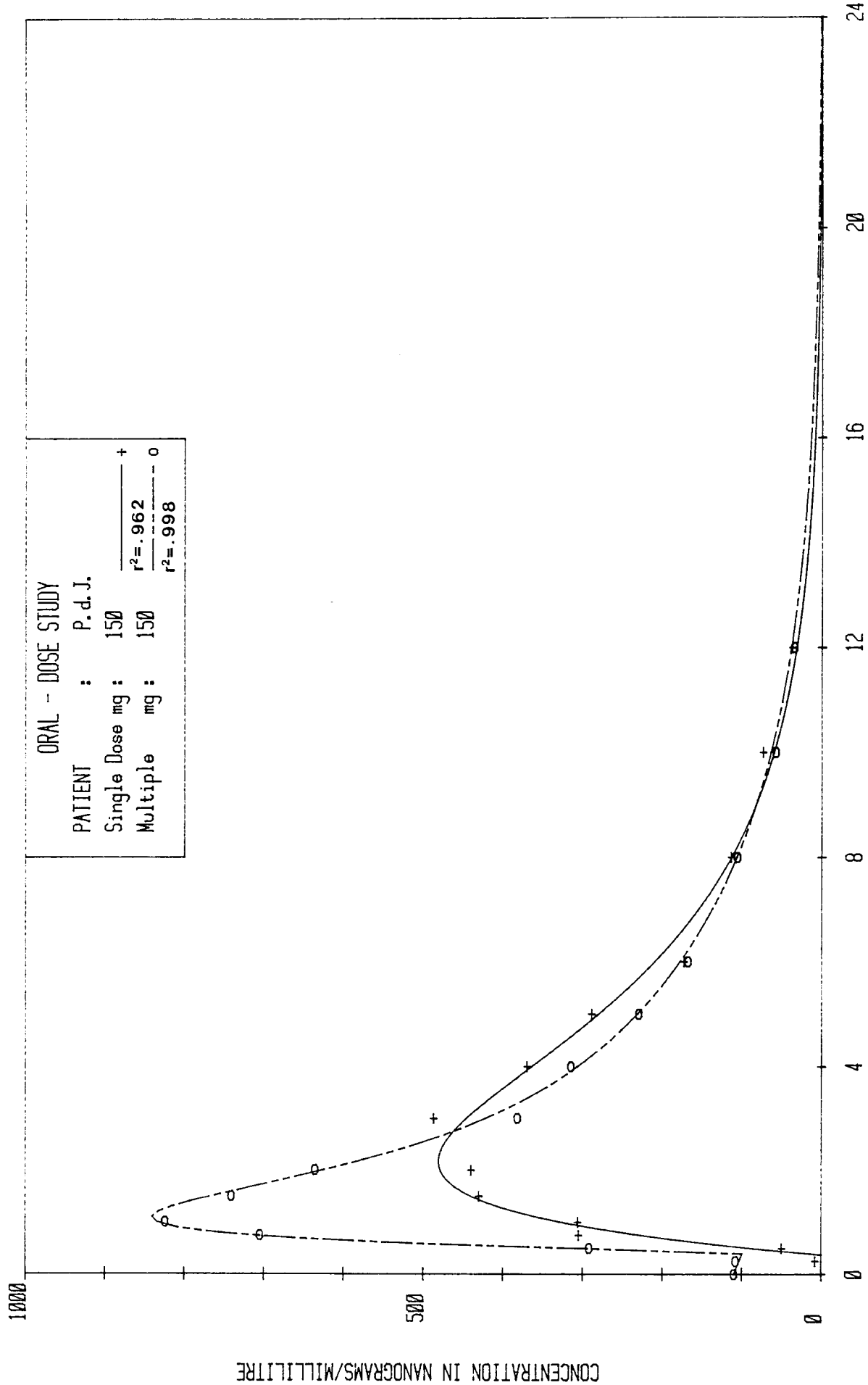
ORAL - DOSE STUDY
PATIENT : P.d.J.
Single Dose mg : 150
Multiple mg : 150
r²=.962
r²=.998
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.7.

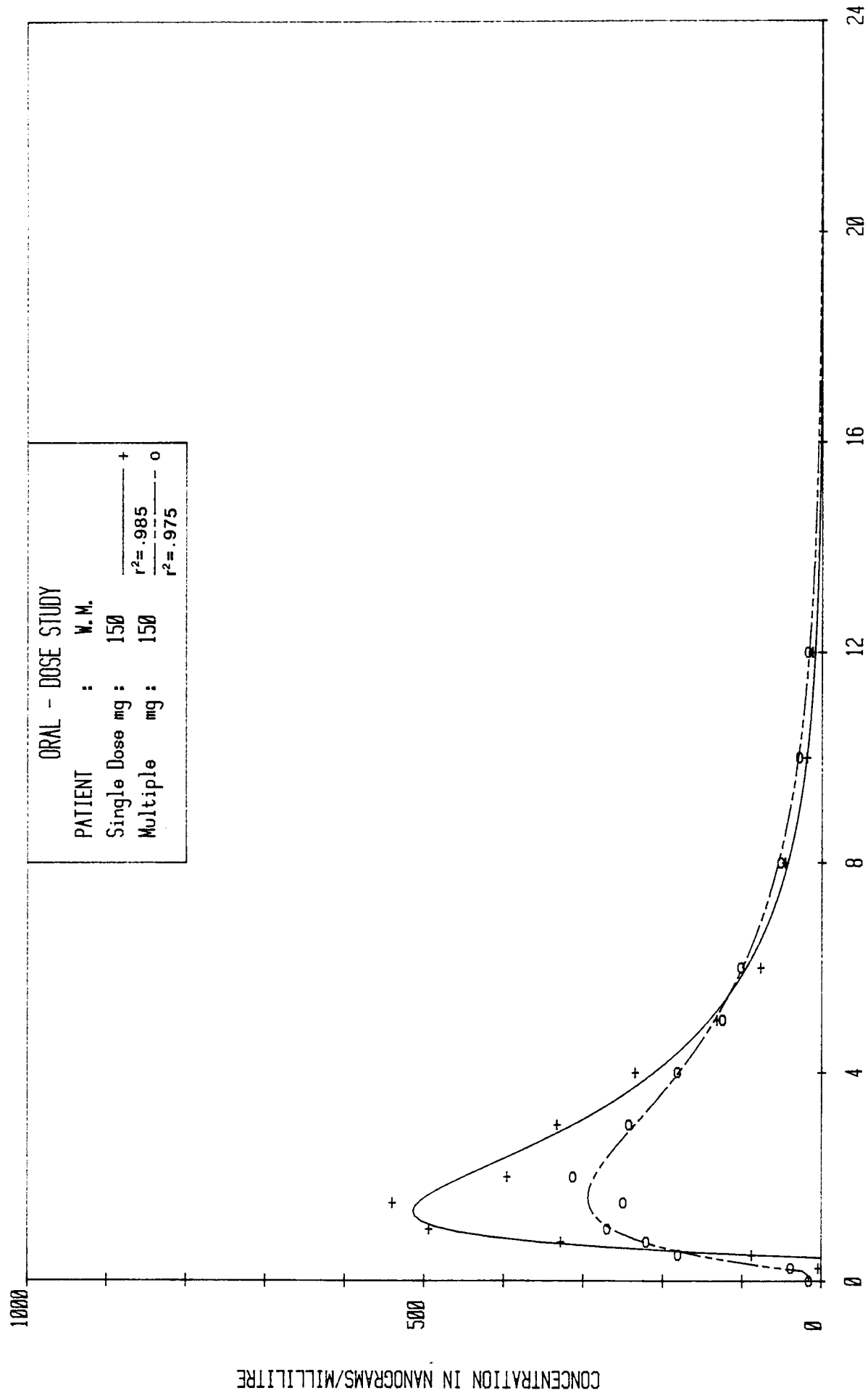
ORAL - DOSE STUDY
PATIENT : W.M.
Single Dose mg : 150
Multiple mg : 150
r²=.985
r²=.975
CONCENTRATION IN NANOGRAMS/MILLILITRE
TIME IN HOURS
1000
500
0
0
4
8
12
16
20
24

Figure 3.8.

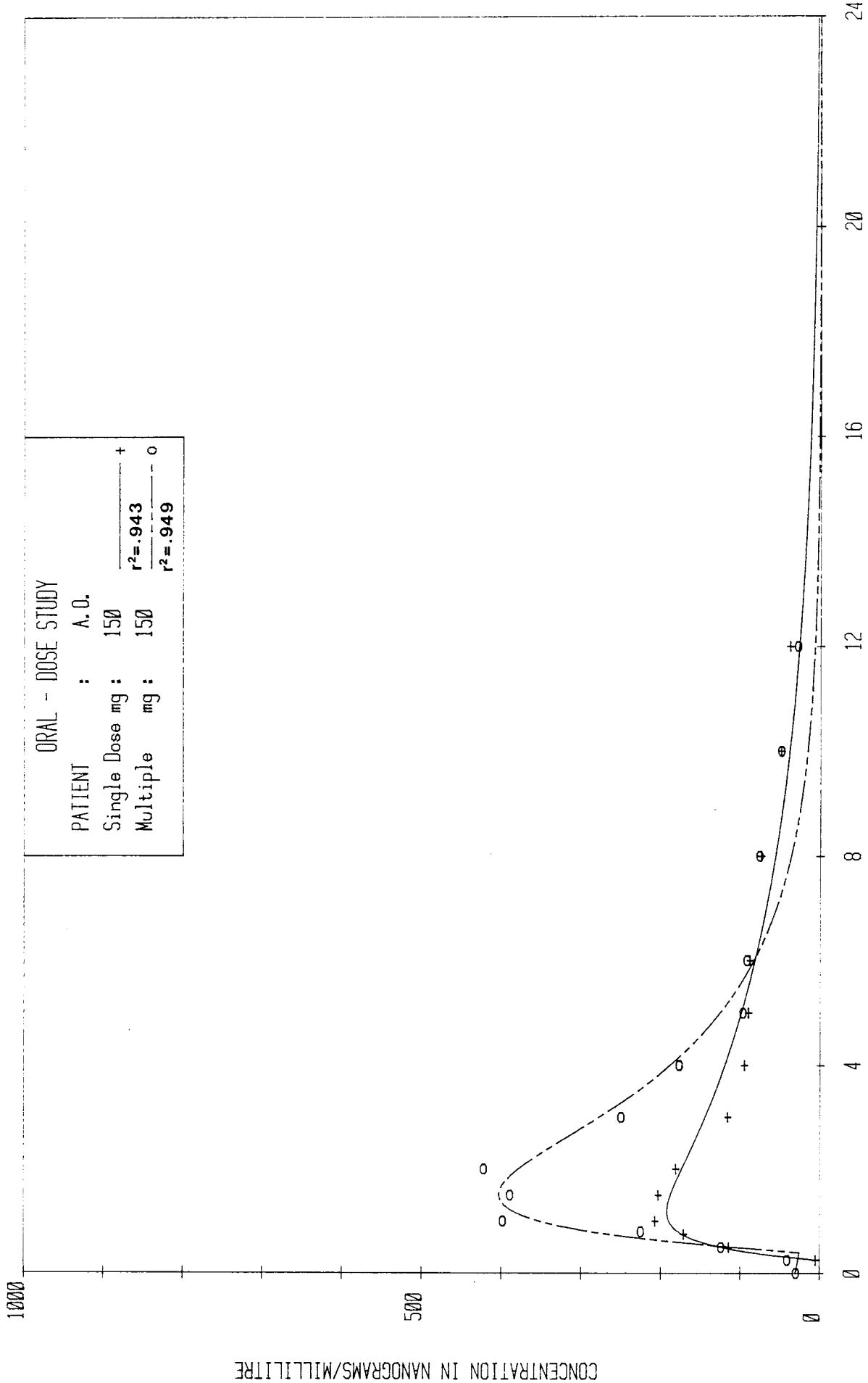
ORAL - DOSE STUDY
PATIENT : A.O.
Single Dose mg : 150
Multiple mg : 150
r²=.943
r²=.949
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.9.

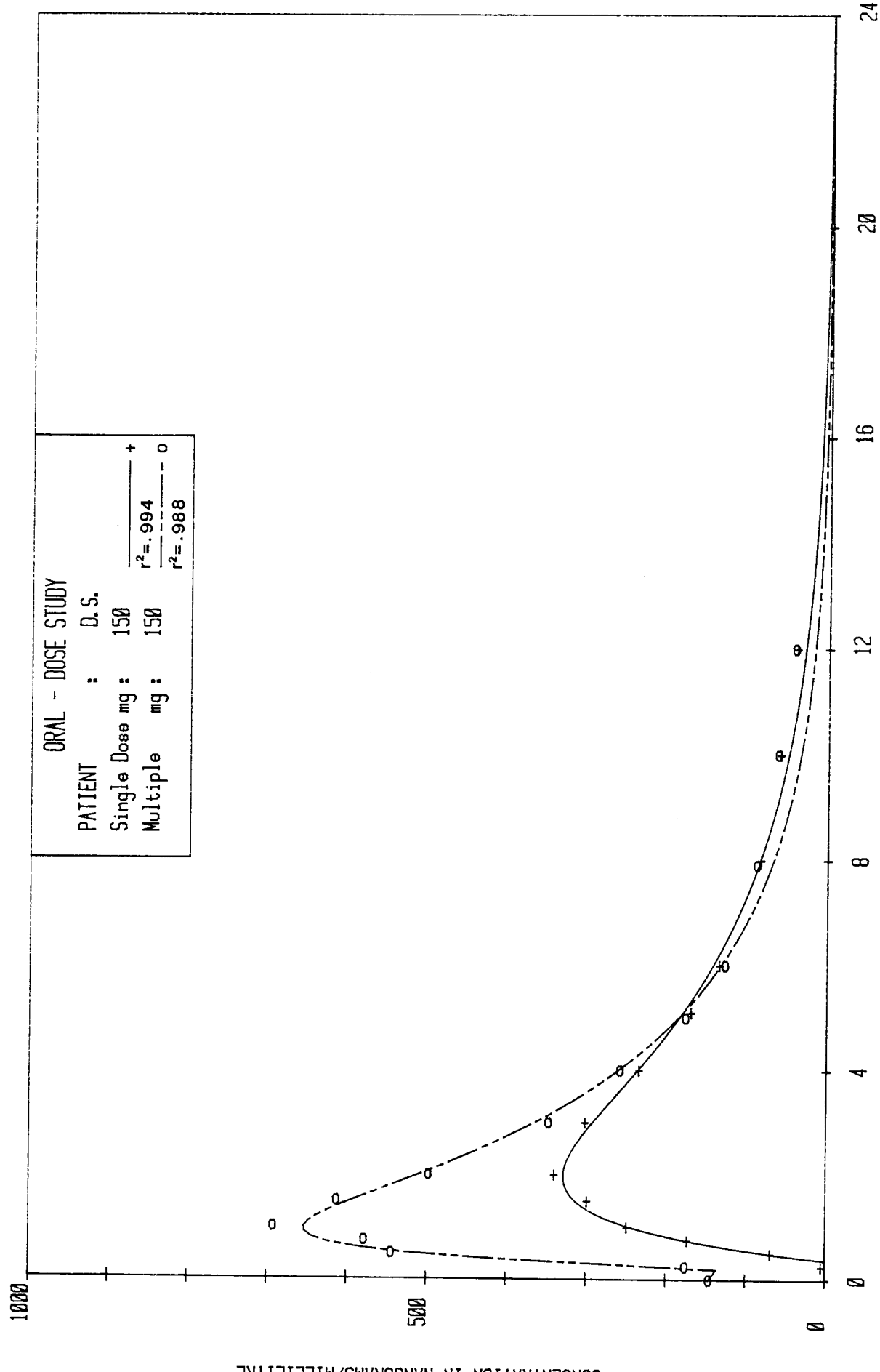
ORAL - DOSE STUDY
PATIENT : D.S.
Single Dose mg : 150
Multiple mg : 150
r²=.994
r²=.988
CONCENTRATION IN NANOGRAMS/MILLILITRE
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS

Figure 3.10.

The areas under the curve (AUC) are shown in Table 3.11. The AUC after multiple-dosage is significantly larger than after single dosage ($p < 0,05$) with median values of 2 108 and 1 844 ng/ml respectively.

The total amounts of ranitidine excreted in urine in the 24 hours following a single dose, expressed as a percentage of the dose administered are shown in Table 3.12, together with the uncorrected creatinine clearance values determined from the same urine sample and the creatinine clearances calculated from serum creatinine corrected for age, sex and weight (Lot and Hayton 1978).

TABLE 3.12. The amount of ranitidine excreted unchanged in the urine in 24 hours after a single 150 mg ranitidine dose expressed as a percentage of dose, uncorrected creatinine clearance calculated from the same urine sample and creatinine clearance estimated from serum creatinine concentration.

Initials	% Unchanged ranitidine in 24 hr. urine	Creatinine clearance (ml/min)	Estimated creatinine clearance (ml/min)
J.H.	26	-	106
T.W.	26	-	69
A.d.S.	35	135	109
M.S.	15	73	79
S.M.	-	-	80
D.F.	21	71	106
P.d.J.	38	65	77
W.M.	48	132	125
A.O.	28	102	93
D.S.	23	68	109
mean	29	-	95
median	26	-	100
range	15-48	-	69-125

Key: - incomplete urine collection

TABLE 3.13. The percentage of unchanged ranitidine excreted in the urine in the 24 hours after multiple-dosing, together with the uncorrected creatinine clearance calculated from the same urine sample and the creatinine clearance estimated from the serum creatinine concentration.

Initials	% Unchanged ranitidine in 24 hr. urine	Creatinine clearance (ml/min)	Estimated creatinine clearance (ml/min)
J.H.	28	-	107
T.W.	22	-	75
A.d.S.	30	94	88
M.S.	24	97	89
S.M.	10	123	81
D.F.	24	84	82
P.d.J.	105	119	90
W.M.	21	34	127
A.O.	29	87	-
D.S.	-	-	143
mean	33	-	98
median	24	-	89
range	10-105	-	75-143

Key: - incomplete urine collection.

There was no significant difference in the percentage of ranitidine excreted in 24 hours after multiple dosing when compared to single-dosing ($p > 0,05$). The creatinine clearances had not changed significantly after multiple-dosing from those obtained at the time of the single-dose study. The completeness of the 24-hour urine collection for the multiple-dose study in one patient (W.M.) was suspect as the creatinine clearances calculated by the two methods differed widely (73%).

3.1.2. Recycling study

The plasma concentrations measured at 10 minute intervals after a standard hospital breakfast when the morning ranitidine tablet was withheld, are given in Table 3.14. These concentrations were close to the lower limit of the reliable assay range. The apparent slight increase in the levels in patient D.F. was possibly due to assay error. This did not support a theory of recycling and reabsorption of ranitidine from the previous evenings' dose in relation to breakfast in these three patients.

TABLE 3.14. Plasma concentrations (ng/ml) in three patients taken at 10 minute intervals following breakfast after the morning dose was withheld.

Patient	Time (minutes) 0	10	20	30	40	50	60
D.F.	23	20	21	26	20	-	14
S.M.	35	32	29	-	27	27	25
J.S.	24	21	21	20	21	19	19

3.1.3. Intravenous study.

Four responders and one non-responder were given 20 mg ranitidine intravenously over 2 minutes as a 1 mg/ml solution in normal saline. The concentration-time data are given in Table 3.15. The time was taken from the end of the infusion period. The data when fitted to a two-compartment model using the NONLIN computer programme gave regression coefficients varying from 0,997-0,999, which made trial of another model unnecessary.

The computed pharmacokinetic parameters appear in Table 3.16. There is a 3-fold variation in the rate constants of transfer into and out of the peripheral compartment (k_{12} and k_{21}) as well as in k_{10} which is the elimination rate constant from the central compartment. The apparent volume of distribution of the central compartment (V_c) ranged from 10,5 to 28,4ℓ which was not improved when corrected for weight (range 190,4 to 436,9 ml/kg). The distribution rate constant (α) and the disposition rate constant (β), moreover, varied 2,6-fold and 2,3-fold respectively.

The computer generated pharmacokinetic parameters were used to calculate $AUC_{0-\infty}$, V_{dext}, V_{darea}, V_{dss}, C, $t_{\frac{1}{2}\alpha}$ and $t_{\frac{1}{2}\beta}$ (Table 3.17). The variation was greatest for the AUC and clearance.

There was no apparent correlation between V_c, AUC, V_{dss} and the weights of the patients. There was, however, a fairly strong correlation between V_{dext} and age (r^2=0,90, $p < 0,01$), V_{darea} and age (r^2=0.89, $p < 0,01$) and V_{dss} and age (r^2=0,76, $p < 0,05$) despite the narrow age range of the five patients. The half-life ($t_{\frac{1}{2}}$) was not age-related (r^2=0,002).

Half-life could not be correlated with the creatinine clearance (calculated from serum creatinine) (r^2=0,45, $p > 0,05$) but total plasma clearance showed a significant correlation with creatinine (r^2=0,71, $p < 0,05$) (Figure 3.11). However, our patient sample is very small.

TABLE 3.15

PLASMA CONCENTRATIONS (ng/ml) FOLLOWING THE INTRAVENOUS ADMINISTRATION OF 20mg RANITIDINE IN DUODENAL ULCER PATIENTS.

Initials	Time (hrs) .00	.03	.10	.17	.33	.50	.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0	8.0	12.0
P.d.J	0	-	1034 (.13)	-	488 (.38)	349 (.47)	-	267 (252 at 1.25)	194	174	128	86	69	43	27	11
W.M.	0	585	374	300	211 (.37)	147	115	93	71	54	34	21	14	11	10	0
S.M.	32	1176	674	368 (.23)	305 (.42)	205 (.57)	175 (.80)	151	105	85	63	43	29	22	15	7 (11.9)
D.S.	0	796	391	282	223 (.25)	139	103	90	70	54	34	24	19	12	10	5
R.L.	0	834	710 (.08)	442	204 (.38)	179	124 (.78)	100	75	61	44	32	23	18	11	6

Key: Figures in brackets are the times of sampling when these differ from the column headings.
- No sample taken.

TABLE 3.16. Computer generated pharmacokinetic parameters from fitting of a two-compartment model to intravenous data.

Initials	k_{12} (h^{-1})	k_{21} (h^{-1})	k_{10} (h^{-1})	V_c (ℓ)	V_c (ml/kg)	α (h^{-1})	β (h^{-1})
P.d.J.	3,61	1,43	1,48	10,5	210,0	6,18	0,34
W.M.	4,77	3,56	2,02	28,4	436,9	9,61	0,75
S.M.	6,79	3,08	2,61	13,0	228,0	11,80	0,68
D.S.	8,69	3,51	3,28	17,9	190,4	14,70	0,78
R.L.	2,97	1,11	1,89	20,3	302,9	5,59	0,38
median	4,77	3,08	2,02	17,9	228,0	9,61	0,68
range	2,97-8,69	1,11-3,56	1,48-3,28	10,5-28,4	190,4-436,9	5,59-14,70	0,34-0,78

TABLE 3.17. Calculated pharmacokinetic parameters after intravenous administration of 20 mg ranitidine.

Initials	AUC (ng/ml.h)	V_{dext} (ℓ)	V_{darea} (ℓ)	V_{dss} (ℓ)	C (ml/min)	$t_{\frac{1}{2}\alpha}$ (min)	$t_{\frac{1}{2}\beta}$ (min)
P.d.J.	1 288	56,3	45,7	37,0	258,9	6,7	122,3
W.M.	348	89,5	76,6	66,5	957,0	4,3	55,4
S.M.	590	60,2	49,9	41.7	565,5	3,5	61,1
D.S.	341	75,0	75,3	62,2	978,9	2,8	53,3
R.L.	523	144,9	100,7	74,6	637,8	7,4	109,4
median	523	75,0	75,3	62,2	637,8	4,3	61,1
range	341-1 288	56,3-144,9	45,7-100,7	37,0-74,6	258,9-978,9	2,8-7,4	53,3-122,3

TABLE 3.18. Statistical analysis of correlations between age or creatinine clearance and ranitidine pharmacokinetic parameters.

Parameter	Slope of regression	Intercept of regression	Coefficient of determination (r^2)	Statistical significance (p)
V_c (ℓ) vs age	0,48	51,00	0,23	p >0,05
V_{dext} (ℓ) vs age	-39,71	3,57	0,90	p <0,01
V_{darea} (ℓ) vs age	- 7,95	2,22	0,89	p <0,01
V_{dss}(ℓ) vs age	4,39	1,49	0,76	p <0,05
$t_{\frac{1}{2}}$(min) vs age	75,57	0,14	0,00	p >0,05
$t_{\frac{1}{2}}$(min) vs C_{cr}	158,68	-0,73	0,36	p >0,05
C (ml/min) vs C_{cr}	-320,48	9,38	0,71	p <0,05
AUC vs C_{cr}	521,23	-8,53	0,35	p >0,05

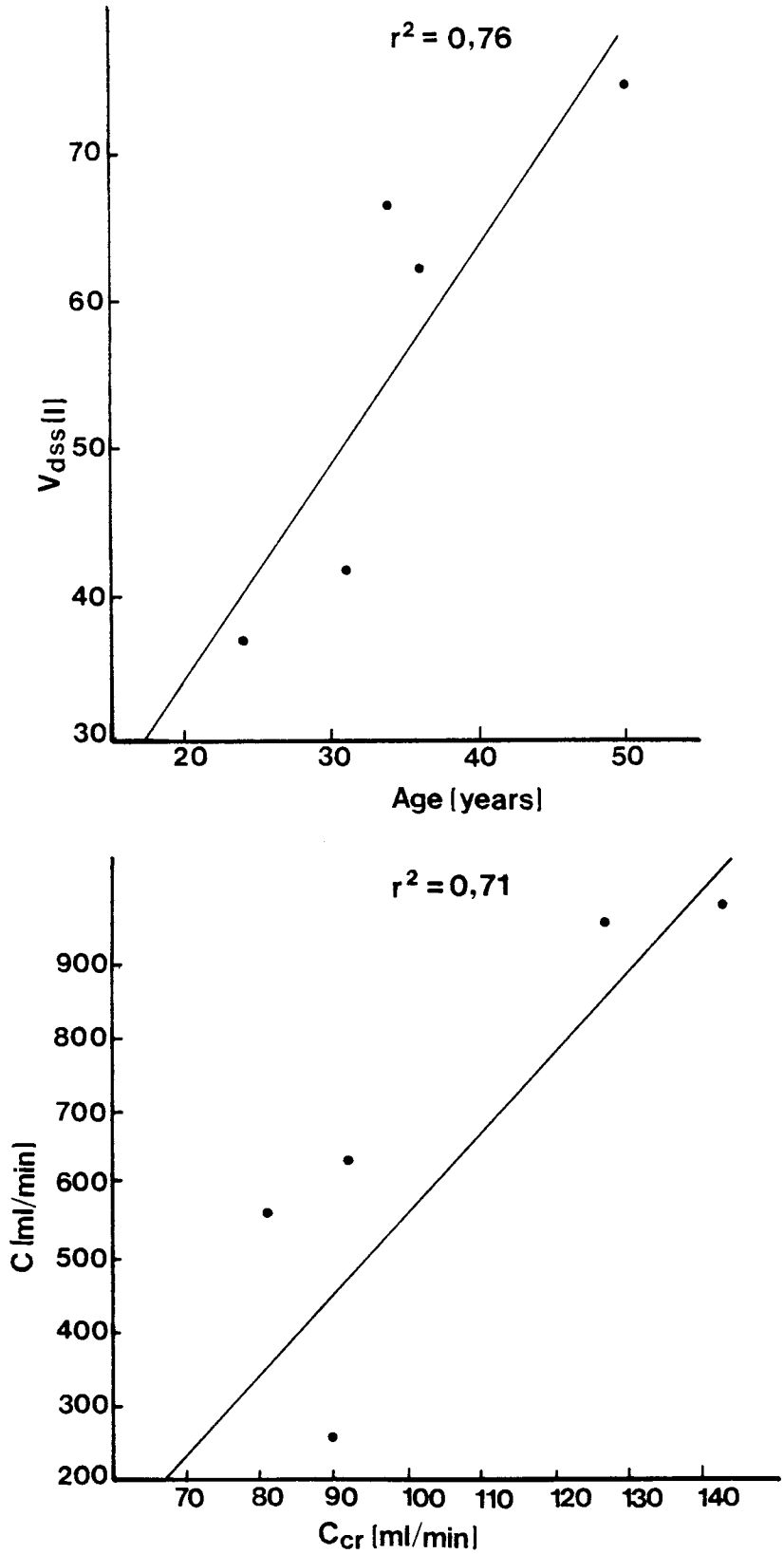

Figure 3.11 Relationship between volume of distribution steady state (V_{dss}) and age; total ranitidine clearance (C) and creatinine clearance (C_{cr}).

TABLE 3.19. Bioavailability after a single oral 150 mg ranitidine tablet and the dosage and areas under the curve (AUC) used to calculate bioavailability.

Patient	AUC oral (ng/ml-hr)	Dose oral (mg)	AUC_{iv} (ng/ml-hr)	$Dose_{iv}$ (mg)	Bioavailability (%)
P.d.J.	2 688	150	1 288	20	28
W.M.	1 845	150	348	20	71
S.M.	1 738	150	590	20	39
D.S.	1 950	150	341	20	76
R.L.	1 540	150	523	20	39

The bioavailability after a single 150 mg ranitidine calculated by the AUC method was extremely variable, ranging from 28% to 76% with a median value of 39% (mean 51%) (Table 3.18).

The theoretical plasma concentration-time curves for the intravenous data are given in Figures 3.12-3.16.

Complete 24-hour urine collections were made in only two patients (P.d.J. and D.S.) who excreted 13% and 7% of the dose respectively as unchanged ranitidine in the 24 hours following the dose.

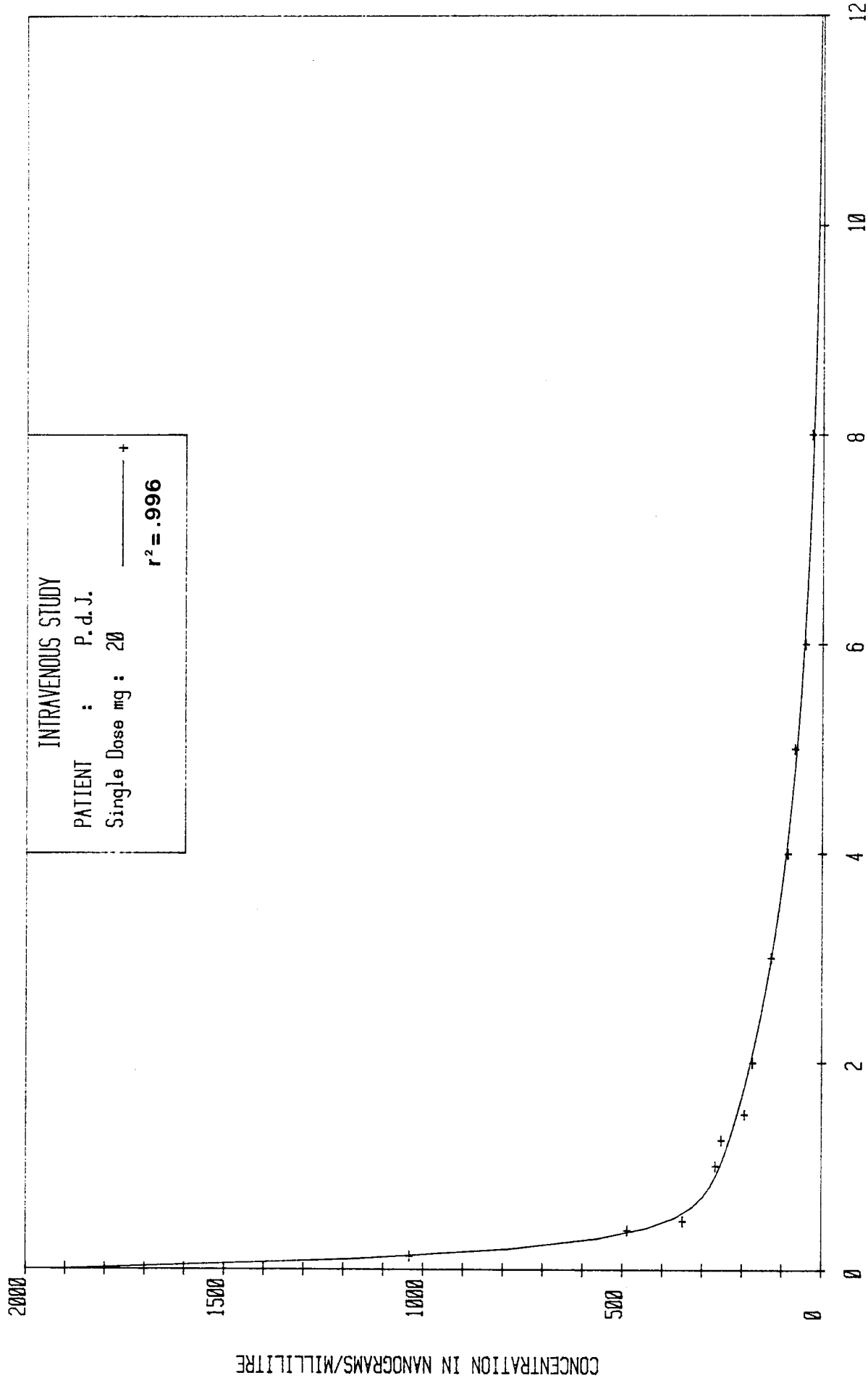
INTRAVENOUS STUDY
PATIENT : P.d.J.
Single Dose mg : 20
r^2 = .996
CONCENTRATION IN NANOGRAMS/MILLILITRE
2000
1500
1000
500
0
0
2
4
6
8
10
12
TIME IN HOURS

Figure 3.12.

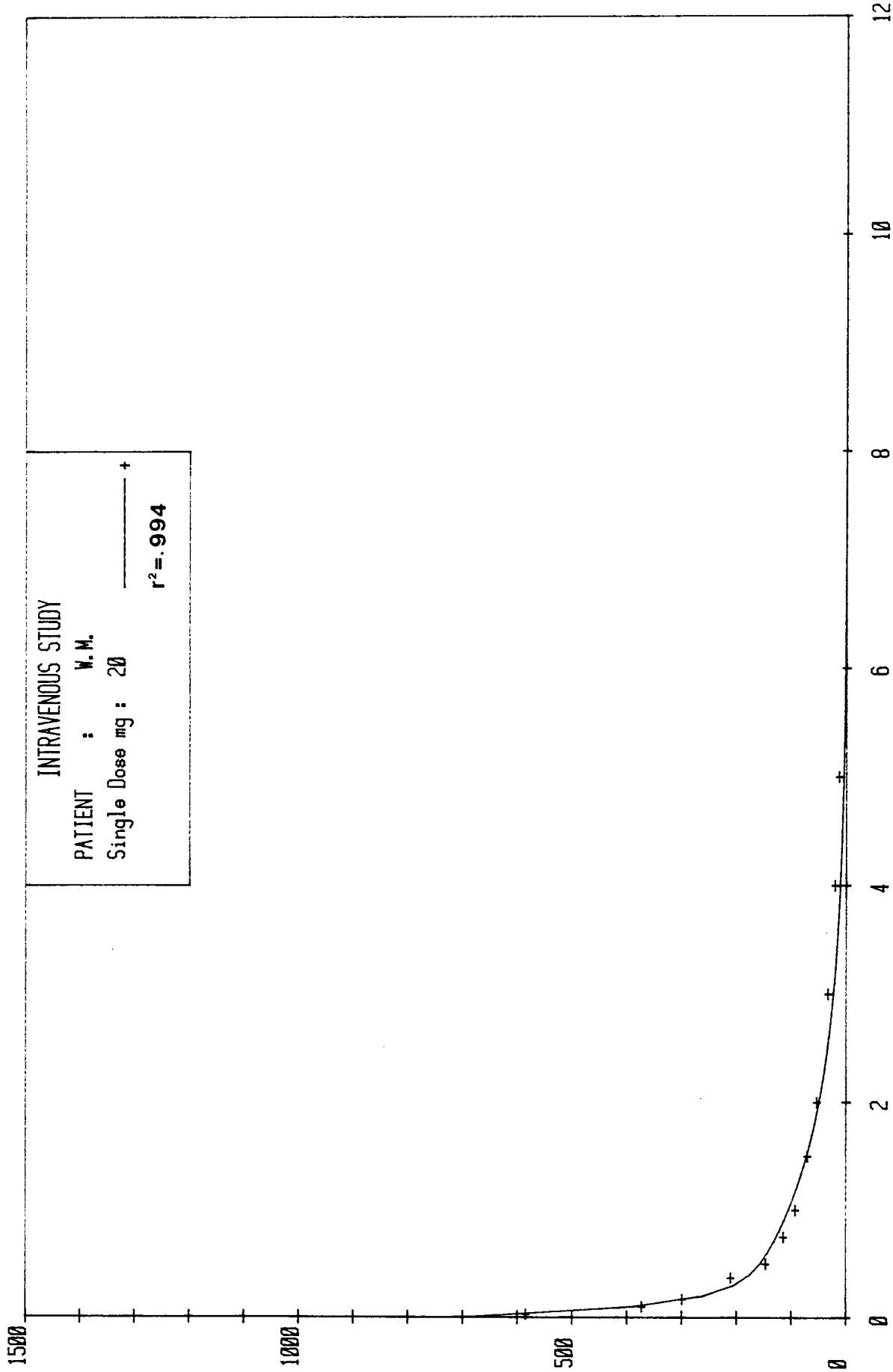
INTRAVENOUS STUDY
PATIENT : W.M.
Single Dose mg : 20
r²=.994
CONCENTRATION IN NANOGRAMS/MILLILITRE
1500
1000
500
0
0
2
4
6
8
10
12
TIME IN HOURS

Figure 3.13.

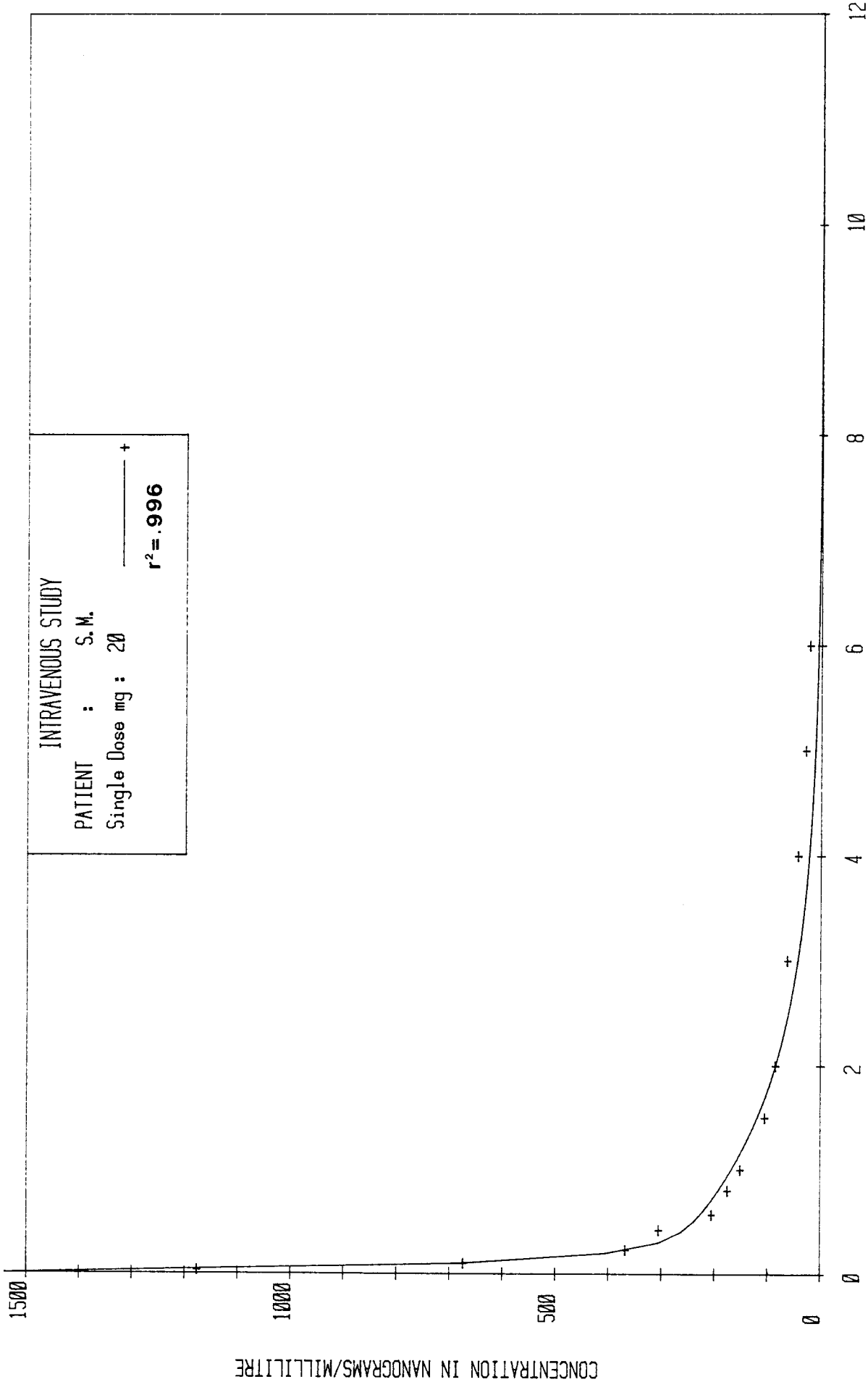
INTRAVENOUS STUDY
PATIENT : S.M.
Single Dose mg : 20
r²=.996
CONCENTRATION IN NANOGRAMS/MILLILITRE
1500
1000
500
0
0
2
4
6
8
10
12
TIME IN HOURS

Figure 3.14.

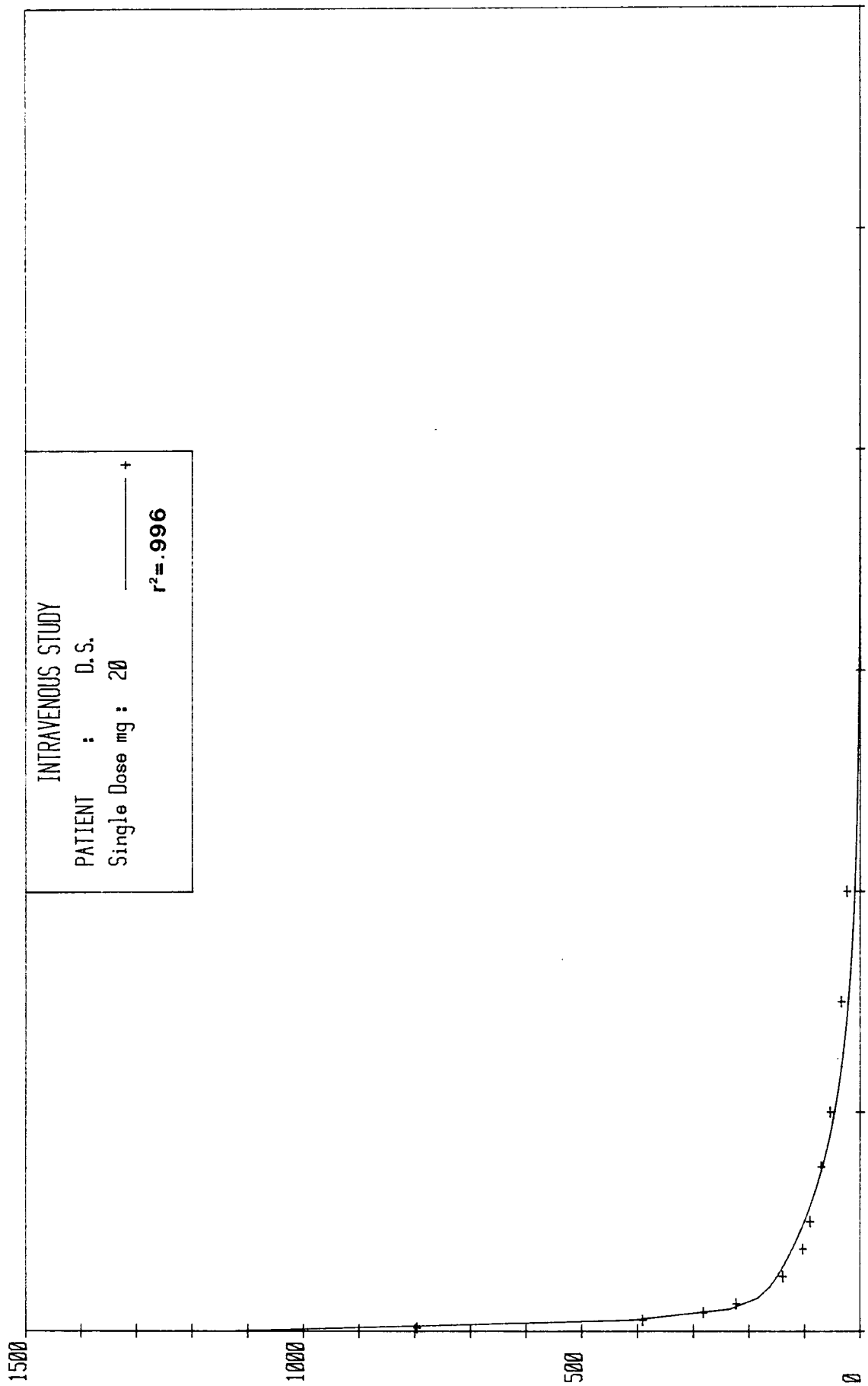
INTRAVENOUS STUDY
PATIENT : D.S.
Single Dose mg : 20
r²=.996
CONCENTRATION IN NANOGRAMS/MILLILITRE
1500
1000
500
0
0
2
4
6
8
10
12
TIME IN HOURS

Figure 3.15.

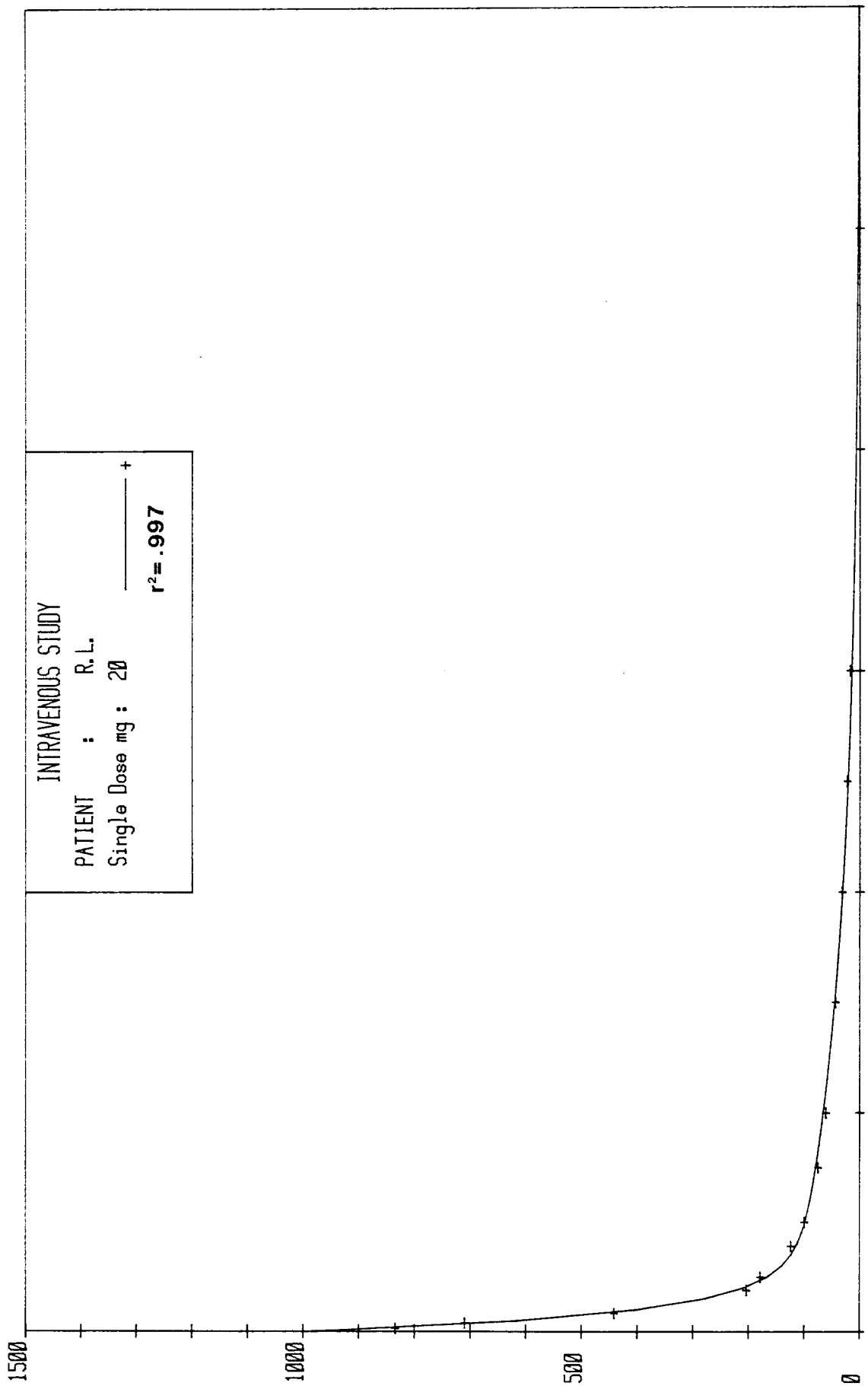
INTRAVENOUS STUDY
PATIENT : R.L.
Single Dose mg : 20
r²=.997
CONCENTRATION IN NANOGRAMS/MILLILITRE
1500
1000
500
0
0
2
4
6
8
10
12
TIME IN HOURS

Figure 3.16.

3.2. PATIENTS WITH CHRONIC DUODENAL ULCERATION - NON-RESPONDERS.

This group of patients had endoscopic evidence of unhealed duodenal ulcers at the end of at least 8 weeks' treatment with ranitidine. Endoscopy reports are included in the case histories in Appendix I. These patients were all studied after multiple dosing and one patient (R.L.) had a single-dose study and another (J.S.) an increased dosage multiple-dose study in addition. The plasma concentration-time data are given in Table 3.20 and the data for the additional studies in Table 3.21.

Results of basal acid output (BAO) and pentagastrin stimulated maximum acid output (MAO) for 6 of these patients are given in Table 3.22, together with the fasting serum gastrin taken at the time of the pharmacokinetic study. The fasting serum gastrin levels ranged from 12,2-67,8 pg/ml, all of which were well within the normal range of 0-100 pg/ml. The acid studies were carried out in 4 patients just prior to the start of the ranitidine trial while J.S. had an acid study on being classified as a non-responder 12 weeks after starting the ranitidine trial. The only gastric acid levels available on P.M. were carried out a year after the study. Three patients had BAO and MAO well above the range for responders.

The median values for Cmax, tmax, Cmin (0) and Cmin (12) were 599 ng/ml, 1,5 h, 48 ng/ml and 44 ng/ml (Table 3.23 with corresponding values for responders given in brackets). There were no significant differences between the responders and the non-responders.

The following values were obtained after a single-dose in patient R.L.:

TABLE 3.20

PLASMA CONCENTRATIONS (ng/ml) AFTER MULTIPLE-DOSE RANITIDINE ADMINISTRATION (150mg TWICE DAILY FOR AT LEAST ONE WEEK) TO DUODENAL ULCER PATIENTS (NON-RESPONDERS)

Patient	Time (hrs) 0	.25	.50	.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0	8.0	10.0	12.0	24.0
J.S.	21	40	243	235	204	206	234	175	133 (3.9)	81	60	47 (7.9)	31	20	10 (23.8)
R.L.	21	101	548	575	449	399	304	158	131	104	79	35	19	16	4
D.S.	196	166	249	446	673	779	714	453	411	336	243	170	102	58	8
D.M.	48	38	60	311	442	599	500	429	422	279	165	102	72	44	0
S.S.	58	70	313	531	584	611	583	494	390	291	243	163	95	62	12
P.P.	56	56	102	235	347	395	426	359	314	277	204	122	59	35	6
P.M.	7	25	319	607	735	721	547	432	350	260	221	145	94	62	10

Figures in brackets are the times of sampling when these differ from the column headings.

TABLE 3.21

PLASMA CONCENTRATIONS FOLLOWING A SINGLE DOSE (150mg) IN PATIENT R.L. AND MULTIPLE DOSAGE OF 300mg TWICE DAILY IN PATIENT J.S.

Patient	Time (hrs) 0	.25	.50	.75	1.0	1.5	2.0	3.0	3.5	4.0	5.0	6.0	8.0	10.0	12.0	24.0	Dose
R.L.	0	420 (.3)	-	-	365	386	371	306	227	186 (3.75)	143	104	69 (8.2)	46 (9.75)	33 (11.75)	0	Single dose 150mg
J.S.	34	72	271	350	356	386	403	348	300 (3.7)	-	262 (5.1)	204	125	98	74	0	300mg twice daily for 1 month

TABLE 3.22. Basal acid output (BAO) and pentagastrin stimulated maximum acid output (MAO) and fasting serum gastrin levels for non-responders.

Initials	BAO (meq/h)	MAO (meq/h)	Fasting gastrin (pg/ml)
J.S.[1]	16,5	45,9	12,2
R.L.[2]	22,5	59,6	27,9
D.S.	-	-	67,8
D.M.[2]	29,4	93,9	44,7
S.S.[2]	1,6	33,7	66,5
P.P.[2]	4,4	30,4	53,7
P.M.[3]	4,4	25,3	29,2
range	1,6-29,4 (0,0-9,1)	25,3-93,9 (16,2-39,1)	12,2-67,8

Key: 1 Acids measured after 8 weeks' ranitidine

2 Acids measured prior to ranitidine trial

3 Acids measured 1 year after trial

( ) Range for responders

TABLE 3.23. The maximum concentrations (Cmax), time to reach Cmax (tmax), minimum concentration at zero time (Cmin(0)) and at 12 hours post-dosing (Cmin(12)) for non-responders.

Initials	Cmax (ng/ml)	tmax (h)	Cmin(0) (ng/ml)	Cmin(12) (ng/ml)
J.S.	243	0,5	21	20
R.L.	573	0,75	21	16
D.S.	779	1,5	196	58
D.M.	599	1,5	48	44
S.S.	611	1,5	58	62
P.P.	426	2,0	56	35
P.M.	735	1,0	7	62
median	599 (562)	1,5 (1,0)	48 (33)	44 (30)
range	243-779 (313-824)	0,5-2,0 (0,5-2,0)	7-196 (8-146)	16-62 (16-42)

( ) values for responders

Cmax = 420 ng/ml, tmax = 0,3 h, Cmin(12) = 33 ng/ml. This patient had very rapid absorption with other parameters similar to responders. From Table 3.23 it can be seen that Cmax for patient J.S. was 243 ng/ml, the lowest value observed in any patient. After multiple-dosing with 300 mg twice daily Cmax of the same patient was increased to 403 ng/ml at 2 hours; the Cmin(0) was 34 ng/ml and the Cmin(12) 74 ng/ml.

From Table 3.24 it can be seen that in all cases except one (R.L.), the one compartment model yielded the lower AIC value. One patient (R.L.) exhibited two compartment characteristics after single- and multiple-dosing. The same patient was also studied after administration of intravenous ranitidine (see Section 3.1.3).

TABLE 3.24. Akaike's Information Criteria (AIC) for one- and two-compartment model fittings for non-responders.

Initials	A I C	
	1 Compartment	2 Compartments
J.S.	134,1*	142,3
J.S.[1]	120,7*	125,5
R.L.	130,1	128,5*
R.L.[2]	136,1	121,7*
D.S.	152,7*	153,5
D.M.	139,7*	157,4
S.S.	119,5*	130,1
P.P.	125,0*	164,4
P.M.	144,2*	146,7

* Model chosen for analysis

1 Multiple-dose 300 mg

2 Single-dose 150 mg

TABLE 3.25. Computer generated multiple-dose pharmacokinetic parameters for non-responders.

Initials	k_a (h^{-1})	t_{lag} (min)	FD/V (ng/ml)	k_{el} (h^{-1})	α (h^{-1})	β (h^{-1})
J.S.	9,52	14,5	250,5	0,22		
R.L.	7,45	14,0	689,6	-	0,81	0,24
D.S.	3,78	37,4	751,8	0,25		
D.M.	1,82	29,2	740,7	0,27		
S.S.	2,49	18,9	739,2	0,22		
P.P.	1,34	25,3	564,0	0,24		
P.M.	4,31	23,6	844,6	0,26		
median	3,78	23,6	739,2	$0,24^{++}$		
	(2,39)	(13,2)	(850,9)	(0,31)		
range	1,34-9,52	14,0-37,4	250,5-844,6	0,22-0,27		
	(0,70-11,05)	(0,0-28,2)	(416,2-3 381,1)	(0,26-0,80)		

Key: ++ $p < 0,002$

( ) values for responders

The computer generated pharmacokinetic parameters for the chosen model are given in Table 3.25. When compared to the parameters in responders, no significant differences were found in non-responders except in the disposition rate constant (k_{el}) which was smaller in non-responders than responders with median values of 0,24 h^{-1} and 0,31 h^{-1} respectively ($p < 0,002$). Non-responders had a longer median $t_{\frac{1}{2}}$ of 173 minutes compared to 135 minutes in responders (Table 3.26). Contrary to what was expected, this would tend to keep plasma levels higher for a longer time period in non-responders.

In humans the plasma concentration of ranitidine at which pentagastrin stimulated acid secretion is inhibited by 50% (IC_{50}) is reported to be

TABLE 3.26. Half-life ($t_{\frac{1}{2}}$), area under the curve (AUC) and time that concentration remained above 100 ng/ml for non-responders.

Initials	$t_{\frac{1}{2}}$ (min)	AUC_{0-12} (ng/ml.h)	Time concentration greater than 100 ng/ml (h)
J.S.	189	1 140	4,0
R.L.	173	1 540	4,75
D.S.	166	3 584	9,75
D.M.	154	2 720	7,75
S.S.	189	3 315	9,75
P.P.	173	2 405	8,0
P.M.	160	3 199	9,25
median	173	2 720	7,75
	(135)	(2 108)	(5,9)
range	154-189	1 140-3 584	4,0-9.75
	(52-160)	(1 458-3 074)	(5,25-7,75)

( ) values for responders

in the region of 100 ng/ml (Peden et al 1979). When the time that plasma concentrations remained above 100 ng/ml was examined in responders and in non-responders, an apparent bimodal distribution of non-responders was observed (Table 3.26). Non-responders fell into two groups at either end of the responders' range. The range for responders was 5,25 - 7,75 h and J.S. and R.L. had levels above 100 ng/ml for 4,0 and 4,75 h only while the 5 other non-responders had levels above 100 ng/ml for 7,75 h and longer.

As a group the AUC values for non-responders did not differ significantly from responders, although J.S. and R.L. again fell at the lower end of the range (Table 3.26).

The theoretical plasma concentration-time curves for the multiple dose situation are given in Figures 3.17-3.23.

The proportion of the total ranitidine dose excreted unchanged in the urine 24 hours post-dosing was highly variable (10-59%) (Table 3.27) and not significantly different to responders (10-105%). Creatinine clearance (calculated from serum creatinine) is shown in the same table.

TABLE 3.27. Percentage of total ranitidine dose excreted unchanged in the urine in the 24 hours after dosing and creatinine clearance (C_{cr}) estimated from serum creatinine.

Initials	Ranitidine in 24 h urine (%)	C_{cr} (ml/min)
J.S.	-	103
R.L.	32	92
D.S.	13	101
D.M.	45	114
S.S.	59	106
P.P.	13	91
P.M.	10	79

In summary non-responders as a group did not show grossly different pharmacokinetic profiles to responders. Two patients (R.L. and J.S.) had relatively low plasma levels, FD/V, AUC, combined with high basal and maximal acid output. These patients may fall into a subgroup of non-responders for whom an increased dose of ranitidine is necessary to inhibit acid secretion. One patient (J.S.) did in fact show evidence of ulcer healing on endoscopy after one month's treatment at 300 mg twice daily; the FD/V was increased to 472 ng/ml, the AUC to 2 789 ng/ml.hr and time that the concentration remained above 100 ng/ml was increased to 9,25 h.

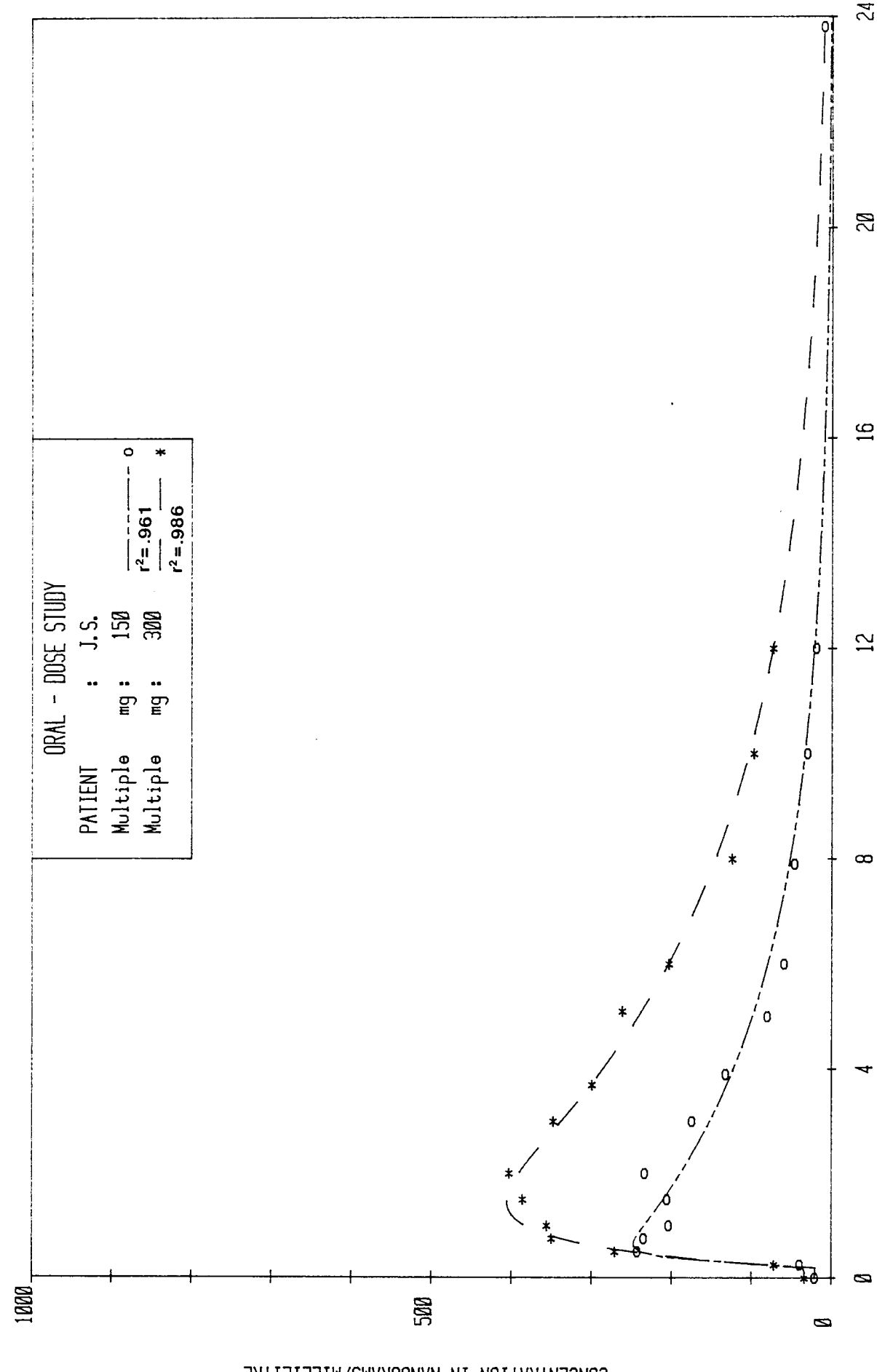
ORAL - DOSE STUDY
PATIENT : J.S.
Multiple mg : 150 r²=.961
Multiple mg : 300 r²=.986
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.17.

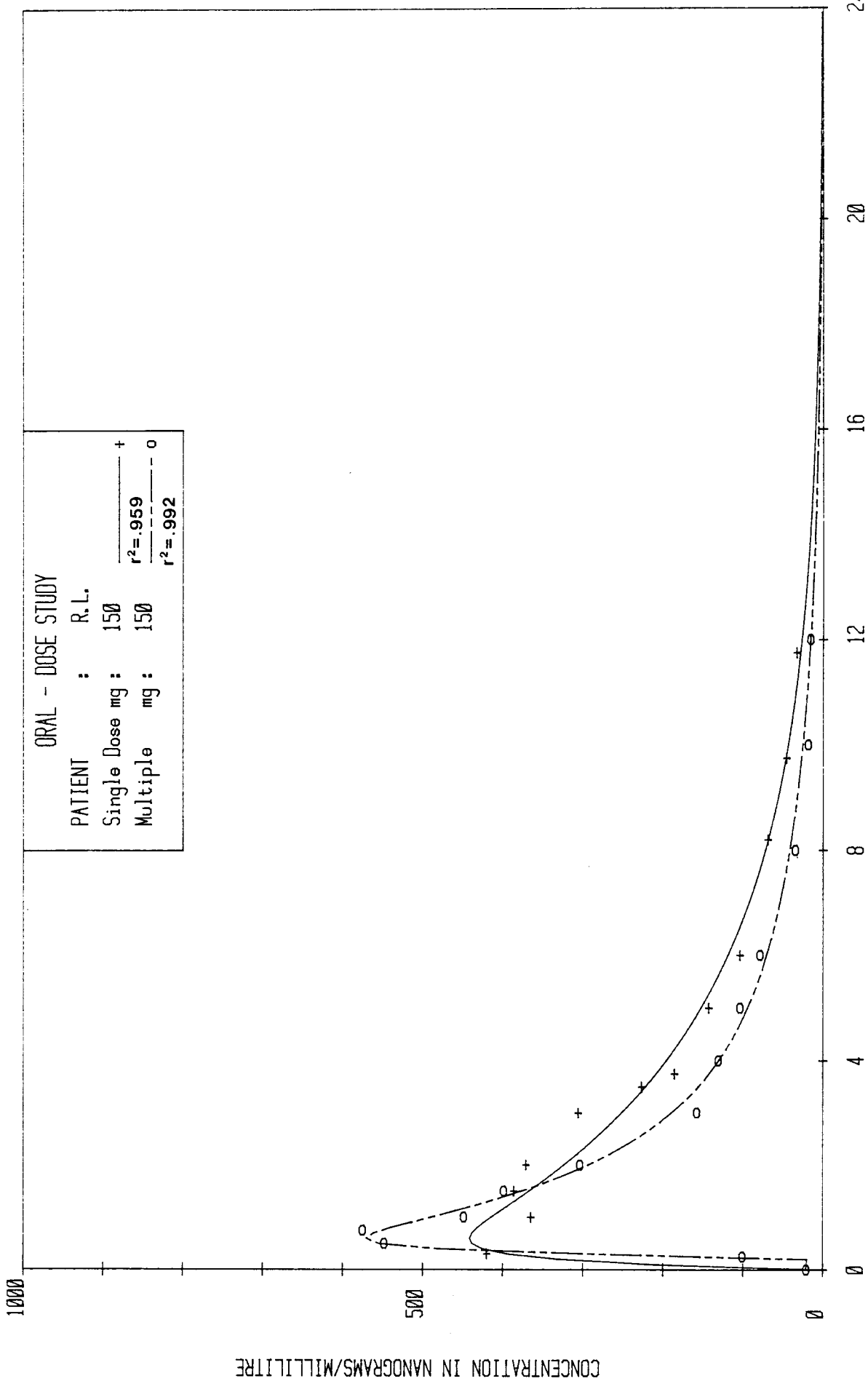
ORAL - DOSE STUDY
PATIENT : R.L.
Single Dose mg : 150
Multiple mg : 150
r²=.959
r²=.992
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.18.

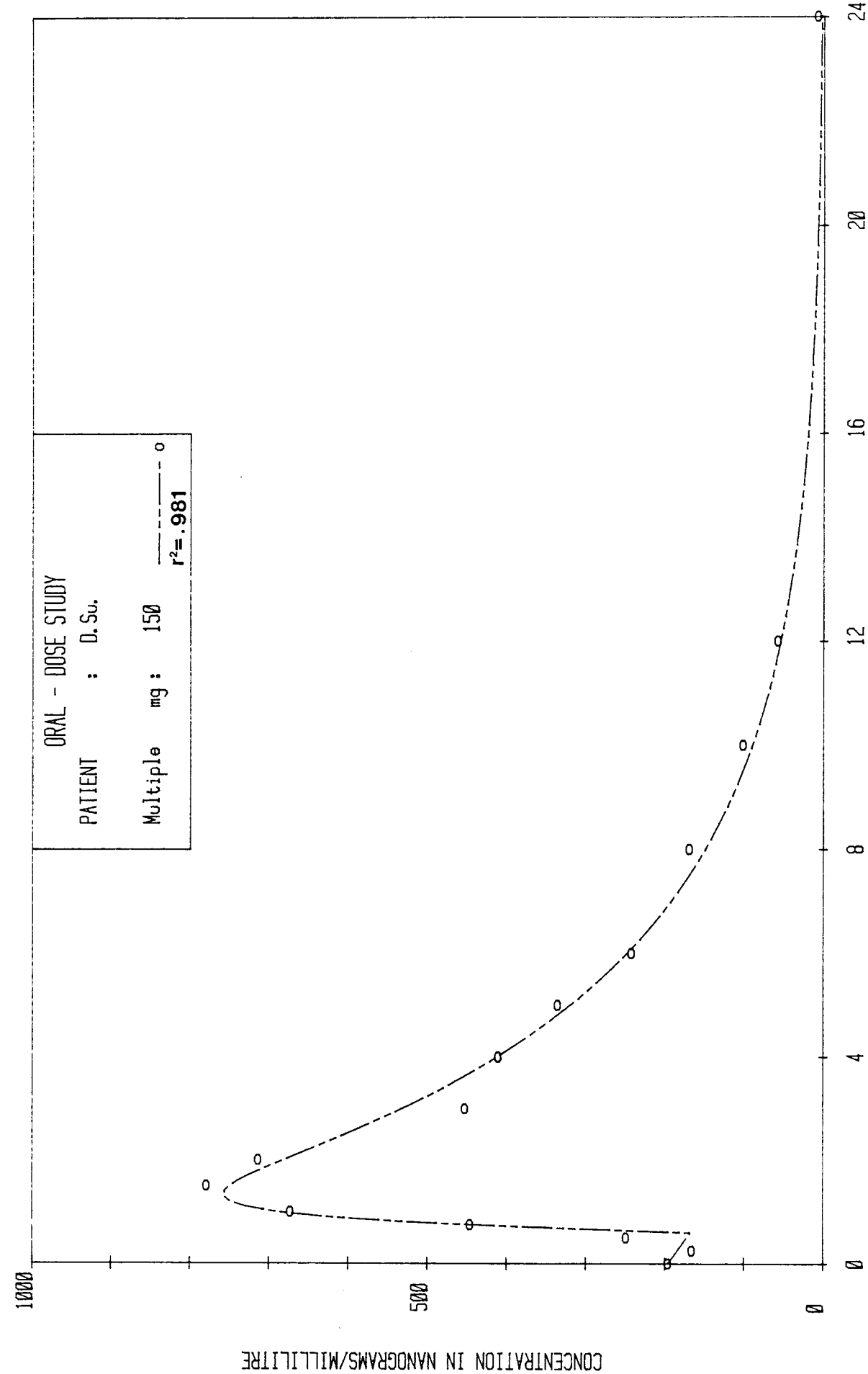
ORAL - DOSE STUDY
PATIENT : D.Su.
Multiple mg : 150
r²=.981
CONCENTRATION IN NANOGRAMS/MILLILITRE
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS

Figure 3.19.

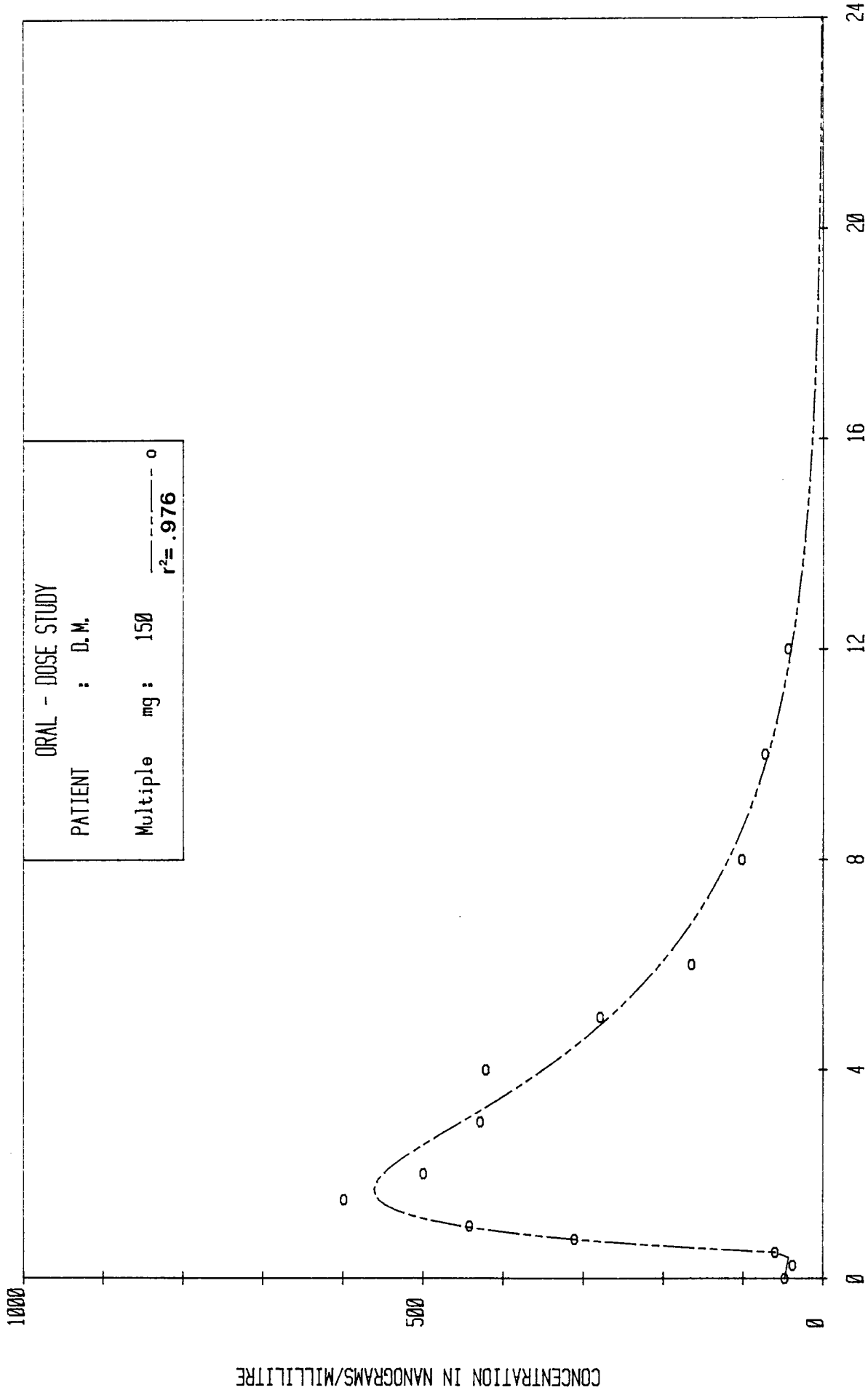
ORAL - DOSE STUDY
PATIENT : D.M.
Multiple mg : 150
r²= .976
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.20.

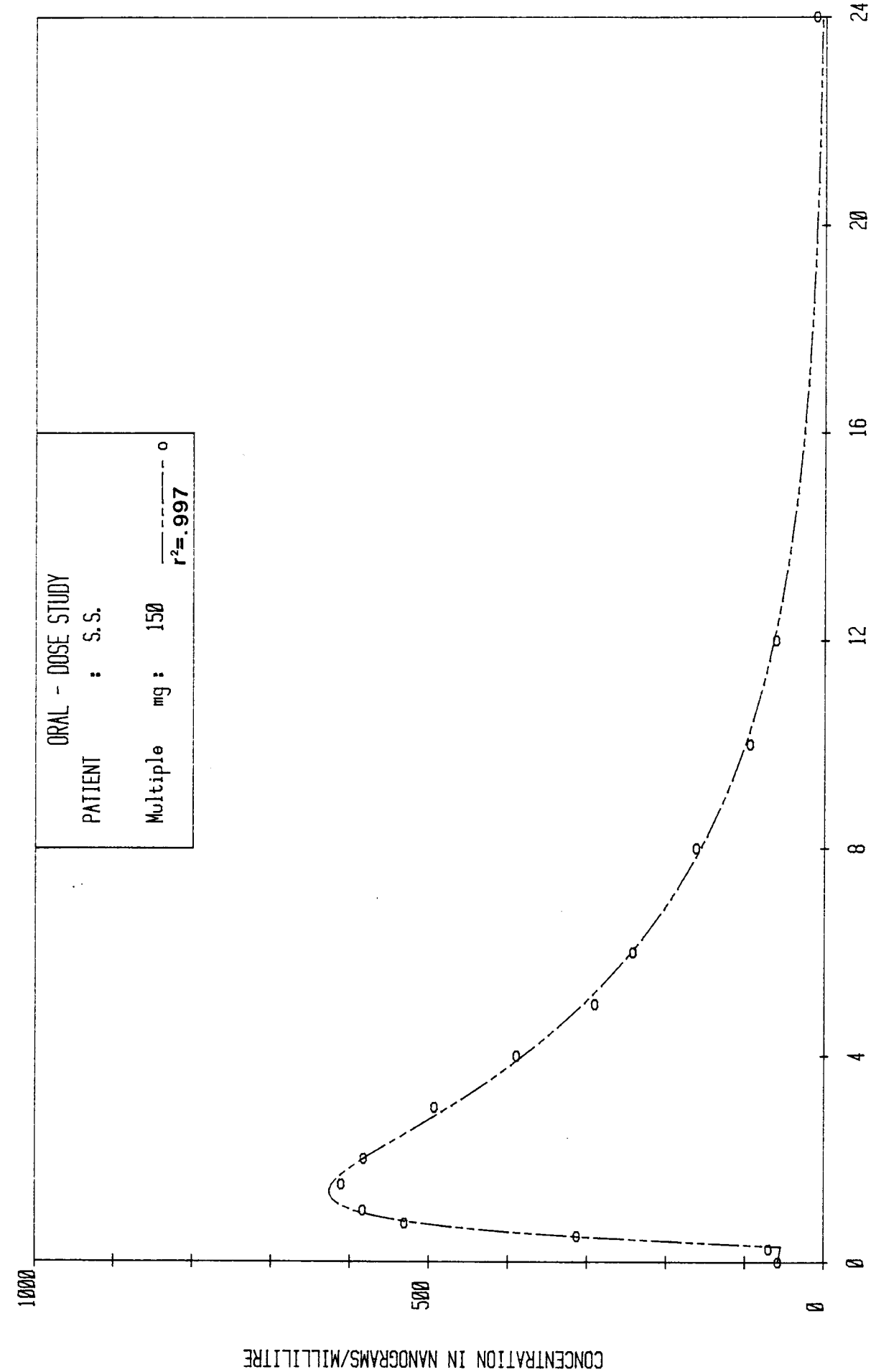
ORAL - DOSE STUDY
PATIENT : S.S.
Multiple mg : 150
r²=.997
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.21.

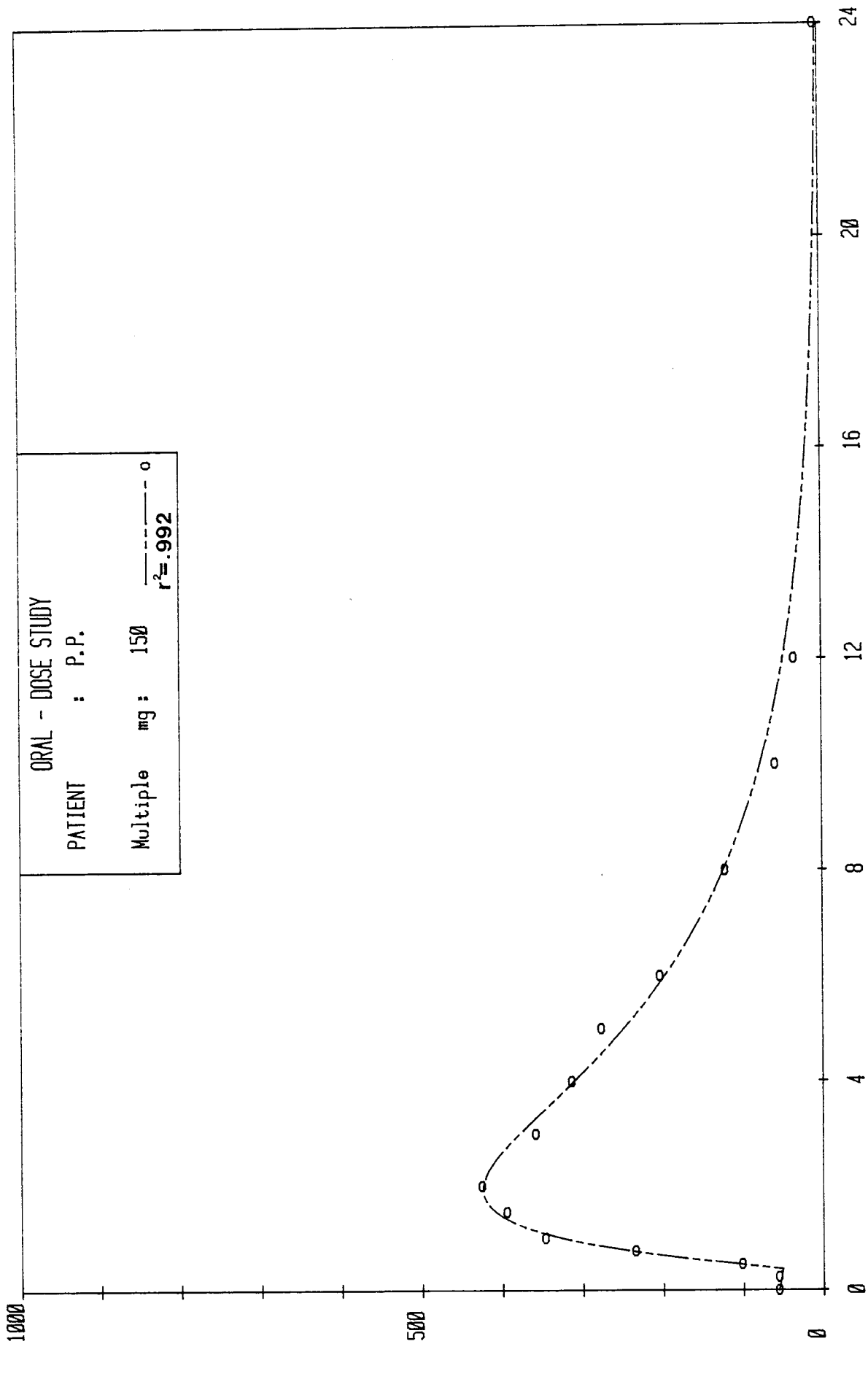
ORAL - DOSE STUDY
PATIENT : P.P.
Multiple mg : 150
r²=.992
CONCENTRATION IN NANOGRAMS/MILLILITRE
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS

Figure 3.22.

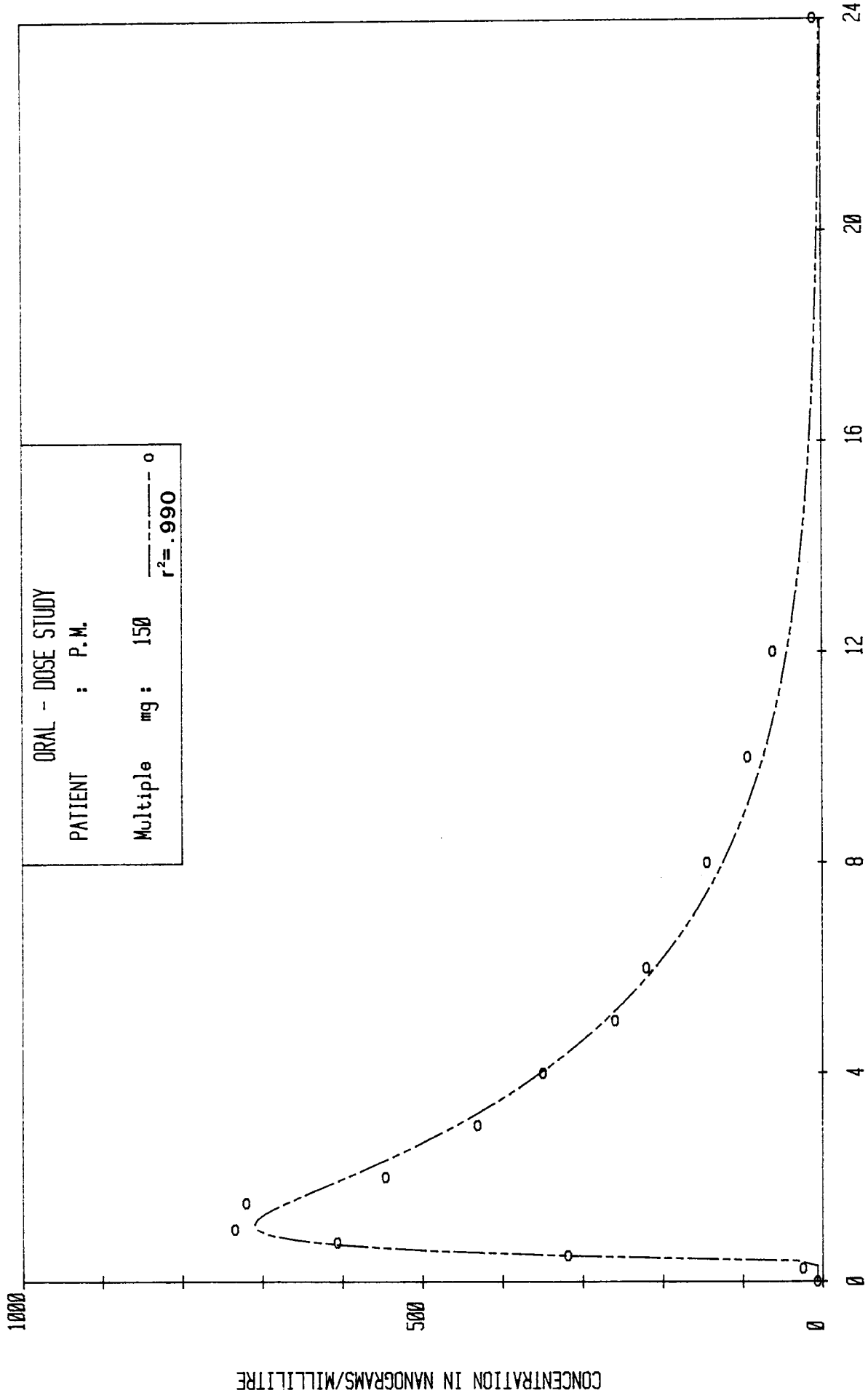
ORAL - DOSE STUDY
PATIENT : P.M.
Multiple mg : 150
r²= .990
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.23.

3.3. PATIENTS SUFFERING FROM CHRONIC RENAL FAILURE.

3.3.1. Single- and multiple-dose pharmacokinetic studies in patients with severe renal failure who were not on haemodialysis.

The plasma concentration-time data following single dose oral administration of 150 mg ranitidine are given in Table 3.28. The multiple-dose study was carried out after one week of ranitidine being taken twice daily. The plasma concentration-time data are given in Table 3.29. I have viewed the multiple-dose data with caution for the following reasons: B.S. received 150 mg ranitidine twice daily throughout the week while the other patients received 75 mg twice daily; B.S. underwent haemodialysis 3 times during the week of the study although not on the day of study; L.A. may have taken 75 mg ranitidine two hours prior to the multiple-dose pharmacokinetic study; it is possible that R.W. did not receive the evening ranitidine dose on the day prior to the multiple-dose study.

The maximum (Cmax) and minimum (Cmin) concentrations and the time to reach Cmax (tmax) after single- and multiple-dosing are shown in Table 3.30. These values are taken from the raw plasma concentration-time data. The multiple-dose Cmax and Cmin were normalised for a 150 mg dose. There was no apparent difference in the absorption phase of ranitidine in uraemic patients, compared with the reference group with duodenal ulceration and normal renal function as Cmax and tmax did not differ significantly in either the single- or the multiple-dose situation. After single- and multiple-dosing in uraemic patients, minimum concentrations (Cmin) were highly significantly different to controls. The median Cmin at 12 hours' post-dosing after a single-dose in patients with renal failure was 164 ng/ml compared with 35 ng/ml in the control group ($p < 0,001$).

TABLE 3.28

PLASMA RANITIDINE CONCENTRATIONS (ng/ml) AFTER A SINGLE 150 mg TABLET WAS ADMINISTERED ORALLY TO PATIENTS WITH RENAL FAILURE

Patient	Time (hrs) 0.0	.25	.50	.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0	8.0	10.0	12.0	24.0
B.S.	0	21	180	267 (.83)	-	356 (1.33)	413	332	272 (4.5)	227	196	144 (8.67)	124 (10.67)	110	46
J.S.	0	0	54	190	274	537	863	847	758	698	642	476 (8.1)	392	344	123
L.A.	0	46	572	693	750 (1.13)	851	750	703	649	542	484	393	268	218 (11.9)	60
H.D.	0	8	104	234	276	283	267 (2.33)	231	199	163 (5.17)	149	124	88	76 (12.08)	28
T.C.	0	7	30	124	240	457	661	698	675	593	526	432	330	281	99
R.W.	0	0	74	333	484	646	618	532	459	371	220	184	118	93	26

Key: ( ) times of sampling when these times differ from column headings.

TABLE 3.29

PLASMA RANITIDINE CONCENTRATIONS (ng/ml) AFTER ADMINISTRATION OF 75 mg RANITIDINE TWICE DAILY TO PATIENTS WITH RENAL FAILURE

Patient	Time (hrs) 0	.25	.50	.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0	8.0	10.0	12.0	24.0
B.S.*	161	184	325	405	462	431	465	419	361	285	221	178	144	110	36 (25.33)
J.S.	382	365	574	663	672	750	759	738	704	645 (5.5)	592 (6.1)	520	-	309	142
L.A.	338	364	475	710	711	666	581	527	463	433	352	279 (7.9)	191 (10.4)	144 (11.75)	32
H.D.	217	280 (.36)	397	427	442	436	420	404	379	314	284	210	160	133	48 (24.1)
T.C.	227	302	367	374	364	337	353	328	289	259	236	191	164	137	65
R.W.**	19	23	170	286	330	302	313	266	232	193	151	103	76	50	14

Key: ( ) Times of sampling when these times differ from column headings.

* Patient B.S. received 150mg ranitidine twice daily.

** Patient R.W. skipped evening dose prior to pharmacokinetic study.

TABLE 3.30. Maximum concentrations (Cmax), minimum concentrations (Cmin) and time to reach maximum concentrations (tmax) for single- and multiple-dose studies in patients with chronic renal failure.

Initials	SINGLE - DOSE			MULTIPLE - DOSE				
	Cmax (ng/ml)	tmax (h)	Cmin(12) (ng/ml)	Cmax (ng/ml)	tmax (h)	Cmin(0) (ng/ml)	Cmin(12) (ng/ml)	Cmax-Cmin0 (ng/ml)
B.S.	413	2,0	110	465	2,0	161	110	304
J.S.	863	2,0	344	1 518	2,0	764	618	754
L.A.	851	1,5	218	1 422	1,0	676	288	746
H.D.	283	1,5	76	884	1,0	434	266	450
T.C.	698	3,0	281	748	0,75	454	274	294
R.W.	646	1,5	93	660	1,0	38	100	560
median	672	1,75	164**	816	1,0	444**	270**	505
	(356)	(2,0)	(35)	(562)	(1,0)	(33)	(30)	(521)
range	283-863	1,5-3,0	76-344	465-1 518	0,75-2,0	38-764	100-618	294-754
	(207-540)	(1,0-3,0)	(12-48)	(313-824)	(0,5-2,0)	(8-146)	(16-42)	(292-811)

** $p < 0,001$

( ) values for patients with normal renal function

TABLE 3.31. Akaike's Information Criteria for one- and two-compartment models in patients with chronic renal failure.

Initials	Single - dose		Multiple - dose	
	1 Compartment	2 Compartments	1 Compartment	2 Compartments
B.S.	118,9	115,7+	133,4+	134,0
J.Se.	147,3+	152,0	133,6+	151,4
L.A.	139,5+	143,8	132,2+	156,7
H.D.	120,0+	123,9	131,2+	146,9
T.C.	159,8+	169,6	114,6+	120,9
R.W.	121,9+	123,6	93,2+	124,3

+ Model chosen for analysis.

The difference was even greater after multiple dosing with median Cmin levels of 270 ng/ml in renal failure and 30 ng/ml in controls ($p < 0,001$).

The concentration-time data were fitted to both one- and two-compartment models and Akaike's Information Criteria (AIC) were calculated in order to choose the simplest model (Table 3.31). The one-compartment model best described the data in all cases except after single dose administration to B.S. where a two-compartment model gave a lower AIC value.

There were no differences in absorption rate (Ka) or lag time to the start of absorption in single- and multiple-dosing between uraemic patients and patients with normal renal function. There did not appear to be any difference in the bioavailability of ranitidine in uraemic patients, as FD/V values were not significantly different from controls.

Elimination of ranitidine was much slower in patients with impaired renal function. The median elimination rate constant (K_{el}) after single-

TABLE 3.32. Computer-generated pharmacokinetic parameter for single-dose (A) and multiple-dose (B) studies in patients with renal failure.

A.

Initials	k_a (h^{-1})	t_{lag} (min)	FD/V (ng/ml)	k_{el} or β (h^{-1})	α (h^{-1})
B.S.	0,74	10,4	857,7	0,07	0,78
J.Se.	0,86	30,0	1 116,2	0,12	-
L.A.	3,22	13,8	923,4	0,12	-
H.D.	2,28	15,0	335,7	0,15	-
T.C.	0,48	15,0	1 132,1	0,16	-
R.W.	1,79	26,9	857,0	0,23	-
median	1,33	15,0	890,6	0,14**	
	(1,31)	(19,3)	(549,5)	(0,31)	
range	0,48-3,22	10,4-30,0	335,7-1 132,1	0,07-0,23	
	(0,37-3,26)	(0,0-33,8)	(229,0-1 138,1)	(0,19-0,82)	

B.

Initials	k_a (h^{-1})	t_{lag} (min)	FD/V[1] (ng/ml)	k_{el} (h^{-1})
B.S.	1,91	12,7	425,7	0,16
J.Se.	1,41	13,7	1 095,2	0,08
L.A.	10,87	28,8	873,0	0,14
H.D.	3,47	15,9	601,2	0,11
T.C.	6,10	8,8	344,0	0,09
R.W.	3,46	20,4	738,6	0,17
median	3,47	14,8	669,9	0,13
	(2,39)	(13,2)	(850,9)	(0,31)
range	1,41-10,87	8,8-28,8	344,0-1 095,2	0,08-0,17
	(0,70-11,05)	(0,0-28,2)	(416,2-3 381,1)	(0,26-0,80)

Key: ** $p < 0,001$
[1] normalised for dose
( ) values for controls

dosing was 0,14 h^{-1} with controls having a median K_{el} of 0,31 h^{-1} ($p < 0,001$). The pattern was similar after multiple-dosing.

The median half-life in renal failure was prolonged by approximately two-fold (312 minutes compared with 135 minutes in controls) (Table 3.33).

TABLE 3.33. The half-lives ($t_{\frac{1}{2}}$) after single- and multiple-dosing in patients with renal failure.

Initials	Single-dose $t_{\frac{1}{2}}$ (min)	Multiple-dose $t_{\frac{1}{2}}$ (min)
B.S.	594	260
J.Se.	347	520
L.A.	347	297
H.D.	277	378
T.C.	260	462
R.W.	181	245
median	312	338
	(135)	(135)
range	181-594	245-520
	(51-219)	(52-160)

( ) Values for patients with normal renal function.

The theoretical plasma concentration-time curves for patients with renal failure are given in Figures 3.24-3.29. Each figure represents the single- and multiple-dose curves for a patient.

The AUC obtained for patients with renal failure were highly variable ranging from 2 673-10 270 ng/ml.h after single-dosing, with a similar wide range after multiple-dosing. Within this group of patients with renal failure there was no linear relationship between AUC and the extent

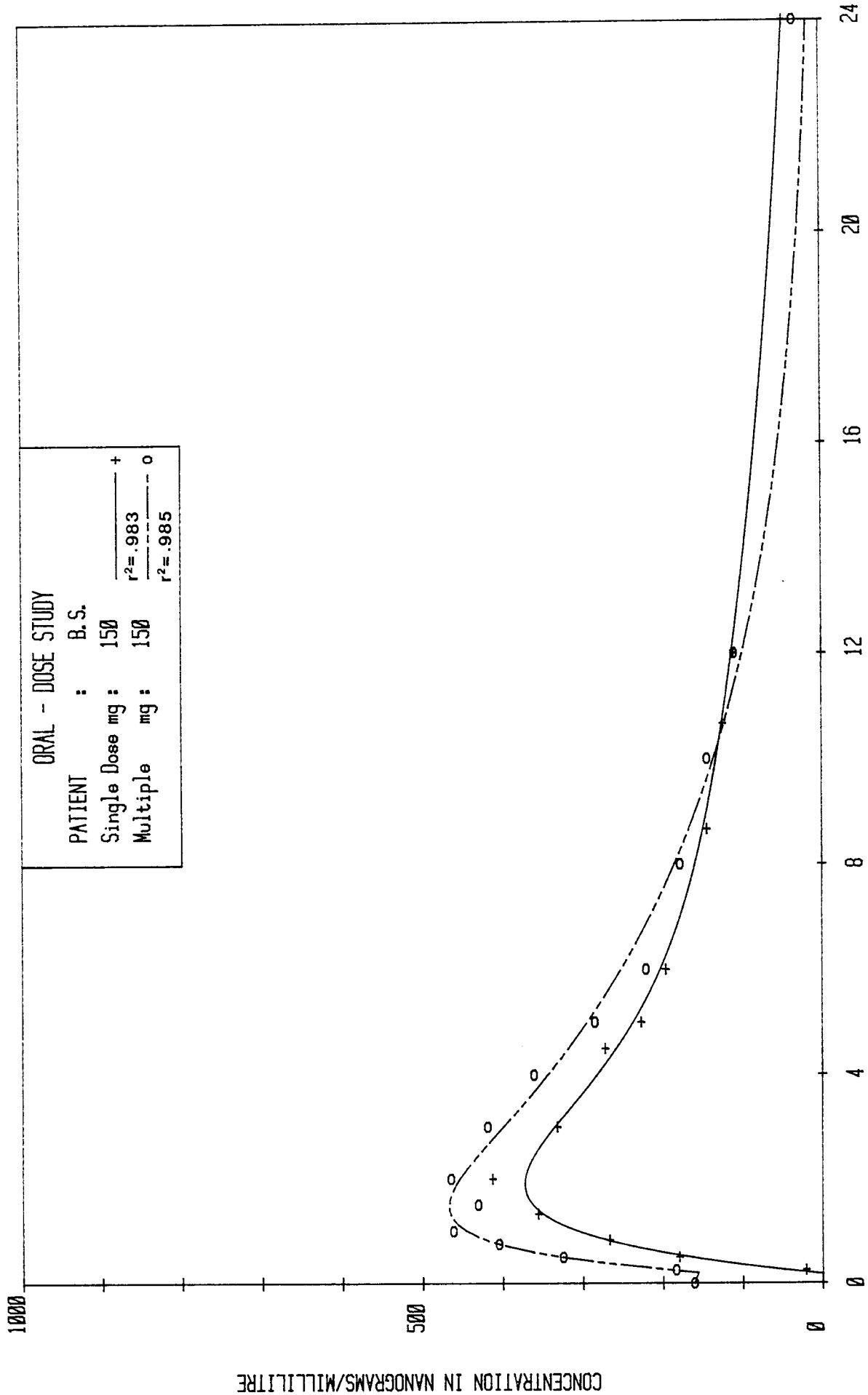
ORAL - DOSE STUDY
PATIENT : B.S.
Single Dose mg : 150
Multiple mg : 150
r²=.983
r²=.985
CONCENTRATION IN NANOGRAMS/MILLILITRE
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS

Figure 3.24.

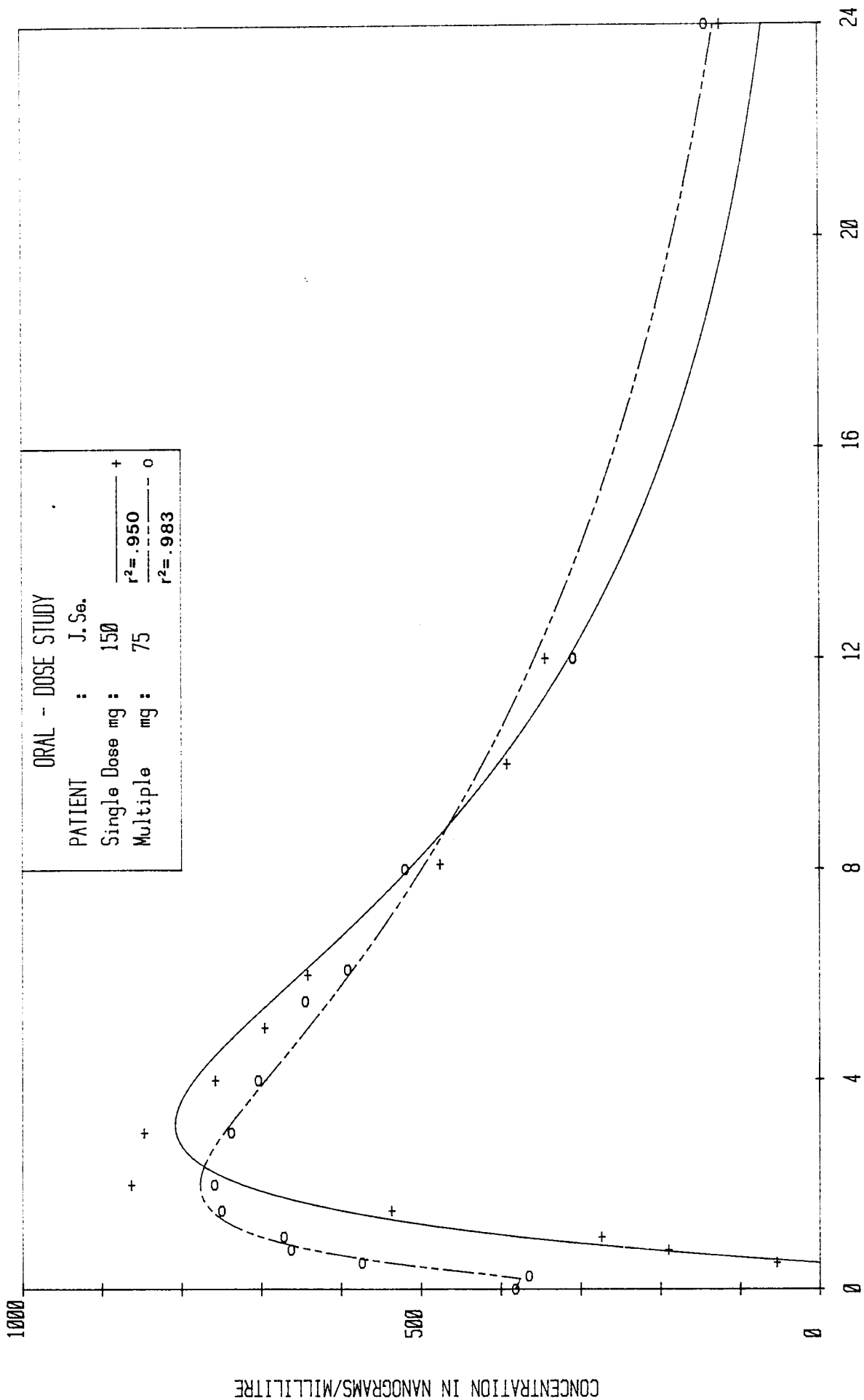
ORAL - DOSE STUDY
PATIENT : J.Se.
Single Dose mg : 150
Multiple mg : 75
r²=.950
r²=.983
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.25.

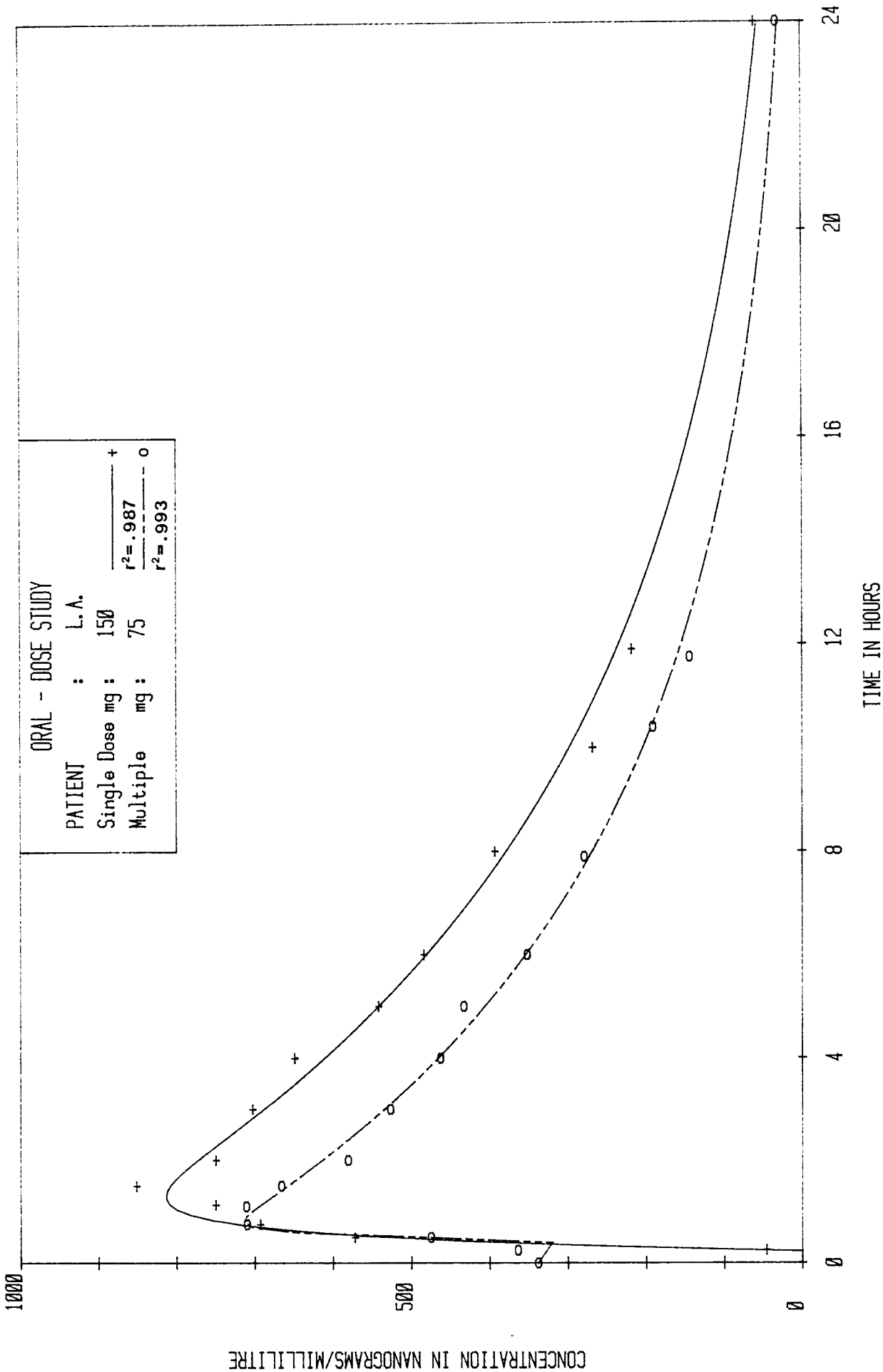
ORAL - DOSE STUDY
PATIENT : L.A.
Single Dose mg : 150
Multiple mg : 75
r²=.987
r²=.993
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.26.

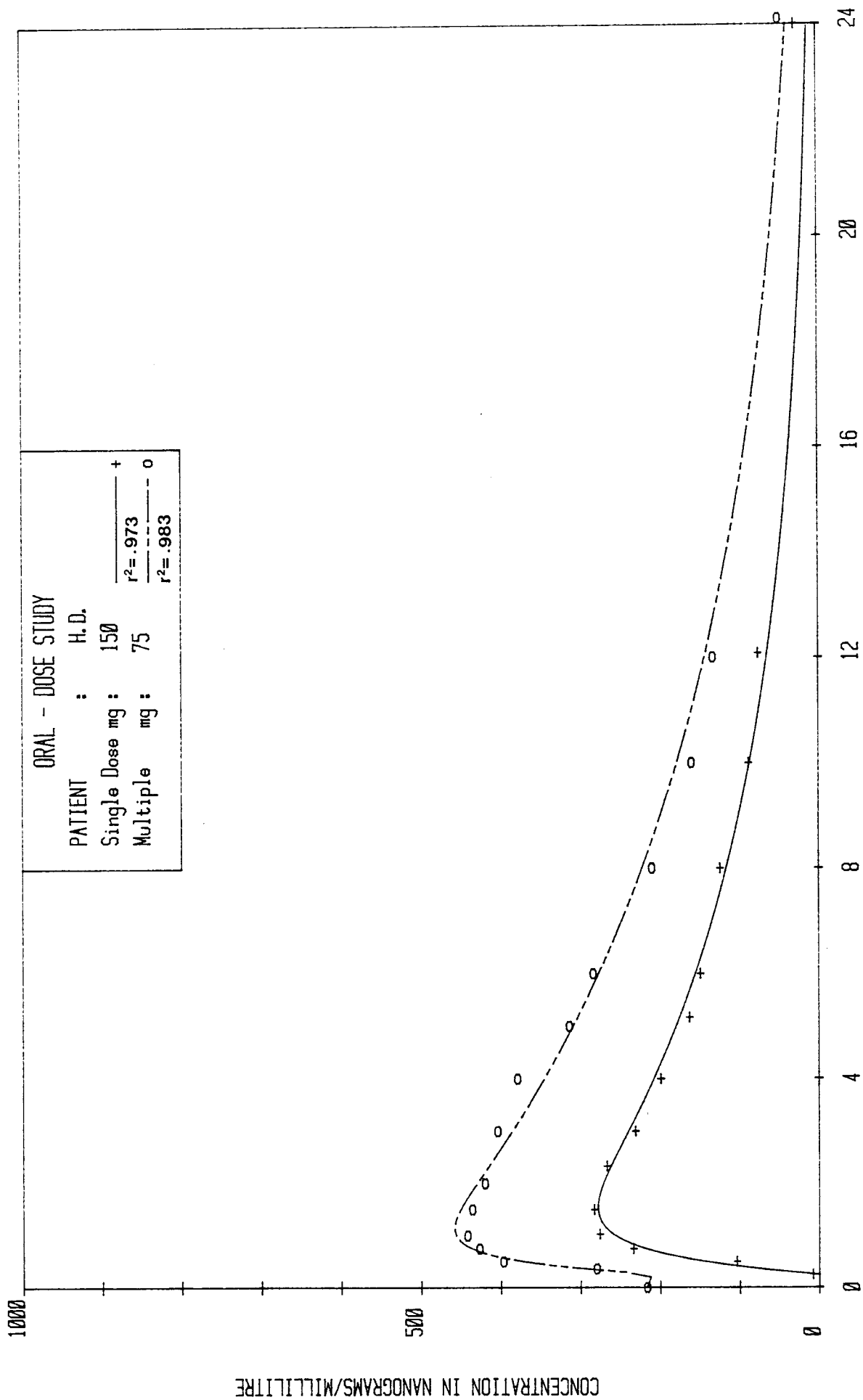
ORAL - DOSE STUDY
PATIENT : H.D.
Single Dose mg : 150
Multiple mg : 75
r²=.973
r²=.983
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.27.

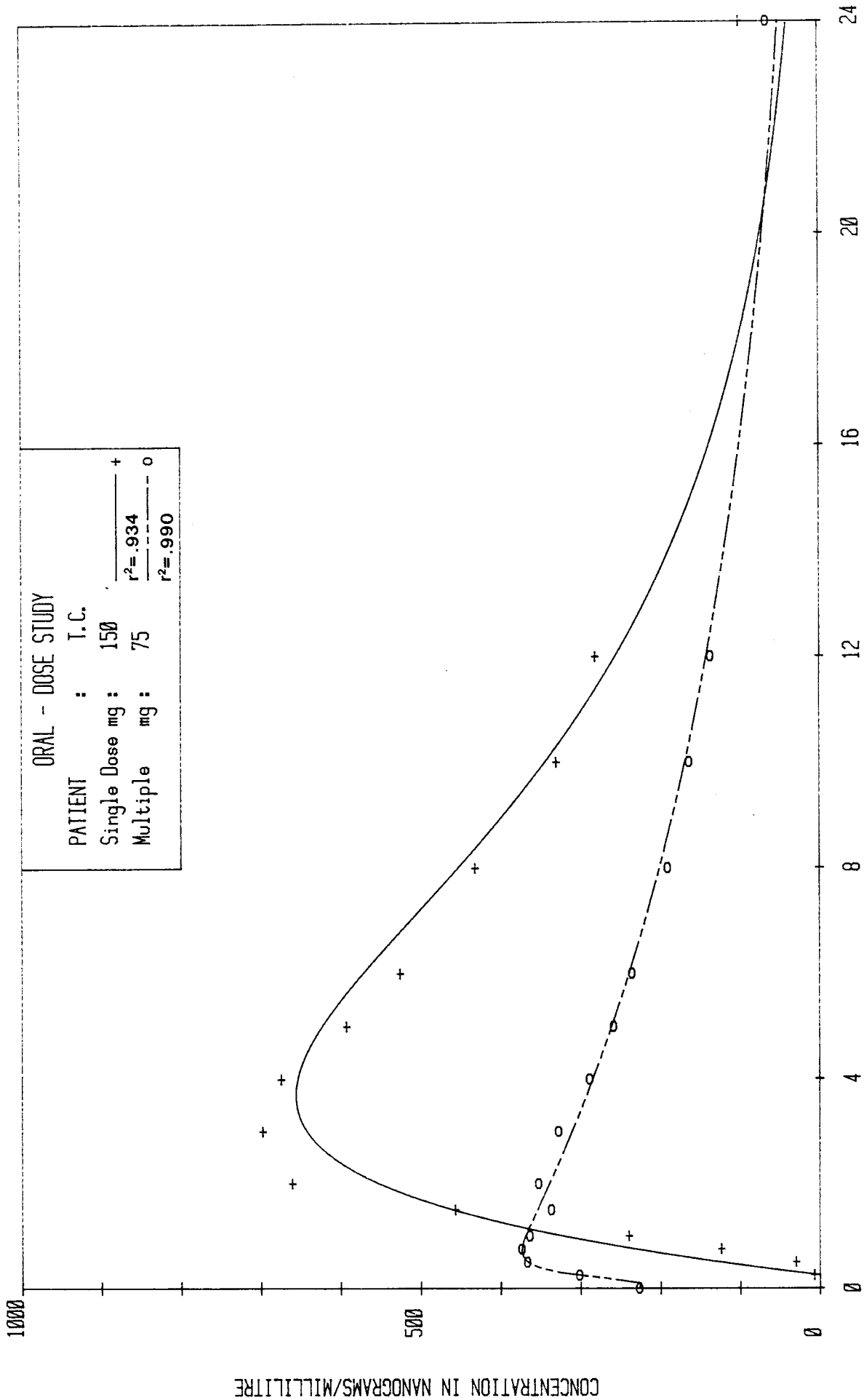
ORAL - DOSE STUDY
PATIENT : T.C.
Single Dose mg : 150 r²=.934
Multiple mg : 75 r²=.990
1000
500
0
0
4
8
12
16
20
24
TIME IN HOURS
CONCENTRATION IN NANOGRAMS/MILLILITRE

Figure 3.28.

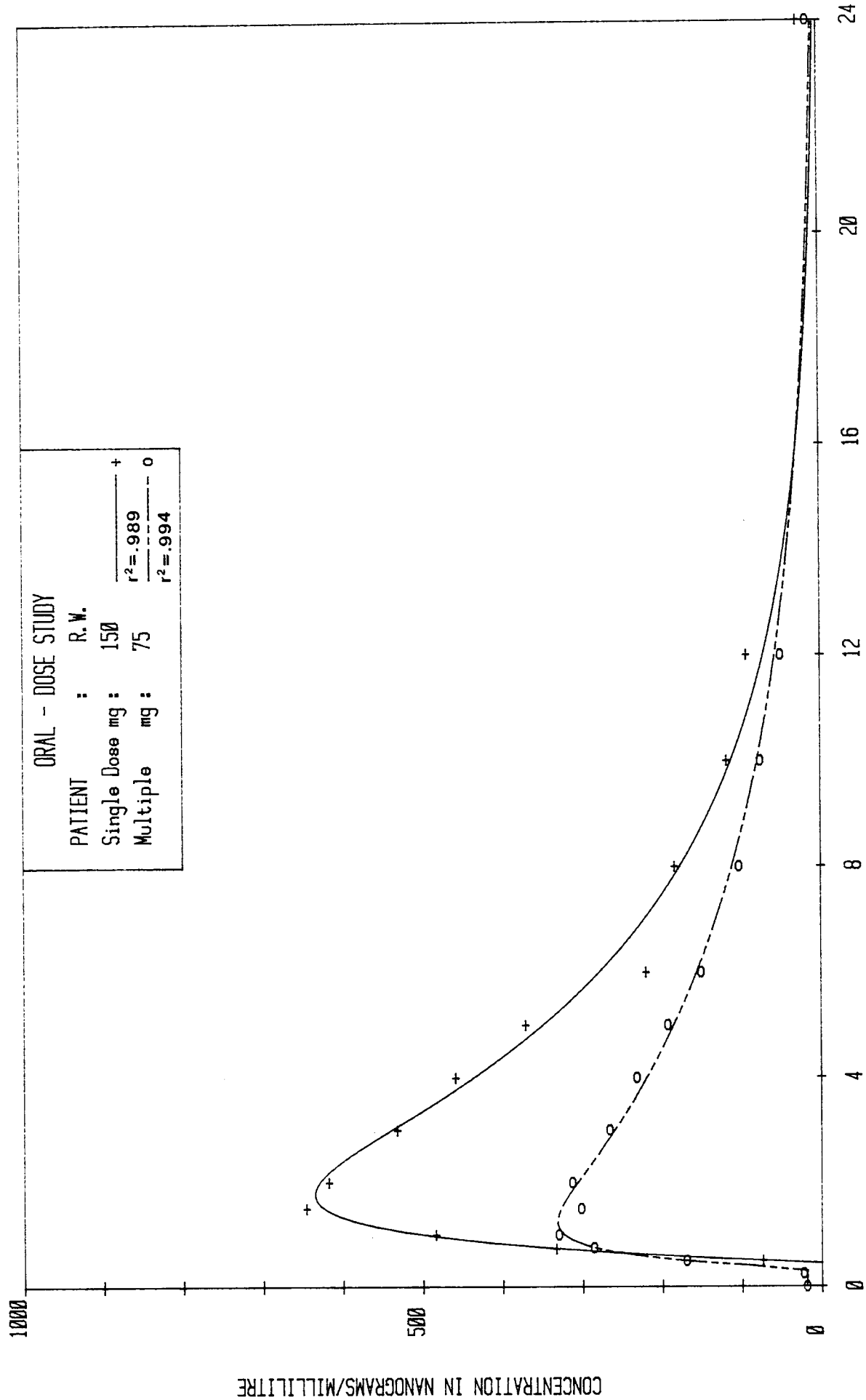
ORAL - DOSE STUDY
PATIENT : R.W.
Single Dose mg : 150
Multiple mg : 75
r²=.989
r²=.994
CONCENTRATION IN NANOGRAMS/MILLILITRE
TIME IN HOURS
1000
500
0
0
4
8
12
16
20
24

Figure 3.29.

of renal impairment as judged by creatinine clearance (r^2 = 0,157 after single-dosing and r^2 = 0,066 after multiple-dosing).

TABLE 3.34. AUC (single- and multiple-dose) for patients with renal failure.

Initials	Single-dose AUC (ng/ml.h)	Multiple-dose AUC[1] (ng/ml.h)
B.S.	4 147	3 137
J.Se.	10 270	13 664
L.A.	7 904	8 958
H.D.	2 673	6 776
T.C.	8 313	5 872
R.W.	4 286	3 914
median	6 095**	6 324**
	(1 844)	(2 108)
range	2 673-10 270	3 137-13 664
	(1 304-2 688)	(1 458-3 074)

** p <0,001
1 normalised for dose
( ) control values

In Figure 3.30 AUC is plotted against creatinine clearance for both patients with renal failure and those with normal renal function. There is a possibility that a hyperbolic relationship exists although the exact relationship could not be determined as no patients were studied in the moderate renal failure range (creatinine clearance 20-60 ml/min). However, AUC for the patients with renal failure was significantly different to that of patients with normal renal function after both single- (p <0,001) and after multiple-dosing (p <0,001). Since AUC is

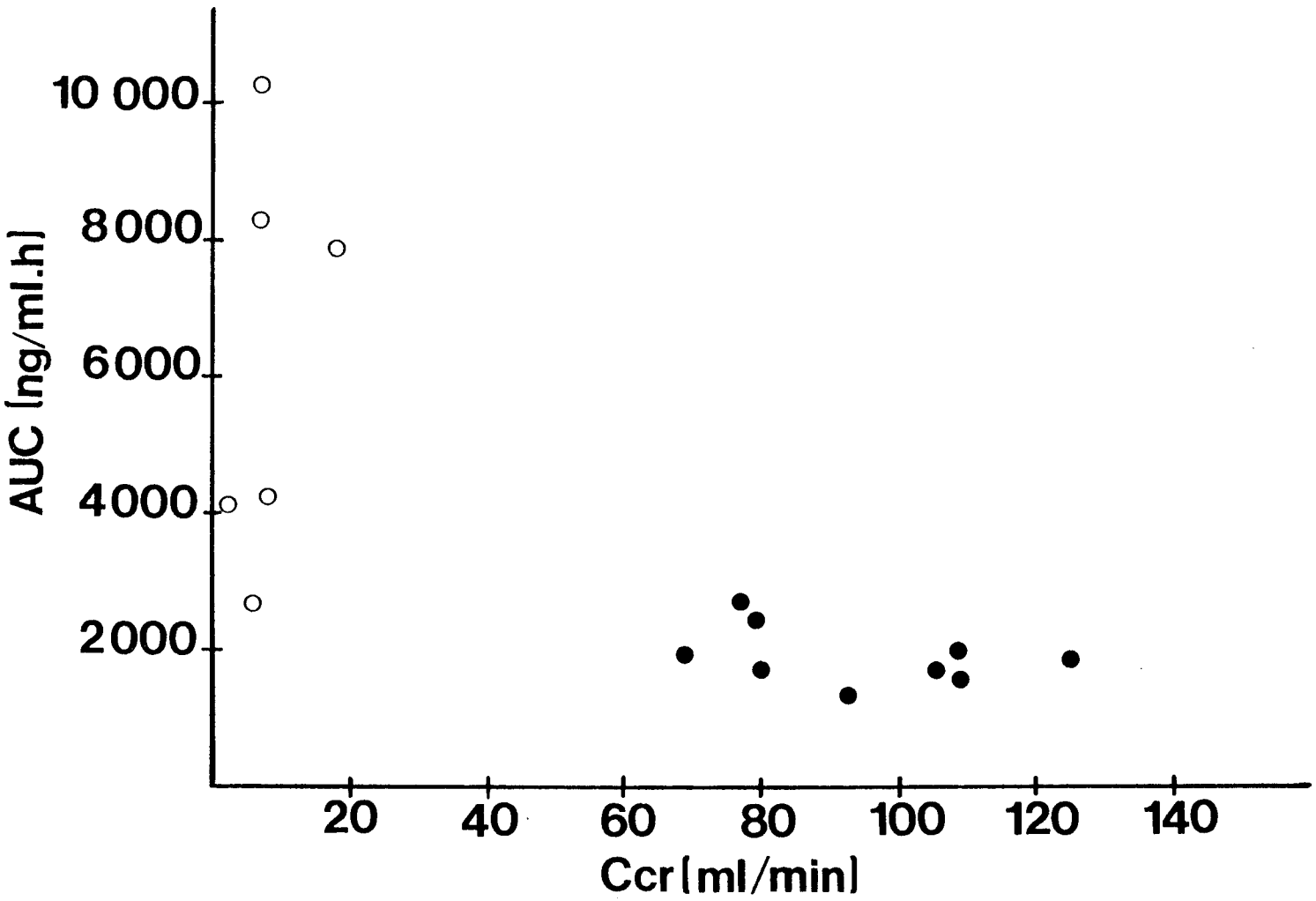

Figure 3.30. AUC vs creatinine clearance [Ccr] for patients with renal failure [○] and patients with normal renal function [●]

inversely proportional to clearance, it is assumed that this increase is due to decreased renal clearance of ranitidine.

The amount of ranitidine excreted unchanged in the 24-hour urine collection expressed as a percentage of dose for each patient after single- and multiple-dosing is shown in Table 3.35, together with the uncorrected creatinine clearance calculated from urine creatinine concentrations and creatinine clearance estimated from serum creatinine with a correction for age, sex and weight (Method 2, Lot and Hayton 1978). The latter creatinine clearance was used for calculations and figures. In the group of patients with renal failure, the amount of unchanged ranitidine in urine was significantly less than that found in the urine of patients with normal renal function ($p < 0,001$) with median values of 5 and 26% respectively. The pattern was similar after single- and multiple-dosing.

TABLE 3.35. Amount of ranitidine (% of dose) excreted in the urine in the 24 hours following dose; creatinine clearance calculated from urine ($C_{cr}(U)$) and creatinine clearance estimated from serum creatinine ($C_{cr}(S)$).

Initials	SINGLE-DOSE Ranitidine (%)	$C_{cr}(U)$ (ml/min)	$C_{cr}(S)$ (ml/min)	MULTIPLE-DOSE Ranitidine (%)	$C_{cr}(U)$ (ml/min)	$C_{cr}(S)$ (ml/min)
B.S.	1	4	2	1	3	6
J.Se.	16	4	7	9	5	6
L.A.	16	30	18	23	18	18
H.D.	2	5	6	12	5	5
T.C.	8	-	7	9	6	5
R.W.	2	4	8	0,4	2	6
median	5**	4	7	9**	5	6
	(26)	-	(100)	(24)	-	(89)
range	1-16	4-30	2-18	0,4-23	2-18	5-18
	(15-48)	-	(69-125)	(10-105)	-	(75-143)

** $p < 0,001$

In Figure 3.31 the amount of ranitidine excreted in the 24 hour urine collection, expressed as a % of dose is plotted against creatinine clearance for both groups of patients after single-dosing. It can be seen that within each group there is a wide variation which is not apparently related to creatinine clearance. However, when both groups are combined there appears to be a linear relationship (r^2 = 0,679, p <0,001) between amount of ranitidine in the urine and creatinine clearance.

Since neither AUC nor $t_{\frac{1}{2}}$ appears to be directly related to creatinine clearance in the patients studied, it is not possible to suggest making dosage adjustments based on creatinine clearance measurements as an index of renal function. In the present study the normal 150 mg dose was arbitrarily halved while maintaining a 12 hour dosage interval for the multiple-dose study in 5 of the 6 patients with renal failure. Plasma ranitidine levels remained above 100 ng/ml (the IC_{50} for acid inhibition in duodenal ulcer patients) for 8 hours in the 5 patients, with most exceeding this level for 12 hours. No untoward central nervous system changes were noted by the patient or the doctors. Blood biochemistry and haematology were monitored regularly in 4 of the 6 patients who remained in hospital for the week of the study. In 3 patients a rise in SGOT levels was noted and there was a rise in alkaline phosphatase levels in 3 patients although no other biochemical tests showed changed levels (Appendix II,Table A4).

Based on the half-life, a two-fold reduction in the 150 mg dose of ranitidine would give plasma levels comparable to those in patients with normal renal function. Prolonging the dosage interval from 12 to 24 hours might result in very low trough levels in patients such as R.W. and B.S. who have relatively small AUC's and trough levels of ranitidine despite very poor renal function.

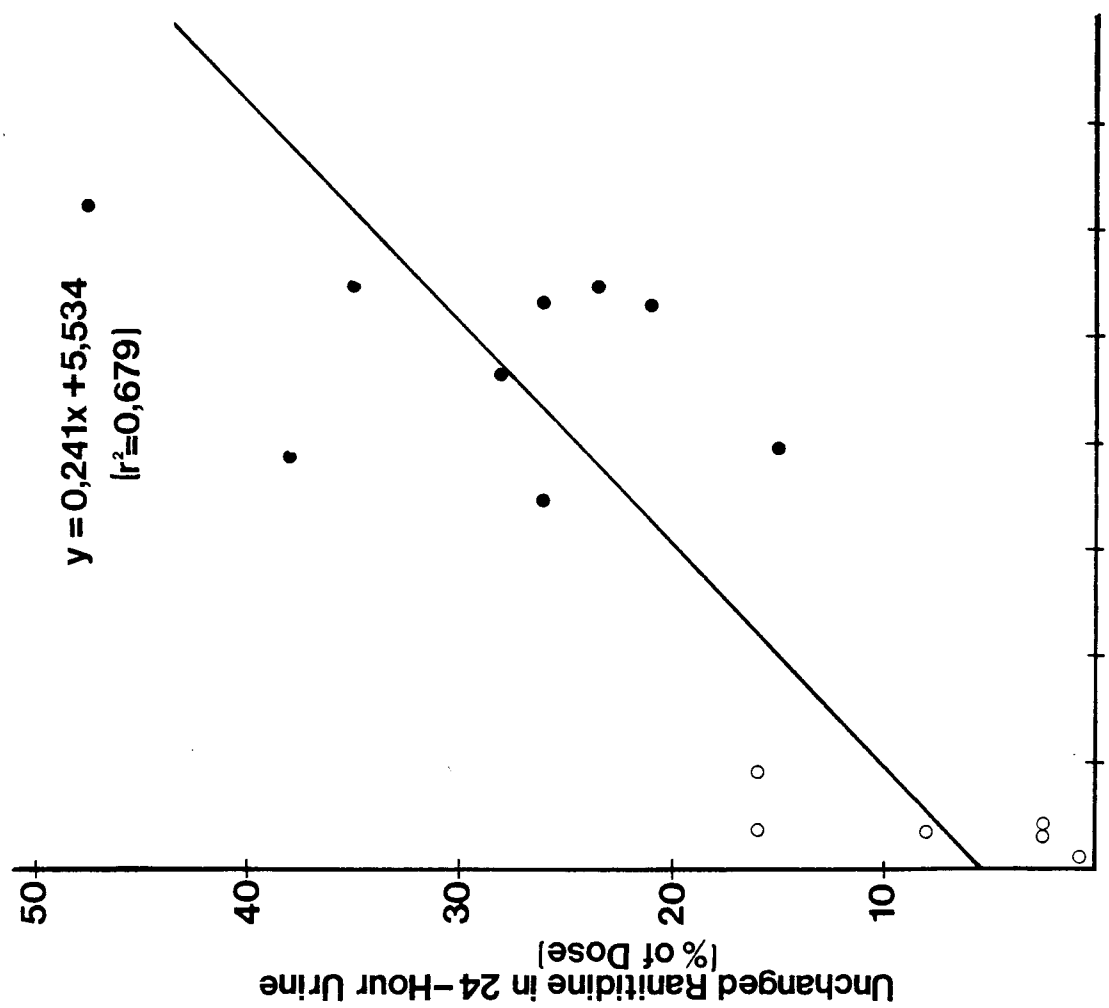

Figure 3.31 Unchanged ranitidine in 24-hour urine vs creatinine clearance in patients with renal failure(○) and with normal renal function (●)

3.3.2. Dialysance of ranitidine.

The 3 patients in this study received 150 mg ranitidine, orally, on one occasion only. Dialysis was commenced approximately 3 hours after administration of the ranitidine tablet. Blood samples were drawn approximately 3 hours after the commencement of haemodialysis and in two cases this was done at two flow rates (Table 3.36). Ranitidine is partially cleared by dialysis with a dialysance of 40 ml/min at a flow rate of 175 ml/min and 50 ml/min at a flow rate of 275 ml/min.

TABLE 3.36. Concentration into (Bi) and out of (Bo) dialyser, flow rate (Q_B), dialysance (Q_D) and times after dosage and from start of dialysis for 3 patients with chronic renal failure on chronic haemodialysis.

Initials	Bi (ng/ml)	Bo (ng/ml)	Flow rate Q_B (ml/min)	Dialysance Q_D (ml/min)	Time after dose (h)	Time from start of dialysis (h)
F.P.	566	463	275	50	6,0	2,83
	448	347	175	39	7,0	3,92
O.P.	567	466	275	49	5,9	2,67
	484	371	175	41	7,1	3,83
R.D.	380	304	250	50	6,0	2,75

CHAPTER 4

4. DISCUSSION

It is of importance that the pharmacokinetic behaviour of a drug is studied in the patient population that will ultimately receive the medication, as the absorption, distribution, metabolism or elimination of a drug may be altered by the disease state, thereby reducing therapeutic effects or increasing the likelihood of toxic effects. In the case of ranitidine, it is the ulcer patient or the patient at risk of developing ulcers who will receive the drug. It is likely that the elderly patient or the patient with renal dysfunction will be most at risk for development of adverse effects.

The present study encompasses a group of patients with duodenal ulceration who responded to ranitidine therapy, a subgroup who did not respond, and a small number of patients with advanced renal disease who did not have peptic ulceration. The results of these three groups will be discussed in that order.

In patients with duodenal ulceration ranitidine was rapidly absorbed, reaching peak levels within two hours in most cases. There was a trend for the peak to be reached earlier after multiple dosing. There was a lag time for absorption varying from nil to approximately half an hour and this tended to be a little shorter after multiple dosing. There was a wide range in the bioavailability of oral ranitidine (28-76% with a mean of 51%) when this was studied in 4 responders and 1 non-responder. This variation has similarly been described for cimetidine in peptic ulcer patients and was ascribed to the disease state (Somogyi et al 1980a). The findings for ranitidine are in agreement with the 49% (Woodings et al 1980) and 52% (Garg et al 1981) bioavailability reported for healthy volunteers, although in another study 81% bioavailability has been reported in healthy subjects (McNeil et al 1980). In the present study with oral ranitidine

relative bioavailability after single- and multiple-dose studies can be assessed by comparing the respective FD/V values. The dose remained constant and it was assumed that the volume of distribution of the drug remains constant in any individual. Thus, any change in FD/V is attributed to the fraction of the dose available systemically. There was a marginal increase in the median FD/V with multiple dosing compared with the same parameter after single dosing. This increase in rate and extent of absorption may in part be due to the more alkaline conditions present in the stomach and duodenum in patients receiving ranitidine. This might facilitate absorption of ranitidine which is a weak base. Another possible explanation is a contribution from the previous dose through enterohepatic recycling. In this study no evidence for recycling of ranitidine was found 12 hours after dosage. However, in another study, bioavailability and hepatic and renal clearance values for ranitidine in normal volunteers suggest a significant 'first-pass' metabolism following oral administration (Garg et al 1981).

The elimination half-life ($t_{\frac{1}{2}}$) of 135 minutes in the patients in this study after oral dosage corresponds with that reported for healthy volunteers (Garg et al 1981, McNeil et al 1980, Woodings et al 1980). The $t_{\frac{1}{2}}$ after intravenous (IV) administration was somewhat shorter, with a median of 61 minutes. A possible explanation is that the lack of sensitivity of the assay method did not allow the very low levels after 6 hours to be accurately measured after IV administration. In certain patients there appeared to be a very slow release from a deep compartment contributing to a longer $t_{\frac{1}{2}}$ after the higher oral dose.

It is interesting to note that although ranitidine has a $t_{\frac{1}{2}}$ only slightly longer than the 2 hours of cimetidine (Burland et al 1975, Griffiths et al 1977, Somogyi et al 1980a, Walkenstein et al 1978), it has a longer duration

of action with adequate control of 24-hour gastric acidity with a twice daily dosage schedule (Walt et al 1980, Walt et al 1981). This is borne out by clinical evidence of ulcer healing on a twice daily dose schedule (Barbier et al 1979, Langman et al 1980). In this respect ranitidine is similar to another new H_2-antagonist tiotidine (Kaojarern et al 1981).

Not only is the half-life of ranitidine similar to that of cimetidine but the volume of distribution of the central compartment and volume of distribution steady state for ranitidine in this study were very similar to values Somogyi et al found in a study of cimetidine pharmacokinetics in peptic ulcer patients (Somogyi et al 1980a). McNeil et al found a larger total volume of distribution of ranitidine in healthy volunteers than was found in this study (McNeil et al 1980). From the present study it appears that ranitidine distributes into two compartments with similar volumes of distribution to those of the two compartments of cimetidine. In one study of cimetidine a 3-compartment model gave the best fit for certain patients (Somogyi et al 1980a) and this may be the case with ranitidine although a 3-compartment model fit was not attempted.

The mean total body clearance of ranitidine was 680 ml/min in the 5 patients studied and this was in agreement with 709 ml/min found in healthy volunteers (Garg et al 1980, McNeil et al 1980). The clearance of cimetidine in peptic ulcer patients has been reported as 495 ml/min and this was age dependent (Somogyi et al 1980a).

A clear-cut relationship between age and ranitidine disposition such as that demonstrated for cimetidine (Somogyi et al 1980a) was not observed probably because of the small numbers and narrow age range of patients in this study. A surprising age-related increase in V_{dext}, V_{dss} and V_{darea} was shown but this was greatly influenced by one patient who happened to

be a non-responder and who therefore was possibly not truly representative of duodenal ulcer patients.

No correlation between creatinine clearance and half-life of elimination of ranitidine was found but total plasma clearance was related to creatinine clearance in the duodenal ulcer patients. The renal clearance of cimetidine is less strongly related to creatinine clearance than is expected (Somogyi et al 1980a) and ranitidine may be similar. In this study renal clearance was not calculated as 24-hour urine collections were made in only two cases after intravenous administration.

All the patients in this study had ranitidine administered together with food and the bimodal plasma concentration-time pattern seen with ranitidine (Woodings et al 1980) and cimetidine (Bodemar et al 1979, Somogyi et al 1980a, Walkenstein et al 1978) when administered on a fasting stomach was not observed.

Ranitidine and cimetidine effect similar healing rates and there are non-responders to ranitidine just as there are patients with cimetidine-resistant ulcers (Berstad et al 1980, Langman et al 1980). The multiple-dose pharmacokinetic pattern was studied in non-responders in order to see if this pattern differed from responders. The degree of inhibition of gastric acid in response to ranitidine was not studied in either group. In two drug trials of a total of 130 patients only 7 patients who did not respond to treatment were considered sufficiently compliant and accordingly qualified for inclusion as non-responders (Section 2.2.). Fasting serum gastrin levels in all 7 of these patients were within normal limits, ruling out the Zollinger-Ellison syndrome as the cause of the lack of response.

Three of the 6 non-responders in whom gastric acid secretion studies were carried out had high basal and maximal acid output compared with the 10 responders. In addition, two of these had relatively low plasma levels,

AUC and FD/V values. This seems to indicate that the standard ranitidine dosage of 150 mg twice daily may not be adequate for the control of acid in some patients. The lack of response in the other patients cannot be as simply explained. Non-responders as a group did not differ significantly from responders with respect to any of the pharmacokinetic parameters besides the half-life which was unexpectedly longer in non-responders. Non-responders tended to be older and to smoke more than responders. The five patients with plasma levels comparable to responders were of Asiatic origin.

There are a few reports in which investigators attempted to find the reason for lack of response to H_2-antagonists. There is a single case report where acid secretion was unaffected by cimetidine treatment despite adequate plasma levels (Kisloff 1980). In another cimetidine study it was observed that patients with lower pretreatment rates of gastric acid secretion had a higher incidence of ulcer healing and patients with ulcers which healed, had a lower mean peak acid output than those whose ulcers had not healed. It was suggested that the standard cimetidine dose was inadequate in patients with higher secretory rates (Binder et al 1978). In a study of duodenal ulcer patients, Rune et al found that a group of patients with a low sensitivity to cimetidine and a high maximum acid output improved more slowly than other patients (Rune et al 1979). It appears that some patients require higher doses and possibly longer treatment periods than others. Wormsley et al have identified two subgroups of non-healing patients - one group in which acid secretion is not adequately suppressed by standard doses of ranitidine, and another group in which residual duodenal ulceration was present despite complete suppression of gastric secretion. They found the former group to have increased ulcer healing when the dose was increased to 300 mg twice daily while the latter were healed by the addition of a drug

such as carbenoxolon to the regime (Wormsley et al 1981). It is therefore important to carry out gastric secretory studies of H_2-antagonist treatment failures in order to treat them correctly. Five of the 7 non-responders in the present study were subsequently treated surgically and the remaining two are at present being considered for surgery.

The incidence of peptic ulceration occurring in conjunction with renal failure may range from 0 to 20% and there is a marked increase (of up to 50%) when patients undergo chronic haemodialysis (Wormsley 1980). It can therefore be anticipated that ranitidine will be administered to patients in renal failure. Ranitidine, like cimetidine, is excreted primarily unchanged by the kidney (Bell et al 1980) and it is therefore expected to accumulate when renal function is impaired.

In the present study the pharmacokinetics of ranitidine in advanced renal failure (creatinine clearance below 25 ml/min) were compared with those in duodenal ulcer patients with normal renal function (creatinine clearance above 60 ml/min) in order to minimize toxicity which may occur due to accumulation of the drug. At present there is no published information concerning the overall elimination rate constant of ranitidine, its $t_{\frac{1}{2}}$ and the relationship to glomerular filtration rate.

The absorption of ranitidine in uraemic patients does not differ from absorption in the patients with normal renal function in this study. Bioavailability, as assessed by FD/V, which is independent of elimination, did not differ significantly between the two groups.

However, there were highly significant differences in the 12-hour minimum concentrations, elimination rate constants (and consequently $t_{\frac{1}{2}}$) and in the areas under the curve (AUC) with very little overlap in any of these parameters between the two groups.

No linear relationships between the degree of renal failure, using creatinine clearance as a measure, and half-life could be found. Similarly AUC could not be related to creatinine clearance within the renal failure group. The probable reason for this lack of correlation is that endogenous creatinine clearance is of questionable value in patients with severe kidney disease (Dettli 1976). The possible relationships between creatinine clearance and parameters such as $t_{\frac{1}{2}}$ and AUC could not be determined overall as there was no overlap between the two groups with respect to creatinine clearance. It is possible that the relationship is hyperbolic with AUC and $t_{\frac{1}{2}}$ increasing dramatically only when creatinine clearance is below 20 ml/min.

Since the relationship between accumulation of ranitidine and renal function could not be determined, it is not possible to draw up a nomogram for dosage adjustment based on creatinine clearance.

The median $t_{\frac{1}{2}}$ in the patients with advanced renal failure in my study is twice that of the group with normal renal function and AUC was three times larger in patients with renal failure. I would suggest a decrease in dosage to 75 mg ranitidine administered twice daily in patients with advanced renal failure (creatinine clearance below 25 ml/min) without altering the already long 12-hour dosage interval to lessen fluctuations in ranitidine concentrations in the body.

Ranitidine was well tolerated in all the patients studied, including the small sample of patients with severe renal failure. I assumed that ranitidine would behave in a similar manner to cimetidine in renal failure and therefore halved the standard 150 mg ranitidine dose for chronic treatment of patients with renal failure. Despite an approximate 5-fold higher trough level (12 hours) found in these patients on reduced dosage no side effects were noted.

No gastric secretory studies were performed on patients with renal failure and it is impossible to assess whether plasma concentrations obtained were associated with inhibition of gastric acid secretion. Assuming comparable effects on gastric acidity with those in patients with normal renal function, the plasma ranitidine concentrations obtained with 75 mg ranitidine are more than adequate.

Within the group of patients with renal failure there was a wide inter-individual variation in drug concentrations, $t_{\frac{1}{2}}$ and AUC which bore no direct relationship to the degree of renal failure. Two patients with advanced renal failure excreted less than 2% of the dose as unchanged ranitidine in urine but had the smallest areas under the curve, and another patient with creatinine clearance of 18 ml/min who excreted 16% of dose as unmetabolised ranitidine had a relatively large AUC. These differences may reflect variation in the apparent volume of distribution of ranitidine or perhaps an alternative ranitidine excretory pathway may be utilised in younger patients whose other organs such as the liver may be better able to cope with drug detoxification. Schentag et al have reported that cimetidine trough concentrations were consistently raised only in those patients with serious impairment of both renal and liver function (Schentag et al 1977). Cimetidine and ranitidine undergo oxidation (Bell et al 1980, Burland et al 1975b) and in renal failure oxidation reactions are for the most part normal (Reidenberg and Drayer 1980). It would therefore not be surprising if in certain patients metabolism by the liver may compensate for the renal impairment to some extent.

On the basis of the present study, it is not possible to make precise dosage recommendations for ranitidine administration in renal failure. Until further studies are carried out which establish the overall body clearance of ranitidine and ranitidine renal clearance over the whole

range of renal decompensation, halving of the standard 150 mg ranitidine dose would seem advisable, bearing in mind the individual variation. Ideally there should be individualization of dose in these patients based on monitoring of drug plasma levels.

In this study ranitidine was found to undergo limited dialysis (50 ml/min). An additional dose at the end of the period of haemodialysis would seem unnecessary although a standard 150 mg dose on the morning of a day on which haemodialysis is carried out, may be useful.

APPENDIX I

Abbreviations:

GSH - Groote Schuur Hospital

KE - King Edward VIII Hospital, Durban

NSH - New Somerset Hospital, Green Point

BAO - Basal acid output

MAO - Maximal acid output

PAO - Peak acid output

CASE HISTORIES

A. PATIENTS WITH CHRONIC DUODENAL ULCERATION

No. 1

INITIALS AND FOLDER NUMBER: J.H. 12199705 (GSH)

AGE: 25 years

SEX: male

WEIGHT: 70 kg

OCCUPATION: security guard

DIAGNOSIS: duodenal ulceration

PAST ILLNESSES:
1975: Duodenal ulcer diagnosed on barium meal, treated with antacids.
1977: Recurrence of epigastric pain with vomiting and loss of weight. Endoscopy showed a deformed duodenum with a healed duodenal ulcer.
1978: June. Epigastric pain and vomiting. Treatment with antacids.
August. Repeat endoscopy showed a deformed pylorus and in the duodenum a small area posteriorly with a healed scar and surrounding duodenitis. Treated with antacids.

FAMILY HISTORY: One brother with peptic ulceration. No other significant family history.

PRESENT ILLNESS (November 1979):
Presented to the Gastrointestinal Clinic with recurrence of epigastric pain which had been severe for the previous week. He also had sinusitis which was being treated with tetracyclines.
Endoscopy: deformed pylorus and duodenum with an 0,8 cm superior superficial duodenal ulcer just behind the pylorus.
Pentagastrin stimulated gastric secretory study: BAO 2,6 meq/h, MAO 16,2 meq/h.

RESPONSE TO RANITIDINE (December 1979):
The patient responded symptomatically within one day of the initiation of treatment. After 28 days' treatment follow-up endoscopy showed the duodenum to be scarred and hyperaemic. On the anterior aspect of the greater curve, duodenitis and a long linear scar were noted. The patient was placed on the maintenance study of ranitidine.
No adverse effects of ranitidine were noted.

CONCOMITANT MEDICATION:
Tetracyclines: 250 mg four times daily were prescribed for 7 days on two occasions coinciding with the single- and multiple-dose pharmacokinetic studies.

No. 2

INITIALS AND FOLDER NUMBER: T.W. 62416626 (GSH)

AGE: 42 years

SEX: male

WEIGHT: 47,5 kg

OCCUPATION: unemployed

DIAGNOSIS: chronic duodenal ulceration

PAST ILLNESSES:
1963: From this time onwards chronic dyspepsia.
1979: Patient had complained of nausea and vomiting for several years. In addition he had had a burning sensation in the upper abdomen, unrelated to meals, and a poor appetite. He was treated with antacids and in 1978 with cimetidine.
A barium meal examination showed a deformation of the first part of the duodenum and an active ulcer. Treatment was given with metoclopramide and "Mucaine" (aluminium hydroxide, oxethazaine and magnesium hydroxide).

FAMILY HISTORY: No significant family history.

PRESENT ILLNESS (November 1979):
Despite the above medication there was no abatement of symptoms over the previous two months.
Endoscopy: Stomach showed two small areas of gastritis on the greater curve (possibly related to medication) and a deformity of the pyloric antrum. The pylorus was patent. A small shallow duodenal ulcer was noted superiorly.
Pentagastrin stimulated gastric secretory study: BAO 2,4 meq/h, MAO 27,8 meq/h.

RESPONSE TO RANITIDINE (December 1979):
The symptoms abated but did not disappear over the first two weeks. Endoscopy at four weeks revealed a small linear scar on the anterior duodenal wall. A duodenal diverticulum was noted.
No adverse effects were noted.

No. 3

INITIALS AND FOLDER NUMBER: A.d.S. 52340130 (GSH)

AGE: 26 years

SEX: male

WEIGHT: 69 kg

OCCUPATION: mechanic's assistant

DIAGNOSIS: chronic duodenal ulceration

PAST ILLNESSES:

1977: Epigastric pain not related to meals. This had recurred off and on over a number of years but had been more noticeable in the previous two years.
Barium meal examination showed a central crater in the duodenum.
Treatment was with antacids with a good response.

1978: Symptoms returned and were treated with antacids and propantheline.

FAMILY HISTORY: No significant family history.

PRESENT ILLNESS (March 1980):

The symptoms had been present for a year but were more severe in the previous week. The pain was worse when the patient was hungry and at night.
Endoscopy: The duodenum was deformed with a 1,0 x 0,6 cm ulcer on the anterior aspect of the greater curve of cap which was oedematous with erosive duodenitis surrounding it.
Pentagastrin stimulated gastric secretory study: BAO 2,4 meq/h, MAO 26,4 meq/h.

RESPONSE TO RANITIDINE (April 1980):

Endoscopy 28 days after initiation of treatment showed evidence of ulcer healing but erosions were noted at the previous ulcer site. There was duodenitis of the anterior wall and two new erosions of the roof of the duodenum.
The patient complained of tiredness, possibly attributable to medication, but there were no other adverse effects.

No. 4

INITIALS AND FOLDER NUMBER: M.S. 55220636 (GSH)

AGE: 26 years

SEX: male

WEIGHT: 50 kg

OCCUPATION: unemployed

DIAGNOSIS: chronic duodenal ulceration

PAST ILLNESSES:
Epigastric pain and nausea intermittently for several years.
1980: February. Epigastric pain; barium meal showed a marked pyloric spasm and deformity of the duodenal cap.

FAMILY HISTORY: No significant family history.

PRESENT ILLNESS (March 1980):
Epigastric pain, nausea and haematemesis two nights prior to present visit. Right-sided chest pain with coughing and breathing had developed. The latter was attributed to bronchitis, and tetracyclines were prescribed.
Endoscopy: Mild gastritis with fundal erosions. The pylorus was deformed and oedematous. There was an ulcer crater just inside the pylorus, 0,5 cm in diameter, post-inferiorly.
Pentagastrin stimulated gastric secretory study: BAO 3,2 meq/h, MAO 25,5 meq/h.

RESPONSE TO RANITIDINE (April 1980):
Endoscopy: normal stomach and pylorus with a scar in the duodenal cap.
No adverse effects to ranitidine were noted.

CONCOMITANT MEDICATION:
Tetracyclines 250 mg 4 times daily for 7 days after initiation of ranitidine therapy.

No. 5

INITIALS AND FOLDER NUMBER: S.M. 54606942 (GSH)

AGE: 31 years

SEX: male

WEIGHT: 57 kg

OCCUPATION: gardener

DIAGNOSIS: chronic duodenal ulceration

PAST ILLNESSES:

1978: The patient had a duodenal ulcer which was treated with cimetidine.

1979: On endoscopy the patient was found to have a polyp in the stomach as well as gastritis.
In the duodenum there was a superficial ulcer 0,4 cm in size in the base of the cap. This was treated with antacids.

FAMILY HISTORY: There is no history of ulcer disease in the family.

PRESENT ILLNESS (March 1980):

The patient presented with continuous epigastric pain which was not relieved by antacids.
Endoscopy: There was a swollen pre-pyloric fold, inferiorly. In the duodenum there was an 0,4 cm ulcer at the beginning of the second part.

RESPONSE TO RANITIDINE (April 1980):

The patient responded symptomatically within 7 days of initiation of therapy.
Endoscopy: The ulcer was healed but erosions were present.
Six months later while the patient was on maintenance ranitidine therapy, he returned for a bioavailability study when ranitidine was administered intravenously in a dose of 20 mg. An ECG was done after administration of the drug: rate 65, sinus rhythm, occasional ventricular premature systole beats, PR = 0,16 secs, normal axis, voltage changes of left ventricular hypertrophy.
No untoward effects were noted while he was treated with ranitidine.

No. 6

INITIALS AND FOLDER NUMBER: D.F. 57465502 (GSH)

AGE: 23 years

SEX: male

WEIGHT: 48 kg

OCCUPATION: machinest

DIAGNOSIS: chronic duodenal ulceration

PAST ILLNESSES:
A two year history of epigastric pain, nausea and occasional vomiting after meals. These symptoms were usually relieved by antacids.
1980: April. Symptoms became more severe.
Barium meal examination showed a grossly deformed duodenal cap and an ulcer crater with radiating folds.

FAMILY HISTORY: No significant family history.

PRESENT ILLNESS (May 1980):
Endoscopy: The pylorus was narrowed and the duodenum was deformed and hyperaemic. An oval ulcer, 0,4 by 0,8 cm, was seen on an oedematous mound in the anterior aspect of the cap.

RESPONSE TO RANITIDINE (June 1980):
The patient became asymptomatic within one week.
Endoscopy done 4 weeks after initiation of therapy showed coffee grounds in the fundus and antrum. In the duodenum an oedematous mound was noted in the roof of the cap with an erosion on top of it.

No. 7

INITIALS AND FOLDER NUMBER: P.d.J. 55627772 (GSH)

AGE: 24 years

SEX: male

WEIGHT: 50 kg

OCCUPATION: clerk

DIAGNOSIS: bleeding duodenal ulcer

PAST ILLNESSES:
1973: He had had a barium meal and barium enema with negative results.
1974: Operation for haemorrhoids.
1979: Repeat operation for haemorrhoids.
The patient had suffered from frequent headaches over a number of years for which he had taken salicylates.

FAMILY HISTORY: No family history of peptic ulcer disease.

PRESENT ILLNESS (July 1980):
The patient presented with epigastric pain unrelated to meals but which was worse in the morning. There was no improvement with antacids. Patient had noticed a melaena stool two weeks prior to admission and again immediately prior to admission. No haematemesis was noted.
A barium meal examination showed a 0,75 cm ulcer crater in the duodenal bulb.
Endoscopy: Blood-stained fluid was noted in the stomach and in the duodenum two ulcers - a 1,0 cm ulcer on the posterior curve and a 0,6 cm ulcer on the floor of the anterior wall.
Alkaline phosphatase levels were slightly raised.

RESPONSE TO RANITIDINE (August 1980):
Endoscopy: After 28 days' ranitidine therapy there was complete healing of the posterior wall ulcer with a pit and two peripheral ulcers remaining. The anterior ulcer was now a large shallow erosion. The patient was asymptomatic.
The patient was at that stage given 20 mg ranitidine intravenously for a pharmacokinetic study without ill effect.

No. 8

INITIALS AND FOLDER NUMBER: W.M. 54127576 (GSH)

AGE: 34 years

SEX: male

WEIGHT: 64,5 kg

OCCUPATION: unemployed seaman

DIAGNOSIS: chronic duodenal ulceration

PAST ILLNESSES:
1965: Pulmonary tuberculosis.
1978: Patient complained on a number of visits to the hospital of low backache which may have been related to a fall a few months earlier. X-ray did not reveal anything wrong.

FAMILY HISTORY: No significant family history.

PRESENT ILLNESS (July 1980):
1980: August. The patient complained of severe epigastric pain over the previous ten days, particularly related to meals. This was apparently brought on by a heavy bout of alcohol. Barium meal examination showed prominent duodenal ulcer. Endoscopy: Some deformity of the antrum was noted. In the duodenum there was a 0,8 cm ulcer on big fold in the roof of cap, which was oedematous and hyperaemic. Blood chemistry: Raised gamma glutamyl transpeptidase was probably related to alcohol.

RESPONSE TO RANITIDINE (August 1980):
After treatment the patient felt much better. Endoscopy: The duodenum showed a swollen fold with duodenitis and an ulcer scar on posterior wall side of roof. This patient received an intravenous dose of 20 mg ranitidine with no ill effect. An ECG done after administration of the drug was normal. The gamma glutamyl transpeptidase levels were normal at the end of 4 weeks' treatment with ranitidine.

No. 9

INITIALS AND FOLDER NUMBER: A.O. 58016478 (GSH)

AGE: 42 years

SEX: male

WEIGHT: 73 kg

OCCUPATION: unemployed

DIAGNOSIS: active duodenal ulcer disease

PAST ILLNESSES:

1980: The patient had a four month history of dyspepsia. July. On barium meal examination the duodenum was not adequately visualized and a duodenal ulcer could not be excluded.

FAMILY HISTORY: No gastrointestinal disease in the family.

PRESENT ILLNESS (August 1980):

The patient had symptoms of post-prandial epigastric pain with pain at night. Antacids gave moderate relief of pain. There was loss of appetite.
Endoscopy: A swollen circumferential fold with a 0,6 x 0,4 cm ulcer at its base was seen in the duodenum.

RESPONSE TO RANITIDINE (September 1980);

The patient responded symptomatically.
Endoscopy: The duodenum was deformed. The mucosa tended to pit of anterior wall on the greater curve. There were multiple small erosions at the site of the ulcer.

No. 10

INITIALS AND FOLDER NUMBER: D.S. 610087 (GSH)

AGE: 36 years

SEX: male

WEIGHT: 94 kg

OCCUPATION: works in the medical school animal house

DIAGNOSIS: chronic duodenal ulcer disease

PAST ILLNESSES:
There is a longstanding history of duodenal ulceration.
1971: There was a duodenal ulcer presenting as a melaena which was treated with antacids.
1976: Barium meal examination showed a duodenal ulcer crater in the duodenal cap with accompanying deformity.
1977: The patient took part in a cimetidine trial. A 0,4 x 0,4 cm duodenal ulcer healed when treated with cimetidine.
1979: The patient presented with epigastric pain and a burning sensation. On endoscopy a 0,4 cm duodenal ulcer with duodenitis was seen. He was treated with cimetidine and antacids.
The patient had a moderate to heavy intake of alcohol.

FAMILY HISTORY: Mother was diabetic but no history of gastrointestinal disease in the family.

PRESENT ILLNESS (September 1980):
The patient had a recurrence of symptoms with hunger pains and flatulence.
Endoscopy: A 0,3 cm duodenal ulcer in the roof of cap with surrounding duodenitis was seen.

RESPONSE TO RANITIDINE (October 1980):
The patient became asymptomatic soon after starting ranitidine therapy.
Endoscopy: After 4 weeks' ranitidine treatment, the duodenum was deformed with radiating folds from the area of the previous ulcer.
The patient received an intravenous dose of 20 mg ranitidine on one occasion. The drug was well tolerated with no change in blood pressure or pulse rate. An ECG done at this stage showed voltage changes indicative of left ventricular hypertrophy.

CHRONIC DUODENAL ULCER PATIENTS (NON-RESPONDERS)

No. 11

INITIALS AND FOLDER NUMBER: J.S. 56670052 (GSH)

AGE: 52 years

SEX: male

WEIGHT: 66 kg

OCCUPATION: supervisor at a meat factory

DIAGNOSIS: duodenal ulceration, polycythaemia vera

PAST ILLNESSES:

1974: Since 1974 the patient has had dyspepsia with classical periodicity. Discomfort occurred up to half an hour after meals and was relieved by vomiting and alkalis.

1979: There was a two year symptom-free period until the current episode of severe epigastric pain which was unrelated to meals and was worse when he lay on his right side. He had three episodes of melaena but no haematemesis. The patient was a heavy drinker (up to a bottle of wine per day) up until a few months prior to admission.

FAMILY HISTORY: One sister suffers from duodenal ulcer disease.

PRESENT ILLNESS: (January 1980)

The patient did not respond to conservative therapy. An endoscopy in November 1979 showed a swollen and closed pylorus while the duodenum was oedematous and deformed. There was a large ulcer 0,8 cm in diameter, inferior to the duodenal cap. The patient was entered into the ranitidine trial.

In March 1980 the patient was still symptomatic and on endoscopy an ulcer was still present (0,4 cm on floor of cap just immediately distal to the pylorus) despite two months of ranitidine treatment. A detailed pharmacokinetic study was performed and it was found that the plasma levels of ranitidine were relatively low. The dose was therefore increased from 150 to 300 mg twice daily.

Two weeks later the patient was admitted to hospital because of raised liver enzymes thought to be related to an alcoholic binge, which soon returned to normal. A liver scan revealed slight hepatomegaly with no intra-hepatic focal lesions. The spleen was slightly enlarged on posterior view.

Gastric secretion test: BAO 16,5 meq/h, MAO 45,9 meq/h.

Gastrin: 12,2 pg/ml.

Chest X-ray: mild hyperinflation.

There was a raised haemoglobin of 18,8 g/dl but no other features of polycythaemia vera.

After one month of high dose ranitidine treatment, endoscopy showed that the duodenum was deformed and there was mild duodenitis, but the ulcer was healed and a linear scar remained. The deformity had improved.
The patient subsequently had a recurrence of the ulcer and was treated with sucralphate with some temporary improvement. When symptoms again became severe, he was treated with cimetidine. This was not effective and the patient was later sent for surgery.

No. 12

INITIALS AND FOLDER NUMBER: R.L. 56240591 (GSH)

AGE: 50 years

SEX: male

WEIGHT: 67 kg

OCCUPATION: cleaner

DIAGNOSIS: chronic duodenal ulceration

PAST ILLNESSES:

There was a longstanding history of peptic ulcer disease.

1977: He was treated at Somerset Hospital for duodenal ulceration.

1979: He was again treated at Somerset for the same complaint.

1980: The patient complained of weakness and stiffness in the arms and legs. This was diagnosed as cervical spondylosis with compression. He was operated on for this condition in August. A decompressive cervical laminectomy was carried out.

FAMILY HISTORY: No significant family history.

PRESENT ILLNESS (April 1980):

The patient was referred to the Gastrointestinal Clinic because of recurrent epigastric pain.
Endoscopy: The patient was found to have a duodenal ulcer in the superior position with anterior erosions and duodenitis.
Acid test: BAO 12,2 meq/h. MAO 54,9 meq/h.

RESPONSE TO RANITIDINE:

1980: May. On endoscopy one prepyloric ulcer erosion was seen and also an ulcer 0,5 x 0,3 cm in the roof of the duodenal cap. There were surrounding duodenal erosions and erosions on the anterior wall.

1980: June. The endoscopy showed a deformed pylorus and cap with a small 0,3 x 0,1 cm ulcer on roof and duodenitis at one edge. Fasting serum gastrin levels were normal.

1980: July. On repeat endoscopy a superior 0,4 cm ulcer with deformity and duodenitis were seen.
At this stage it was decided to increase the ranitidine dose from 150 mg twice daily to 300 mg twice daily. The patient did not return for his next appointment and was not seen until hospitalized for the laminectomy operation.

1980: September. The patient was then brought back for a pharmacokinetic study following 20 mg ranitidine given intravenously. This study was completed without problems except that the patient complained of epigastric pain. He had an endoscopy at this point and was again found to have a large duodenal ulcer. He was treated with cimetidine.

1980: October. The duodenal ulcer persisted and surgery has now been considered.

No. 13

INITIALS: D.S. (KE)

AGE: 56 years

SEX: male

WEIGHT: 72 kg

OCCUPATION: worker in sweet factory

DIAGNOSIS: duodenal ulceration, diabetes mellitus.

FAMILY HISTORY: no significant family history

PAST ILLNESSES:
Diabetes mellitus.
Five year history of recurring dyspepsia.

PRESENT ILLNESS:

1979: October. Patient presented to the clinic with symptoms of nausea and vomiting which had worsened over the previous 3 months.
Endoscopy showed a small antral nodule which was biopsied. A single deep anterior duodenal ulcer was noted. The patient was treated with placebo for 28 days.
Endoscopy after 28 days showed gastritis and a single deep duodenal ulcer. Patient then started ranitidine therapy.

1979: November. An endoscopy showed stomach and oesophagus to be normal but multiple flat ulcers were noted in the duodenum. Another 1 month course of ranitidine was prescribed.

1980: January. Patient complained of slight epigastric pain. Endoscopy showed area of flat ulceration on a broad ridge.

1980: April. Ranitidine was discontinued and treatment with colloidal bismuth subcitrate was initiated.

1980: May. The patient was much improved although endoscopy still showed ulceration.

1980: June. Endoscopy showed scanty ulcers.

1981: March. In the intervening months the patient was treated with colloidal bismuth subcitrate but symptoms recurred. Surgery is at present being considered.

CONCURRENT MEDICATION:
Chlorpropamide.

No. 14

INITIALS: D.M. (KE)

AGE: 20 years

SEX: male

WEIGHT: 54 kg

OCCUPATION: factory hand

DIAGNOSIS: chronic duodenal ulceration

FAMILY HISTORY:
There are two brothers who have had surgical treatment for peptic ulceration.

PAST ILLNESSES:
4½ year history of dyspepsia.

PRESENT ILLNESS:

1979: October. Patient presented with severe epigastric pain, nausea and vomiting.
Endoscopy revealed gross pylorospasm with a deep, superior duodenal ulcer.
Gastric secretion test: BAO 29,4 meq/h, MAO 93,9 meq/h, PAO 122,4 meq/h.
Started treatment with ranitidine.

1979: November. A deep posterior duodenal ulcer was seen on endoscopy. Patient continued on ranitidine.

1980: January. Patient still complained of epigastric pain although not as severe as previously.
Endoscopy showed a normal stomach and oesophagus. There was duodenitis, a deformed duodenal cap and a large duodenal ulcer with extensive flat ulceration.

1980: February. After a further month's ranitidine treatment, endoscopy showed multiple prepyloric and duodenal ulcers. There was duodenitis, a deformed duodenal cap and erosions. The patient was experiencing severe pain and nausea. Ranitidine treatment was discontinued.

1980: July. Ranitidine treatment was recommenced one week prior to the pharmacokinetic study. The patient was subsequently treated with colloidal bismuth subcitrate until he underwent surgery.

No. 15

INITIALS: S.S. (KE)

AGE: 50 years

SEX: male

WEIGHT: 72 kg

OCCUPATION: labourer

DIAGNOSIS: diabetus mellitus, chronic duodenal ulceration

PAST ILLNESSES:
Diabetes mellitus. 20 year history of dyspepsia.
1979: February. Gastric secretion test: BAO 7,4 meq/h, MAO 55,6 meq/h.

FAMILY HISTORY: No significant family history

PRESENT ILLNESS:
1979: October. There were symptoms of epigastric pain, nausea, vomiting and acidity over the previous 4 months. On endoscopy there was a large deep anterior duodenal ulcer enveloping the pylorus.
Gastric secretion test: BAO 1,6 meq/h. MAO 33,7 meq/h, PAO 37,8 meq/h.
Patient was treated with ranitidine.
1979: November. Patient reported slight epigastric pain with nausea and vomiting.
Endoscopy showed no improvement of the large deep duodenal ulcer enveloping the pylorus.
There was 1% sugar in the urine.
Patient continued on ranitidine.
1979: December. Repeat endoscopy showed no change in the large deep duodenal ulcer enveloping the pylorus.
Ranitidine was continued for a further month at the standard 150 mg twice daily dosage.
1980: January. The patient was still experiencing some epigastric pain although the endoscopy showed that the duodenal ulcer was healing. + Sugar in the urine was noted.
1980: May. Patient was treated with colloidal bismuth subcitrate but endoscopy showed a scarred narrow pylorus with an active duodenal ulcer. Patient was referred to the surgeons.
1980: July. Ranitidine treatment was recommenced for one week prior to the pharmacokinetic study.
1980: September. Prior to surgery a gastric secretion test was carried out. BAO 7,2 meq/h, MAO 43,1 meq/h and PAO 48,4 meq/h.

CONCURRENT MEDICATION:
Chlorpropamide.

No. 16

INITIALS: P.P. (KE)

AGE: 24 years

SEX: male

WEIGHT: 57 kg

OCCUPATION: cleaner at hospital

DIAGNOSIS: chronic duodenal ulceration

FAMILY HISTORY: no significant family history

PAST ILLNESSES:

Recurrent episodes of dyspepsia from 1974 onwards.

1979: May. Gastric secretion test: BAO 4,4 meq/h, MAO 30,4 meq/h, PAO 37,6 meq/h.

PRESENT ILLNESS:

1979: October. Patient complained of 'acid', full feeling, nausea and vomiting which had been recurring over the previous two months.
Endoscopy showed stomach and oesophagus to be normal but a single deep inferior duodenal ulcer was present.
The symptoms worsened over two weeks while the patient was on placebo. He was therefore placed on ranitidine therapy.

1979: November. The patient still had slight pain although he was much improved. The endoscopy done 28 days after initiation of ranitidine therapy showed a deep inferior duodenal ulcer to be present. He continued on ranitidine.

1980: January. Symptoms were much improved although still present. Endoscopy showed a single small duodenal ulcer.
The patient was subsequently treated with colloidal bismuth subcitrate except for a week in July when ranitidine was administered prior to the pharmacokinetic study.

1980: November. The patient underwent gastric surgery.

No. 17

INITIALS: P.M. (KE)

AGE: 47 years

SEX: male

WEIGHT: 62 kg

OCCUPATION: labourer in sweet factory

DIAGNOSIS: chronic duodenal ulceration

FAMILY HISTORY: One brother has gastric problems. No other significant family history.

PAST ILLNESSES: Seven year history of dyspepsia.

PRESENT ILLNESS:

1979: October. Epigastric pain, nausea and acidity had been experienced.
Endoscopy showed a pyloric channel ulcer on the lesser curve. There were multiple duodenal ulcers, gross distortion with flat anterior ulcer plus a deep posterior ulcer. Treatment was with placebo for the first 28 days.

1979: November. Slight epigastric pain was present after one month's placebo treatment.
Endoscopy showed no improvement of the multiple duodenal ulcers. Ranitidine treatment was initiated.

1979: December. Patient became asymptomatic after 2 weeks' ranitidine treatment. Endoscopy at 4 weeks showed the small deep duodenal ulcer to be active although the flat ulceration had healed.
Ranitidine treatment was continued.

1980: January. The single small duodenal ulcer on endoscopy was noted to be healing.
Colloidal bismuth subcitrate treatment was commenced.

1980: February. Patient was asymptomatic although an ulcer was still present as well as a small hiatus hernia.

1980: July. Ranitidine pharmacokinetic study was performed.

1980: August. Patient had a relapsed duodenal ulcer.

1981: March. Patient was referred for surgery.
Gastric secretion test: BAO 4,4 meq/h, MAO 25,3 meq/h, PAO 28,2 meq/h.

CASE HISTORIES

B. PATIENTS WITH RENAL FAILURE

No. 1

INITIALS AND FOLDER NUMBER: B.S. 072043 (NSH)

AGE: 35 years

SEX: male

WEIGHT: 64,5 kg

OCCUPATION: manager of a garage

DIAGNOSIS: chronic glomerulonephritis (proliferative)
chronic renal failure
atypical migraine
hypertension

PAST ILLNESSES:

1971: Symptoms started when the patient developed swelling of the body and pain in the right loin with dysuria and nocturia.

1975: He developed haematuria and proteinuria. Renal biopsy showed features compatible with those of acute focal glomerulonephritis. Blood pressure was 120/70. The heart was not enlarged clinically or radiologically. Intravenous pyelogram (I.V.P.) was normal, as was renal size.

1979: He was admitted with severe headaches and in addition dull loin pain. Blood pressure was 190/120. Grade 3 retinopathy. 2+ proteinuria. Twelve hour creatinine clearance was 15,5 ml/min. Serum creatinine 625 µmol/l. Blood urea 20 mmol/l. Protein excretion 4,9 gm/24 hrs. I.V.P. at this stage showed extremely poor renal function. The fall-off in renal function was attributed to hypertension or progression of nephritis. His hypertension was fairly easily controlled on atenolol 100 mg daily, hydrallazine 100 mg twice daily. An additional problem was recurrent attacks of headache put down to migraine.

1980: May. Blood pressure on readmission was 210/120. This was brought down to 150/90 with the same antihypertensive treatment.

1980: July. He was readmitted because of deteriorating renal function. Blood urea was 35 mmol/l. Serum creatinine 1 175 µmol/l. Creatinine clearance 5 ml/min.
X-ray of chest showed slight cardiomegaly. He was admitted to the long-term renal failure programme. An arterio-venous fistula was inserted.

1980: September and October. He came back into hospital because of fluid overload.

FAMILY HISTORY: No significant family history.

HOSPITAL COURSE:

The patient was excreting approximately 1 500 ml urine/day. Blood pressure was 140/100. Serum creatinine was 1 800 µmol/l Serum urea was 145 mmol/l on the strength of which he was entered into the dialysis programme on the day after starting the ranitidine treatment. His blood pressure was controlled with atenolol, hydrallazine and furosemide.
The patient felt well throughout the week of ranitidine therapy.

CONCOMITANT THERAPY:

aluminium hydroxide gel
sodium bicarbonate
furosemide
atenolol
hydrallazine

No. 2

INITIALS AND FOLDER NUMBER: J.S. 0123810 (NSH)

AGE: 39 years

SEX: male

WEIGHT: 73 kg

OCCUPATION: school teacher

DIAGNOSIS: malignant hypertension
chronic renal failure
accelerated hypertension
type 4 hyperlipidaemia

PAST ILLNESSES:
1948: Appendectomy
1950: Tonsillectomy
1974: In July/August he was admitted with epistaxis. Blood pressure was 220/150 although this settled rapidly on hospitalization to 150/110. There had been blurring of vision for several weeks.
X-ray chest: heart slightly enlarged and left ventricular in configuration. Blood urea 56 mg%, creatinine 1,5 mg%.
Treatment was with alpha-methyldopa and furosemide.
1978: January. He was readmitted following deterioration with severe occipital headaches and recent development of nocturia. 3+ proteinuria. The patient had mild normochromic normocytic anaemia. Haemoglobin 11,8 g/dl. Creatinine clearance 6,8 ml/min. I.V.P. showed both kidneys to be 10 cm in length. Diazoxide was necessary to control the blood pressure.
1980: March. Readmitted due to lack of compliance, elevation of blood pressure and development of chest pain, thought to be angina pectoris. Blood pressure 150/95. Urine normal. No evidence that the patient had had an acute myocardial infarction.

FAMILY HISTORY: Both parents were hypertensive.

HOSPITAL COURSE: The patient felt well throughout the study. Blood pressure was in the order of 160/100. Ranitidine was well tolerated despite high plasma ranitidine levels.

CONCOMITANT THERAPY:
hydrallazine 75 mg four times daily
atenolol 100 mg twice daily
furosemide 120 mg daily

No. 3

INITIALS AND FOLDER NUMBER: L.A. 087207 (NSH)

AGE: 75 years

SEX: female

WEIGHT: 57,5 kg

OCCUPATION: retired

DIAGNOSIS: longstanding insulin diabetic
longstanding insulin-dependent diabetic with hypertension
transient cerebral ischaemia with left-sided weakness
chronic renal impairment

PAST ILLNESSES:

1963: She had diabetes mellitus (insulin-dependent) and was hypertensive for the past 17 years.

1980: July. The patient was admitted to hospital and on examination had mild left-sided hemiparesis. Blood pressure 180/90. Pulse 52/min. Presumptive evidence of digoxin toxicity as pulse increased on stopping digoxin. Serum creatinine 200 µmol/l and urea 12 mmol/l.
Chest X-ray showed minimum cardiomegaly. ECG showed some left ventricular strain and damage. No protein in the urine.
Transient cerebral ischaemia.

FAMILY HISTORY: No significant family history.

HOSPITAL COURSE:
No change in the patient's condition during the week of treatment. She felt very well while taking ranitidine.

CONCOMITANT MEDICATION:
80 lente insulin 35 units daily
digoxin 0,125 mg daily
dipyridamole 50 mg daily
acetyl salicylic acid 1 daily
cyclopenthiazide with potassium chloride two tablets daily

No. 4

INITIALS AND FOLDER NUMBER: H.D. 260804

AGE: 34 years

SEX: male

WEIGHT: 55 kg

OCCUPATION: head porter at a hotel

DIAGNOSIS: acute glomerulonephritis
malignant hypertension
probable acute tubular necrosis
microangiopathic haemolytic anaemia

PAST ILLNESSES:

1974: Pulmonary tuberculosis (T.B.). He was carefully followed up with annual checkups and was perfectly well until 1980.

1980: October. He presented with sore throat, shortness of breath, ankle and facial oedema, loin pain. This brought him to hospital where he was admitted in a serious condition. He was in cardiac failure and had pulmonary oedema. The jugular venous pressure was raised +6 cm. Blood pressure 280/160. There was parasternal heave and a gallop rhythm was heard. No papilloedema but florid grade 3 hypertensive changes were seen in the retina. 3+ proteinuria. 2+ haematuria.
X-ray of chest showed evidence of old pulmonary T.B. Electrocardiograph (ECG) showed evidence of left ventricular hypertrophy.
No acid fast bacilli were found in the sputum.
Renal biopsy: Four glomeruli showing slight hypercellularity and one with fairly advanced sclerosis. These changes could not account for the anuria present at the time nor the hypertension. No evidence of fibrinoid necrosis. No obvious cause for the anuria could be found. The patient underwent peritoneal dialysis. Anuria lasted 8-9 days and then settled rapidly. There was evidence of microangiopathic haemolytic anaemia.
Control of blood pressure was achieved with labetalol, hydrallazine, guanethadine and furosemide.

FAMILY HISTORY: No significant family history.

HOSPITAL COURSE: During the week of ranitidine therapy, the patient's condition remained stable. No adverse effects to ranitidine were noted.

CONCOMITANT THERAPY:
hydrallazine 150 mg 12 hourly
furosemide 750 mg daily
labetalol 200 mg 8 hourly

No. 5

INITIALS AND FOLDER NUMBER: T.C. 259879 (NSH)

AGE: 40 years

SEX: male

WEIGHT: 68,5 kg

OCCUPATION: labourer with the South African Railways

DIAGNOSIS: previous acute glomerulonephritis
chronic glomerulonephritis
chronic renal failure
accelerated hypertension
anaemia

PAST ILLNESSES:
Childhood: repeated sore throats and tonsillitis, the last attack occurring 10 years ago.
1956: Epileptic attacks which continued until 5 years ago.
1970: Fractured left wrist.
1976: Acute nephritis associated with hypertension. This attack lasted 1 month.
1980: In May he was admitted with severe hypertension. Blood pressure 220/140. Blood urea 26 mmol/l. Serum creatinine 685 µmol/l. Haemoglobin 9,8 g/dl. Proteinuria 3+.
1980: The patient was admitted again in October. On examination he was found to be pale and had peripheral oedema. Pulse 72/min, regular. Blood pressure 230/145. Clinical evidence of left ventricular hypertrophy. A_2 was accentuated. Proteinuria 4+. Fundi showed grade 3 retinopathy. Electrocardiograph showed left ventricular hypertrophy and strain.
Chest X-ray showed no obvious cardiomegaly. Abdomen X-ray showed the right renal outline to be 11,2 cm. The left kidney was not visualised to assess size.
X-ray hand and midstream urine were normal. Astrup normal.

FAMILY HISTORY: One aunt has hypertension. No other family history of hypertension.

HOSPITAL COURSE: (while on ranitidine)
Put out 1 500-2 200 ml of urine daily. Weight remained constant. Felt well throughout the admission. Blood pressure (standing) was in the order of 190/110, settling during the week's hospitalization to 130/90. The recumbent blood pressure during the course of the week was fairly constant at 150/100. At the time of discharge blood pressure was 220/110.
No adverse effects to ranitidine were noted.

CONCOMITANT THERAPY:
hydrallazine 50 mg 4 times daily
atenolol 100 mg daily
furosemide 250 mg daily
aluminium hydroxide gel 20 ml 4 times daily
hydrallazine 6,125 mg intramuscularly was administered when the diastolic blood pressure went above 120.

No. 6

INITIALS AND FOLDER NUMBER: R.W. 267080 (NSH)

AGE: 21 years

SEX: male

WEIGHT: 60 kg

OCCUPATION: labourer

DIAGNOSIS: chronic renal failure with bilateral chronic glomerulonephritis

PAST ILLNESSES:

Childhood: Renal problems from the age of 11 years. He had frequent urinary tract infections. He was investigated at Livingstone Hospital for rheumatic fever, outcome of which is unknown.

1981: The patient was weak and unwell for a week prior to admission on 2 February. He had nocturia for about three weeks before admission. Dysuria was followed by an acute illness which had lasted for about 10 days. There was swelling of the legs. Examination on admission showed the patient to be confused, drowsy, sick and distressed. The face was puffy and the body oedematous. Pulse 60/min. Blood pressure 210/140. Jugular venous pressure raised + 3 cm.
Heart in anterior axillary line suggesting left ventricular hypertrophy. Slight systolic murmur. Proteinuria 2+. Blood 1+. ECG showed sinus rhythm.
Problems were acute or chronic renal disease with hypertension and anaemia.
The patient underwent peritoneal dialysis. The fluid overload was controlled but severe hypertension and uraemia persisted.
Small kidneys bilaterally on X-ray suggestive of chronic glomerulonephritis. Excretion concentrate extremely poor. The fundi showed narrowed arterioles. High K^+ levels.

FAMILY HISTORY: Mother has asthma.

HOSPITAL COURSE (while on ranitidine):

The patient did not feel well. This was, however, not thought to be due to ranitidine but to the renal disease. Urinary output was dropping slightly. Blood pressure was controlled; he was in fluid balance with slight ankle oedema. Jugular venous pressure was not raised.

CONCOMITANT THERAPY:

prazosin 4 mg 8 hourly
aluminium hydroxide gel 10 ml 3 times daily
kayexalate 15 g 4 times daily

DIALYSIS PATIENTS

No. 1.

INITIALS AND FOLDER NUMBER: F.P. 129843 (NSH)

DIAGNOSIS: nephrotic syndrome

systemic lupus erythematosus (renal biopsy)

hypertension (severe)

renal failure

secondary hyperparathyroidism

renal osteodystrophy

proximal myopathy

chronic bronchitis

haemodialysis (chronic)

No.2.

INITIALS AND FOLDER NUMBER: O.P. 217942 (NSH)

DIAGNOSIS: chronic renal failure

diabetes mellitis

diverticulosis

haemodialysis (chronic)

No.3.

INITIALS AND FOLDER NUMBER: R.D. 211716 (NSH)

DIAGNOSIS: chronic renal failure

hypertension

pneumonia

previous cardiac failure

haemodialysis (chronic)

APPENDIX II

TABLE A1

HAEMATOLOGY DUODENAL ULCER PATIENTS (RESPONDERS)

		Hb (g/dl)	RBC ($x10^{12}/\ell$)	MCHC (%)	PCV (%)	MCV (fl)	Platelets ($x10^{9}/\ell$)	ESR	WBC ($x10^{9}/\ell$)	DIFFERENTIAL LEUCOCYTES (%) L	M	N	E	B
	Normal	m 13,3-17,3 11,6-15,6	m 4,5-5,9 3,7-5,3	33-35	-	m 81-93 f 81-95	140-420	m 0-5 0-7	4-11	20-45	2-10	40-75	1-6	1
J.S.	Pre-dose	16,1	5,0	33	47	93	-	-	10,7	-	-	-	-	-
	2 weeks	15,8	5,0	32	47	94	260	-	8,8	-	-	-	-	-
	4 weeks	16,2	5.1	33	47	93	250	2	9,7	21	1	77	1	0
T.W.	Pre-dose	13,2	4,5	33	38	87	242	8	5,8	39	9	47	3	-
	2 weeks	13,3	4,5	35	38	84	253	12	7,1	43	3	52	1	1
	4 weeks	13,0	4,4	34	37	84	203	15	6,7	33	11	50	3	3
A.d.S	Pre-dose	15,8	5,1	35	44	88	-	-	5,2	-	-	-	-	-
	2 weeks	14,2	4,6	33	42	90	323	-	5,0	-	3	53	-	44
	4 weeks	14,5	4,6	35	41	89	331	8	4,0	32	2	62	4	-
M.S.	Pre-dose	17,0	5,2	34	48	92	275	8	6,0	29	10	58	4	1
	2 weeks	15,4	5,1	36	42	83	346	-	8,4	40	11	45	4	0
	4 weeks	15,2	4,9	35	42	87	292	-	9,8	54	3	43	0	0

TABLE A1 CONTINUED

HAEMATOLOGY DUODENAL ULCER PATIENTS (RESPONDERS)

		Hb (g/dl)	RBC ($x10^{12}/\ell$)	MCHC (%)	PCV (%)	MCV (fl)	Platelets ($x10^{9}/\ell$)	ESR	WBC ($x10^{9}/\ell$)	DIFFERENTIAL LEUCOCYTES (%) L	M	N	E	B
	Normal	m 13,3-17,3 11,6-15,6	m 4,5-5,9 3,7-5,3	33-35	-	m 81-93 f 81-95	140-420	m 0-5 f 0-7	4-11	20-45	2-10	40-75	1-6	1
S.M.	Pre-dose	10,9	5,8	32	52	90	336	-	10,8	34	5	56	4	1
	2 weeks	15,2	5,0	34	43	85	415	6	5,2	24	8	64	3	1
	4 weeks	-	-	-	-	-	-	-	-	-	-	-	-	-
D.F.	Pre-dose	15,9	4,8	37	41	88	-	-	6,9	-	-	-	-	-
	2 weeks	13,9	4,6	33	42	90	158	10	5,4	26	6	68	0	0
	4 weeks	15,7	5,0	34	46	90	193	7	5,3	50	2	42	4	2
P.d.J	Pre-dose	13,4	4,2	36	36	86	248	28	8,4	19	3	77	3	1
	2 weeks	14,0	4,5	35	40	88	174	8	5,5	30	9	58	3	0
	4 weeks	15,2	5,1	33	45	88	189	6	5,3	44	3	46	4	0
W.M.	Pre-dose	13,5	4,1	34	38	93	396	15	6,2	45	8	42	2	2
	2 weeks	14,2	4,8	31	45	92	-	20	6,5	41	7	50	2	0
	4 weeks	14,2	4,6	33	43	92	295	13	9,2	25	10	60	4	1

TABLE A1 CONTINUED

HAEMATOLOGY DUODENAL ULCER PATIENTS (RESPONDERS)

		Hb (g/dl)	RBC ($x10^{12}/\ell$)	MCHC (%)	PCV (%)	MCV (fl)	Platelets ($x10^{9}/\ell$)	ESR	WBC ($x10^{9}/\ell$)	DIFFERENTIAL LEUCOCYTES (%) L	M	N	E	B
	Normal	m 13,3-17,3 11,6-15,6	m 4,5-5,9 3,7-5,3	33-35	-	m 81-93 f 81-95	140-420	m 0-5 f 0-7	4-11	20-45	2-10	40-75	1-6	1
A.O.	Pre-dose	16,5	5,3	34	48	92	210	2	5,3	34	8	50	2	0
	2 weeks	16,1	5,0	33	47	94	228	9	3,6	33	12	51	3	1
	4 weeks	15,4	4,9	34	45	91	-	-	3,4	37	7	54	2	0
D.S.	Pre-dose	15,3	5,0	33	45	90	249	5	4,2	28	8	57	5	2
	2 weeks	15,5	5,2	32	47	91	290	18	4,5	27	10	59	4	0
	4 weeks	14,7	4,9	32	45	90	283	7	5,9	-	-	-	-	-

TABLE A2

BLOOD CHEMISTRY DUODENAL ULCER PATIENTS (RESPONDERS)

		Urea (mmol/ℓ)	Sodium (mmol/ℓ)	Potassium (mmol/ℓ)	Creatinine (µmol/ℓ)	Calcium (mmol/ℓ)	Alk.Phos. (units/ℓ)	Bilirubin (µmol/ℓ)	Total Protein (g/ℓ)	Albumin (g/ℓ)	Gamma GT (units/ℓ)	SGOT (units/ℓ)	SGPT (units/ℓ)
	Normal	1,7-6,7	135-145	3,5-5,0	75-115	2,1-2,6	30-85	2-17	60-80	35-50	6-28	0-12	0-12
J.H.	Pre-dose	4,5	141	6,6	98	-	66	7	66	43	11	8	5
	2 weeks	4,3	140	4,9	98	-	77	-	68	43	8	-	-
	4 weeks	-	-	-	-	2,3	58	8	67	46	9	7	4
T.W.	Pre-dose	5,2	142	4,2	88	2,0	72	5	57	36	-	6	3
	2 weeks	4,7	144	4,0	72	2,2	73	5	67	39	7	5	2
	4 weeks	5,4	142	3,9	81	2,3	86	4	68	42	7	5	2
A.d.S.	Pre-dose	4,4	139	3,9	93	2,4	42	13	78	43	16	10	5
	2 weeks	6,0	-	-	93	2,3	36	12	71	43	12	5	3
	4 weeks	5,4	142	4,2	115	2,3	44	12	71	42	-	6	4
M.S.	Pre-dose	5,1	138	3,9	93	-	41	6	77	43	9	6	7
	2 weeks	6,1	139	4,0	79	2,3	42	8	74	43	8	7	4
	4 weeks	4,2	140	4,6	83	2,4	48	6	77	45	8	-	-
S.M.	Pre-dose	6,0	139	3,6	100	2,3	54	8	72	42	10	7	4
	2 weeks	4,8	139	4,1	106	2,2	52	13	71	49	9	11	2
	4 weeks	5,4	139	4,1	99	2,4	54	8	76	43	8	10	4

TABLE A2 CONTINUED

BLOOD CHEMISTRY DUODENAL ULCER PATIENTS (RESPONDERS)

		Urea (mmol/ℓ)	Sodium (mmol/ℓ)	Potassium (mmol/ℓ)	Creatinine (μmol/ℓ)	Calcium (mmol/ℓ)	Alk.Phos. (units/ℓ)	Bilirubin (μmol/ℓ)	Total Protein (g/ℓ)	Albumin (g/ℓ)	Gamma GT (units/ℓ)	SGOT (units/ℓ)	SGPT (units/ℓ)
	Normal	1,7-6,7	135-145	3,5-5,0	75-115	2,1-2,6	30-85	2-17	60-80	35-50	6-28	0-12	0-12
D.F.	Pre-dose	4,7	142	3,6	69	2,4	65	16	79	46	13	7	3
	2 weeks	4,1	134	6,1	63	2,1	51	10	73	42	13	11	2
	4 weeks	3,7	138	5,1	89	2,2	54	10	74	44	10	7	3
?.d.J	Pre-dose	6,5	144	4,9	97	2,4	145	8	68	47	18	8	6
	2 weeks	3,7	147	4,1	83	2,4	119	9	67	47	13	7	6
	4 weeks	4,6	145	4,5	84	2,7	133	11	73	50	13	8	5
W.M.	Pre-dose	6,8	144	5,0	72	2,4	84	6	70	47	61	4	6
	2 weeks	-	-	-	-	-	-	-	-	-	-	-	-
	4 weeks	4,5	140	4,2	71	2,4	81	7	69	46	17	23*	8**
A.O.	Pre-dose	6,1	143	3,8	100	2,3	74	9	66	44	8	4	4
	2 weeks	4,3	-	-	-	2,4	60	7	67	44	4	17*	5**
	4 weeks	-	-	-	-	2,3	71	11	66	42	8	5	4
D.S.	Pre-dose	5,8	146	3,7	115	2,5	84	6	72	44	64	12	15
	2 weeks	4,9	139	4,4	98	2,7	71	6	79	52	46	7	7
	4 weeks	6,0	138	3,8	89	2,5	78	5	72	45	51	7	8

* Normal SGOT 0-40 units/ℓ

** Normal SGPT 0-53 units/ℓ

TABLE A3

HEAMATOLOGY RENAL FAILURE PATIENTS

		Hb (g/dl)	RBC ($x10^{12}/\ell$)	PCV (%)	MCV (fl)	Platelets ($x10^9/\ell$)	WBC ($x10^9/\ell$)	DIFFERENTIAL LEUCOCYTES (%) L	M	N	E	B
	Normal	m 13,3-17,3 f 11,6-15,6	m 4,5-5,9 f 3,7-5,3		m 81-93 f 81-95	140-420	4-11	20-45	2-10	40-75	1-6	1
B.S.	Pre-dose	-	2,76	-	-	-	-	-	-	-	-	-
	1 week	8,1	3,09	26,0	87	155	6,5	35	9	54	1	1
J.S.	Pre-dose	12,0	3,97	-	91	normal	9,3	23	8	68	1	0
	1 week	10,0	3,88	35,4	93	302	8,8	17	12	67	4	0
L.A.	Pre-dose	13,8	5,10	41,0	85	normal	6,8	20	6	69	5	-
	1 week	10,9	3,98	32,3	82	198	5,9	23	6	66	4	1
H.D.	Pre-dose	10,1	3,55	31,6	88	normal	6,2	18	1	79	1	1
	1 week	9,7	3,24	29,0	-	288	7,3	20	4	76	0	0
T.C.	Pre-dose	8,4	3,22	28,0	86	140	5,4	16	4	80	0	0
	1 week	11,1	-	-	-	194	7,4	21	2	75	2	0
R.W.	Pre-dose	7,6	-	-	-	-	5,7	30	6	52	11	1
	1 week	6,5	2,30	20,0	89	138	7,6	19	9	63	8	1

TABLE A4

BLOOD CHEMISTRY RENAL FAILURE PATIENTS

		Urea (mmol/ℓ)	Sodium (mmol/ℓ)	Potassium (mmol/ℓ)	Creatinine (μmol/ℓ)	Calcium (mmol/ℓ)	Alk.Phos (Units)	Biliburin (μmol/ℓ)	Total Protein g/ℓ	Albumin g/ℓ	SGOT Units/ℓ	LDH Units/ℓ	CPK Units/ℓ
	Normal	2,5-6,0	135-145	3,5-5,5	75-115	2,1-2,6	30-85	0-17	60-80	35-50	0-18	120-240	
B.S.	Pre-dose	43,5	142	6,0	1800	2,30	84,0	10	56,0	34,0	4,0	200	-
	1 week	23,5	138	4,8	975	2,30	86,0	10	64,0	39,0	15,0	150	62
J.S.	Pre-dose	43,0	138	4,8	925	2,50	66,0	10	72,0	44,0	4,0	200	50
	1 week	36,5	141	4,1	1000	2,70	64,0	10	71,0	-	3,0	204	43
L.A.	Pre-dose	14,0	141	3,6	220	2,50	128,0	10	73,0	41,0	6,0	226	27
	1 week	16,0	140	3,5	225	2,45	156,0	10	71,0	33,0	15,0	-	50
H.D.	Pre-dose	20,0	139	3,9	875	2,50	46,0	10	67,0	36,0	7,0	-	-
	1 week	19,8	136	3,6	950	2,45	60,0	10	61,0	38,0	20,0	-	54
T.C.	Pre-dose	34,0	138	4,0	875	-	94,0	10	56,0	32,0	7,0	-	-
	1 week	35,5	133	4,2	1050	2,32	74,0	10	57,0	35;0	4,0	-	8
R.W.	Pre-dose	27,5	145	6,5	985	1,90	73,0	10	65,0	33,0	11,0	250	-
	1 week	33,0	140	7,0	860	1,95	86,0	10	63,0	33,0	11,0	300	-

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