Drug Therapy in Patients Undergoing Peritoneal Dialysis
Clinical Pharmacokinetic Considerations

Thomas W. Paton, William R. Cornish, M. Arifie Manuel
and *Brian G. Hardy*

Departments of Pharmacy and Medicine, Sunnybrook Medical Centre and
The University of Toronto, Toronto

Summary

Peritoneal dialysis has become an accepted treatment modality for end-stage renal disease. The introduction of continuous ambulatory peritoneal dialysis (CAPD) has further popularised this technique. The need for adjustment of drug dosage in patients with end-stage renal disease and the need for supplemental dosages following haemodialysis are well recognised. Little documentation exists concerning the need for supplemental drug dosage in patients on peritoneal dialysis. Knowledge of the influence of peritoneal dialysis on the elimination of specific drugs is essential to the rational design of dosage regimens in patients undergoing this dialysis technique.

This review addresses the clinical pharmacokinetic aspects of drug therapy in patients undergoing peritoneal dialysis and considers: (1) the efficiency of the peritoneal membrane as a dialysing membrane; (2) the effects of peritoneal dialysis on the pharmacokinetics of drugs; (3) the pharmacokinetic models and estimation methods for peritoneal dialysis clearance and the effects of peritoneal dialysis on drug elimination; (4) the influence of the pharmacokinetic parameters of drugs on drug dialysability; and (5) the application of pharmacokinetic principles to the adjustment of drug dosage regimens in peritoneal dialysis patients. Data on drugs which have been studied in peritoneal dialysis are tabulated with inclusion of pharmacokinetic and dialysability information.

In the management of patients with end-stage renal disease, peritoneal dialysis (PD) has become an accepted treatment modality. The technique may be performed as intermittent peritoneal dialysis (IPD), continuous ambulatory peritoneal dialysis (CAPD) or continuous cycling peritoneal dialysis (CCPD). Clearly, the introduction of CAPD and more recently CCPD has renewed interest in peri-toneal dialysis and at present, it is estimated that these methods are being used to treat approximately 5000 patients in the United States and Canada (Harrington, 1982).

Both methods take advantage of prolonged 'dwell times' (dialysate remains in the peritoneal cavity for approximately 4 to 6 hours), and the resulting continuous removal of urea. Blood urea ni-

trogen and serum creatinine stabilise at levels of approximately 80 mg/dl and 8.0 mg/dl, respectively. The basic principles and techniques of CAPD can be learned in 2 to 3 weeks. This method has the advantage of requiring neither anticoagulation nor vascular access and it results in better patient well-being, improved biochemical control, lack of dietary or fluid restrictions, an increase in haemoglobin levels, and easier management of bone disease and hypertension compared with haemodialysis (Gokal et al., 1981). However, it does suffer from a major disadvantage, that of peritonitis. As techniques improve, the incidence of peritonitis is likely to decrease and patients not previously considered candidates for peritoneal dialysis may qualify for CAPD.

The need for adjustment of drug dosage in patients with end-stage renal disease is well recognised, and guidelines have been established to facilitate drug dosage in such patients (Bennett et al., 1983). Similarly, dosage modification in patients on haemodialysis (Keller et al., 1982) and pharmacokinetic considerations of drug therapy in haemodialysis (Lee and Marbury, 1984) have also been reviewed. However, little attention has been paid to the extent to which peritoneal dialysis alters drug disposition from that described for end-stage renal disease. A tabulation of the pharmacokinetic data for drugs in patients on peritoneal dialysis with accompanying dosage recommendations has recently been published (Manuel et al., 1983). Difficulties in dosage adjustment in IPD arise due to potential differences in drug removal between the dialysis and non-dialysis days. In contrast, since most CAPD patients are dialysed continuously 7 days a week, a single well-constructed dosing schedule is feasible. It should be cautioned, however, that the application of such data for a particular patient may be difficult due to large intersubject variabilities in drug clearance. Whenever feasible therefore, dosage adjustment should be supported by serum concentration monitoring.

With the exception of antibiotics which are usually instilled intraperitoneally for the treatment of peritonitis, drugs administered to patients undergoing peritoneal dialysis are given orally or intra-

venously. It is considered appropriate, in most cases, to give a loading dose similar to that given to a patient without renal disease. In the case of antibiotics, the loading dose and the maintenance dose may be given intraperitoneally as has been described for tobramycin (Bunke et al., 1983b), cephazolin (Bunke et al., 1983a) and vancomycin (Bunke et al., 1983c).

Factors which affect the rate of removal of a drug in peritoneal dialysis have not been well-characterised. Generally, the following are thought to be of importance:

1. *The physiochemical properties of the drug.* These include molecular weight, water solubility and lipid partition.

2. *The physiology of the peritoneal membrane* – specifically the surface area, vascularity and the ultrafiltrability of the membrane which may be affected by peritonitis and other drugs.

3. *The solution type, flow rate and osmolality.*

4. *The pharmacokinetic properties of the drug* – in particular its protein binding and volume of distribution.

This review addresses the clinical pharmacokinetic aspects of drug therapy in peritoneal dialysis patients. Pharmacokinetic principles will be discussed with particular emphasis on those drugs in which peritoneal dialysis is of major importance in altering the elimination pattern. Little discussion will be devoted to specific dosage recommendations or the use of peritoneal dialysis as a treatment modality for accidental or intentional overdose. For a detailed review of these issues, readers are referred to recent articles by Manuel et al. (1983) and Blye et al. (1984), respectively.

1. The Peritoneum and Peritoneal Cavity

The peritoneal membrane is a continuous mesothelial layer of cells lining the inner surface of the peritoneal cavity and is called the parietal peritoneum. When this same membrane is reflected onto the abdominal organs it is known as the visceral peritoneum. According to Boen (1964), the surface area of the peritoneum is approximately

equal to that of the skin. Using the nomograms suggested by Dubois (1916) for body surface area, the peritoneal surface area for a 70kg human whose height is 172cm is estimated to be 1.8 square metres. According to Pappenheimer (1955), however, the peritoneal surface area is almost equal to that of the glomerular capillaries (range, 0.5 to 1.5 square metres per 100g of kidney). Since an average kidney weighs approximately 150g this would equate to an effective surface area of 1.5 to 4.5 square metres for the two kidneys.

The blood supply of the parietal peritoneum is an extension of vasculature of the abdominal wall. The visceral peritoneum, on the other hand, receives blood from vessels supplying the abdominal organs. The terminal arterioles of the peritoneum have a discontinuous muscle layer and thus participate in the exchange with dialysis fluid only at sites where endothelial lining cells and basement membrane are devoid of muscle (Renkin, 1979). Although the capillaries do not have a muscular layer, most of the endothelial cells lining the peritoneum do not possess fenestrations (Miller, 1981). Transport of solutes and fluid may occur via the fenestrations, intercellular junctions or by transcellular diffusion via vesicle formation (Nolph et al., 1980). Vesicles, which are found in the basal and luminal surfaces as well as in the cytoplasm, most likely contribute to transport of solute across vessel walls (Bruns and Palade, 1968).

Fluid and solute transfer may also occur via intercellular gaps. These gaps are smaller on the arterial than the venule side of the capillaries and may contribute to the explanation of ultrafiltration and protein loss across the peritoneal membrane. Less glucose from dialysis fluid diffuses across the peritoneal membrane into the bloodstream near the arteriole end of the capillary network.

Consequently in peritoneal dialysis, a large glucose gradient is established and maintained that draws water from the bloodstream into the peritoneal fluid. As blood reaches the venule end of the capillary bed, protein more readily moves out of, and glucose into, the capillary lumen, dissipating the glucose gradient required for ultrafiltration (Nolph et al., 1981).

1.1 Factors Influencing Solute Transport

There are a number of factors which will influence the movement of solute into and out of the capillary lumen. These factors have been discussed in detail by Nolph and Sorkin (1981), and are briefly summarised here.

Solute encounters a number of anatomical and physical resistances as it moves across the peritoneal membrane. In the capillary lumen, the first resistance is a stagnant fluid layer adjacent to the lumen. The second resistance is the endothelial layer itself – both the endothelial cell and the intercellular gaps. This is followed by the interstitium, the mesothelial channels, and finally a stagnant layer of peritoneal dialysis fluid in the peritoneal cavity.

Dialysis clearance rates for solutes are dependent on the physical nature of the peritoneal membrane. This can be illustrated by comparing the peritoneal membrane with the hollow fibres of an artificial kidney. The peritoneal membrane capillary has a lumen diameter of 7 to 10 microns and a wall thickness of 1 to 2 microns. In contrast, a hollow fibre synthetic 'capillary' has a diameter of 200 to 215 microns and a wall thickness of 16 to 30 microns (Nolph and Sorkin, 1981). The peritoneal capillary thus has a very small luminal surface area and, according to Pappenheimer (1953), only 0.2% of that surface will contain functional pore area. Intercellular gaps may be separated from each other by as much as 200 microns. In contrast, the cellulose fibres consist of a mesh of fibrils with many spaces between their interstices. The average pore size in the capillary is about 40 Ångströms compared with 20 Ångströms in the cellulose fibre. Thus the peritoneal capillary has a relatively high mean pore diameter and a low pore density, whereas the cellulose capillary has a low pore diameter, but a high pore density.

There is abundant evidence to suggest that the clearance of small molecular weight substances is not influenced to a major extent by changes in blood flow (Nolph and Sorkin, 1981). Regardless of the peritoneal dialysis technique used, peritoneal clearance rarely exceeds 30 to 40 ml/min

(Tenckhoff et al., 1965) despite the fact that the splanchnic blood flow in adult humans is approximately 1200 ml/min (Wade et al., 1956). Vasodilators are known to increase the number of capillaries perfused and the vascular permeability in the peritoneum (Nolph, 1979), yet only a modest 20% increase in urea clearance will occur. However, vasodilators increase the clearance of larger solutes dramatically and may exceed 100% of control. Thus for small solutes, interstitial and fluid films may be a more important barrier than blood flow changes. In contrast, vascular permeability and total effective pore area of the peritoneal capillaries significantly influence the clearance of larger molecular weight solutes. This latter point is supported by the following observations: (a) protein losses increase with the topical application of substances known to increase vascular permeability; (b) a proportionately larger increase in inulin than urea clearance occurs following intraperitoneal administration of vasodilators; and (c) during peritonitis, peritoneal membrane vasodilatation occurs which has been associated with a corresponding increase in glucose absorption and substantial loss of peritoneal fluid into the peritoneum (Nolph et al., 1981).

1.2 Membrane Failure

Membrane failure is an uncommon but important complication of CAPD since it will prevent the use of this technique as long term therapy for end-stage renal disease (Manuel and The University of Toronto Collaborative Dialysis Group, 1983).

Two types of membrane failure are now recognised. In *type 1,* there is a loss of ultrafiltration despite the use of high glucose concentrations in the dialysis fluid. However, solute removal is not affected. This type of failure is reversible if the CAPD is discontinued for weeks to months. The mechanism is unclear but appears to be related to the rapid dissipation of the glucose concentration from the peritoneal dialysis fluid. Such rapid glucose absorption is felt to occur due to vasodilatation and an increase in pore size of the capillaries

or alternatively, to an increase in the intercellular gaps of the mesothelial cells. If either event occurs, it is possible that the absorption of drugs from the peritoneal cavity will be favoured.

Faller and Marichal (1984) have suggested that the loss of ultrafiltration capacity may in fact be related to the acetate found in the dialysis solutions. Limited data from their group suggest that patients using lactate-containing dialysis solutions had a lower incidence of membrane failure than those using acetate-containing solutions. It is clear that the reason for loss of ultrafiltration (type 1) remains to be determined.

In *type 2* membrane failure, there is loss of total surface area of the peritoneal membrane. This may be due to recurrent episodes of peritonitis, adhesions and formation of stagnant pools within the peritoneal cavity. In this condition, there is loss of ultrafiltration and solute removal; recovery is unlikely.

2. Effects of Peritoneal Dialysis on the Pharmacokinetics of Drugs
2.1 Effects on Drug Absorption and Bioavailability

Little specific information is available on drug absorption and bioavailability in peritoneal dialysis. It is generally accepted the gastrointestinal disturbances associated with end-stage renal disease may in some way affect drug absorption and accordingly in patients on peritoneal dialysis. Furthermore, any effect of peritoneal dialysis on absorption is usually inferred by differences between peritoneal dialysis patients and those with end-stage renal disease or patients without renal disease. The first absolute bioavailability study in patients on either IPD or CAPD are awaited with interest.

During CAPD, it has been demonstrated that no clinically important changes in absorption characteristics occur with digoxin (De Paoli Vitali et al., 1981), co-trimoxazole (sulfamethoxazole-trimethoprim) [Singlas et al., 1982], and metronidazole (Bush et al., 1983). Procainamide bioavailability following the administration of a single oral dose appears to be similar to that reported for

patients with end-stage renal disease (Yonce et al., 1984). Similarly during IPD, amoxycillin serum concentrations following a 750mg dose are comparable to those reported in normal subjects (Jones et al., 1979). In contrast, the absorption of ketoconazole in 6 patients studied on CAPD was severely impaired, with peak concentrations around 25% of those achieved with the same dose in normal subjects (Chapman and Warnock, 1983).

Following intraperitoneal administration of antibiotics, drug absorption is rapid and extensive. It has been suggested that this process occurs rapidly and in a relatively unrestricted manner since little protein is available in the dialysis solution to retard absorption. Theoretically, the rate of absorption and the degree of protein accumulation in the peritoneal cavity may vary over the exchange period. This phenomenon, unfortunately, has not been examined in detail.

Studies addressing the state of hepatic blood flow and resultant effects on the bioavailability of high extraction drugs in peritoneal dialysis remain to be done.

2.2 Effects on Protein Binding

The therapeutic consequences of alterations in plasma protein binding in renal failure have been described for numerous drugs (Reidenberg, 1977a). Unfortunately, few such studies exist for peritoneal dialysis patients. It is generally agreed that changes in drug protein binding during peritoneal dialysis are likely to be secondary to the nutritional status of the patient, as reflected by serum protein concentrations, the resultant peritoneal losses of protein during the dialysis process, and the accumulating endogenous compounds that may displace highly bound drugs.

Protein losses during maintenance IPD and CAPD average 12.9g per 10 hours of dialysis and 8.8g per 24 hours, respectively (Blumenkrantz et al., 1981). In spite of these losses, serum protein concentrations are usually at the lower end of the normal range. With peritonitis, protein losses in the dialysate are enhanced but rapidly normalise to baseline losses with prompt institution of anti-

biotic therapy. Whether or not clinically significant changes in drug protein binding occur is, as yet, unclear.

The influence of protein binding changes on the total and free concentrations of digitoxin was reported by Peters et al. (1981) for CAPD and control haemodialysis patients. The protein binding of digitoxin during CAPD was 94.7 ± 1.5%, significantly less than the 96.2 ± 1.3% observed binding in control haemodialysis patients. Following a 0.1mg daily oral dose, the mean steady-state serum concentrations of total drug in CAPD and haemodialysis patients of 14.3 and 22.8 ng/ml, respectively, suggests a higher clearance of digitoxin during CAPD. However, when protein binding alterations were considered, the mean free serum concentrations in CAPD and haemodialysis patients of 0.8 and 0.9 ng/ml, respectively, were not significantly different.

2.3 Effects on the Volume of Distribution

Changes in the volume of distribution of drugs have been described in patients with end-stage renal disease and for the most part reflect changes in protein binding and tissue uptake. These changes are best illustrated with digoxin (Reuning et al., 1973) and phenytoin (Odar-Cederlöf and Borgå, 1974) with resultant changes required in dosing.

At present, those pharmacokinetic studies that have examined volume of distribution have been unable to discern a true difference between peritoneal dialysis patients and those with normal renal function or end-stage renal disease. Difficulties arise in making comparisons with the small number of subjects studied. This is due, in part, to the large intersubject variability reported in peritoneal dialysis and the overlap in values reported for normal subjects and end-stage renal disease patients.

In patients on IPD, the volumes of distribution of those drugs that have been studied are similar to those in patients with normal renal function. The notable exception is an increased volume of distribution of sulphamethoxazole (0.55 L/kg) compared with normal subjects (0.14 to 0.36 L/kg) [Singlas et al., 1982].

During CAPD, volume of distribution infrequently changes in comparison with normal or end-stage renal disease patients. However, with cefoxitin, the volume of distribution was reported to be 0.27 L/kg as compared with normal values of 0.16 L/kg (Greaves et al., 1981). This change is thought to be due to the protein binding alterations that occur in end-stage renal disease, with the percentage protein binding approaching 20% compared with 73% in subjects with normal renal function (Garcia et al., 1979). For latamoxef (moxalactam) [Singlas et al., 1983] and cefotaxime (Alexander et al., 1984) the distribution volumes are significantly reduced. The reasons for these changes are not apparent.

2.4 Effects on Drug Metabolism

The effect of peritoneal dialysis on drug metabolism has not been extensively studied. Whether or not defects in biotransformation, as documented in renal failure (Reidenberg, 1977b) will be influenced by long term peritoneal dialysis is unknown. Preliminary work in CAPD with metronidazole and its 2 major metabolites suggests that oxidative metabolism may be normal in such patients (Guay et al., 1984). Clearly, more work in this area is needed.

3. Peritoneal Dialysis and Drug Clearance
3.1 Pharmacokinetic Models of Peritoneal Dialysis

Pharmacokinetic relationships have been developed in an effort to characterise the distribution and elimination of drugs by peritoneal dialysis (Babb et al., 1973; Boen, 1961; Jusko et al., 1976; Popovich and Moncrief, 1979; Sargent and Gotch, 1980). These mathematical models and clearance concepts can be used to describe the bi-directional and frequently unequal transfer of drugs across the peritoneum by passive diffusion or ultrafiltration with solvent drag. Within limitations, models of peritoneal dialysis offer an accountable means by which the peritoneal flux of drugs can be studied.
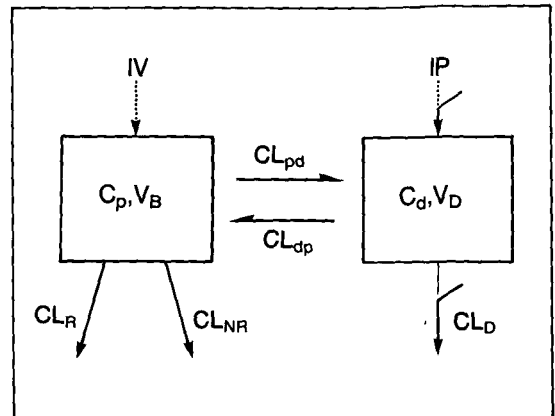
An example of a 2-compartment pharmacokin-

Fig. 1. Pharmacokinetic model describing the distribution and elimination of a drug during peritoneal dialysis. C_p and C_d are drug concentrations in plasma and dialysis fluid; V_B and V_D are volumes of the body and dialysis fluid compartments; CL_R, CL_{NR} and CL_D are renal, non-renal and peritoneal clearances; CL_{pd} and CL_{dp} are transfer clearances between plasma and dialysis fluid; and IV and IP (with dashed arrows) represent potential intravenous and intraperitoneal routes of administration. The solid arrows indicate continuous drug transport processes and the interrupted arrows represent the intermittent draining and replacing of dialysis fluid in the peritoneum (adapted from Jusko et al., 1976; with permission of the International Society of Nephrology).

etic model (plasma and dialysis fluid) for peritoneal dialysis of drugs is shown in figure 1. This model is appropriate for those drugs for which a 1-compartment model adequately describes their disposition during non-peritoneal dialysis conditions. For drugs better characterised by a multicompartment model the mathematical descriptions are more complex; however, the principles of bi-directional clearance between plasma and dialysis fluid remain applicable.

For specific information on the differential pharmacokinetic equations that have been derived to describe the rate of change of plasma or dialysis fluid drug concentration following intravenous or intraperitoneal administration, readers are referred to articles by Sargent and Gotch (1980) and Jusko et al. (1976).

3.1.1 Assumptions of Pharmacokinetic Models
Pharmacokinetic estimates generated from these equations are only as accurate as the mathematical

and descriptive models upon which they are based. A number of assumptions have been made in designing these pharmacokinetic models that limit their general applicability. For example, the original models assumed that transfer of drug across the peritoneal membrane was exclusively by passive diffusion. Subsequently, it was recognised that there are at least 6 resistance sites in the transfer of drug from the capillaries to the peritoneal cavity involving passive and ultrafiltrative processes with or without solvent drag (Babb et al., 1973; Nolph, 1979). A second assumption of these models is that the volume of the dialysis fluid compartment remains constant. If appreciable ultrafiltration occurs, either by hydrostatic (across capillary walls) or osmotic mechanisms (induced by hypertonic dialysis solutions), the dialysate volume instilled may vary from that removed at the end of a 'dwell' period. These differences may become notable when one compares techniques with variable dwell times (IPD *versus* CAPD). In addition, the pharmacokinetic models of bi-directional transfer clearances do not take into account the possibility of changes in the transfer clearances with variations in dialysis fluid compartment volume.

Lastly, drug distribution following intravenous or intraperitoneal administration is presumed to be instantaneous within the respective compartments. This latter point is of concern for drugs in dialysate instilled and removed over a half-hour exchange period.

In practical terms, most clinicians are less interested in the individual transfer clearances between plasma and dialysate than the net removal rate of drug from plasma or dialysate following intravenous or intraperitoneal administration, respectively. The following discussion relates to these net clearance and absorptive processes.

3.2 Calculation of Peritoneal Clearance

Peritoneal clearance is defined as the volume of plasma fluid from which a given amount of drug is removed by peritoneal dialysis per unit of time. This parameter can be calculated following intravenous or intraperitoneal administration of a drug.

The latter route requires plasma sampling during the absorptive phase and following exchange with drug-free dialysate. The removal of drug from plasma is dependent on 'dwell' time, dialysate volume and osmolality. As will be discussed, these factors often vary between reported studies and are dependent on the dialysis-type chosen. Independently of whether IPD or CAPD is employed, the following 2 methods are used for the purposes of calculating net peritoneal clearance.

3.2.1 Time-Specific Method

The general equation used clinically to calculate drug removal during peritoneal dialysis is:

$$CL_D = C_d \cdot V_D / \bar{C}p \cdot t \qquad \text{(Eq. 1)},$$

where CL_D is the net peritoneal clearance, C_d is the drug concentration in peritoneal effluent at the end of the exchange, V_D is the volume of peritoneal effluent at the end of the exchange, $\bar{C}_p$ is the plasma drug concentration at the midpoint of the dialysate collection, and t is the duration of the exchange. This method is most applicable when dialysate sampling or exchange is frequent. At least 2 such measurements should be obtained for confirmation of results, especially if the midpoint plasma drug concentration is an interpolated value.

The method is time-specific, as it relies on the validity of the dialysate collection midpoint as the most appropriate time to obtain plasma samples. Although this arithmetic mean time is acceptable for drugs with longer half-lives, the method errs when rapid exponential changes in plasma drug concentrations occur over a collection interval. In addition, the method is also dependent on dialysate flow and processes that alter dialysate volume, e.g. ultrafiltration.

3.2.2 Time-Average Method

The following model-independent calculation of peritoneal clearance requires that the area under the plasma concentration *versus* time curve (AUC) be analysed for a given dialysate 'dwell'. The equation is given as:

$$CL_D = \frac{A_{d\,(t_1 \to t_2)}}{AUC_{(t_1 \to t_2)}} \qquad \text{(Eq. 2)},$$

where A_d is the total amount of drug collected in the dialysate from time t_1 to t_2, and AUC is determined for the same time interval. In the case of a single intravenous dose $t_1 = 0$; following intraperitoneal administration t_1 is some time after systemic absorption when exchange with drug-free dialysate is complete. The dialysate sampling interval, $t_2 - t_1$, should not be excessively long, relative to the half-life of the drug, as to preclude a meaningful estimation of AUC.

As the time-average peritoneal clearance derived from equation 2 is independent of dialysate flow rate and unaffected by ultrafiltration, it is preferred to the time-specific method where such factors are uncontrolled or unknown.

3.2.3 Assumptions of Clearance Calculations

Estimations of peritoneal clearance inherently rely on the accuracy and sensitivity of the assay used to measure drug concentrations in plasma and dialysate. This may be of particular concern for drugs that have poor dialysability (low effluent concentration) or estimations based on single-point determinations (equation 1). In addition, it is assumed that the assay is specific enough to differentiate between parent compound, metabolites and degradation products of a drug. In the latter case, in vitro chemical deterioration of a drug must be ruled out by performing stability studies of the parent compound in dialysate solution at body temperature.

Drug concentrations are invariably reported as total drug, with little or no reference to the degree of protein binding in plasma or dialysate. During multiple 'dwell' periods, protein loss into the peritoneal fluid may be of such magnitude as to alter the free drug concentration available for therapeutic effect. Time-dependent protein losses of the order of 8 to 10 g/day have been reported in CAPD patients with 4 exchanges per day (Blumenkrantz et al., 1981; Twardowski et al., 1981). Up to 60% of the variability of this protein loss was dependent on the initial total protein and body surface area (and indirectly on the anatomical peritoneal surface area) of the patients. Studies on protein losses during 10 hours of IPD gave higher losses of 12g

(Blumenkrantz et al., 1981). Removal of endogenous protein binding displacing substances, e.g. urea, may potentially contribute to variability in free drug concentrations. It follows that increasing efforts are required to characterise the disposition and elimination of both total and free drug by peritoneal dialysis.

Calculation of peritoneal clearance following intraperitoneal administration of drug assumes that any residual drug and dialysis fluid from the previous exchange will be negligible prior to instillation of drug-free dialysate. However, complete evacuation of the peritoneal effluent may not always be achievable, the result being a potential overestimation of the apparent peritoneal clearance.

3.3 Effects of Peritoneal Dialysis on Drug Elimination

Although peritoneal dialysis has been shown to be an effective method for removal of uraemic waste products, it contributes little to the clearance of most drugs (table I). The greatest contribution to total clearance occurs with drugs which are almost exclusively removed by the kidney.

3.3.1 Drugs Principally Eliminated by the Kidney

Intermittent Peritoneal Dialysis

During IPD, the aminoglycosides, amikacin (Madhavan et al., 1976; Matzke et al., 1980), gentamicin (Hamann et al., 1982; Jusko et al., 1976), kanamycin (Atkins et al., 1973), and tobramycin (Jaffe et al., 1974; Malacoff et al., 1975; Ramos et al., 1979) are cleared sufficiently as to warrant a change in dosage relative to that used in end-stage renal disease. The peritoneal clearance accounts for 50 to 75% of the total body clearance with a correspondingly high recovery in the dialysate. Of the cephalosporin antibiotics studied, cephalexin (Yamasaku et al., 1970), cefuroxime (Local et al., 1981) and ceftazidime (Tourkantonis and Nicolaidis, 1983) require dosage modification relative to dosages required in end-stage renal disease. Changes

Table I. The disposition and elimination of drugs in patients undergoing intermittent peritoneal dialysis (IPD) and continuous ambulatory peritoneal dialysis (CAPD) for which meaningful pharmacokinetic data are available, as compared with normal adult and end-stage renal disease (ESRD) patients. Pharmacokinetic parameters of clinical importance include half-life, volume of distribution (Vd), total body clearance, peritoneal clearance, and percentage removal of drug over specified dialysis dwell times. Values are reported as means (± standard deviation) or range, as available

Drug	Dialysis type	Half-life (hours)			Vd (L/kg)		Clearance (ml/min)		Removal		No. of patients	Reference
		normal	ESRD	study	normal	study	total body	peritoneal	%	time (h)		
Amikacin	IPD	2	24-60	25.8 (± 12.9)	0.22-0.29	0.26	9.7 (5.4-19)	6.7 (± 6)	23.1	8	5	Matzke et al. (1980)
	IPD			18 (± 3.2)			6.4 (± 2)	3.9 (± 2.1)			4	Regueur et al. (1977)
	IPD			29					20	12	3	Madhavan et al. (1976)
Amino-caproic acid	IPD	1-2		31	0.9	0.9	24-29	13.8			2	Fish et al. (1981)
Amoxycillin	IPD	0.5-2.3	5-20	15 (8.6-22)	0.25-0.45						19	Jones et al. (1979)
Ampicillin	IPD	0.8-1.5	6-20	13.5 (10.9-14.6)	0.17-0.31				7	12	4	Reudy (1966)
Azlocillin	IPD	0.8-1.5	5.6	2.5 (± 0.25)	0.18-0.23				5.4	7.5	6	Whelton et al. (1983)
Aztreonam	CAPD	1.8-2.2	5-8	7.08	0.17-0.22		23.8	2.1	9.74	48	2	Bolton et al. (1984)
Carbenicillin	IPD	1.0	10-20		0.12-0.20			6.8 (± 2.5)			2	Eastwood and Curtis (1968)
Cefamandole	IPD	0.5-1.8	6-20	7 (± 1.4)	0.16-0.25			10 (± 1)	14	12	4	Ahern et al. (1976)
	IPD			12 (2)		0.3					2	Meyers and Hirschmann (1977)
	CAPD			10.4 (± 7.3)	0.16-0.25	0.25 (± 0.08)	20 (± 6.2)	3.2 (± 1.6)	7.3 (± 2.3)	24	5	Pancorbo and Comty (1983)
Cefoperazone	CAPD	1.6-2.4	4-6	2.25 (± 0.61)	0.14-0.23						5	Keller et al. (1984)
Cefotaxime	IPD	0.8-1.5	1.4-3.6	38 (±1.4)	0.20-0.27		39 (± 16)	5.5 (± 3)	6	8	5	Schurig et al. (1981)
	IPD			2.9 (± 1)								Wise et al. (1981)
	CAPD							3.2				Schurig et al. (1981)

Drug	Route										n	Reference
Cefotaxime	CAPD			1.8 (± 1.2)		0.13 (± 0.02)	65 (± 25)	2.4 (± 0.3)			3	Alexander et al. (1984)
Desacetyl-cefotaxime	CAPD	1.1-1.8	8.2-11.8	11 (± 5)				3.8 (± 0.9)			3	Alexander et al. (1984)
Cefoxitin	CAPD	0.7	10-22	7.8 (± 2.7)	0.10-0.13	0.27 (± 0.05)	20.4 (± 3.9)	1.44 (± 0.67)			6	Greaves et al. (1981)
Ceftazidime	IPD	1.3-2.0	18-28	8.7 (± 3.1)	0.11-0.16		8.46 (± 2.7)				5	Tourkantonis and Nicolaidis (1983)
Ceftazidime	IPD	1.3-2.0	18-28	8.7 (± 3.1)	0.11-0.16		8.46 (± 2.7)				5	
Ceftazidime	CAPD						4.0-3.0		4.3-7.0	4-6	5	Comstock et al. (1983)
Ceftizoxime	CAPD	1.4-2.0	20-30	9.7 (± 5.1)	0.26	0.23 (± 0.05)	17.1 (± 7.4)	2.8 (± 0.7)			12	Burgess and Blair (1983)
Ceftizoxime	CAPD			11.1 (± 5.8)		0.27 (± 0.07)	25.3 (± 9.8)	3.2 (± 1.0)	15 (± 5)	6	14	Gross et al. (1983)
Ceftriaxone	CAPD	4.6	12-18 (7.4-14.4)	12.2	0.15-0.20	0.12 (0.08-0.18)	7.4 (4-12.9)				3	Ti et al. (1984)
Cefuroxime	IPD	1.6-2.2	15-22	11.8 (± 2)	0.13-0.18		16 (± 2)	4.7 (± 2)	20	24	6	Local et al. (1981)
Cefuroxime	IPD			13.6 (± 4)							3	Kosmidis et al. (1977)
Cephalexin	IPD	1-2	12-30	6.4	0.18-0.38			16.3	30	7	3	Yamasaku et al. (1970)
Cephalexin	CAPD			8.6 (± 2.0)	0.18-0.26	0.22 (± 0.04)	18.5 (± 6.1)	2.29 (± 1.4)			5	Bunke et al. (1983a)
Cephaloridine	IPD	1-1.5	10-23	8.3				7.5			4	Yamasaku et al. (1970)
Cephalothin	IPD	0.5-1.0	3-18	5.1	0.15-0.31						6	Yamasaku et al. (1970)
Cephazolin	IPD	1.4-2.0	28-40	32 (± 4)	0.1-0.15				19.6	30	3	Madhavan et al. (1975)
Cephazolin	IPD			33 (20-46)							2	Levison et al. (1973)
Cephazolin	CAPD			33 (± 9.8)		0.24 (± 0.06)	5.7 (± 0.6)	1.0 (± 0.3)			6	Bunke et al. (1983a)
Chloramphenicol	IPD	2-4	3-7	3.8 (± 1)	0.57-1.0						7	Greenberg and Sanford (1967)
Cimetidine	IPD	1.4-2.4	3-10		0.45-1.1			3.1-9.98			2	Vaziri et al. (1979)
Chloramphenicol	CAPD			6.9 (± 0.4)			167 (± 20)	2.7 (± 0.9)	1.63	24	6	Paton et al. (1982a)
Cimetidine	CAPD			4.3 (2.9-7.3)		0.96 (± 0.21)	191 (± 55)	4.2 (± 3.1)			6	Kogan et al. (1983)

Table I. (contd)

Drug	Dialysis type	Half-life (hours) normal	ESRD	study	Vd (L/kg) normal	study	Clearance (ml/min) total body	peritoneal	Removal %	time (h)	No. of patients	Reference
	CAPD			4.3 (2.9-7.3)		0.96 (± 0.21)	191 (± 55)	4.2 (± 3.1)			6	Kogan et al. (1983)
Clindamycin	IPD	3.0	3.0	4.6 (± 1.2)	0.61-1.1			4			3	Malacoff et al. (1975)
Colistin sulphomethate (colistimethate)	IPD	3-8	10-20	14 (± 6.8)	0.54			5.8 (± 1.9)			6	Goodwin and
	IPD						31	11 (± 6.5)	16	48	3	Greenberg and Sanford (1967)
Digoxin	IPD	160	160		0.4-0.7			0.7 (± 0.3)	13.4	24	8	Risler et al. (1981)
	CAPD	30-40	80-140	88 (52-118)	5-7.5			8.0	3	32	14	Ackerman et al. (1967)
	IPD			89.2 (57-141)			28.4 (11-52)	2.74 (2.3-3.1)	10	96	5	De Paepe et al. (1982)
	CAPD							3.6 (2.5-6)	7.6	24	5	Gloor et al. (1982)
	CAPD			97.9			12.6	2.0			1	Pancorbo and Comty (1980)
Gentamicin	CAPD	2	24-60	6.5-7	0.23-0.26		21.2 (19.8-22.6)				2	Hamann et al. (1982)
	IPD			21 (± 12)		0.33	5.5 (± 3)	4 (± 2.6)			5	Jusko et al. (1976)
	IPD						13.5 (8-19)				2	Gary (1971)
	IPD			14.7				9 (5-12)	4	22	4	Smithivas et al. (1971)
	CAPD			36 (± 9.0)		0.22 (± 0.07)		2.9 (± 0.4)	20 (± 6.9)	24	7	Pancorbo and Comty (1981)
	CAPD			27.4 (± 11.7)		0.3 (± 0.01)	11.3				5	Somani et al. (1982)
Kanamicin	IPD	1.7	24-60	12.1 (8-17)	0.22-0.27			8.2 (6-11)	31	22	15	Atkins et al. (1973)
Latamoxef (moxalactam)	CAPD	2-3	15-30	16.7 (± 2.1)	0.31-0.41	0.21 (± 0.01)	10.6 (± 2)	2.7 (± 0.5)			8	Singlas et al. (1983)

Drug												Reference
Lincomycin	IPD	4.5	12		0.31-0.6					7.5	4	Reinarz and McIntosh (1965)
Metronidazole	IPD	6-10	6-10	13.2 (10.3-15.4)	0.59-0.85	0.56 (± 0.16)	80.1 (± 17.1)	15.8 (± 1.6)	10.2 (± 2.7)		5	Cassey et al. (1983)
	CAPD	6-10		5.6 (± 1.0)		0.75 (± 0.15)	50.2 (± 18.6)	4.5 (± 0.9)			5	Guay et al. (1984)
Mezlocillin	IPD	1.0	2-4	10.9 (± 2.0)	0.22		96 (± 51)	7.4 (± 3.9)			6	Kampf et al. (1980)
Oxacillin	IPD	0.5	1.4	3.2	0.19-0.41				5	12	3	Reudy (1966)
Procainamide	CAPD	2.5-4.7	5.3-20	1.4	2			< 3	0.016	1	5	Yonce et al. (1984)
N-acetyl-procainamide	CAPD	4.3-8.7	27-44	24	1.3-1.8			< 7	0.096	1	5	Yonce et al. (1984)
Quinidine	IPD	4-6	5-8		2-3		277	1.2	4.5	6	1	Hall et al. (1982)
	CAPD			5.4			154.2	0.79	0.61	24	1	Chin et al. (1981)
Sulphamethoxazole	IPD	10-13	20-50	18 (± 11)	0.14-0.36	0.55 (± 0.22)	26 (± 18)	1.2 (± 0.6)	2	12	10	Singlas et al. (1982)
	CAPD			107 (± 33)		0.17 (± 0.22)	1.3 (± 0.3)				8	Matzke et al. (1983a)
Theophylline	IPD	3-12		5.1-6.8	0.3-0.7			11.7 (± 2.4)			3	Brown et al. (1981)
Ticarcillin	IPD		10-20	10.6 (± 0.8)				13.4-13.7	3.3-4.4	4	2	Lee et al. (1983)
	IPD	1-1.5			0.14-0.21			7.2 (± 1.8)			2	Parry and Neu (1976)
Tobramycin	IPD	2	24-60	18-50	0.22-0.25				23-38	48	10	Ramos et al. (1979)
	IPD			25.4 (18-37)					30-69	36	4	Jaffe et al. (1974)
	IPD		10-20	16 (± 4)		0.3		15 (± 4)	34	12	5	Malacoff et al. (1975)
	CAPD		24-60	34.6 (± 18)		0.23 (± 0.06)	8.0 (± 2.5)	3.8 (± 1.0)	16.5-26	24	6	Paton et al. (1982b)
	CAPD			39.5 (± 18)		0.34 (± 0.06)	7.57 (± 3.1)	1.11 (± 0.8)			6	Bunke et al. (1983b)
	CAPD			38.7 (± 10.6)		0.3 (± 0.07)	6.9 (± 1.2)				4	Halstenson et al. (1984)
Trimethoprim	IPD	10-13	24-46	23.7 (± 13)	1-2	2.2 (± 1.5)	66 (± 36)	5 (± 1.6)	3	12	10	Singlas et al. (1982)
	CAPD			33.7 (± 10.5)		1.28 (± 0.32)	32.8 (± 10)				8	Matzke et al. (1983a)

Table 1. (contd)

Drug	Dialysis type	Half-life (hours)			Vd (L/kg)		Clearance (ml/min)		Removal		No. of patients	Reference
		normal	ESRD	study	normal	study	total body	peritoneal	%	time (h)		
Vancomycin	IPD	4-8	80-250	18	0.47-0.84			6.1 (4.2-9.8)	39.7	15	11	Nielsen et al. (1979)
	IPD			205.2 (± 62.24)		1.07 (± 0.38)	4.25 (± 0.6)	2.4			4	Magera et al. (1983)
	CAPD			90 (± 24)		0.73 (± 0.1)	6.4 (± 1.1)	1.4 (± 0.4)			4	Matzke et al. (1983b)
	CAPD			77 (± 27)			9.8 (± 5.0)	1.4 (± 0.95)			4	Bunke et al. (1982)
	CAPD			67 (± 12)		0.43 (± 0.1)		2.4 (± 0.8)			4	Pancorbo and Comty (1982)
	CAPD			93 (± 15.5)		0.7 (± 0.03)	4.85 (± 0.72)	3.82 (± 0.45)			7	Harford et al. (1984)
	CAPD			81 (± 10.8)		0.88 (± 0.07)	9.4 (± 1.9)	1.48 (± 0.36)			6	Bunke et al. (1983c)

Abbreviations: IPD = intermittent peritoneal dialysis; CAPD = continuous ambulatory peritoneal dialysis; ESRD = end-stage renal disease.

in vancomycin clearance are unresolved with reports of profound changes in half-life (18 hours) compared with end-stage renal disease (80 to 200 hours) [Nielsen et al., 1979] to no changes compared with end-stage renal disease (Magera et al., 1983). For all other drugs examined during IPD the peritoneal clearance contributes little to the total body clearance (table I).

Continuous Ambulatory Peritoneal Dialysis

Likewise during CAPD, the peritoneal clearance relative to total body clearance is significant for gentamicin (Pancorbo and Comty, 1981; Somani et al., 1982) and tobramycin (Bunke et al., 1983b; Paton et al., 1982b). For tobramycin, the peritoneal clearance contributes 15 to 40% of the total body clearance with up to 20% of the dose recovered in the dialysate over 24 hours. With the cephalosporin antibiotics cephalexin (Bunke et al., 1983a), ceftazidime (Comstock et al., 1983) and ceftizoxime (Burgess and Blair, 1983; Gross et al., 1983), the peritoneal clearance contributes significantly to the total body clearance (approximate contributions for cephalexin and ceftazidime are 12% and 10 to 15%, respectively). For vancomycin, the peritoneal clearance contributes 15 to 25% to the total body clearance. Corresponding half-lives range from 67 (Pancorbo and Comty, 1982) to 90 hours (Bunke et al., 1983c; Matzke et al., 1983b).

3.3.2 Drugs Eliminated Significantly by Metabolism

It appears that for agents in which metabolism contributes significantly to the total body clearance, dialysate clearance is low and removal in dialysate is of little importance. For cimetidine, dialysate clearance in CAPD accounts for only 1.5 to 2.5% of the total body clearance (Kogan et al., 1983; Paton et al., 1982a). Similarly, quinidine removal by CAPD is negligible with < 1% removed in 24 hours, and the dialysate clearance represents < 1% of the total body clearance (Chin et al., 1981).

3.3.3 Antibiotics in Treatment of Peritonitis

For the majority of the antibiotics studied, the penetration into the peritoneal cavity is low. Treat-

ment of peritonitis with such antibiotics must therefore be by the intraperitoneal route to ensure resolution of the infection. It should be noted that for gentamicin and tobramycin, even though the drugs are removed by peritoneal dialysis, the antibiotic concentrations are too low to be effective. However, with the newer cephalosporin antibiotics, despite low peritoneal clearances, intravenous therapy may produce adequate dialysate drug concentrations in excess of the minimum inhibitory concentration (MIC) of susceptible causative organisms. This appears to be the case with latamoxef (Singlas et al., 1983). In addition, metronidazole appears to accumulate in the peritoneal cavity in adequate concentrations to be effective for anaerobic peritonitis even though the dialysate clearance accounts for only 9% of total body clearance (Bush et al., 1983; Guay et al., 1984).

The effect of peritonitis on dialysate clearance has not been adequately studied. However, the intraperitoneal absorption of gentamicin (De Paepe et al., 1983; Somani et al., 1982) and trimethoprim (Singlas et al., 1982) from the peritoneal cavity to blood is enhanced in the presence of peritonitis.

3.3.4 Metabolite Removal
Few studies exist examining the effect of dialysate clearance on metabolite removal. Recent work with metronidazole (Guay et al., 1984) would suggest that CAPD contributes little to the metabolite clearance. Similar work with cefotaxime and its active metabolite, desacetyl-cefotaxime, suggests that the dialysate clearance of the metabolite is low (3.8 ml/min) with a corresponding half-life of 11 hours (Alexander et al., 1984) as compared with a value of 1.3 hours in normal subjects (Luthy et al., 1981).

4. Influence of Pharmacokinetic Parameters on Drug Dialysability

The dialysability of a drug in peritoneal dialysis appears to be determined by its route of elimination, protein binding and by its volume of distribution. This is most apparent when one considers the aminoglycosides which have low protein binding, relatively small volumes of distribution and

are eliminated unchanged by the kidney. In this circumstance peritoneal dialysis can contribute up to 40% of the total body clearance of an aminoglycoside in end-stage renal disease. For other agents, such as latamoxef (Singlas et al., 1983), which are eliminated essentially unchanged by the kidney, dialysability is limited by, as yet, unidentified factors. Further difficulties arise in making such predictions when one considers agents which are only partially eliminated by the renal route. Therefore any generalisations regarding a drug's dialysability on the basis of its route of elimination is difficult.

4.1 Protein Binding

4.1.1 Influence on Dialysability in IPD
During IPD, drugs which are highly protein-bound are poorly dialysed regardless of their route of elimination. In contrast, agents which are primarily renally eliminated and with low protein binding are significantly cleared. This is especially true for the aminoglycosides (Atkins et al., 1973; Jaffe et al., 1984; Matzke et al., 1980), vancomycin (Nielsen et al., 1979), cephalexin (Yamasaku et al., 1970), and ceftazidime (Tourkantonis and Nicolaidis, 1983). Cefuroxime, which is 35% protein-bound, is efficiently removed by IPD (Local et al., 1981). However, if hepatic metabolism contributes significantly to a drug's elimination, as with cimetidine (Pizzella et al., 1980), regardless of the degree of protein binding, its dialysability will be low.

4.1.2 Influence on Dialysability in CAPD
Similarly, in CAPD, the aminoglycosides (Bunke et al., 1983b; Pancorbo and Comty, 1981; Paton et al., 1982b; Somani et al., 1982), vancomycin (Bunke et al., 1983c; Matzke et al., 1983b; Pancorbo and Comty, 1982) and ceftazidime (Comstock et al., 1983) are sufficiently removed as to require dosage adjustment in comparison with that used in end-stage renal disease. This increased elimination in CAPD is consistent with the drugs' low protein binding. Cephalexin is not as efficiently removed during CAPD (Bunke et al., 1983a) as during IPD,

Table II. The absorption characteristics of antibiotic drugs following intraperitoneal (IP) administration in patients undergoing intermittent peritoneal dialysis (IPD) and continuous ambulatory peritoneal dialysis (CAPD). Pharmacokinetic considerations of importance in the development of dosing regimens include the amount of drug administered intraperitoneally per litre of dialysis solution (Dose), dialysate flow rate, percentage absorbed (mean ± standard deviation), and achievable serum drug concentrations (mean ± standard deviation) at specified blood sampling times

Drug		Dose (mg/L)	CAPD dwell time (h)	IPD flow rate (L/h)	Percentage absorbed	Serum concentrations		No. of Patients	Reference
						(mg/L)	time (h)		
Ampicillin		25		1.25	75	7.5 (± 1.2)	12	6[a]	Reudy (1966)
Cefamandole		500	6		71.7 (± 12.8)	31.3 (± 5.4)	6	5	Pancorbo and Comty (1983)
Cefotaxime		100	8		90			26	Schurig et al. (1981)
		1000	6		56 (± 10)	18-38	3	5	Alexander et al. (1984)
Ceftazidime		200		2		25.3 (± 3.1)	12	3	Tourkantonis and Nicolaidis (1983)
		1g (no dianeal)	8			44.7 (± 10.5)	2.75 (± 2.2)	4	Tourkantonis and Nicolaidis (1983)
Ceftizoxime		250	6		78 (± 4)	12.5	5	4	Gross et al. (1983)
Cefuroxime		50		2	44 (± 20)	14.0 (± 8.1)	24	5	Local et al. (1981)
		250		5		60.9	6	7	LaGreca (1982)
Cephalothin		100	6			3.5 (± 1.7)	2.3	7	Munch et al. (1983)
						5.6 (± 2.2)	25		
Cephazolin		50		2		30.3 (± 12.8)	24	3	Kaye et al. (1978)
		150		2		71.9 (± 43.0)	24	6[a]	
		10 mg/kg	4		73.7	36	4	5	Bunke et al. (1983a)
	LD[b]	500	6		88	54.8 (± 6.7)	6	5[a]	Paton et al. (1983)
	MD[c]	250	6		65	110.9 (± 6.7)	24	5[a]	
Gentamicin		5		2		1.7-5.0	12-24	8[a]	Smithivas (1971)
		15		0.6-1.2		3.76-10.2	10	5	Jusko et al. (1976)
	LD	50	6		49 (± 14.7)	3.9 (± 1.5)	6	8	Pancorbo and Comty (1981)
	LD	1.5 mg/kg	6		84	3.22 (± 2.5)	6	5	Somani et al. (1982)
	MD	7.5	6		79.3 (± 2.7)			5[a]	De Paepe et al. (1983)
					64.0 (4.8)			5	
Kanamycin		15		3.5	55	6.7	16	7	Atkins et al. (1973)
Latamoxef (moxalactam)	LD	100				2.5 (± 0.9)	1	5[a]	Stephens et al. (1983)
	MD	30		2		10.3 (± 4.8)	24	5[a]	
Sulphamethoxazole		80		3	40	26	12	5[a]	Singlas et al. (1982)
						29 (± 3.2)	48	5[a]	
						12	24	8	
Tobramycin		10				6.8-8.4		5	Ramos et al. (1979)
	LD	1.5 mg/kg	4		52	1.8	4	6	Bunke et al. (1983b)
	LD	1.7 mg/kg	6			5-6	6	20[a]	Williams et al. (1982)
	LD	50	6		85	4.3 (± 0.6)	6	5[a]	Paton et al. (1983)
	LD	1.93 (± 0.26) mg/kg	6			6.6 (± 1.1)	48 (peak)	4[a]	Halstenson et al. (1984)
	MD	8	6			5-6	6	20	Williams et al. (1982)
	MD	7.5	6		50	3.7 (± 0.15)	24-72	5[a]	Paton et al. (1983)
	MD	5	6		48	1.3 (± 0.12)	24	4[a]	Paton et al. (1983)
						2.1 (± 0.2)	48		

Table II. (contd)

Drug		Dose (mg/L)	CAPD dwell time (h)	IPD flow rate (L/h)	Percentage absorbed	Serum concentrations		No. of Patients	Reference
						(mg/L)	time (h)		
Tobramycin	MD	0.96 (± 0.29) mg/kg	6			6.9 (± 0.7) 2.6 (0.4)	48 (peak) 48 (trough)	4[a]	Halstenson et al. (1984)
Trimethoprim		16		3	89	1.2 3.8 (± 0.3) 0.6	12 48 12	5[a] 5[a] 8	Singlas et al. (1982)
Vancomycin		50		2	35	10	15	11	Nielsen et al. (1979)
		500	6		53.6 (± 17.4)	23.7 (15.8-31.5)	6	4	Pancorbo and Comty (1982)
		10 mg/kg	4		61.5 (± 29.4)	6.3	4	6	Bunke et al. (1983c)

a   Patients infected at the time of the study.
b   Loading dose.
c   Maintenance dose.

but nevertheless its increased clearance compared with other cephalosporin antibiotics can be explained at least in part by its low protein binding.

As with IPD, drugs which have low protein binding (< 30%), and are significantly metabolised such as cimetidine (Kogan et al., 1983; Paton et al., 1982a) are not significantly removed during CAPD. Drugs with intermediate protein binding (30 to 75%) are not commonly dialysable whether or not they are exclusively renally cleared. This is the case, for example, with cefotaxime (Alexander et al., 1984) and latamoxef (Singlas et al., 1983). Ceftizoxime, which is 30 to 50% protein-bound is significantly cleared by CAPD (Gross et al., 1983). Drugs which are highly protein-bound, regardless of the route of elimination, are poorly dialysable in CAPD. This is best exemplified by cefoperazone (Keller et al., 1984) and cephazolin (Bunke et al., 1983a) which are 90% and 80% protein-bound, respectively.

In summary, the degree of protein binding contributes significantly to the dialysability of a drug in peritoneal dialysis. Other factors however,

namely route of elimination and volume of distribution also contribute to drug dialysability.

4.2 Volume of Distribution

As discussed by Lee et al. (1984), the volume of distribution determines in part, the dialysability of a drug, particularly in haemodialysis. With peritoneal dialysis, a volume of distribution of less than 1 L/kg with correspondingly low protein binding (< 20%), and low total body clearance, favours drug removal. For the aminoglycosides and vancomycin these conditions are met. However, for many drugs, particularly the cephalosporin antibiotics, the apparent volume of distribution is < 1 L/kg and nonrenal clearance is usually low, but the majority are poorly dialysable. It appears that the degree of protein binding limits their dialysability.

For a drug such as cimetidine, both protein binding and volume of distribution are relatively low, but its removal in peritoneal dialysis is limited by its considerable hepatic elimination. As such, neither peritoneal dialysis nor haemodialysis

will enhance drug elimination if the pre-existing non-renal clearance is inherently large.

As with haemodialysis, drugs with a large volume of distribution (> 1 L/kg), such as digoxin, have negligible removal by peritoneal dialysis.

5. Application of Pharmacokinetic Principles to Drug Dosage Adjustment in Peritoneal Dialysis

For the most part, dosage recommendations for patients on peritoneal dialysis are similar to those established for patients with end-stage renal disease. Such dosage modifications have been comprehensively reviewed elsewhere (Bennett et al., 1983). Selecting a suitable dosage regimen for a patient on IPD can often become difficult when one considers that a difference in drug clearance exists between the 'on' and 'off' dialysis days. This is especially true for the aminoglycosides. In contrast, with CAPD, dosage modifications are less complex due to the 'continuous' nature of the dialysis process. Using the pharmacokinetic parameters listed in table I suitable dosage schedules can be formulated.

For antibiotics, it has become clear that in addition to the treatment of peritonitis, intraperitoneal administration is likely to be satisfactory for systemic infection. Table II shows the absorption characteristics of the antibiotics studies to date, together with the corresponding peak concentrations to be expected in serum. This information combined with the individual pharmacokinetic data in table I will allow for the construction of suitable intraperitoneal dosing regimens.

Examples of recommended dosage adjustments are discussed below for the drugs in which peritoneal dialysis alters their elimination so as to require modifications significantly different from that in end-stage renal disease.

5.1 Tobramycin

5.1.1 Patients on IPD
IPD reduces the half-life of tobramycin from 69 hours in end-stage renal disease to 36 hours (range 18 to 50 hours) [Jaffe et al., 1974; Malacoff et al., 1975; Ramos et al., 1979]. Patients dialysed twice weekly should receive a loading dose of 1.5 to 2.0 mg/kg followed by 1.0 mg/kg every 3 days. In those circumstances in which dialysis occurs every 2 days, a loading dose of 1.5 mg/kg after the first dialysis and 0.75 mg/kg after each subsequent dialysis appears appropriate. Serum concentrations should be determined to facilitate subsequent dosage modifications.

For peritonitis, tobramycin intraperitoneally at a dosage of 10 mg/L of dialysis solution is recommended. Steady-state serum concentrations at this dosage approach 6 to 8.5 mg/L. If systemic symptoms are present at the onset, a loading dose of 1.5 mg/kg given intravenously or intraperitoneally is recommended.

5.1.2 Patients on CAPD
Following intravenous or intraperitoneal tobramycin in CAPD, tobramycin half-life approaches 36 hours (Bunke et al., 1983b; Halstenson et al., 1984; Paton et al., 1982b). Intravenous therapy should consist of a loading dose of 1.5 mg/kg followed by 0.75 mg/kg every 36 hours. Intraperitoneal administration for systemic infection (in the absence of peritonitis) should consist of a loading dose of 4 mg/kg followed by 1.5 mg/kg every 24 hours (Bunke et al., 1983b). With peritonitis *and* systemic symptoms, therapy should begin with an intraperitoneal loading dose of 1.5 to 2 mg/kg followed by 15 to 20 mg/2L of dialysis fluid every 6 hours. Steady-state serum concentrations with this dosage will approach 4 to 6 mg/L (Paton et al., 1983; Williams et al., 1982). Concerns regarding ototoxicity are real due to the relatively high serum concentrations of tobramycin achieved, but it is clear that for peritonitis the drug must be administered in every exchange of dialysis solution.

5.2 Vancomycin

The total body clearance of vancomycin in end-stage renal disease is low with a reported half-life approaching 200 hours (Moellering et al., 1981). Nielsen et al. (1979) reported a mean half-life of

18 hours in patients undergoing IPD. In contrast, Magera et al. (1983) reported a mean half-life of 205.2 hours, not significantly different from that in end-stage renal disease patients. In both studies, the corresponding peritoneal clearances were 6.1 and 2.4 ml/min, respectively. Although discrepancies in the data may be attributed to the large intersubject variability reported for vancomycin, even with normal renal function (Krogstad et al., 1980), such differences are not readily explained.

In CAPD, the half-life of elimination of vancomycin varies between 67 and 93 hours (Bunke et al., 1983c; Harford et al., 1984; Matzke et al., 1983b; Pancorbo and Comty, 1982). Peritoneal clearance contributes 15 to 18% of the total body clearance, ranging from 1.48 to 3.82 ml/min.

Treatment of peritonitis appears to be adequate with either intravenous (Krothapalli et al., 1983) or intraperitoneal vancomycin administration. System infections in such patients may be managed with intraperitoneal therapy according to the following schedule (Bunke et al., 1983c): a loading dose of 30 mg/kg intraperitoneally followed by 7 mg/kg once daily or 1.5 mg/kg every 6 hours intraperitoneally will provide serum concentrations in excess of 10 mg/L.

5.3 Ceftizoxime

In CAPD, the half-life of ceftizoxime approaches 12 hours (Burgess and Blair, 1983; Gross et al., 1983) compared with 30.2 hours in end-stage renal disease (Ohkawa et al., 1982). The peritoneal clearance contributes approximately 15% to the total body clearance. However, the concentrations of the drug in the peritoneal fluid are above the MIC of most susceptible organisms; therefore intravenous therapy alone is likely to be adequate for the treatment of peritonitis.

5.4 Ceftazidime

Tourkantonis and Nicolaidis (1983) reported that 47.1% of a dose of 200mg ceftazidime given in the dialysis fluid was recovered at 12 hours in the dialysate of patients on IPD. After intravenous administration of 1g elimination half-life while on IPD was 8.7 hours compared with 26.9 hours while off dialysis.

During CAPD, a 6- and 4-hour exchange removed 7.0% and 4.3%, respectively, of the total body ceftazidime stores (Comstock et al., 1983). Ceftazidime treatment of peritonitis may be given by either the intravenous or intraperitoneal route.

5.5 Cephalexin

Yamasaku et al. (1970) demonstrated that 7 hours of IPD removed 30% of an orally administered dose of cephalexin, with a corresponding half-life of 6.4 hours. In patients on CAPD, Bunke et al. (1983a) reported an elimination half-life of 8.6 hours with a peritoneal clearance of 12% of the total body clearance. Importantly, the peritoneal concentrations following this single oral 500mg dose were low or absent. However, Drew et al. (1984) showed that following multiple oral dose administration in patients with peritonitis, adequate dialysate concentrations can be achieved. The authors suggested that the dosing regimen for peritonitis due to susceptible organisms should include a 1g loading dose of cephalexin followed by 500mg orally after each 6-hour exchange.

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Address for correspondence and reprints: *Thomas W. Paton*, Department of Pharmacy, Sunnybrook Medical Centre, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5 (Canada).