METOCLOPRAMIDE DISPOSITION IN NORMAL AND UREMIC HUMANS

by

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We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

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ABSTRACT

Metoclopramide (MCP) is a potent antinauseant/antiemetic and gastrointestinal motility modifier. MCP finds clinical use in a wide variety of situations and is administered on both an acute and chronic basis.

This thesis examines the pharmacokinetics of MCP in both normal, healthy volunteers and in uremic subjects on a maintenance hemodialysis program. Specifically, in the normal, healthy volunteers, the dose-linearity, and absolute and relative bioavailabilities are examined. In the uremics, the effects of chronic renal failure on MCP kinetics, the removal of MCP by hemodialysis, and the effects of hemodialysis on MCP kinetics are examined.

Based on early reports, the pharmacokinetics of MCP were claimed to be dose-dependent and the absolute bioavailability extremely variable. However, many of these early studies suffered from methodological problems which limit the credibility of their findings. Based on a four-way crossover study involving six normal, healthy volunteers we find, in contrast to previous results, that the kinetics of MCP are linear over the dose range of 5 - 20 mg, the absolute bioavailability is 76 ± 38 %, and the relative bioavailability of a solution dosage form vs the tablet dosage form is approximately 1.
Although renal clearance accounts for only about 20% of the total body clearance of MCP in normals, uremia has been shown to substantially alter MCP kinetics in both rat and man. There appears to be at least a two-fold decrease in total body clearance with an attendant, proportional increase in elimination half-life and insignificant change in volume of distribution. Hemodialysis is relatively ineffective in clearing MCP from the body and this inefficiency is probably related to the relatively large volume of distribution of MCP. Hemodialysis also has no effects on the apparent kinetic parameters following its termination. In addition, results from a single patient who received a kidney transplant show that the renewed renal function is accompanied by an apparent reversion of all kinetic parameters to within normal limits within 15 days of transplantation.
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<tr>
<td>AAG</td>
<td>Alpha-1-Acid Glycoprotein</td>
<td></td>
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<td>A.D.M.E.</td>
<td>Absorption, Distribution, Metabolism, Elimination</td>
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<td>Alk Phos</td>
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<td>ARE</td>
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<td>Clint</td>
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<td>CRTZ</td>
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<td>C.V.</td>
<td>Coefficient of Variation</td>
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<td>E</td>
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<td>ECD</td>
<td>Electron Capture Detection</td>
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<td>F</td>
<td>Bioavailability</td>
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<td>FID</td>
<td>Flame Ionization Detection</td>
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<td>g</td>
<td>Acceleration due to gravity</td>
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<tr>
<td>GC-ECD</td>
<td>Gas Chromatographic Electron Capture Detection</td>
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<td>GI</td>
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<td>HFB</td>
<td>Heptafluorobutyryl</td>
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<td>Ka</td>
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<td>$K_n$ or $K_E$</td>
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<td>$r^2$</td>
<td>Coefficient of Determination</td>
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<td>RBC</td>
<td>Red Blood Cell</td>
<td></td>
</tr>
<tr>
<td>Scr</td>
<td>Serum Creatinine</td>
<td></td>
</tr>
<tr>
<td>SD or s.d. or std dev</td>
<td>Standard deviation</td>
<td></td>
</tr>
<tr>
<td>SGOT</td>
<td>Serum Glutamate Oxalate Transaminase</td>
<td></td>
</tr>
<tr>
<td>SGPT</td>
<td>Serum Glutamate Pyruvate Transaminase</td>
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\( t_{1/2} \)  
\( V \) or \( V_d \)  
\( V_c \)  

Elimination half-life  
Volume of Distribution  
Volume of the Central Compartment
ACKNOWLEDGEMENTS

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To the memory of my grandfather, Rev. K. St. C. Thomas.
1. INTRODUCTION

1.1 Metoclopramide Pharmacology and Clinical Applications

Introduction of a methoxy group onto the heterocyclic ring of procainamide produces compounds with antiemetic activity (Clinton and Laskowsky, 1955). The antiemetic activity of these congeners can be enhanced by the addition of a halogen atom para to the methoxy group (Besancon et al., 1964). Metoclopramide is the 2-methoxy, 5-chloro analogue of procainamide (see Figure 1).

![Figure 1: Metoclopramide](image)

The pharmacology and clinical applications of metoclopramide (MCP) have been extensively reviewed by several authors (Pinder et al., 1976; Harrington et al., 1983; Albibi and McCallum, 1983; Shaughnessy, 1985; Desmond and Watson, 1986). Although it is an analog of procainamide, MCP does not possess significant
antiarrhythmic or local anaesthetic properties (Harrington et al., 1983). The pharmacological actions of MCP are most pronounced in the gastrointestinal tract where a generalized increase in motility is seen after either oral or intravenous administration (Pinder et al., 1976; Schulze-Delrieu, 1981).

Segmentally, within the GI tract, MCP has several effects. In the esophagus, MCP raises the pressure of the lower esophageal sphincter (LES), in a dose-dependent fashion, in both normal volunteers and patients with hiatus hernia and to a lesser extent in pregnant women (Baumann et al., 1979; Behar and Biancania, 1976; Brock-Utne et al., 1978). In addition, MCP also enhances the amplitude and duration of esophageal peristalsis as well as improving acid clearance from the esophagus (Desmond and Watson, 1986). MCP significantly accelerates gastric emptying and the amplitude of gastric contraction (Harrington et al., 1983). The effects of MCP on the stomach are most readily seen in patients with slow gastric emptying rates or small and/or slow antral and duodenal contractions (Harrington et al., 1983). The most pronounced effects within the stomach are on the antral region where MCP induces contraction as well as improving coordination of antral and duodenal contraction (Pinder et al., 1976). MCP has no effects on the amount of gastric acid secreted or on serum gastrin levels.
(Cohen et al., 1976). In the small intestine, MCP decreases intestinal transit time via a stimulation of smooth muscle contraction which can be antagonized by anticholinergic agents (Pinder et al., 1976). As well, improvement of antral/duodenal contraction coordination and an increase in the amplitude of duodenal contraction has been noted (Harrington et al., 1983). MCP appears to be a stronger stimulant of intestinal motility than is pyridostigmine bromide (Oigaard and Fleckenstein, 1975). Although a stimulant of both amplitude and frequency of contraction in in vitro strips of colonic circular smooth muscle (Schulze-Delrieu, 1979), no consistent effects of MCP on the large intestine have been demonstrated in vivo (Harrington et al., 1983). No consistent effects of MCP on the gall bladder in vivo in animals or humans have been noted (Pinder et al., 1976).

The exact mechanism of MCP action in the GI tract is unclear. However, many actions are inhibited by anticholinergic agents (Harrington et al., 1983). MCP has no anticholinesterase activity and its actions are not influenced by ganglionic blocking agents (Pinder et al., 1976). Since vagotomy does not affect MCP activity, the site of action in the GI tract is thought to be at the peripheral nerve endings in the gut smooth muscle (Stadaas and Aune, 1971). There are three proposed
mechanisms used to explain the activity of MCP in the GI tract:

1. **Potentiation of cholinergic activity**

   Although MCP is not cholinomimetic in the manner of traditional cholinergic agonists, many actions of MCP are antagonized by anticholinergic agents (Eisner, 1968). Vagotomy, however, does not abolish MCP activity (Stadaas and Aune, 1971), suggesting that activity depends on intramural cholinergic neurons (Desmond and Watson, 1986). Using the isolated guinea pig stomach Hay and Man (1979) have demonstrated that MCP activity is dependent on the release of acetylcholine from neuronal stores within the enteric nervous system. Further evidence from isolated human and guinea pig GI smooth muscle suggests that MCP augments acetylcholine release and sensitizes muscarinic receptors (Beani et al., 1970).

2. **Dopamine Antagonism**

   Dopamine is well known to be a neurotransmitter in the central, peripheral, and enteric nervous systems. MCP has been shown to be able to antagonize L-dopa mediated delays of gastric emptying and L-dopa antagonizes MCP induced increases in LES tone (Berkowitz and McCallum, 1980; Baumann et al., 1979).
3. Direct Action on Smooth Muscle

In an in vitro preparation of oppossum esophageal muscle, application of MCP resulted in dose-related increases in tension (Cohen and DiMarino, 1976). Although tenuous, this observation suggests that some direct action of MCP may be possible.

In addition to its effects on the GI tract, MCP possesses central effects that are likely as important to its overall antiemetic efficacy as the increased GI tract motility (Desmond and Watson, 1986). MCP is believed to raise the threshold of the chemoreceptor trigger zone (CRTZ) and decrease the sensitivity of visceral afferents which project to the emetic centre in the lateral reticular formation (Pinder et al., 1976). Since stimulation of the CRTZ is relatively specific to dopamine agonistic drugs, centrally acting agents which block this are generally considered to be dopamine antagonists (Cannon, 1975). MCP also demonstrates behavioural effects in animals and adverse effects in man consistent with the proposition that it is a dopamine antagonist (Harrington et al., 1983). Jenner et al. (1978) have determined that the benzamides interact with a non-adenylate cyclase coupled dopamine receptor, thus MCP may be classified as a selective D-2 receptor antagonist.
Since MCP is a dopamine antagonist it is also able to affect the release of various hormones. MCP stimulates prolactin release as well as slightly increasing serum thyrotropin, aldosterone, and arginine vasopressin levels (Desmond and Watson, 1986). In contrast, MCP causes slight reductions in growth hormone, luteinizing hormone, and follicle-stimulating hormone levels (Desmond and Watson, 1986).

Although MCP is structurally related to procainamide, it does not have significant effects on blood pressure or intracardiac electrical conduction in animal studies (Harrington et al., 1983). However, isolated instances of hypotension under general anaesthesia, hypertensive crisis in patients with pheochromocytoma, and cardiac arrhythmias have been reported in man. MCP, however, has been reported to decrease renal plasma flow in oncology patients (Israel et al., 1986) by less than 20%. Alternatively, Tam et al. (1981) demonstrated a decrease in hepatic blood flow, brought about by MCP, in the rat.

MCP has found clinical use in a wide variety of settings both in Europe and North America. Several reviews have extensively examined these uses (Pinder et al., 1976, Harrington et al., 1983; Alibi and McCallum, 1983; Shaughnessy, 1985; Desmond and Watson, 1986). MCP
has found use in controlling nausea and vomiting resulting from a variety of etiologies. More specifically MCP is effective in controlling the nausea and vomiting associated with uremia (Jones, 1968), in postoperative patients (Pinder et al., 1976), narcotic therapy (Assaf et al., 1974), cancer chemotherapy (in particular cis-platin) (Harrington et al., 1983), radiation sickness (Ward, 1973), and pregnancy (Singh and Lean, 1973). Additionally MCP has found use in gastroesophageal reflux treatment (Harrington et al., 1983), gastroparesis associated with vagotomy and gastric resection or diabetes (Desmond and Watson, 1986), migraine therapy to enhance the delivery of antimigrainous agents (Matts, 1974), GI tract diagnostic and radiological procedures (Christie and Ament, 1976; James and Hume, 1968), and significantly prior to anaesthetic induction as in emergency caesarian section (Schulze-Delrieu, 1981). Furthermore, other trials have examined the effectiveness of MCP in defective lactation, treatment of patients with hypomotile ureter, orthostatic hypotension, hiccups, tardive dyskinesia, and vertigo (Harrington et al., 1983).

Adverse effects of MCP are generally transient and reversible and occur in approximately 11% of patients in some of the larger clinical surveys (Harrington et al., 1983). Several patient groups, e.g. uremics and
children, appear to be at somewhat higher risk for the development of adverse effects to MCP. Drowsiness and restlessness appear to be the most common side effects occurring in about 10% of patients while extrapyramidal side effects occur in about 9% of patients (Harrington et al., 1983). Other side effects appear to occur in less than 5% of patients (Harrington et al., 1983).

1.2 Effect of Route of Administration on Drug Kinetics

Based on studies using p-aminohippuric acid and several sulfonamide antibacterials, which were administered to experimental animals both IV and orally, Dost (1958) and Gladtke (1964) proposed a relationship between dose and area under the plasma concentration vs time curve (AUC) known as "the law of corresponding areas". This "law" suggested that, if distribution, metabolism and excretion are first-order processes, then the AUC is directly proportional to the dose and is independent of the route of administration. Unfortunately, the drugs used to formulate this proposition are only negligibly or slowly metabolized by the liver and are not representative of enough drugs to establish such a generality (Harris and Riegelman, 1969). In fact, it has become quite clear that for many drugs the AUC is dependent not only upon the dose but also on
the route of administration, physiological factors of the experimental animal, and the physico-chemical properties of the drug and dosage form. This concept is best expressed by the term bioavailability, which, in its simplest terms refers to the rate and extent of drug absorption (Gibaldi and Perrier, 1982). As previously mentioned, and as is somewhat intuitive, the amount of drug reaching the systemic circulation is affected by both physiological factors of the test animal and the physico-chemical factors of the drug and dosage form, as outlined in the following table (Riegelman and Rowland, 1973).

The most reliable determination of bioavailability is made by the comparison of the AUC's of equal doses of drug to experimental subjects on a crossover basis by oral and IV routes. For a drug displaying n compartmental kinetics:

\[
\text{AUC}_{\text{oral}} = \frac{F \text{ Dose}_{\text{oral}}}{V_B K_n}
\]

and

\[
\text{AUC}_{\text{IV}} = \frac{\text{Dose}_{\text{IV}}}{V_B K_n}
\]

therefore:

\[
\frac{\text{AUC}_{\text{oral}}}{\text{AUC}_{\text{IV}}} = \frac{F \text{ Dose}_{\text{oral}}}{\text{Dose}_{\text{IV}}}
\]
### TABLE 1

Factors affecting drug bioavailability
(Riegelman and Rowland, 1973)

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<tr>
<th>Physiological Factors</th>
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<td>water solubility</td>
</tr>
<tr>
<td>mucous interaction</td>
<td>lipid solubility</td>
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<tr>
<td>complexing components</td>
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thus:
\[ F = \frac{AUC_{\text{oral}} \cdot \text{Dose}_{\text{IV}}}{AUC_{\text{IV}} \cdot \text{Dose}_{\text{oral}}} \]

This equation suggests that unequal doses may be used to determine bioavailability, however, this presupposes that dose-linear kinetics exist. Therefore, in the absence of information regarding dose-linearity, equal doses should be used.

Independently of the AUC determined from plasma sampling, bioavailability may be also be determined from the total amount of drug excreted intact in the urine. This method requires complete urine collection for a period of at least 7 half-lives with at least 10% of the dose being excreted unchanged. Generally, this assessment should be carried out in conjunction with determination of the bioavailability from plasma data since it gives independent confirmation of the results obtained from plasma.

As stated previously, the literature contains many examples of drugs that are not completely bioavailable (i.e. \( AUC_{\text{oral}} < AUC_{\text{IV}} \)). In many cases, the disposition of these drugs is markedly influenced by the route of administration. If a drug is given by a peripheral route (e.g. sublingual, intramuscular, intravenous, subcutaneous), such that it directly enters a systemic artery or vein, distribution occurs so that only \( \sim 30\% \) of
the dose of the drug reaches the liver on its first circulation through the body. In contrast, if a drug is given by a hepatic route (e.g. *per os*, intraperitoneal, portal or splenic vein infusion), absorption occurs across that part of the GI epithelium drained by the hepatic portal system (Blaschke, 1979). In these cases, the entire absorbed dose is exposed to the liver prior to mixing with the systemic circulation and, if hepatic metabolism occurs, a certain percentage of the dose will be extracted prior to exposure to the rest of the body. Thus, for certain drugs a substantial portion of an oral dose may be metabolized prior to the systemic circulation and site of pharmacological action. This process is known as hepatic first-pass metabolism or first-pass effect (Harris and Riegelman, 1969).

1.3 Dose-Linearity of Kinetics

The velocity of a chemical reaction can generally be expressed by the equation:

\[
\frac{dC}{dt} = K C^n
\]

where \( C \) is the concentration of reactant, \( K \) is the kinetic rate constant and \( n \) is the order of the reaction (Holtzman, 1983). In the pharmacokinetics of most drugs it appears that over some finite range \( n=1 \) thus producing
an integrated equation that is termed "linear". It should be noted that the use of the term "linear" in this context is not truly mathematically rigorous but is entrenched in pharmacokinetic literature. As well, the time course of drug concentration for many drugs cannot be expressed by a single exponential term and is instead equated to a sum of several apparently first order processes (Holtzman, 1983). These "linear" models assume that the pharmacokinetic parameters for a drug do not change when different size or multiple doses are administered (Shargel and Yu, 1985). However, this view is clearly flawed since many of the pharmacokinetic processes of absorption, distribution, biotransformation and elimination are mediated by enzymatic or carrier systems which clearly have some limitation to their capacity. Saturation of these systems leads to deviation from apparently "linear" kinetics and, hence, the display of "nonlinear" or dose-dependent kinetics.

In general, drugs displaying dose-dependent kinetics display the following characteristics (Shargel and Yu, 1985):

1) Drug elimination is not a simple first-order process.

2) As dose increases so does elimination half-life.

3) AUC does not increase proportionately to an increase in dose.
4) Capacity limited processes may be affected, at saturation, by other drugs requiring the same system(s).

5) The composition of metabolites may be altered as the dose is changed.

Since the pharmacokinetic parameters may be altered as additional doses are given, prediction of drug levels at steady-state based on data gathered from single dose studies is difficult. Although it is unexpected that any drug will display "linear" kinetics over an infinite concentration range most drugs do display linear kinetics over a significant range. It is therefore important to characterize the "linearity" of kinetics of a drug over the usual therapeutic dose range in order to optimize safety and efficacy of drug treatment to patients on multiple dose therapy.

1.4 Effects of Chronic Renal Failure on Pharmacokinetics

Although the kidneys are commonly viewed as organs of excretion for many drugs, chronic renal failure can alter all of the A.D.M.E. processes, either singly or simultaneously. The changes in the A.D.M.E. processes brought about by chronic renal failure reflect, in many cases, the physiological roles of the kidney that are
dissociated from simple excretion and the importance of this organ system to homeostasis.

1.4.1 Absorption and Bioavailability

Little intensive study has been made on the effects of chronic renal failure on drug absorption. Yet many sequelae of chronic renal failure and its therapy can lead to changes in the absorption and bioavailability of pharmaceuticals. Some of the most pronounced features of the uremic syndrome are displayed in the gastrointestinal tract. Features such as nausea, vomiting, diarrhea, pancreatitis, and colitis are common (Hoffsten and Klahr, 1983). These processes can alter the motility of the GI tract and therefore can change the extent of absorption of many drugs (Riegelman and Rowland, 1973). In addition, the absorption of many drugs is related to the degree of gastric acidity. Patients with chronic renal failure may have altered gastric pH, either raised due to the swallowing of urea and subsequent conversion to ammonia, or lowered due to an increased excretion of hydrogen ion into the stomach. Thus drugs whose absorption depends on the pH of the GI tract may have an altered bioavailability in patients with renal failure (Anderson and Granbertoglio, 1976). As well, ammonia could have a significant irritant effect on the GI mucosa, which may affect both permeability and the
surface area available for absorption, and also alter the absorption process through changes in GI motility.

Many patients routinely take aluminium hydroxide tablets to decrease the absorption of dietary phosphate (Lee and Marbury, 1984). It is well known that antacids can decrease the absorption of many drugs through complexation, alteration of gastric pH, or a delay in gastric emptying (Hurwitz, 1974; Welling, 1984).

Several reports of decreased first-pass effect in uremia exist (Balant et al., 1983). Both Lowenthal et al. (1974) and Bianchetti et al. (1976) have shown a decreased extent of first-pass metabolism for propranolol. These findings have, however, been challenged by Wood et al. (1979) on the basis that the control and renal failure groups of Bianchetti's study, in particular, were not age matched. Terao and Shen (1985) have subsequently shown that a circulating fraction present in uremic rat blood inhibits extraction of propranolol by rat liver which lends some credence to the earlier reports in man. Similarly the extent of first-pass effect for d-propoxyphene has been shown to be decreased in chronic renal failure (Gibson et al., 1977).

In summary, several processes due to the pathophysiology and therapy of chronic renal failure can alter the rate and extent of drug absorption.
1.4.2 Distribution and Protein Binding

The volume of distribution of a drug is a complex term which is the result of such physiological factors as body fluid pH, tissue composition, plasma protein binding, membrane permeability, tissue blood flow and capillarisation (Klotz, 1976). In somewhat simpler terms, the volume of distribution is an overall reflection of drug-protein binding, drug-RBC partitioning, and tissue drug uptake (Lee and Marbury, 1984).

Perhaps the most notable change in distribution is the alteration of the extent of protein binding of many drugs. Several reviews have appeared on this topic including two notable older reviews (Reidenberg, 1977; Tillement et al., 1978) whose findings have remained largely unchanged since publication. In general, the patient with chronic renal failure is hypoalbuminemic due to dietary protein restriction, decreased albumin synthesis, and shifts in the total body distribution of albumin (Tillement et al., 1978). Furthermore the affinity of the albumin for drugs may be altered due to the presence of endogenous binding inhibitors (e.g. free fatty acids), the presence of metabolic acids, and possibly structural changes in the albumin binding site(s) (Tillement et al., 1979). In contrast, the
concentration of the acute phase reactant, alpha-l-acid glycoprotein (AAG, orosomucoid) has been shown to be increased in hemodialysis patients (Henriksen et al., 1982).

The changes in protein concentration and affinity, associated with renal failure, cause the following general processes to occur. The binding of acidic drugs is generally decreased while that of basic or neutral drugs is unchanged or increased (Reidenberg and Drayer, 1984). Examples of both abound with representative examples shown by the acidic drug phenytoin

\[
\begin{align*}
V_{d_{\text{normal}}} &= 0.5 - 0.7 \text{ L/kg, } \% \text{ bound } = \sim 90 \%; \\
V_{d_{\text{uremic}}} &= 1 - 1.8 \text{ L/kg, } \% \text{ bound } = 75 - 85 \%
\end{align*}
\]

(Gibaldi, 1977) and with the basic drug digoxin \(V_{d_{\text{normal}}} = 7.3 - 8.1 \text{ L/kg, } \% \text{ bound } = 25 \%; \\
V_{d_{\text{uremic}}} = 4.4 - 4.7 \text{ L/kg, } \% \text{ bound } = \sim 17\%
\)

(Jusko and Weintraub, 1974).

The influence of changes in protein binding on clearance has been reviewed by Rowland (1984). The influence of protein binding changes on clearance depends on the affinity of the drug for tissues outside the extracellular fluids and on the intrinsic clearance of the drug by an organ. If unbound drug clearance is low in comparison to organ blood flow, then organ clearance will be sensitive to the extent of protein binding. If, however, organ clearance is high then elimination becomes
perfusion rate-limited and relatively insensitive to the extent of protein binding.

Chronic renal failure is also often accompanied by a severe anemia which results from decreased erythropoietin production and a decreased life span of the red blood cell. Therefore, drugs which partition into erythrocytes could have their distribution altered in chronic renal failure. For example, anemic patients demonstrate significantly higher plasma gentamicin levels than subjects with a normal haematocrit (Riff and Jackson, 1971).

End-stage renal failure may also affect the tissue uptake of many drugs. Possibly the best example of this is with digoxin (Jusko and Weintraub, 1974). With decreasing creatinine clearance, it was noted that the myocardial/serum concentration ratio decreases. This implies that the uptake of digoxin into the heart decreases as renal failure worsens.

Thus, the physiological changes brought about by renal failure may substantially alter the distribution of many drugs.
1.4.3 Metabolism

Although the liver is commonly thought of as the primary metabolic organ for drugs, the kidney plays a significant role in the metabolism of many endogenous substances and xenobiotics (Gibson, 1986). The alteration of drug metabolism in renal failure has been the subject of several recent reviews (Reidenberg, 1977; Verbeeck et al., 1981; Balant et al., 1983; Gibson, 1986).

Reidenberg (1977), based on examinations of studies to that time, made the following generalizations with respect to rates of metabolic drug elimination in uremia: a) oxidative types of reactions appeared to occur at normal or increased rates; b) reductive type reactions were slowed; c) synthetic reactions (e.g. glucuronidation, sulphation, glycination, acetylation) occurred at apparently normal rates d) hydrolytic reactions were slowed. More recent studies (Gibson, 1986), however, suggest that these generalizations may be too broad since they are based on too limited a spectrum of studies. Verbeeck et al. (1981) highlight the possibility of hydrolysis and recirculation of inactive conjugates, particularly glucuronides, which may result in an apparently prolonged activity of the parent drug. Examples of this process may occur for oxazepam, lorazepam, diflunisal, and clofibrate (Verbeeck et al.,
Balant et al. (1983) demonstrate the effects of renal failure on the kinetics of a variety of beta blockers and the cephalosporin, cefoperazone. These authors, however, do not relate any precise causes of the alterations in hepatic metabolism to the existence of renal failure. Recently, Gibson (1986) reviewed many studies with respect to the effect of renal failure on drug metabolism, both hepatic and extra-hepatic. This review provides a more comprehensive and updated approach to the work of Reidenberg (1977). In summary, the findings of Gibson (1986) concur with those of the previous authors (Reidenberg, 1977; Verbeeck et al., 1981; Balant et al., 1983), in that (1) renal disease may alter hepatic drug metabolism and (2) that the kidneys may play an important role in xenobiotic metabolism.

Although it is difficult to demonstrate specific mechanisms causing alterations of drug metabolism in renal failure, several possibilities exist. Massive retention of metabolites, normally excreted by the kidney, may result in "negative feedback", thereby inhibiting the conversion of the parent drug (Verbeeck, 1982; Gibson, 1986). The activity of the mixed function oxidase system in rats has been shown to be diminished in experimentally induced renal failure (Gibson, 1986) but comparable findings in man have not been reported. Recently, Terao and Shen (1985) demonstrated that a
soluble fraction of uremic rat blood reduced the extraction of propranolol by an isolated rat liver, thus raising the possibility of a circulating metabolic inhibitor. This result may explain findings by Bianchetti et al. (1976) and Lowenthal et al. (1974) of decreased clearance of propranolol in uremic patients. It has also been demonstrated that renal failure decreases organic anion transport into the liver, although similar results for organic cations have not been reported (Yates et al., 1985).

1.4.4 Elimination of Intact Drug and Metabolites

Perhaps the most obvious change in pharmacokinetics in renal failure is the diminished excretion and hence increased serum half-life of the parent drug and metabolites that are normally excreted by the kidney. The clearance of the endogenous substance, creatinine, allows an estimation of glomerular filtration rate that, for a number of drugs, reflects drug elimination (Gibaldi and Perrier, 1982). It is recognized, however, that the kidney is also capable of secretion, particularly in the S_3 segment of the proximal tubule, as well as resorption along the nephron. These processes may alter the accuracy of kinetic estimates based on creatinine clearance derived glomerular filtration rate.
Several authors have reviewed the effects of renal disease on drug elimination (Dettli, 1976; Levy, 1977; Fabre and Balant, 1976; Jusko, 1980; Vree et al., 1983; Lee and Marbury, 1984). Their approaches stem from the fact that the overall elimination rate constant $K_E$ can be expressed as the sum of renal and non-renal elimination rate constants.

$$K_E = K_{\text{renal}} + K_{\text{non-renal}}$$

and, assuming for most drugs that $K_{\text{renal}}$ is a linear function of creatinine clearance, then:

$$K_E = A \left( Cl_{cr} \right) + K_{\text{non-renal}}$$

where: $A = \text{constant}$

$Cl_{cr} = \text{creatinine clearance}$,

Thus, drugs can be broken up into three general kinetic classes; a) those eliminated solely by renal routes, b) those eliminated solely by non-renal routes, and c) those eliminated by both routes (Dettli, 1976). A plot of $K_E$ vs $Cl_{cr}$ for each class of drugs is shown in Figure 2:
Thus, it can be seen that those drugs relying on exclusively renal mechanisms for elimination will accumulate, since their half-lives will be much prolonged. It also appears that those drugs removed exclusively by non-renal routes will have their half-lives substantially unaltered, however as previously discussed, this may be an over-simplification. Finally, the magnitude of change for those drugs eliminated by both routes will depend on the relative magnitudes of renal and non-renal elimination.

As well as accumulation of the parent drug, accumulation of polar metabolites may also occur in renal failure. This phenomenon has been extensively reviewed by Verbeeck et al. (1981). Appreciation of this is important since accumulation of metabolites may lead to
altered therapeutic or toxic effects in a renally impaired patient.

In summary, chronic renal failure can produce significant changes in almost all pharmacokinetic parameters due to the fact that the kidney fulfills many other physiological roles besides maintenance of fluid and electrolyte balance.

1.5 Influence of Hemodialysis on Drug Removal

Dialysis may be defined as the separation of crystalline substances (e.g. NaCl) from colloidal substances (e.g. serum albumin) utilizing differences in their rates of movement across a semi-permeable membrane. Hemodialysis involves passing the patients blood through an "artificial kidney" with a semi-permeable membrane around which flows a dialysate of similar composition to normal plasma. Solutes then are free to move from blood to dialysate or vice versa by passive diffusion or accompanying water movement (solvent drag). In addition to removing solutes from the uremic plasma, dialysis also removes water from the dialysis patient via ultrafiltration.

The movement of a substance across the semi-permeable membrane is influenced by several factors
(Gibson and Nelson, 1977; Lee and Marbury, 1984). Since the semipermeable membrane has discrete pores, solute shape, molecular size, and molecular weight significantly influence the ability of the molecule to pass through easily. Generally, hemodialysis is effective in removing solutes with molecular weights below 5000 Daltons. Substances that are water soluble are generally removed more readily than those that are more lipophilic. The surface area, porosity, and thickness of the semipermeable membrane also influence the rate of solute removal. The rates of flow of the blood and dialysate and the proximity of the entire system to sink conditions are also significant factors influencing the rate of solute movement.

Drugs, as solutes in the plasma, can also be removed by hemodialysis. The removal of pharmaceuticals by hemodialysis has been reviewed by many authors (Gibson et al., 1977; Maher, 1977; Gibson and Nelson, 1977; Watanabe, 1977; Lee and Marbury, 1984). Although governed by the same requirements as plasma solutes for removal by hemodialysis, several pharmacokinetic parameters can give an indication of whether a drug will be dialysable or not (Lee and Marbury, 1984). Since the existence of a concentration gradient is essential as a driving force for passive diffusion, Vd is of primary importance to drug dialysability. Generally, drugs with
Vd < 1 L/kg will be dialysable while those with Vd > 2 L/kg will not. Furthermore, since only free drug can be removed, drugs that are highly protein bound are not likely to be extensively removed by hemodialysis. Those drugs normally excreted primarily by the kidney will be more dialysable than those primarily excreted by metabolism. Drugs with very long or very short elimination half-lives are usually not dialysable. Since maximal dialyser clearances are on the order of 100 mL/min, those drugs with metabolic clearances > 200 mL/min (e.g., tricyclic antidepressants) are not dialysable since removal by dialysis is rendered non-competitive by the high intrinsic clearance. Levy (1977) states that for hemodialysis to be a significant contributor to total body clearance of drug it must account for > 30% of total body clearance. Mathematically, dialysis may be treated as any other first-order route of drug elimination. Several authors have described the equations necessary to describe drug removal by dialysis (Maher, 1977; Gibson and Nelson, 1977, Watanabe, 1977; Gwilt, 1981; Lee and Marbury, 1984). Wellhoner (1981) has extended these calculations to a two-compartment system.

Two extensive reviews of drug removal by peritoneal dialysis have also recently appeared (Janknegt and Koks, 1984; Paton et al., 1985).
1.6 Metoclopramide Pharmacokinetics

1.6.1 Animal Models

Animal experiments (rabbit, rat, and dog) have shown that metoclopramide (MCP) is well absorbed, extensively metabolized, and rapidly excreted in the species studied (Tunon et al., 1974; Bakke and Segura, 1976; Bateman et al., 1980; Tam et al., 1981). Metabolism occurs via sulphate and glucuronide conjugation at the N\(^4\) position [rabbit, dog] (Arita et al., 1970; Cowan et al., 1976; Bateman et al., 1978), O-demethylation, N-de-ethylation and amide hydrolysis [rat, rabbit, dog] (Arita et al., 1970; Bakke and Segura, 1976; Cowan et al., 1976).

Peak plasma concentrations occur 30-120 minutes after oral MCP dosing. Early reports (Bakke and Segura, 1976) gave the elimination half-life of MCP following IV injection as 20, 28, and 36 minutes in the rat, rabbit, and dog respectively. Somewhat in contrast to this, Tam and Axelson (1978) demonstrated a half-life of 50 minutes in the rat with dose-dependent changes in \( t_{1/2} \) at doses above 15 mg/kg. Furthermore studies in the rat by Kapil et al. (1984) and Tam et al. (1981) suggest that MCP undergoes saturable first-pass metabolism at doses below 1 mg/kg and unusual dose-dependent kinetics due to apparently MCP induced hepatic blood flow changes at doses above 15 mg/kg.
Tam et al. (1981a) have also carried out kinetic studies in rats with experimentally induced renal and hepatic failure. Experimentally induced (CCl₄) hepatic failure leads to an approximate 3 fold increase in plasma half-life and area under the plasma concentration vs time curve (AUC). Volume of distribution, however, was shown to remain essentially unchanged. Urinary excretion of intact MCP was approximately doubled in these animals yet the formation of the N-de-ethylated metabolite was unchanged, suggesting extrahepatic formation of this substance. Investigations of animals with experimentally induced renal failure (5/6 two-step nephrectomy, bilateral ureteral ligation, or uranyl nitrate) showed at least a two-fold increase in plasma half-life and AUC with a proportional decrease in total body clearance. Volume of distribution was slightly decreased in these animals. Although these investigators postulated diminished extrahepatic metabolism as the mechanism for the alterations seen in renal failure, this has been ruled out by Kapil et al. (1984). A more likely mechanism is the decrease in hepatic metabolism secondary to renal failure (Bateman et al., 1981; Kapil et al., 1984)
1.6.2 Human Studies

Several studies have been completed on the pharmacokinetics and bioavailability of MCP in normal, healthy volunteers. The kinetic studies have tended to focus either on the doses used in cancer chemotherapy (1-2 mg/kg as a short infusion) (Taylor et al., 1984; Bryson et al., 1985; Saller et al., 1985) or on lower doses (5-50 mg) (Graffner et al., 1979; Schuppan et al., 1979; Bateman et al., 1980; Ross-Lee et al., 1981; Bateman et al., 1981; Block et al., 1981; Bateman, 1983). While the more recent "high-dose" chemotherapy studies have been generally well done, unfortunately, many of the existing "low-dose" studies suffer from analytical and/or methodological problems that cast some degree of doubt on their findings. Basically these deficiencies fall into three general categories: (1) poor assay sensitivity/selectivity (Schuppan et al., 1979; Bateman et al., 1980) (2) the use of a tablet or capsule as the oral reference dosage form in bioavailability assessments (Schuppan et al., 1979; Graffner et al., 1979; Bateman et al., 1980; Ross-Lee et al., 1981) (3) failure to compare equal oral and IV doses (Schuppan et al., 1979; Graffner et al., 1979; Block et al., 1981).

The failure of many of the previous assay methods to be sensitive and selective has resulted in several
problems. The most significant of these is the lack of ability to sample plasma long enough after dosing to produce an accurate estimate of the true biological half-life. Gibaldi and Weintraub (1971) have shown that truncation of the sampling interval can lead to an underestimation of the biological half-life. The inaccuracy in half-life determination has led to claims of dose-dependency of MCP kinetics (Bateman et al., 1980; Bateman, 1983) which may be artifactual.

The use of a tablet or capsule as the oral reference dosage form in bioavailability studies can be inappropriate in some instances since disintegration and dissolution rates can substantially alter bioavailability (Riegelman and Rowland, 1973). A more appropriate dosage form is the commercially available oral solution.

Although it is possible to determine bioavailability from unequal oral and IV doses, such a determination is based on the existence of linear kinetics over the dose range in question. Prior to 1984, no such determination had been made, in fact the evidence from animal models (Kapil et al., 1984; Tam et al., 1981) was quite to the contrary. Recently, Wright et al. (1984) have demonstrated linear kinetics in the range of 20 - 100 mg. Linear kinetics have also been observed in the high-dose cancer chemotherapy trials (Bryson et al., 1985). These
dosages are, however, cover a different range from those examined in the following study.

In general, MCP appears to be rapidly absorbed from the GI with a significant first-pass effect (Bateman et al., 1979; Ross-Lee et al., 1981). MCP appears to be widely distributed in man with volume of distribution ranging from 2.2 - 3.4 L/kg (Harrington et al., 1983). MCP is ~40% bound to plasma proteins particularly to AAG (Webb et al., 1986). In man, MCP is predominantly metabolized to the N\textsuperscript{4}-sulphonate (~32-40% of IV or oral dose) (Bateman et al., 1980; Teng et al., 1977) as well as a minor (<5%) contribution from the N\textsuperscript{4}-glucuronide. Approximately 25% of the dose is excreted as intact drug (Teng et al., 1977). Total body clearance is relatively high (11.61 mL/min/kg) (Harrington et al., 1983) with renal clearance accounting for about 20% of this value. Elimination half-life ranges from 2.6 - 5.1 hours (Harrington et al., 1983) and claims of dose dependency have been made (Graffner et al., 1979; Bateman, 1983).

Given the pharmacokinetic information available about MCP in normal human volunteers it was unexpected that the kinetics should be significantly altered in patients with renal failure. However, several reports to Lancet showed a higher incidence of side effects in uremic patients given MCP (Caralps, 1979;
Bateman and Davies, 1979; Bateman and Gokal, 1980). This was later attributed to an unexpectedly large decrease in total body clearance of MCP in uremic patients (Bateman et al., 1981). Recently another study (Lehmann et al., 1985) has been completed in patients with renal failure. These studies have shown at least a two-fold decrease in total body clearance with a proportional increase in plasma elimination half-life. Preliminary evidence suggests that hemodialysis (Bateman et al., 1981, Lehmann et al. 1985) and peritoneal dialysis (Berardi et al., 1986) are ineffective at removing MCP from the body. This is probably the result of the large volume of distribution of MCP. No mechanism has been proven to be responsible for the unexpected changes in MCP kinetics shown by uremic patients. Lehmann et al. (1986) have suggested a circulating metabolic inhibitor but this has not been substantiated.
2. EXPERIMENTAL

2.1 Materials and Supplies

2.1.1 Chemicals

The following were supplied by A.H. Robins Canada Inc., Montreal, Quebec:
4-amino-5-chloro-2-methoxy-N-(2-diethyl aminoethyl) benzamide monohydrochloride monohydrate (MCP.HCl.H₂O) (Lot Nos. A105 and F058), MCP.HCl 5 mg/mL (Reglan \(^R\) Injectable, 2 mL Ampule) (Lot No. 84637), MCP.HCl Syrup 1mg/mL (Reglan \(^R\), 100 mL bottle) (Lot No. 8474), MCP.HCl \(H_2O\) Tablets 10 mg (Reglan \(^R\)) (Lot No. 84707).

Maprotaline.HCl (MAP HCl) (N-methyl -9-10-ethanoanthracene-9(10H) propanamide Hydrochloride)
Lot A11663096472-0 was supplied by Ciba Pharmaceuticals, Mississauga, Ontario.

2.1.2 Reagents

ACS reagent grade Sodium Hydroxide pellets were obtained from Fisher Scientific Co., Fair Lawn, NJ, U.S.A.. ACS reagent grade Hydrochloric Acid 37% was obtained from American Scientific and Chemical, Seattle, WA, U.S.A.. Ammonia Solution Strong 27% was obtained from Mallinckrodt Inc., St. Louis, MI, U.S.A..
Heptafluorobutyric Anhydride and Triethylamine Sequanal Grade were obtained from Pierce Chemical Co., Rockford, IL, U.S.A.

2.1.3 Solvents

Benzene and toluene (distilled in glass) were obtained from Caledon Laboratories Inc., Georgetown, Ont.. Deionized water was produced on site via a Milli-RO^R System, Millipore Corp., Bedford, MA., U.S.A.. Methanol ACS reagent grade and acetone ACS reagent grade were obtained from BDH Chemicals, Toronto, Ontario.

2.1.4 Gases

Nitrogen U.S.P. and Medical Air were obtained from Union Carbide Canada Ltd., Toronto, Ontario. Hydrogen UHP and Argon/Methane (95:5) were obtained from Matheson Gas Products Canada Ltd; Edmonton, Alberta.

2.1.5 Supplies for Human Experiments

Intravenous drug administration was made through a sterile Argyle^R Venocut^TM infusion set (19 gauge needle) obtained from Sherwood Medical, St. Louis, MI, U.S.A.. A Butterfly^R-19 INT cannula (Abbott Ireland, Sligo, Republic of Ireland) was implanted in the contralateral arm to facilitate blood sampling. Glass 1 mL (Glaspak^R), plastic 1 mL and 3 mL syringes, 22 and 25 gauge needles,
and luer adapters were obtained from Becton-Dickson Canada, Mississauga, Ontario. Urine samples were collected in Whirl-pak\textsuperscript{R} bags (AHS Canada, Richmond, B.C.). Whole blood was collected into heparinized vacutainer tubes (Vacutainer Systems, Rutherford, NJ, U.S.A.). Following centrifugation the plasma was stored frozen in sterile Pyrex\textsuperscript{R} tubes (Corning Glass Works, Corning, NY, U.S.A.).

2.2 Equipment

A model 5840A Hewlett-Packard gas chromatograph equipped with a $^{63}$Ni electron capture detector (ECD), a model 18850A GC terminal and integrator, and a packed column compatible model 18835B capillary inlet system, Hewlett Packard Co., Avondale, PA, U.S.A.; a bonded phase fused silica capillary column (5\% phenyl methyl silicone stationary phase, cross-linked; film thickness 0.52 um, phase ratio 150, column I.D. 0.31 mm, column length 25m), Hewlett-Packard Co., Palo Alto, CA, U.S.A.; vortex-type mixer (Vortex-Genie\textsuperscript{R}), incubation oven (Isotemp\textsuperscript{R}, model 350), Fisher Accumet\textsuperscript{R} pH meter Model 620, water bath with temperature control, (Haake D1 model), Fisher Scientific Industries, Springfield, IL, U.S.A.; IEC Model 2K Centrifuge, Damon/IEC division, Needham Hts., MA, U.S.A.; rotating-type tube mixer (Labquake\textsuperscript{R}, model 415-110), Labindustries, Berkeley, CA, U.S.A.; 15 mL
Pyrex\textsuperscript{R} culture tubes with Teflon\textsuperscript{R} lined screw caps, Canlab, Vancouver, B.C.

2.3 Preparation of solutions

2.3.1 Metoclopramide.HCl

Approximately 11.81 mg of MCP.HCl.H\textsubscript{2}O (equivalent to ~10 mg of MCP free base) was accurately weighed, transferred to a 100 mL volumetric flask and dissolved in deionized water. A volume, (0.2 mL), of this solution was diluted to 100 mL in a volumetric flask with deionized water. The final working stock solution was produced by taking a 10 mL aliquot of the second solution and diluting this in a 50 mL volumetric with deionized water. The concentration of the final working stock solution was ~0.04 ug/mL.

2.3.2 Maprotaline (MAP).HCL

Approximately 11.31 mg of MAP HCl (equivalent to ~10 mg of MAP free base) was accurately weighed and transferred to a 100 mL volumetric flask and dissolved in deionized water. A volume, 0.2 mL, was then diluted to 50 mL with deionized water in a volumetric flask. The concentration of this working solution was ~0.4 ug/mL.
2.3.3 Reagent Solutions

Hydrochloric Acid 1 N was prepared by diluting 8.3 mL ACS reagent grade concentrated HCl (37%) to 100 mL with deionized water in a volumetric flask.

Sodium Hydroxide (NaOH) 1 N and 5 N solutions were prepared by dissolving 4 and 20 g, respectively, of NaOH pellets in deionized water in 100 mL volumetric flasks.

Ammonium Hydroxide 4% was prepared by diluting 13.3 mL of Strong Ammonia solution (30%) to 100 mL with deionized water in a volumetric flask.

Triethylamine, 0.0125 M in toluene, solution was prepared by diluting 0.125 mL triethylamine to 100 mL with toluene in a volumetric flask. Four or five NaOH pellets were then added to the solution.

2.4 Sample Extraction procedure

2.4.1 Biological Fluid Extraction

The method used is identical to that developed by Riggs et al. (1983) and is outlined in Scheme 1. Normal or uremic plasma, 0.1 - 0.5 mL, or 0.01 to 0.10 mL of urine, containing MCP following dosing, were added to a clean Pyrex\textsuperscript{R} tube containing 0.50 mL 1 N NaOH, 0.2 mL MAP internal (0.4 ug/mL) standard solution. The tubes were
then made up to a volume of 2.2 mL with distilled water. Following the addition of 6 mL benzene the tubes were capped, with Teflon\textsuperscript{R}-lined caps, and rotated for 20 minutes on a rotating rack (Labquake\textsuperscript{R}) to extract the metoclopramide and maprotaline. After centrifugation at 2300 g for 2 X 5 minutes the organic phase was removed and back-extracted using 2 mL of 1 N HCl then rotated for 20 minutes on a rotating rack. Following centrifugation for 5 minutes (@ 2300 g) the organic layer was aspirated and discarded (water vacuum aspirator). The remaining aqueous layer was washed twice with 4 mL of benzene, which were subsequently aspirated. The remaining aqueous layer was alkalinized with 0.5 mL 5 N NaOH and then extracted for 20 minutes following the addition of 6 mL benzene. Following centrifugation (5 min @ 2300 g), 5 mL of the organic layer was removed and dried under a gentle flow of nitrogen in a 40 °C water bath. The nitrogen dried residues were then derivatized as follows prior to GC-ECD analysis.

2.4.2 Derivative Formation

The nitrogen dried residue was reconstituted with 800 uL of 0.0125 M Triethylamine in toluene. Following reconstitution 20 uL of heptafluorobutyric anhydride were added and the samples briefly vortexed to ensure complete mixing. The samples were then incubated at 55°C for
EXTRACTION PROCEDURE

Blank plasma spiked with MCP standard solutions.

Plasma samples (0.2-0.5 mL) or urine (0.01-0.5 mL) from normal/uremic subjects.

0.5 mL 1N NaOH, 0.2 mL
0.4 mcg/mL Maprotaline, 6 mL benzene, mix, 20 min
centrifuge, 10 min

discard aqueous layer

Organic layer

2 mL 1N HCl, mix, 20 min
centrifuge, 5 min

discard organic layer
wash twice with 4 mL benzene

Aqueous layer

0.5 mL 5N NaOH, 6 mL benzene mix, 20 min
centrifuge, 5 min

discard aqueous layer

Organic layer

evaporate to dryness
under nitrogen @ 40°C.
0.8 mL 0.125 M triethylamine in toluene, 20 uL HFBA,
derivatize for 1 hour @ 65°C.
cool to room temperature.
0.5 mL H2O, vortex, 10 sec.
0.5 mL NH4OH, vortex, 10 sec.
centrifugé, 1 min. Transfer organic layer to vials

Inject into GC (2 uL)

Scheme 1: Extraction Procedure (Riggs et al., 1983)
1 hour. Following incubation the tubes were allowed to cool to room temperature, at which time the excess HFBA reagent was hydrolyzed by the addition of 0.5 mL distilled water and vortexing for 10 seconds. The excess acid was then neutralized by the addition of 0.5 mL 4% NH₄OH and vortexing for 10 seconds followed by centrifugation (@ 2300 g) for 1 minute. The organic layer was then immediately transferred to clean autosampler vials from which 2 uL were injected for GC-ECD analysis.

2.5 Standard Curve Preparation for Fused Silica Capillary GC-ECD Analysis.

Volumes of 0.05, 0.1, 0.2, 0.4, 0.6, and 0.8 mL of MCP HCL stock solution (0.04 ug/mL) were pipetted into clean Pyrex tubes containing 0.2 mL blank human plasma, 0.2 mL MAP.HCl stock solution (0.4 ug/mL), and 0.5 mL 1 N NaOH. Each tube was then made up to a volume of 2.2 mL with distilled water and extracted and derivatized as in Sections 2.4.1 and 2.4.2.

2.6 Capillary GC-ECD

2.6.1 GC-ECD Parameters

The parameters for the GC-ECD system are as follows: Injection temperature 260 °C; initial column temperature 205 °C; detector (ECD) temperature 350 °C; carrier gas
(Hydrogen) flow 30 mL/min; carrier gas (Argon-Methane 95:5) flow rate 60 mL/min; inlet pressure 10 p.s.i.; attenuation $2^6$; chart speed 0.4 cm/min; slope sensitivity 0.15 - 0.4; valve open time 0.1 min, valve closed time 1.75 min.; rate of temperature increase 4 °C/min after 0.81 minutes.

2.6.2 Application of Assay to Uremic Plasma

The applicability of the assay method had previously been shown to human plasma and urine samples, as well as sheep plasma, amniotic fluid, tracheal fluid and urine. However, the ability of the assay to quantify MCP in the presence of the components of uremic serum was unknown. A series of blank plasma samples were drawn from several uremic volunteers and aliquots of 150, 200, 250, and 500 uL were extracted and derivatized as outlined in sections 2.4.1 and 2.4.2 to determine whether any component of the blank uremic plasma would interfere with the detection and quantitation of either MCP or MAP.

2.7 Pharmacokinetic Studies in Normal and Uremic Humans.

2.7.1 Experimental Protocol in Normal, Healthy Volunteers

Six male, non-smoking volunteers gave informed, written consent prior to the initiation of the study.
All volunteers were healthy as assessed by a physical examination and by standard hematological and biochemical laboratory tests. More specifically none showed, or had prior history of, any abnormality of hepatic function, (as demonstrated by SGOT, SGPT, or ALK PHOS measurements), or renal function (as demonstrated by BUN, serum creatinine, and creatinine clearance). All subjects were fasted for 12 hours prior to dosing and for 4 hours following drug administration. All volunteers were instructed to avoid other medications, including over-the-counter medications, for one week prior to the study and were also required to abstain from alcohol for 48 hours prior to and during the study.

The study was conducted on a four-way crossover basis. All volunteers received a 10 mg MCP IV dose (Reglan® Injectable, A.H. Robins Canada Inc., Montreal, Que), a 5 and 20 mg dose of MCP in oral solution form (Reglan®, A.H. Robins). Three volunteers then received a 10 mg dose of MCP oral solution while the other three volunteers received a 10 mg MCP dose as an oral tablet (Reglan®, A.H. Robins). All drug administrations were separated by at least one week to allow for complete drug washout. On a study day, an indwelling cannula (Butterfly-19® INT, Venisystems, Abbott Ireland Ltd.) was placed in a forearm vein prior to drug administration to facilitate blood sampling, a blank blood sample taken and
the patency of the cannula maintained throughout the experiment using heparinized saline (50 U/mL).

On the day of the IV administration, another cannula was implanted in the forearm contralateral to the sampling cannula. The 10 mg MCP dose was then given as a short IV infusion over 3.5 minutes using a Harvard Model 944 infusion pump (Millis, MA). Oral drug administration was accompanied by ~200 mL of water. Blood samples (5 mL) were taken at -5, 2, 4, 6, 10, 20, 40, and 60 minutes, and 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, 24, 48, and 72 hours following IV drug administration. Following oral drug administration, blood samples (5 mL) were drawn at 15, 30, 45, and 60 minutes, and 1.5, 2, 3, 5, 6, 8, 10, 12, 14, 16, 24, 48, and 72 hours. Blood was drawn from the cannula, after removal of the heparinized saline, into 10 mL glass Vacutainer tubes containing lithium heparin (Vacutainer\textsuperscript{R}, Vacutainer Systems, Rutherford, NJ, U.S.A.). The plasma was separated by centrifugation, placed in fresh glass (Pyrex\textsuperscript{R}) tubes with screw-on Teflon\textsuperscript{R} lined caps, and frozen until analysis. On all occasions, a total urine collection for 72 hours, at hourly intervals for the first 12 hours, was made. Urine was carefully gathered in plastic Whirl-pak\textsuperscript{R} bags, the volume and pH immediately measured, and an aliquot stored, frozen until analysis.
6 Normal, healthy volunteers well matched for age, height, and weight

- Fasted 12 h prior to and for the first 4h post-dose
- No medications for 1 week prior to or during study
- No alcohol 48 h prior to or during study

Blood and urine sampled for 72 h

Electron-capture gas-chromatographic analysis

Scheme 2: Study Protocol in Normal Healthy Volunteers
2.7.2 Quantitative Analysis in Normals

Plasma samples 0.2-0.5 mL were extracted and derivatized as described in Sections 2.4.1 and 2.4.2. Maprotaline HCl (0.4 ug/mL) was used as the internal standard. Each sample was measured in duplicate. Each duplicate was injected (2 uL) twice into the ECD-GC. Quantitative determination of MCP was made by fitting the area-ratios of the HFB derivatives of MCP/MAP to the standard curve regression line (area ratio MCP/MAP vs MCP concentration). Standard curve samples were extracted, derivatized, and chromatographed on the same day as the volunteer samples. The study in normals is summarized in Scheme 2.

2.7.3 Experimental Protocol for Uremic Volunteers

Eight patients, 7 male and 1 female, with severe renal impairment (creatinine clearance < 10 mL/min) and on maintenance hemodialysis were studied. Following approval of the study protocol by the Human Ethics Committee of the University of British Columbia, all patients gave informed, written consent. Values for standard hematological and biochemical tests, taken as part of the routine clinical monitoring of these patients, were recorded prior to drug administration.
All patients fasted for 12 hours prior to drug administration and for at least 1 hour after drug administration. The uremic subjects continued any medications required for therapy (see Appendix), however, no interference was noted in the metoclopramide assay from any of these substances.

The uremic patients received a 10 mg IV dose of MCP on two separate occasions. The first drug administration occurred 24 hours prior to a dialysis session. The dose was given by a short IV infusion, using a Harvard Model 944 infusion pump, over 3.5 minutes. Blood samples, 1 mL, were taken from an indwelling cannula (Butterfly-19-INTR, Venisystems, Abbott Ireland Ltd.) into a glass 1 mL tuberculin syringe (Glaspak, Becton and Dickson, Rutherford NJ, U.S.A,) and processed as outlined for the normal volunteers (see Section 2.7.1). Blood samples were drawn at -15, 5, 15, 30, 45, and 60 minutes, and 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours following drug administration and at half-hourly intervals from the dialyser arterial and venous lines for the duration of hemodialysis. Following a period of at least one week, to allow for complete drug washout, the uremic patients were given a second 10 mg IV dose 1 hour prior to dialysis. Blood samples were taken at -15, 5, 15, 30, 45, and 60 minutes, then half-hourly from the dialyser arterial and venous lines during dialysis, and then at 5,
8 Uremic volunteers (creatinine clearance < 10 mL/min) on hemodialysis 3 times per week

n = 8  n = 7  n = 1

10 mg IV MCP 24 h prior to hemodialysis
10 mg IV MCP 1 h prior to hemodialysis
10 mg IV MCP 16 days post-transplant
10 mg IV MCP 3 months post-transplant

plasma sampled for 24 h and during dialysis
plasma sampled for 24 h (incl. dialysis)
plasma and urine sampled for 24 h

Electron-capture gas-chromatographic analysis

Scheme 3: Study Protocol in Uremic Patients and Kidney Transplant Recipient
6, 8, 10, 12, and 24 hours. Again, the blood samples were processed as for the normal healthy volunteers (see Section 2.7.1).

2.7.4 Quantitative Plasma Analysis in Uremic Patients

A volume, 0.1 - 0.3 mL, of the plasma samples were extracted and derivatized as previously outlined (see Sections 2.4.1 and 2.4.2). Maprotaline HCl (0.4 ug/mL) was used as the internal standard. Each sample was measured in duplicate and each duplicate was injected twice, 2 uL, into the ECD-GC for analysis. Quantitation was made by fitting the area ratios for the HFB derivatives of MCP/MAP to the standard curve regression line (area ratio MCP/MAP vs MCP concentration). Standard curve samples were extracted, derivatized, and chromatographed on the same day as the volunteer samples. The study in uremics is summarized in Scheme 3.

2.7.5 Experimental Protocol for the Kidney Transplant Recipient

Subsequent to the first administration of MCP to a uremic male volunteer (BM), this patient received a kidney transplant. The patient then received two further doses of 10 mg IV MCP as a short infusion, over 3.5 minutes, at 16 days post-surgery and again at 3 months after transplantation. Informed written consent was
obtained on all occasions. The sampling protocol and biological sample processing were the same as outlined for the uremic volunteers receiving the dose 24 hours prior to dialysis. In addition, urine was collected for 24 hours as described for the normal, healthy volunteers (see Section 2.7.1). Laboratory indices were recorded from the patients' chart.

2.7.6 Quantitative Analysis in Kidney Transplant Recipient

Plasma, 0.1 - 0.3 mL, or 10 uL of urine were extracted and derivatized as outlined in Sections 2.4.1 and 2.4.2. Maprotaline (0.4 ug/mL) was used as the internal standard throughout the study. Each sample was measured in duplicate using two injections of 2 uL each into the GC-ECD. Quantitative determination of MCP was made by fitting the area ratio of the HFB derivative of MCP/MAP to the standard curve regression line (area ratio MCP/MAP vs MCP concentration). Standard curve samples were extracted, derivatized, and chromatographed on the same day as the volunteer samples.

2.8 Data Analysis

2.8.1 Computer Fitting

Following analysis of the biological samples for metoclopramide content, the data were plotted manually to
obtain initial kinetic parameter estimates. The concentration vs time data were then run by the decision making program AUTOAN (Sedman and Wagner, 1976) to give computer generated estimates of the kinetic parameters and model. These estimates were then independently confirmed by using the iterative program JANA (Dunne, 1985) to also fit the data. The initial estimates were then used by the computer program NONLIN (Metzler et al., 1974) to yield final estimates of the kinetic parameters which were used in further calculations.

2.8.2 Pharmacokinetic Calculations

Area under the plasma concentration vs time curve was determined by the trapezoidal approximation. The pharmacokinetic values of clearance, volume of distribution, and bioavailability are based on standard calculations given by Gibaldi and Perrier (1982). The dialysis parameters, extraction efficiency and dialyzer clearance, were calculated by the A-V difference method described by Lee and Marbury (1984) using the formula:
Extraction efficiency \( E = \frac{C_a - C_v}{AUC_a - AUC_v} \)

where: 
\( C_a \) = plasma MCP concentration entering dialyser 
\( C_v \) = plasma MCP concentration exiting dialyser 
\( AUC_a \) = area under the plasma concentration vs time curve entering the dialyser 
\( AUC_v \) = area under the plasma concentration vs time curve exiting the dialyser 

Dialyser Clearance \( Cl_d \) = \( Q (1-Hct) E \)

where: 
\( Q \) = blood flow through the dialyser 
\( Hct \) = patients' hematocrit 
\( E \) = extraction efficiency 

This method assumes that the blood to plasma ratio of metoclopramide is approximately 1. This has been reported by Ross-Lee et al. (1981) in human blood.

2.8.3 Statistical Tests

Statistical evaluations were performed using either a two-sample t-test, paired t-test, or one-way ANOVA to compare mean values between groups. A significance level of \( p < 0.05 \) two-tailed was used.
3. RESULTS

3.1 Applicability of assay to uremic serum

3.1.1 Extraction of blank plasma

Since many of the components of uremic plasma have been shown to interfere with the determination of many drugs, aliquots (150, 250, 500 uL) of uremic plasma were extracted using the method of Riggs et al. (1983), to determine potential interferences with MCP or MAP. The retention times for MCP and MAP are ~9.3 and ~11.8 minutes, respectively. As can be seen in Figure 3, there are no interfering peaks eluting close to the retention times of MCP and MAP. Overall the chromatograms of the extracted uremic plasma appear to be somewhat less complex than comparable chromatograms from normal, healthy volunteers.

3.1.2 Standard curve

Figure 4 shows a representative standard curve extracted from uremic plasma. The slope and area ratios of the points agree quite closely with those observed from normal healthy volunteers. Comparison with results obtained by Riggs et al. (1983) also demonstrates good correlation. Since no significant differences were noted between the standard curve from uremic plasma and normal
Figure 3: Representative chromatograms of blank uremic plasma, extracted as per Riggs et al (1983).

1. 500 μL uremic plasma.
2. 250 μL uremic plasma.
3. 150 μL uremic plasma.

MCP elutes at approximately 9.3 minutes.
MAP elutes at approximately 11.8 minutes.
Figure 4: Standard Curve

$r^2 = 0.996$

slope = 0.023

$y$ intercept = 0.033

<table>
<thead>
<tr>
<th>SAMPLE</th>
<th>AREA RATIO ± STD. DEV.</th>
<th>C.V.</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>0.7674 ± 0.0110</td>
<td>1</td>
</tr>
<tr>
<td>24</td>
<td>0.6547 ± 0.0321</td>
<td>5</td>
</tr>
<tr>
<td>16</td>
<td>0.4069 ± 0.0300</td>
<td>7</td>
</tr>
<tr>
<td>8</td>
<td>0.2444 ± 0.0207</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>0.1204 ± 0.0041</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>0.0699 ± 0.0070</td>
<td>10</td>
</tr>
</tbody>
</table>

1. n=2, units are ng/mL.
2. Mean ± 1 std. dev. for duplicate injections of each sample.
3. Coefficient of Variation, units are %.
plasma, normal plasma was used in the subsequent preparation of standard curves simultaneous to the extraction of the patient samples. The minimum acceptable correlation coefficient ($r^2$) was 0.995 and the maximum acceptable y-intercept was ~10% of the highest area ratio. The maximum coefficient of variation of any point on the standard curve was 10%.

3.2 Normal pharmacokinetics

3.2.1 Plasma Kinetics

The bioavailability and pharmacokinetics of MCP were studied on a four-way crossover basis in six normal healthy volunteers. The mean kinetic parameters from the plasma data are given in Table 3. The mean value of the terminal elimination rate constant is $0.130 \pm 0.060 \text{ h}^{-1}$. The larger values for oral clearance, as compared with the total body clearance following IV dosing, suggests that MCP undergoes first-pass metabolism. Total body clearance when calculated from either oral or IV dosing is $28.70 \pm 6.46 \text{ L/h}$. The volume of distribution, calculated via the area method, is $270.26 \pm 127.70 \text{ L}$. There are no statistically significant differences, as determined by one-way ANOVA, between the dose groups for terminal elimination rate constant, bioavailability, total body clearance, or volume of distribution.
<table>
<thead>
<tr>
<th>Parameters:</th>
<th>DOSE: 5mg Sol.</th>
<th>10mg sol.</th>
<th>10mg Tab.</th>
<th>20mg Sol.</th>
<th>10mg IV</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Ka $(h^{-1})$</td>
<td>$3.21±1.68$</td>
<td>$3.28±2.71$</td>
<td>$2.78±0.51$</td>
<td>$3.64±1.93$</td>
<td>----</td>
<td>$3.29±1.71$</td>
</tr>
<tr>
<td>$\alpha (h^{-1})$</td>
<td>$0.6±0.3$</td>
<td>$0.2$</td>
<td>$0.7$</td>
<td>$0.8±0.3$</td>
<td>$7.3±5.3$</td>
<td>*</td>
</tr>
<tr>
<td>$\beta (h^{-1})$</td>
<td>$0.12±0.07$</td>
<td>$0.13±0.06$</td>
<td>$0.12±0.04$</td>
<td>$0.12±0.05$</td>
<td>$0.15±0.08$</td>
<td>$0.13±0.06$</td>
</tr>
<tr>
<td>AUC (ug.h/L)</td>
<td>$155.7±111$</td>
<td>$427.9±226$</td>
<td>$255.2±41$</td>
<td>$608.0±383$</td>
<td>$362.1±66$</td>
<td>---------</td>
</tr>
<tr>
<td>CLint (L/h)</td>
<td>$28.7±7.0$</td>
<td>$31.3±9.2$</td>
<td>$25.9±1.2$</td>
<td>$28.8±7.0$</td>
<td>$28.7±7.0$</td>
<td>$28.7±6.5$</td>
</tr>
<tr>
<td>$V_d$ area (L)</td>
<td>$273.2±115$</td>
<td>$318.5±166$</td>
<td>$235.5±67$</td>
<td>$287.9±133$</td>
<td>$242.9±128$</td>
<td>$270.3±128$</td>
</tr>
<tr>
<td>F (%)</td>
<td>$83±54$</td>
<td>$124±38$</td>
<td>$66±10$</td>
<td>$84±44$</td>
<td>---------</td>
<td>$83±47$</td>
</tr>
</tbody>
</table>

* Determined for those volunteers whose data fit a two-compartment model (n= 3, 1, 1, 3, 6)
Figure 5: Mean Area under the Plasma Concentration vs Time Curve (± 1 s.d.) for the Normal, Healthy Volunteers.
Figure 6: Representative Plasma Concentration vs Time Profiles for a Single Healthy Volunteer.  
5 mg Oral Solution (○—○), 10 mg Oral Solution (□—□), 10 mg IV Bolus (●—●), 20 mg Oral Solution (■—■).
Although the absorption rate constant, $K_a$, and the
two-compartment distributional rate constant, $\alpha$, have
been calculated and tabulated, their values appear to be
quite variable among the volunteers. Due to the large
potential errors in their estimation no statistical tests
have been performed on them. AUC appears to increase
linearly with dose as is shown in Figure 5. A
representative set of plasma concentration vs time curves
is shown in Figure 6 for a normal volunteer who received
5 mg MCP oral solution, 20 mg MCP oral solution, 10 mg IV
MCP, and 10 mg MCP oral solution. In this figure, and in
all volunteers, the time to peak and slope of the decline
phase appear constant and the plasma concentrations and
AUC's appear to increase proportionately with dose. The
plasma data gathered from most volunteers fit a
two-compartment open model with insignificant lag time
following the oral doses.

3.2.2 Urinary Excretion

For the normal volunteers a complete urine
collection was made for 72 hours following dosing. The
data was then analysed using the amount remaining to be
excreted (ARE) methods. Figure 7 shows a representative
set of ARE plots for a normal healthy volunteer. Linear
regression generally
Figure 7: Representative Amount Remaining to be Excreted in the Urine for a Single, Healthy Volunteer. 5 mg Oral Solution (○-○), 10 mg Oral Solution (□-□), 10 mg IV Bolus (●-●), 20 mg Oral Solution (■-■).
resulted in a correlation coefficient of $\geq 0.95$. Mean kinetic parameters from the urine data are reported in Table 4. One-way ANOVA shows no statistically significant differences across the dose groups. Two-sample t-testing shows no significant differences, for comparable parameters determined from either urine or plasma data. Therefore, the best overall estimates of these parameters are the overall means which are reported in Table 5. The average percent of dose excreted intact was $20.4 \pm 9.3\%$. The terminal elimination rate constant was $0.14 \pm 0.04$ h$^{-1}$ and the bioavailability was $0.68 \pm 0.26$. Renal clearance ($7.6 \pm 5.3$ L/h) accounts for approximately 25% of total body clearance.

3.3 Uremic Pharmacokinetics

The clinical hematological and biochemical results, taken from the medical records of the uremic volunteers are displayed in Table 6. The details pertaining to the dialysis of the uremic patients are presented in Table 7.

3.3.1 24 h Pre-dialysis Dose

The pharmacokinetic parameters obtained from a 10 mg IV dose of MCP in the uremic volunteers are presented in Table 9. A typical plasma concentration vs time curve is shown in Figure 8. The kinetic parameters show a much
### TABLE 3

<table>
<thead>
<tr>
<th>DOSE:</th>
<th>5 mg Sol.</th>
<th>10 mg sol.</th>
<th>10 mg Tab.</th>
<th>20 mg Sol.</th>
<th>10 mg IV</th>
<th>Mean±SD</th>
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<tbody>
<tr>
<td>n</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>% dose</td>
<td>16.4±5.5</td>
<td>20.6±0.4</td>
<td>11.7±0.2</td>
<td>19.5±4.7</td>
<td>29.7±12.3</td>
<td>20.4±9.3</td>
</tr>
<tr>
<td>excreted</td>
<td></td>
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<td>intact</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>β (h⁻¹)</td>
<td>0.15±0.04</td>
<td>0.14±0.05</td>
<td>0.13</td>
<td>0.15±0.04</td>
<td>0.12±0.04</td>
<td>0.14±0.04</td>
</tr>
<tr>
<td>CLR (L/h)</td>
<td>8.8±9.4</td>
<td>5.7±2.4</td>
<td>4.2±0.2</td>
<td>7.4±2.1</td>
<td>8.7±4.1</td>
<td>7.6±5.3</td>
</tr>
<tr>
<td>F (%)</td>
<td>62±24</td>
<td>56±12</td>
<td>81±25</td>
<td>76±34</td>
<td>--------</td>
<td>68±26</td>
</tr>
</tbody>
</table>
TABLE 4

Metoclopramide kinetic parameters from the cumulated urine and plasma results of the normal, healthy volunteers

DOSE:  5 mg Sol. 10 mg sol. 10 mg Tab. 20 mg Sol. 10 mg IV

<table>
<thead>
<tr>
<th>Parameters:</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>6</td>
</tr>
<tr>
<td>$\beta (h^{-1})$</td>
<td>0.14±0.06</td>
</tr>
<tr>
<td>F (%)</td>
<td>73±42</td>
</tr>
</tbody>
</table>
### TABLE 5

Clinical details of uremic patients

<table>
<thead>
<tr>
<th>PATIENT:</th>
<th>PB</th>
<th>WL</th>
<th>BM</th>
<th>GM</th>
<th>JS</th>
<th>SS</th>
<th>JT</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE (yr)</td>
<td>34</td>
<td>24</td>
<td>20</td>
<td>41</td>
<td>33</td>
<td>37</td>
<td>33</td>
<td>68</td>
</tr>
<tr>
<td>WEIGHT (kg)</td>
<td>50.2</td>
<td>50</td>
<td>77.3</td>
<td>84.5</td>
<td>68.7</td>
<td>40.3</td>
<td>65.2</td>
<td>75</td>
</tr>
<tr>
<td>Scr* (mg/dL)</td>
<td>11.0</td>
<td>17.2</td>
<td>13.6</td>
<td>15.1</td>
<td>16.1</td>
<td>11.5</td>
<td>17.4</td>
<td>15.1</td>
</tr>
<tr>
<td>BUN* (mg/dL)</td>
<td>83</td>
<td>73</td>
<td>106</td>
<td>108</td>
<td>89</td>
<td>82</td>
<td>82</td>
<td>69</td>
</tr>
<tr>
<td>Alk Phos (I.U.)</td>
<td>-</td>
<td>-</td>
<td>38</td>
<td>51</td>
<td>128</td>
<td>145</td>
<td>250</td>
<td>79</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>34.2</td>
<td>19.2</td>
<td>14.0</td>
<td>15.5</td>
<td>13.0</td>
<td>20.6</td>
<td>23.6</td>
<td>31.0</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>11.5</td>
<td>7.2</td>
<td>5.4</td>
<td>7.2</td>
<td>4.5</td>
<td>6.7</td>
<td>7.8</td>
<td>10.3</td>
</tr>
</tbody>
</table>

* Pre-dialysis values
* Serum creatinine and blood urea nitrogen concentrations.
' Patients are hyperparathyroid.
TABLE 6

Details pertaining to the dialysis of uremic patients.

<table>
<thead>
<tr>
<th>PATIENT</th>
<th>DIALYSER FILTER TYPE</th>
<th>DURATION OF DIALYSIS (h)</th>
<th>BLOOD FLOW RATE (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB</td>
<td>CF 1200</td>
<td>4.5</td>
<td>200</td>
</tr>
<tr>
<td>WL</td>
<td>CF 1211</td>
<td>4.0</td>
<td>200</td>
</tr>
<tr>
<td>BM</td>
<td>CF 1211</td>
<td>5.1</td>
<td>200</td>
</tr>
<tr>
<td>GM</td>
<td>CF 1200</td>
<td>4.0</td>
<td>200</td>
</tr>
<tr>
<td>JS</td>
<td>CF 1211</td>
<td>4.5</td>
<td>200</td>
</tr>
<tr>
<td>SS</td>
<td>CF 1211</td>
<td>3.5</td>
<td>200</td>
</tr>
<tr>
<td>JT</td>
<td>CF 1211</td>
<td>4.5</td>
<td>200</td>
</tr>
<tr>
<td>RT</td>
<td>CF 1211</td>
<td>4.0</td>
<td>200</td>
</tr>
</tbody>
</table>

The CF 1200 and CF 1211 dialyser filters are both hollow fibre capillary flow cuprophane membranes models (Travenol Laboratories, Deerfield, ILL). The effective surface area of the CF 1200 is ~1.3 sq. m while that of the CF 1211 is ~ 0.9 sq. m.
<table>
<thead>
<tr>
<th>PATIENT</th>
<th>( \alpha ) (h(^{-1}))</th>
<th>( \beta ) (h(^{-1}))</th>
<th>AUC (ug.h/L)</th>
<th>CLt (L/h.kg)</th>
<th>Vd area (L/kg)</th>
<th>Vc (L/kg)</th>
<th>E (%)</th>
<th>CLd (L/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB</td>
<td>3.11</td>
<td>0.045</td>
<td>1370.7</td>
<td>0.14</td>
<td>3.11</td>
<td>2.93</td>
<td>2.0</td>
<td>0.10</td>
</tr>
<tr>
<td>WL</td>
<td>0.97</td>
<td>0.032</td>
<td>1682.4</td>
<td>0.12</td>
<td>3.71</td>
<td>2.02</td>
<td>17.0</td>
<td>1.00</td>
</tr>
<tr>
<td>BM</td>
<td>3.50</td>
<td>0.12</td>
<td>713.8</td>
<td>0.18</td>
<td>1.52</td>
<td>1.09</td>
<td>30.0</td>
<td>3.10</td>
</tr>
<tr>
<td>GM</td>
<td>7.94</td>
<td>0.058</td>
<td>471.5</td>
<td>0.25</td>
<td>4.33</td>
<td>1.06</td>
<td>5.0</td>
<td>0.50</td>
</tr>
<tr>
<td>JS</td>
<td>3.16</td>
<td>0.028</td>
<td>999.7</td>
<td>0.15</td>
<td>5.15</td>
<td>2.78</td>
<td>7.5</td>
<td>0.78</td>
</tr>
<tr>
<td>SS</td>
<td>14.39</td>
<td>0.015</td>
<td>4016.3</td>
<td>0.06</td>
<td>4.13</td>
<td>0.48</td>
<td>5.3</td>
<td>0.50</td>
</tr>
<tr>
<td>JT</td>
<td>15.66</td>
<td>0.099</td>
<td>784.7</td>
<td>0.19</td>
<td>1.94</td>
<td>0.16</td>
<td>35.0</td>
<td>2.80</td>
</tr>
<tr>
<td>RT</td>
<td>9.55</td>
<td>0.065</td>
<td>725.5</td>
<td>0.18</td>
<td>2.83</td>
<td>0.70</td>
<td>22.0</td>
<td>1.00</td>
</tr>
<tr>
<td>MEAN</td>
<td>7.29</td>
<td>0.058</td>
<td>1345.6</td>
<td>0.16</td>
<td>3.34</td>
<td>1.40</td>
<td>15.5</td>
<td>1.22</td>
</tr>
<tr>
<td>S.D.</td>
<td>5.53</td>
<td>0.04</td>
<td>1148.2</td>
<td>0.06</td>
<td>1.23</td>
<td>1.05</td>
<td>12.5</td>
<td>1.11</td>
</tr>
</tbody>
</table>

E is the extraction efficiency of the dialyser and CLd is the clearance by dialysis.
larger degree of interindividual variability than do the results of the normal, healthy volunteers.

3.3.2 1 h Pre-dialysis Dose

The results from the 10 mg IV MCP dose administered 1 h prior to the start of hemodialysis are presented in Table 10. A typical plasma concentration vs time profile is shown in Figure 10. These results, although in some individual cases different, do not show statistically significant difference from the results displayed in Table 9, as determined by paired t-testing. Again, the apparent decreases in total body clearance and terminal elimination rate constant can be seen. Furthermore, hemodialysis is ineffective at clearing MCP from the body. These results suggest that hemodialysis has little or no effects on MCP kinetics.

3.4 Pharmacokinetics in Kidney Transplant Recipient

The relevant clinical parameters for the kidney transplant recipient are presented in Table 11.

3.4.1 Plasma Kinetics

The kinetic parameters obtained are displayed in Table 12 and the plasma concentration vs time profiles are presented in Figure 11. Prior to the kidney
Figure 8: Representative Plasma Concentration vs Time Profile for a 10 mg IV Bolus Dose Given to a Uremic Volunteer 24 h Prior to Hemodialysis. Prior to Dialysis (●—●), Dialysis; arterial concentration (■—■), venous concentration (□—□).
<table>
<thead>
<tr>
<th>KINETIC PARAMETER:</th>
<th>alpha (h⁻¹)</th>
<th>β (h⁻¹)</th>
<th>AUC (ug.h/L)</th>
<th>CLtb (L/h.kg)</th>
<th>Vd area (L/kg)</th>
<th>Vc (L/kg)</th>
<th>E (%)</th>
<th>CLd (L/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB</td>
<td>9.00</td>
<td>0.160</td>
<td>488.9</td>
<td>0.41</td>
<td>2.55</td>
<td>1.79</td>
<td>16.0</td>
<td>1.70</td>
</tr>
<tr>
<td>WL</td>
<td>0.76</td>
<td>0.040</td>
<td>1572.0</td>
<td>0.13</td>
<td>3.18</td>
<td>2.60</td>
<td>17.0</td>
<td>1.00</td>
</tr>
<tr>
<td>GM</td>
<td>2.25</td>
<td>0.113</td>
<td>349.9</td>
<td>0.34</td>
<td>2.99</td>
<td>2.53</td>
<td>22.0</td>
<td>2.20</td>
</tr>
<tr>
<td>JS</td>
<td>2.84</td>
<td>0.064</td>
<td>303.1</td>
<td>0.48</td>
<td>7.51</td>
<td>1.55</td>
<td>17.0</td>
<td>1.77</td>
</tr>
<tr>
<td>SS</td>
<td>10.50</td>
<td>0.012</td>
<td>3182.5</td>
<td>0.08</td>
<td>6.50</td>
<td>1.52</td>
<td>19.0</td>
<td>1.80</td>
</tr>
<tr>
<td>JT</td>
<td>16.41</td>
<td>0.102</td>
<td>313.3</td>
<td>0.48</td>
<td>4.71</td>
<td>0.13</td>
<td>38.0</td>
<td>3.40</td>
</tr>
<tr>
<td>RT</td>
<td>0.93</td>
<td>0.052</td>
<td>772.1</td>
<td>0.19</td>
<td>3.65</td>
<td>1.33</td>
<td>12.0</td>
<td>1.00</td>
</tr>
<tr>
<td>MEAN</td>
<td>6.10</td>
<td>0.078</td>
<td>997.4</td>
<td>0.30</td>
<td>4.44</td>
<td>1.64</td>
<td>20.1</td>
<td>1.84</td>
</tr>
<tr>
<td>S.D.</td>
<td>5.98</td>
<td>0.050</td>
<td>1063.3</td>
<td>0.17</td>
<td>1.9</td>
<td>0.83</td>
<td>8.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

# Patient BM received a kidney allograft prior to the second administration of metoclopramide.

E is the extraction efficiency of the dialyser; CLd is the clearance by dialysis.
Figure 9: Representative Plasma Concentration vs Time Profile for a 10 mg IV Bolus Dose Given to a Uremic Volunteer 1 h Prior to Hemodialysis. Prior to Dialysis (●●), Dialysis; arterial concentration (■■), venous concentration (□□), Post-Dialysis (○○).
<table>
<thead>
<tr>
<th>PARAMETER:</th>
<th>BEFORE</th>
<th>16 DAYS AFTER</th>
<th>3 MONTHS AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>DATE</td>
<td>Nov. 20/83</td>
<td>Sept. 10/85</td>
<td>Dec. 6/85</td>
</tr>
<tr>
<td>WEIGHT, (kg)</td>
<td>77.3</td>
<td>73.5</td>
<td>84.5</td>
</tr>
<tr>
<td>SERUM CREATININE, (mg/dL)</td>
<td>13.6</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td>BLOOD UREA NITROGEN, (mg/dL)</td>
<td>106</td>
<td>35</td>
<td>29</td>
</tr>
</tbody>
</table>
Figure 10: Plasma Concentration vs Time profiles for the Kidney Transplant Recipient Following 10 mg IV Bolus Dose. Uremia (●—●), 15 days After Transplant (○—○), 3 months After Transplant (■—■).
transplant the kinetic parameters show a pattern typical of the uremic volunteers, viz., extended half-life and decreased total body clearance. However, following transplantation the kinetic parameters are dramatically altered, as evidenced by Figure 11, and fall within the range displayed by the normal healthy volunteers.

3.4.2 Urinary Excretion

The excretion of MCP in the urine apparently reaches normal levels, although in the lower range seen in normals, following transplantation as evidenced by the percent of dose excreted intact and the renal clearance values of MCP. These results are presented in Table 13.
<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>BEFORE</th>
<th>16 DAYS AFTER</th>
<th>3 MONTHS AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha$, (h$^{-1}$)</td>
<td>6.08</td>
<td>8.70</td>
<td>6.19</td>
</tr>
<tr>
<td>$\beta$, (h$^{-1}$)</td>
<td>0.11</td>
<td>0.21</td>
<td>0.21</td>
</tr>
<tr>
<td>AUC, (ug.h/L)</td>
<td>713.8</td>
<td>316.9</td>
<td>145.9</td>
</tr>
<tr>
<td>Vdarea, (L/kg)</td>
<td>1.52</td>
<td>2.10</td>
<td>3.74</td>
</tr>
<tr>
<td>CLtb, (L/h/kg)</td>
<td>0.18</td>
<td>0.43</td>
<td>0.81</td>
</tr>
<tr>
<td>CLr, (L/h.kg)</td>
<td>---</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>CLnr, (L/h/kg)</td>
<td>0.18</td>
<td>0.37</td>
<td>0.73</td>
</tr>
<tr>
<td>% dose excreted intact</td>
<td>0</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

CLtb, is total body clearance; and CLnr, is nonrenal drug clearance.
TABLE 11

Metoclopramide Pharmacokinetic parameters from the urine of the kidney transplant recipient

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>BEFORE</th>
<th>16 DAYS AFTER</th>
<th>3 MONTHS AFTER</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{CLR, (L/h.kg)} )</td>
<td>---</td>
<td>0.06</td>
<td>0.08</td>
</tr>
<tr>
<td>% dose excreted intact</td>
<td>0</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>
4. DISCUSSION

4.1 Applicability of Assay to Uremic Plasma

Analysis of drugs in biological samples from patients can often present difficulties in both quantitation and interpretation since the patient samples may contain substances not encountered in samples from normal, healthy volunteers (Perucca et al., 1985). This may be of particular significance in uremic patients whose plasma will contain many substances normally excreted or catabolized by the kidney. The ability to overcome these potential problems is a function of both the assay selectivity and the selectivity of the detection mode. For instance, the use of flame ionization detection (FID) is often difficult and limited in the analysis of uremic plasma since many low weight, volatile compounds are carried over during sample extraction and can interfere with drug detection and quantitation.

The chromatograms (Fig. 3) and standard curve (Fig. 4) demonstrate the ability of this assay (Riggs et al., 1983) procedure to detect and quantify MCP in a selective, and linear manner from uremic patient plasma samples. The lack of interference of the contents of the uremic plasma likely stems from the use of a double extraction procedure which removes almost all potentially
interfering compounds, and/or the relative selectivity of the electron capture detector (ECD). Since none of the blank chromatograms showed interference, the volume of plasma chosen to be extracted for most of the uremic plasma samples was 200 µL. This allowed area ratios to be obtained that were approximately in the middle of the standard curve and reserved enough plasma to allow the assay to be performed once more in case of problems with one or both duplicates. If the area ratio fell outside the range of the standard curve, another aliquot as extracted, using a more appropriate volume, to provide an accurate quantitation of drug. In general, however, there was insufficient plasma to measure more than two sets of duplicates for any single sample. In summary, the assay method was found to be adequate to accurately detect and quantify trace levels of MCP in uremic plasma over the entire experimental time period.

4.2 Normal Pharmacokinetics

The crossover study in the normal healthy volunteers was designed to answer two major questions regarding MCP pharmacokinetics:

1) Does MCP display linear pharmacokinetics over the dose range of 5 - 20 mg in spite of the previous literature claims of dose-dependency?
2) Given the experimental limitations of the existing literature what are the absolute and relative bioavailabilities of MCP?

The accumulated data provide enough information to definitively answer these questions and to shed some doubt of the interpretations of previous authors.

Both the urine and plasma results point to the existence of linear pharmacokinetics over the dose range examined. In Table 2 this is demonstrated by several points:

1) The constant values of beta for each dose level.
2) The constant value of total body clearance.
3) The constant value of volume of distribution.
4) The constant value of bioavailability.
5) The proportional increase in AUC with dose (see also Fig. 5).

The plasma concentration vs time curve (Fig. 6) also illustrates the presence of linear kinetics. This can be seen by the parallel nature of the terminal slopes, the similar time to peak plasma concentration following oral dosing, and the proportionate increases in both plasma concentration and AUC with dose. The urine data also confirms, independently, the existence of linear kinetics. Figure 7 shows a parallel decline in the
amount remaining to be excreted (ARE) vs time plots suggesting equivalent elimination half-lives. Further there is a proportional increase in the total amount excreted unchanged with dose. Table 4 also shows this through the constant values of beta, renal clearance, bioavailability, and percentage excreted intact. In addition there is no statistically significant difference between the kinetic parameter values obtained from plasma and urine. Thus it is demonstrated that MCP undergoes linear pharmacokinetics within the dose range from 5 - 20 mg.

The previous finding is in direct contrast to previously published and widely accepted results. However, the data and interpretations that have led to the previous claims of dose-dependency deserve close scrutiny. The two major claims for dose-dependency of MCP kinetics have been made by Graffner et al. (1979) and by Bateman et al. (1980). Graffner et al. (1979) administered IV doses of 5 and 10 mg, and oral solution and slow-release tablet of 20 mg to five male volunteers. Based on observed, but statistically unproven, observations of differences in beta half-life (4.4 ± 1.2 h for the 5 mg IV dose vs 5.4 ± 1.8 h for the 10 mg IV dose) these workers concluded that the elimination half-life of MCP was dose-dependent. Additionally, they cited an observed difference in the percentage excreted
unchanged in the urine (16 ± 4 % for the 5 mg IV dose vs 21 ± 7 % for the 10 mg IV dose) and an average increase of 150% in the AUC on doubling the dose as evidence of non-linear kinetics. There are several problems with the interpretations of these results made by these authors. Firstly, the lack of statistical demonstration of differences in the mean values is inappropriate. Appropriate testing would have demonstrated no significant differences in these values. Secondly, the HPLC-UV detection assay used, provided sufficient sensitivity to measure MCP in plasma for only 8 h after drug administration. The truncation of the sampling period can lead to underestimation of the biological half-life (Gibaldi and Weintraub, 1971) and in this case could explain the shorter half-life noted following the 5 mg IV dose. Finally, the authors mention that the doubling of the dose provides an approximately proportional increase in plasma concentration. This observation contrasts directly with the claim of dose-dependent kinetics. The second study claiming dose-dependency of MCP kinetics (Bateman et al., 1980) is also similarly flawed. MCP was given as 10 mg IV and 10 and 20 mg as oral tablets. Based on statistically significant differences in elimination half-life, particularly following the oral doses, the authors claim that there are dose-dependent changes in MCP elimination
half-life. While the differences do appear to be statistically significant, the entire sampling duration was only 6 hours which could lead to significant inaccuracy in the estimated half-life particularly at the lower dose level. The range of bioavailability observed in this study was from 32 - 97% suggesting the existence of first-pass metabolism following oral dosing. This implies that the actual amounts of drug reaching the systemic circulation following oral administration of 10 and 20 mg are, at least 3.2 - 6.4 mg and, at most, 9.7 - 19.4 mg. The elimination half-life estimated for the 10 mg IV dose, however, is less than that of either the 10 or 20 mg oral dose. If dose-dependent kinetics did in fact exist and a significant first-pass effect did exist, then the half-life following IV administration would be the largest since the IV route would provide the largest amount of drug to the body. In a subsequent review of the literature on MCP kinetics Bateman (1983), compares results from several pharmacokinetic studies, without benefit of statistical tests, to demonstrate that MCP does not obey linear kinetics. This review fails to critically evaluate the early literature and fails to explain some observations of the kinetics of 'high-dose' MCP used in cancer chemotherapy. Results from pharmacokinetic studies in cancer chemotherapy employing doses in excess of 0.5 mg/kg/h (Taylor et al., 1984,
Bryson et al., 1985) have demonstrated the existence of linear MCP kinetics at these dose levels. Recently, Wright et al. (1984) have demonstrated linear kinetics at doses between 20 and 100 mg. It cannot be argued that MCP at lower doses in humans displays the same type of nonlinear kinetics displayed in the rat, since the observations made by Kapil et al. (1984) are qualitatively very different from the claims of the authors with regards to the human work. In addition, it is not possible to extrapolate results from rat directly to humans for MCP since the metabolic patterns of MCP differ substantially between the two species (Arita and Hori, 1970; Teng et al., 1977).

The question of the absolute and relative bioavailabilities of MCP have been addressed by several groups (Schuppan et al., 1979; Graffner et al., 1979; Bateman et al., 1980; Ross-Lee et al., 1981; Block et al., 1981). However, as outlined earlier, all of these studies suffer from limitations which may reduce the credibility of their results. Generally, these limitations are of three types. Many of the early assay procedures had low sensitivity and/or poor selectivity (Schuppan et al., 1979; Bateman et al., 1980). This problem led to short sampling periods following dosing which may not allow accurate estimation of many kinetic parameters (Gibaldi and Weintraub, 1971). Several groups
used a tablet or capsule as the sole oral dosage form (Schuppan et al., 1979; Graffner et al., 1979; Bateman et al., 1980; Ross-Lee et al., 1981). Since dissolution rate can significantly affect bioavailability, a more appropriate comparison to determine absolute bioavailability would have been made with an oral solution. Finally, the comparison of unequal oral and IV doses (Schuppan et al., 1979; Graffner et al., 1979; Block et al., 1980) was not appropriate since the dose-linearity of MCP kinetics within this dose range had not been established and the existing evidence was, in fact, quite to the contrary.

More specifically the weaknesses of each study are as follows. Schuppan et al. (1979) used a thin layer chromatographic method to quantitate MCP. With this method their minimum detectable concentration was entirely inadequate (40 ng/mL) and their assay only allowed for plasma sampling and measurement for 10 h following drug administration. In total, only 8 plasma samples were taken from each subject, furthermore, no assessment of drug excretion in the urine was made. These authors made their kinetic comparisons based on unequal IV and oral doses without demonstration of the existence of linear kinetics (50 mg orally vs 20 mg IV). Additionally, a capsule was used as the oral reference dosage form in spite of the fact that obtaining or making
an oral solution was possible. These authors observed an absolute bioavailability of ~50%.

Graffner et al. (1979) compared the bioavailability of a 20 mg MCP oral tablet with the administration of 5 and 10 mg IV. No clear demonstration of linear kinetics were made by the authors. In fact, these authors suggested the presence of non-linear kinetics. If this were true, then the assessment of bioavailability from unequal doses would have been impossible. However, these workers go on to suggest that the absolute bioavailability is between 25 - 40%.

Bateman et al. (1980) compared the availability of 10 and 20 mg MCP given as the oral tablet with 10 mg given IV. Due to inherent assay insensitivity, plasma was collected for a maximum of 8 h. Consequently, this sampling approach led to a requirement for extensive extrapolation of the blood curve to allow calculation of the AUC from 0 to infinity. As well, administration of a tablet dosage form before a complete assessment was made with an oral solution has led to some confusion since tablet dissolution rate can substantially alter the observed bioavailability for a high clearance drug. These authors noted substantial inter-individual differences in bioavailability ranging from 32 - 97%
with little explanation for the observed variability. Again, no use was made of urine data.

Block et al. (1980) compared the absolute and relative bioavailabilities of MCP in several different dosage forms. Their HPLC method only allowed quantitation up to 12 h following dose thus requiring significant extrapolation to obtain the necessary AUC values. In addition, the accuracy of the dose of the oral solution appears somewhat questionable, since these authors claim that 30 drops was equal to 10 mg MCP. The use of a drop is unscientific since the volume may vary substantially and not allow accurate knowledge of the administered dose. Further, this group did not compare equal oral and IV doses (18 mg IV vs 27 mg orally) in spite of the observations of the possibility of the existence of non-linear kinetics. These authors suggest a bioavailability of 76 - 79 % for oral MCP forms and 53 % for rectally administered MCP.

Ross-Lee et al. used an ECD-GC method to quantitate MCP in plasma and to determine the absolute bioavailability of a 10 mg oral dose vs 10 mg MCP IV. However, quantitation was only possible for 10 h after drug administration; again urine data was not used as an independent confirmation of the findings using plasma
data. These authors claim bioavailability of 77% (range 47 - 114%).

These studies were reviewed by Bateman (1983) but no true critical dissection was made. Subsequent to this work, Wright et al. (1984) have demonstrated bioequivalence between 20 mg as oral solution and 20 mg as oral tablet. No demonstration of bioequivalence has been made at lower doses, 5 - 20 mg, which are more commonly encountered in ambulatory patient therapy.

The present study attempts to overcome the previously mentioned limitations in several ways. The ECD-GC method is much more sensitive and specific than the previous assays allowing more accurate quantitation over a longer sampling period. In addition, this study demonstrates the linearity of MCP kinetics and compares equal doses of IV MCP and a rapidly available oral solution dosage form. Furthermore, a comparison between the oral solution and the oral tablet is also possible. The results of the bioavailability assessments are clear from Tables 3, 4, and 5. The best estimate of the absolute bioavailability of MCP is 78% using the cumulated data from the plasma and urine. It should be noted, however, that there is significant inter-individual variability. The relative bioavailability of the tablet and solution appears to be
~100% suggesting that tablet dissolution rate does not play a significant role in the absorptive step for MCP. This may result from the fact that the hepatic clearance of MCP is more intermediate than truly high. If this is true then MCP clearance would only be partially sensitive to hepatic blood flow or the rate of delivery of drug to the liver (Wilkinson and Shand, 1975). Thus, if the difference in delivery of the solution and tablet are only subtly different they may be indistinguishable to this method of study. The results obtained from the urine data independently confirm those obtained from the plasma of the normal healthy volunteers. This may also be inferred from the fact that the tablet and solutions have approximately the same time to peak and reach approximately the same plasma concentrations.

The individual kinetic parameters in Tables 3, 4, and 5 do not differ greatly from those reported earlier. In summary, the beta half-life appears to be ~5.4 h, with total body clearance being ~28.7 L/h and the volume of distribution being relatively large at ~270.1 L. Renal excretion accounts for ~21% of the total dose. Although most of the healthy volunteer data was best explained using a two-compartment model in some cases the oral dose profile fit a one-compartment open model, which may result from the value of alpha being larger than Ka (Gibaldi and Perrier, 1982).
4.3 Uremic Pharmacokinetics

From the information available in both this study and those that have been previously completed in normal healthy volunteers, there is no apparent reason to expect that the pharmacokinetics of MCP should be substantially altered by kidney disease. In normals, MCP is only about 20% excreted unchanged in the urine. Although a large proportion of the oral dose of MCP is sulphated, at the N\(^4\) position, sulphation is generally believed to be relatively unaffected in chronic renal failure (Reidenberg, 1977). In addition, MCP is only slightly, ~40%, protein bound and renal failure has been shown to have little effect on this value (Webb et al., 1986). Thus, pharmacokinetic changes, which may occur in renally impaired patients, would not be expected to occur for MCP. Clinical experience using MCP as an antiemetic/antinauseant in patients with decreased kidney function, however, has suggested otherwise. Early reports, published in Lancet, noted an much higher incidence of adverse effects to MCP, particularly those of CNS origin, in uremic patients (Caralps, 1979; Bateman and Davies, 1979). Preliminary investigation (Bateman, 1980) suggested that the total body clearance of MCP in uremics was reduced approximately 3 fold in uremic patients with an attendant, proportional increase in elimination half-life.
Three studies, two in humans (Bateman et al., 1981; Lehmann et al., 1985) and one in rats (Tam et al.; 1981), have examined the influence of renal failure on MCP kinetics in more detail. Tam et al. (1981) used bilateral ureteral ligation, uranyl nitrate administration, and 5/6 two step nephrectomy to provide a range of experimentally induced renal failure in rats. Following administration of MCP they noted at least a two fold increase in AUC and elimination half-life in the animals with renal failure. Total body clearance was decreased by a similar proportion. These results have been essentially paralleled in the work of Bateman et al. (1981) and Lehmann et al. (1985) using human subjects. However, given the interspecies differences between rat and man the mechanisms responsible for this change may not be the same. Bateman et al. (1981) examined the kinetics of MCP following IV and oral administration of 10 mg MCP to six patients with varying degrees of renal failure, two of whom were anephric and on hemodialysis. These authors noted a reduction of total body clearance to levels approximately 30 % of those seen in normal healthy volunteers with an attendant, proportional increase in elimination half-life. Volume of distribution (289.6 ± 18.23 L) was not significantly different from that seen in normal, healthy volunteers. No information was provided on the extent of removal of
MCP by hemodialysis. These results suggested that the increased incidence of adverse effects noted in uremic patients given MCP could be related to accumulation of MCP due to reduced total body clearance. Additionally, these authors suggest that the change in kinetics cannot be solely explained by the reduction of renal clearance since this only accounts for ~20% of total body clearance. A more extensive study, covering a large range of renal impairment, in humans has been completed by Lehmann et al. (1985). These authors confirmed the previously mentioned effects of uremia on MCP kinetics but also found a positive correlation between total body clearance of MCP and the degree of renal impairment, as defined by creatinine clearance ($r = 0.78$). Although removal by hemodialysis was examined, the authors interpretation of this is somewhat confused. They state that hemodialysis was responsible for an additional 60% increase in total body clearance yet that it cleared relatively little of the body load of MCP. In addition, the quoted hemodialysis clearances (94.6 mL/min, 111.0 mL/min, 84.9 mL/min, and 73.4 mL/min) are extremely high when compared to total body clearance and if compared with established values for many drugs. Interestingly, a case report (Berardi et al., 1986) describing MCP removal in a single peritoneal dialysis patient removed less than 10 ug of MCP from the body suggesting that peritoneal
dialysis is an inefficient method of removing MCP. These authors (Lehmann et al. 1985) speculate that the reduced total body clearance noted in renal failure may result from changes in renal drug metabolism or enterohepatic recirculation. However, no evidence is offered to support these speculations. Although the authors suggest strongly that the change may be in renal metabolism, this has been shown not to occur in rats (Kapil et al., 1984).

Given the previous investigations on MCP, this study was designed to answer two major questions as well as to more fully describe the kinetics of MCP in patients with severe renal impairment.

1) What is the extent of removal of MCP by hemodialysis?

2) Does hemodialysis have any effects on the subsequently displayed kinetics of MCP?

Subsequently, one of the uremic patients (BM) received a kidney transplant which allowed investigation of the effects of the renewed renal function on the displayed MCP kinetics.

Qualitatively the kinetic results obtained in this study parallel those previously reported. There is at least a two-fold decrease in total body clearance with a
proportionate increase in elimination half-life and insignificant change in volume of distribution. All the uremic patient data was best fit by a two compartmental model. The distributional rate constant, alpha, was very much greater than the beta rate constant. The volume of the central compartment was quite large accounting for an average of approximately 30 - 40 % of the total volume of distribution. The most striking feature of the uremic kinetic data is the degree of inter-individual variation. This large variability implies that, while at least a two-fold increase in terminal half-life may be expected in a uremic subject, substantially longer half-lives may be encountered and excessive drug accumulation may occur on multiple dosing even with reduced doses. The pattern of the plasma concentrations entering and leaving the dialyser appear to behave in a somewhat unpredictable manner with "venous" concentrations sometimes exceeding the "arterial" concentrations. Two possible explanations may rationalize this problem. First, since the removal of MCP by hemodialysis is relatively inefficient, a relatively large amount of water may be removed from the plasma thereby concentrating the MCP and making the "venous" concentration appear higher than the "arterial" concentration. The second explanation may be that MCP adheres to some component of the artificial kidney or tubing and leaches back into the plasma as dialysis
progresses. Given the variability of the kinetics of MCP, rigid dosing guidelines for use in renal failure may be inappropriate. Following a normal loading dose, a maintenance dose reduction of at least 50% while maintaining the dosing interval (tau) may prevent both the accumulation of MCP and adverse effects noted with the initial high concentrations soon after dosing.

The extraction ratios (E) and dialyser clearances (Cld) calculated suggest that hemodialysis does not contribute significantly to the removal of MCP from uremic patients. No statistically significant differences were noted in these two parameters between the two administrations of MCP. The lack of removal of MCP by dialysis probably is due to the high volume of distribution of this drug. The relatively low concentration of MCP in plasma may not provide a large enough concentration gradient to provide an adequate driving force for diffusion.

There are no statistically significant differences between any of the pharmacokinetic parameters between the two administrations of MCP although some intra-individual variation was noted. This suggests that hemodialysis has no effect on the kinetics displayed subsequent to its termination.
The results observed from the kidney transplant recipient provide some interesting information for speculation. The kinetics while the patient was uremic show the typical pattern of diminished total body clearance with extended plasma half-life. However, following the kidney transplant the kinetic parameters revert to within apparently normal limits on both subsequent administrations. On the second administration following the transplant, 3 months following surgery, there appears to be a further improvement in total body clearance. This may be related to an increased volume of distribution since the half-life is relatively unchanged and the patients' body weight had increased. The rapid change in kinetics suggests that the deficit in total body clearance created by uremia is not due to an irreversible effect.

The exact mechanism responsible for the kinetic changes in uremia cannot be elucidated from the data available. Several possibilities exist however. Extrahepatic metabolism does not seem likely. Kapil et al. (1984) showed that the kidney, and lung tissues do not contribute to the metabolism of MCP in the rat. The findings in the rat may not be directly extrapolatable to man due to the metabolic differences between the two species. Recirculation of the conjugates of MCP may occur. In this case the sulphate conjugate, which
accounts for ~40% would have to be excreted in the bile, deconjugated and then reabsorbed. In general, this process is accepted to occur for the glucuronide conjugates of some drugs (Verbeeck, 1982) but does not appear to have been reported for sulphate conjugates. In addition, the sulphate conjugate of MCP appears to be relatively chemically stable. Hydrolysis occurs within 15 minutes at 100 °C in the presence of 1 N hydrochloric acid (Arita et al., 1970). There does not appear to be any evidence of recirculation in the plasma concentration vs time profiles obtained from the uremic volunteers. Thus, such a recirculation process would have to occur at a somewhat constant rate which is at odds with the accepted pattern of biliary recycling. A more plausible explanation may be a change in hepatic MCP metabolism secondary to chronic renal failure. Although a direct effect on the sulphation of MCP may be possible, it has generally been accepted that this conjugation pathway is relatively unaffected by uremia (Reidenberg, 1977). This assumption is made on data derived from the kinetics of acetaminophen where, although the glucuronide and sulphate conjugates accumulated in uremia, the kinetics of the parent drug were unaltered from those seen in healthy volunteers (Lowenthal et al., 1976). However, the existence of several sulphotransferases, with some degree of substrate specificity, exist (Pang, 1982).
may be possible that the enzymes responsible for the sulphation of MCP may be sensitive to the sequelae of uremia. Yet, for MCP, this alteration may be reversible as evidenced by the change in kinetics following kidney transplant. It has been shown that the rate of removal by the liver for organic anions such as indocyanine green and hippurate is decreased from that seen in normal livers (Yates et al., 1984). These authors suggested that the decrease in removal was not the result of a competition for uptake into the liver between the substrate and some component of uremic plasma but could not specify the responsible mechanism. Similar data for organic cations does not appear to be available (Gibson, 1986). Terao and Shen (1985) demonstrated that some component of uremic rat plasma inhibits extraction of 1-propranolol in the isolated perfused rat liver. Although propranolol and MCP are structurally unrelated, it may be possible that a similar process may occur. However, as evidenced by the constant values of the kinetic parameters relative to the time of onset of hemodialysis, if such a substance impairs MCP clearance it is not hemodialysable. Alternatively, or additionally a change in hepatic blood flow secondary to the sequelae of uremia may alter MCP kinetics. Since MCP appears to be a drug with intermediate or high clearance, its kinetics are at least partially a function of liver blood
flow (Wilkinson and Shand, 1975). Although uremia may not in itself cause changes in liver blood flow, several attendant complications of uremia, for example hypertension and cardiac disease, may alter hepatic perfusion and induce changes in drug clearance (George, 1979). While the change in hepatic blood flow may not be able to account for the entire change in MCP kinetics it may offer, at least a partial explanation.
5. SUMMARY AND CONCLUSIONS

1) Metoclopramide undergoes linear kinetics in normal, healthy volunteers at doses between 5 and 20 mg.

2) The absolute bioavailability of MCP is ~0.78 ± and the relative bioavailability of the solution and tablet is ~ 1.00.

3) In spite of the relatively minor contribution of renal clearance to total body clearance in normals, metoclopramide kinetics are substantially altered in uremia viz a decrease in total body clearance of at least two-fold with an attendant proportionate increase in elimination half-life and little or no change in volume of distribution.

4) Hemodialysis is ineffective at removing metoclopramide from the body.

5) Hemodialysis has no effect on the apparent kinetic parameters following its termination.

6) Following kidney transplantation there appears to be a rapid reversion to apparently normal kinetics from the uremic state.
6. REFERENCES


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### 7. APPENDIX

<table>
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<th>PATIENT</th>
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</tr>
<tr>
<td>RT</td>
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</tbody>
</table>

1. Z-Bec (multivitamin)  
2. Beminal c Fortis (multivitamin)  
3. Folic acid  
4. Biotin  
5. Vitamin D  
6. Calcium Lactate  
7. Iron Dextran  
8. Amphojel Suspension (AlOH$_3$)  
9. Amphojel Tablets (AlOH$_3$)  
10. Robalate (dihydroxyaluminium acetate)  
11. Basalgel (AlOH$_3$)  
12. Docusate Sodium a) Colace b) Regulex  
13. Bisacodyl  
14. Pindolol  
15. Propranolol  
16. Metoprolol  
17. Diazepam  
18. Secobarbital  
19. Cephlexin  
20. Captopril  
21. Sulfasoxazole  
22. Phenytoin Na