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Evaluation of the Sorbent Suspension Reciprocating Dialyser in the Treatment of Overdose of Paracetamol and Phenobarbitone

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Abstract—Poisoning with paracetamol (acetaminophen) and phenobarbitone is a common occurrence in the United States and Europe. The removal efficiency of these drugs by a sorbent suspension reciprocating dialyser (SSRD) has been investigated. The SSRD is a parallel plate dialyser with a reciprocating blood flow and free mobile sorbent suspension composed of charcoal and zeolites. This arrangement provided a system with minimal sorbent saturation. High performance liquid chromatography was used for the quantification of the drugs in aqueous and serum fluids. The in-vitro removal efficiency of the dialyser was studied by dialysing a large volume of the drug in solution for 12 to 16 h. The removal efficiency remained relatively constant up to 10 h of dialysis. The in-vivo dialysis studies were performed using normal dogs. Large doses of the drugs were administered orally or intravenously to achieve high blood levels. The clearance values obtained from these studies were comparable with, or in excess of, the values reported in the literature for conventional dialysers. The major advantage of the SSRD is the ability of the unit to be used for prolonged dialysis and to provide a system with minimal sorbent saturation due to mixing and interchange of sorbent granules next to the membrane surface.

Accidental or intentional intoxification is a serious medical problem in the United States and Europe (Winchester et al 1977; Knepshield et al 1973). In patients with respiratory failure and deep coma from drug overdose, a 38 percent mortality rate has been reported despite application of active drug removal methods, such as forced diuresis, peritoneal dialysis, haemodialysis, and haemoperfusion (Arieff & Friedman 1973; Winchester et al 1977). It is in that group of patients that dialytic methods may play a significant role as an adjunct to expert intensive supportive therapy.

Paracetamol (acetaminophen) and phenobarbitone are commonly encountered in self-poisoning attempts (Harvey 1980; Flower et al 1980). Paracetamol is readily available and is considered a 'safe' analgesic and antipyretic drug with no side effects, compared with aspirin (Winchester et al 1981). However, an overdose in the toxic range of 12 g or more can lead to hepatic necrosis (Prescott et al 1971; Clark et al 1973). Liver damage generally takes place if treatment of the patient is delayed by 12 to 15 h or more after its ingestion. The usual therapy during this period is oral or nasogastric tube administration of *N*-acetylcysteine. However, if treatment is delayed beyond 12 h, then other measures are needed. Attempts at reducing the plasma concentration of the drug and shortening the plasma half-life have been attempted in man by the use of peritoneal dialysis (Maclean et al 1968), haemodialysis (Farid et al 1972), or forced diuresis (Jagenburg et al 1968), and haemoperfusion over activated charcoal (Winchester et al 1981).

Persons who take an overdose of phenobarbitone may enter a coma because of the drug's long plasma half-life (Harvey 1980). Methods of shortening the duration of the coma by increasing the total body clearance of the drug have included haemodialysis, haemoperfusion, and alkaline administration with forced diuresis (Linton et al 1967; Kennedy et al 1969; Schreiner & Teehan 1972; Vale et al 1975). Haemoperfusion has proved to be the best method for active drug removal.

In general, the treatment of overdoses of either drug is best performed in a conservative manner (Winchester et al 1977). However, if a patient presents with respiratory failure, stage IV coma, with decreasing blood pressure, or evidence of toxic drug levels, aggressive therapy is usually indicated. Haemoperfusion has proved to be more efficient than haemodialysis in the removal of both drugs from the blood. With the perfusion procedure, the clearance of the drug is high, approaching the blood flow rate through the column. However, this method has disadvantages, such as high cost, relatively short length of effectiveness, complexity, platelet removal, and the requirement of large amounts of heparin (leading to bleeding episodes), as well as the possibility of particle embolization (Winchester & Gelfand 1978).

The sorbent suspension reciprocating dialyser (SSRD) has been designed to serve as an indirect haemoperfusion system (sorbent-aided dialysis) across a membrane which serves as a transport surface. The sorbent dialysate system used contains charcoal, calcium, and sodium-loaded zeolites and urease. The chemical efficiency of the SSRD has been tested and found to be approximately the same as flow-through dialysers in the treatment of uraemia (Ash et al 1981). Another possible application of the SSRD is that of the treatment of drug overdose.

In the present study, we describe the in-vitro and in-vivo tests carried out to evaluate the SSRD as an overdose treatment device for paracetamol and phenobarbitone.

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Materials and Methods

Construction of the dialyser

The in-vitro and in-vivo dialysis experiments were carried out using 15 and 25 membrane packages. Fig. 1 shows an expanded view of a one membrane package of the SSRD. The membrane pairs are stacked with their blood distribution gasket and supports in the order shown in the Figure. The membrane is composed of regenerated cuprommonium cellulose (Coprophane), a standard dialysis membrane. The unit is then sealed and placed inside a cylindrical rigid Plexiglass case for containing the sorbent suspension (1·5 to 2·5 L volume). The sorbent suspension dialysate is composed of 7 wt% finely powdered activated charcoal USP (Mallinkrodt), 20 wt% calcium-sodium loaded zeolites (type W, Union Carbide), and soluble or zeolite-bound urease. Alternation in pressure of the sorbent suspension is used to promote the movement of blood into and out of the dialyser. A pressure-vacuum system is used to change the dialysate pressure during the dialysis studied, as illustrated in Fig. 2. A timer is used to control the length of the negative and positive pressures to the dialysate. Cycle times of 60 and 90 s were used for the in-vivo and in-vitro tests, respectively.

The urease is present in the suspension media to hydrolyse urea in patients with azotaemia and kidney failure. While it has no effect on drug removal by the SSRD, it would be present in the suspension during treatment of end-stage renal disease patients. Drug clearance is important during treatment of these patients even without drug overdose.

In-vitro continuous dialysis tests

These tests were conducted to determine the limit of time the dialysis could continue without attaining saturation. A large tank containing 30 L of buffered (0·9% NaCl) saline drug solution at pH 7·0 was dialysed for 12 to 14 h. The set-up for these experiments is shown in Fig. 2.

The concentration of the drug solution was approximately equal to concentrations encountered in overdose cases. Samples were collected from the tank at various times up to 12 or 16 h. Outflow samples were also collected to determine the efficiency of removal of the drug by the SSRD.

Animal experiments

Two healthy mongrel dogs, 36 and 50 kg, were used for the in-vivo studies. A modified Quinton-Scribner shunt provided vascular access into the jugular vein/carotid artery (Thornhill 1983; Thornhill et al 1985), the procedure used was that described by Ash et al (1981). Before use the device was sterilized on the blood side using a povidone-iodine mixture (Betadine) which was then completely rinsed from the dialyser using sterile saline. A control (no dialysis) study and at least two dialysis experiments were performed on each dog for each drug studied. The drugs were administered either as an oral solution or as an intravenous infusion. Blood samples were collected before, during, and after dialysis. During dialysis, blood samples were obtained simultaneously from inflow (arterial) and outflow (venous). The entire outflow sample was collected from the dialyser, when the cycle was on pressure, into a vinyl bag. The outflow sample was collected from the pooled outflow blood sample. The serum was separated and stored at −20°C pending assay.

Analytical methods

A high pressure liquid chromatograph (Model 6000 A) equipped with a loop-type injector (Model U6K), a stainless steel column packed with 10 μm C-18 or phenyl reverse phase material [μBondapack column (30 cm × 3·9 mm i.d.)] and UV detector (Model 440) were used for the quantitation of the drugs. All the equipment was obtained from Water Associates, Inc., Milford, MA. The signal from the detector was quantified using a Shimadzu Seisakusho Ltd Data

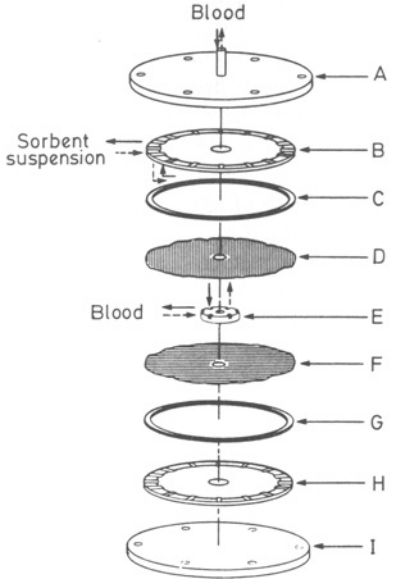

FIG. 1. Expanded view of Purdue sorbent suspension reciprocating dialyser (SSRD). Key: A flat plate, B modified conical support, C sealing ring, D membrane, E blood distribution gasket, F membrane, G sealing ring, H modified conical support, I flat plate

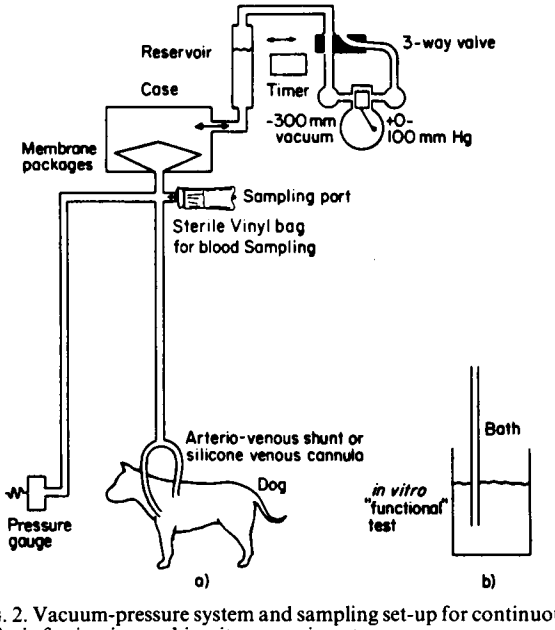

FIG. 2. Vacuum-pressure system and sampling set-up for continuous dialysis for in-vivo and in-vitro experiments.

Processor-Chromatopac-EIA and Houston Instrument Omni-Scribe recorder.

Assay of paracetamol in saline and serum

A sample of saline or serum (0·5 mL) was acidified with 0·5 mL of 1·0 M acetate buffer (pH 4·0) after the addition of 0·25 mL of 100 μg mL solution of *N*-propionyl-*p*-aminophenol (internal standard). The sample was extracted with 5 mL of ethyl acetate. The organic solvent was separated by centrifugation and 2 mL transferred to centrifuge tubes for evaporation under a stream of dry air at 45°C. The residue was dissolved in 0·5 mL of the mobile phase methanol–1% acetic acid 15:85). 25 μL was injected into the HPLC column.

Assay of phenobarbitone in saline and serum

A sample of saline or serum (0·5 mL) and 0·3 mL of hexobarbitone internal standard solution (100 μg mL^{-1}) were acidified with 1 mL of 1·0 M phosphate buffer (pH 6·0). The sample was extracted with 5 mL ethyl acetate and 4 mL was transferred to a centrifuge tube. The solvent was evaporated as for paracetamol. The residue was reconstituted with 0·5 mL of the mobile phase (acetonitrile–0·01 M phosphate buffer, pH 6·7 30:70) and 25 μL were injected onto the HPLC column.

Quantification of the drugs was achieved by reference to a standard curve of the peak height ratio of the drug to internal standard versus different concentrations used to prepare the standard curve. The sensitivity for both assays was 1 μg mL^{-1}. Reproducibility for paracetamol was 3·3% and 6·0% at 1 and 300 μg mL^{-1}, respectively (n = 5). The reproducibility for phenobarbitone varied between 6·4 and 3·4% at 1 and 100 μg mL^{-1}, respectively (n = 5).

Data analysis

In-vitro saturation tests. The clearance (Cl) of the SSRD was calculated by:

$$Cl = \frac{V}{t} \ln \frac{C_i}{C} \quad (1)$$

where V is the volume of the tank, and C_i is the initial concentration in the tank.

The efficiency (E) of removal at different times of dialysis was calculated by:

$$E = (C_i - C_o)/C_i \quad (2)$$

where C_i is the inflow drug concentration and C_o is the outflow drug concentration.

In-vivo control studies. The serum concentration-time profiles after intravenous administration of the drugs were analysed according to a one-compartment open model. The apparent volume of distribution, V_d, was calculated by:

$$V_d = \text{dose}/(AUC_{0\to\infty} k_{el}) \quad (3)$$

where $AUC_{0\to\infty}$ is the area under the curve from zero to infinity and k_{el} is the total elimination rate constant calculated from the slope of the line. The total body clearance (TBC) was calculated by:

$$TBC = \text{dose}/(AUC_{0\to\infty}) \quad (4)$$

In-vivo dialysis studies. The clearance of the drugs by the SSRD at specified times was calculated by the formula:

$$Cl_D = Q_B(C_i - C_o)/C_i \quad (5)$$

where Q_B is the blood flow rate calculated from the V_f divided by the cycle time (V_f/τ). C_i and C_o are the inlet and outlet serum concentrations, respectively. The fraction of drug in the body at the start of dialysis that is removed by the dialyser was calculated using the model independent general equation developed by Gwilt (1981). This equation is expressed as:

$$f = \frac{Cl_D\, AUC_1}{(Cl + Cl_D)\, AUC_1 + Cl\, AUC_2} \quad (6)$$

where Cl_D is the dialyser clearance, AUC_1 is the area under the serum time curve during dialysis, and AUC_2 is the area under the plasma concentration time curve from termination of dialysis to infinity. Cl is the TBC in the absence of dialysis.

The elimination half-lives before, during, and after dialysis were calculated from the linear first order analysis on the serum concentrations versus time. Student's *t*-test was used to compare the slopes of the lines at the different stages of the dialysis experiment (Mendenhall 1975).

Results

In-vitro continuous dialysis experiments

Fig. 3 shows the efficiency of removal for the two in-vitro experiments with the drugs. Table 1 lists the results of the in-vitro dialysis studies. Fig. 4 represents the results for one experiment where a log-linear plot of the concentration versus dialysis time is shown for paracetamol. The efficiency of its removal was high in the beginning of dialysis and values above 50% were obtained from the two experiments (Fig. 3).

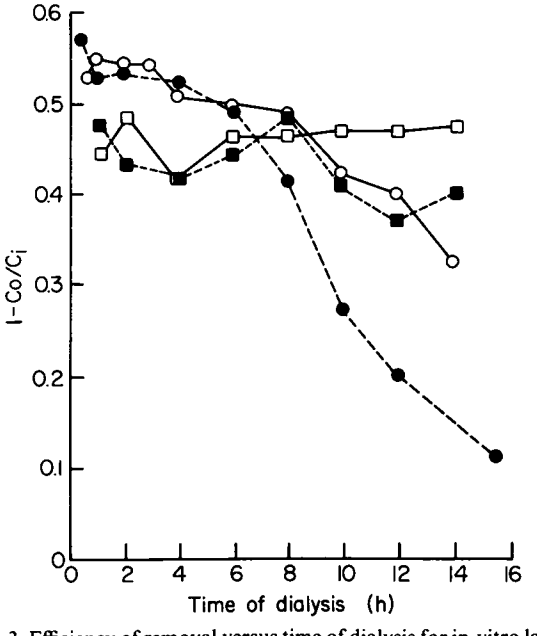

FIG. 3. Efficiency of removal versus time of dialysis for in-vitro large volume saturation tests. C_i = inflow concentration, C_o = outflow concentration paracetamol (●,○) or phenobarbitone (■,□). Open symbols, Exp I; closed symbols, Exp II.

Table 1. Clearance values of paracetamol and phenobarbitone from the in-vitro (large volume) saturation studies using 15 package dialysers and 90 s cycle time.

Drug	Exp. n.	Duration of dialysis (h)	Fill volume (mL)	Overall clearance (mL min^{-1})	Efficiency $(1-C/C_i)$ initial/final (%)
Paracetamol	I	14	120–118	39·4	56/32
				(35·75 ± 5·2)*	
	II	15·6	125–118	32·1	57/11
Phenobarbitone	I	16	145–135	38·2	46/48
				(36·2 ± 2·83)*	
	II	15	126–120	34·2	48/41

* Average of clearance for Exp I and II.

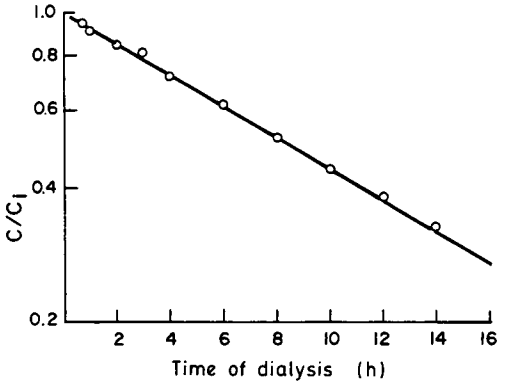

FIG. 4. A log-linear plot of concentration decline in tank during paracetamol in-vitro dialysis saturation test (Exp I) (C_i = initial concentration).

However, in Experiment I, the efficiency remained relatively stable up to 10 h dialysis, then dropped to 32%. In Experiment II, there was a dramatic drop in the efficiency after the 8 h of dialysis, until it reached 11% around the 15th hour. In Experiment II for paracetamol, it was noticed that the sorbent settled into a layer during dialysis. This may have been due to inefficient mixing of the sorbents in the dialyser. Also, a high ultrafiltration rate was observed during these in-vitro experiments. Therefore, the decrease in efficiency may be related to the dilution of the sorbent suspension due to high ultrafiltration or due to inefficient mixing and settling problems.

The efficiency of removal of phenobarbitone remained relatively constant throughout the dialysis period (Fig. 3). This is an indication of a lack of saturation during 15 h of dialysis. The clearance values were comparable with those for paracetamol.

In-vivo studies

Table 2 summarizes the pharmacokinetic parameters obtained from the in-vivo control studies. Tables 3 to 6 summarize the results obtained from the in-vivo dialysis studies. An average clearance of 59·0 mL min^{-1} was obtained for paracetamol and a 49·0 mL min^{-1} mean clearance value for phenobarbitone. The dialyser clearance from paracetamol Experiment I was much higher than the values obtained from Experiments II and III. The reason is mainly due to the large treatment rate obtained from Experiment I compared with the other experiments. The elimination half-life of paracetamol from the predialysis period in Experiment I was significantly higher than the half-life during and after dialysis. This indicates a presence of enzyme saturation in the early stages after administration. However, when the levels

Table 2. Pharmacokinetic parameters for paracetamol and phenobarbitone obtained from control intravenous (no dialysis) studies.

Drug	Dose (g)	R	$t_{\frac{1}{2}}$ (h)	V_d (L kg^{-1}) area	$AUC_{0\to\infty}$ ($\mu g\ h^{-1}\ mL^{-1}$)	TBC (mL min^{-1})
Paracetamol	9·0	0·995	1·84	0·81	698·4	214·8
Phenobarbitone	0·9	0·982	72·70	0·82	3442·0	4·3

Table 3. Summary of the elimination characteristics of paracetamol in the three dialysis experiments.

Dialysis exp no.	Length of dialysis (h)	Half-life (h) with (R)		
		Before dialysis	During dialysis	After dialysis
I (Oral)	4	1·57 (0·994)	1·00 (0·990)	—
II (Oral)	4	2·42 (0·686)	1·30† (0·998)	1·05*† (0·98)
II (i.v.)	3	2·39 (0·992)	1·22† (0·997)	1·3*† (0·992)

The values between parentheses refer to the correlation coefficients (R) obtained from the first order analysis of the serum concentrations versus time.

† The half-lives are significantly different from the predialysis half-lives at $\alpha = 0{\cdot}05$.

* The half-lives are significantly different from the control study half-life (1·84 h) and from the predialysis half-lives.

Table 4. Various clearance values and fill volumes for various times of paracetamol dialysis experiments.

	Exp I (oral)		Exp II (oral)		Exp III (intravenous)	
	V_f (mL)	Clearance (mL min^{-1})	V_f (mL)	Clearance (mL min^{-1})	V_f (mL)	(mL min^{-1})
	164·5	93·1	144·5	57·7	109·0	28·6
	173·5	97·4	141·5	36·8	103·0	30·8
	170·0	97·0	148·0	40·0	117·0	27·0
	173·5	85·3	140·5	33·7	128·0	40·0
	180·0	72·0	141·5	43·2	128·0	46·8
	174·0	96·1	138·5	79·5	128·0	35·2
Mean ± s.d.	172·6 ± 5·113	90·13 ± 9·95	142·4 ± 3·4	52·0 ± 15·8	118·83 ± 10·98	34·73 ± 7·0
Clearance† (mL min^{-1})	190·75		88·65		107·923	
f**	—		0·18		0·12	

* Dialyser clearance calculated from eqn 5.
† Dialyser clearance calculated from the slope of the log-linear line during dialysis.
** f calculated from eqn 6.

Table 5. Summary of the elimination characteristics of phenobarbitone in the dialysis experiments.

Dialysis exp. no.	Length of dialysis (h)	Half-life (h) with (R)	
		During dialysis	After dialysis
I	5	9·0 (0·95)	49·7 (0·992)
II	4	10·7 (0·92)	48·1 (0·993)†

The values between parentheses refer to the correlation coefficients (R) obtained from linear analysis of the natural log of the serum concentration versus time.
† The half-life was calculated from the data point at 39·0 h up to the last sample.

Table 6. Clearance values and fill volumes for various times of dialysis for phenobarbitone dialysis experiments.

	Dialysis Exp I†		Dialysis Exp II	
	V_f (mL)	Clearance (mL min^{-1})	V_f (mL)	Clearance (mL min^{-1})
	220·0	36·9	174·0	74·0
	216·0	43·9	196·0	51·1
	225·0	42·0	200·5	61·0
	226·0	34·7	185·0	53·4
	231·5	36·4	195·0	50·7
	236·5	43·0	—	—
Mean ± s.d.	225·8 ± 7·45	39·6 ± 3·83	190·1 ± 10·63	58·4 ± 9·64
Clearance* (mL min^{-1})	28·2		23·2	
f††	0·48		0·44	

† The microprocessor control system was used instead of the pressure-vacuum pump, with larger cycle time.
* Dialyser clearance calculated from the slope of the log-linear line during dialysis.
†† f calculated from eqn 6.

decreased during dialysis, the half-life also decreased. The dialyser clearance contributed about 27% to the total body clearance of the drug. The f values were between 12 and 18%. These values are not considered of significant importance to justify the use of the dialyser for the treatment of paracetamol overdose (Levy 1977). However, the dialyser clearance can be considered of significant value if the total body clearance of the animal was reduced to a small value due to the administration of higher doses of the drug, and also if the dialyser can be operated for 10 h or more without loss of its removal efficiency.

Although the mean dialyser clearance for phenobarbitone was lower than for paracetamol, the f values obtained from the two experiments (47·0 and 44%) indicated that the dialyser is more efficient in removing larger amounts of phenobarbitone than paracetamol. This is due to the low total body clearance exhibited by phenobarbitone compared with paracetamol (4·3 versus 214 mL min^{-1}). The contribution of the dialyser clearance to the phenobarbitone intrinsic body clearance was manifested by the low half-life of elimination of the drug obtained during dialysis compared with the values obtained after dialysis and from the control studies. The serum blood levels of phenobarbitone in Experiments I and II remained relatively constant before dialysis (Fig. 5). This indicates that saturation of the liver metabolizing enzyme at the high serum levels can account for the long half-life obtained from the in-vivo control study.

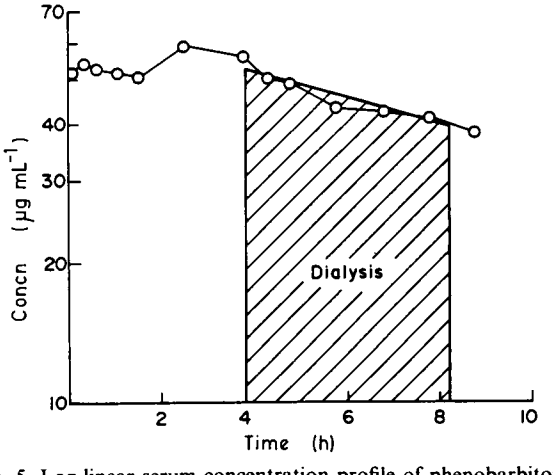

FIG. 5. Log-linear serum concentration profile of phenobarbitone for pre- and interdialysis with dash connecting line between the points. The solid line represents the best fit line for the serum levels in the interdialysis period (Exp II).

Discussion

In the in-vivo studies, the dialysers tested showed no significant dimminution of function during 3–5 h of dialysis. Therefore, the duration of dialysis can possibly be increased further. In-vitro saturation tests indicated that saturation did not occur until 8 to 10 h for paracetamol and no saturation was seen up to 15 h of dialysis for phenobarbitone. In comparing this procedure with therapeutic methods available, such as haemoperfusion and haemodialysis, the clearance values are lower than for haemoperfusion but are comparable or higher than for haemodialysis. Winchester et al (1975) reported a 110 mL min^{-1} haemoperfusion clearance for paracetamol at 200 mL min^{-1} flow rate at the beginning of the procedure. However, saturation of the column occurred at 3 h and the clearance decreased to a very small value. In this investigation, an average in-vivo clearance of $58{\cdot}9 \pm 28{\cdot}3$ mL min^{-1} was obtained for an average flow rate of 114 mL min^{-1}. If the flow rate was 200 mL min^{-1}, then a clearance of 80 mL min^{-1} would be obtained, a value which would be useful clinically if the dialysis treatment continued for a long time (10 h). Farid et al (1972) reported on the use of haemodialysis for the treatment of 15 patients who ingested large amounts of paracetamol. A clearance value of 95 to 100 mL min^{-1} was obtained at 300 mL min^{-1} blood flow rate. A clearance of 122 mL min^{-1} could be obtained for paracetamol if the SSRD was operated at 300 mL min^{-1} (with a proportionately larger dialyser).

The mean phenobarbitone clearance by the SSRD was $49{\cdot}0 \pm 13{\cdot}3$ at an average flow rate of 170 mL min^{-1}. Widdop et al (1975) reported a similar clearance value obtained from their experimental drug intoxication studies in dogs. They reported a haemodialysis clearance of 60 mL min^{-1} for phenobarbitone at a flow rate of 200 mL min^{-1}, while an average clearance of 72 mL min^{-1} was reported from the charcoal haemoperfusion columns. Gelfand (1978) reported on the clinical use of haemoperfusion and haemodialysis in the treatment of drug overdose. Using haemoperfusion for the treatment of phenobarbitone overdose in a 42-year-old female patient, a mean clearance value of 50 mL min^{-1} was reported at a 100 mL min^{-1} blood flow rate. In the same paper, he reported a haemodialysis clearance of 22 mL min^{-1} at the same blood flow rate.

Haemodialysis is a complex, expensive system, and can be risky for the patient when systemic heparin is used to avoid clotting. Haemoperfusion is simple, can be prepared in 15 min, and is more efficient in drug removal than haemodialysis. However, haemoperfusion is also expensive ($250–$400/column), more risky for the patient since larger amounts of heparin are used, and is not biocompatible. Also, the haemoperfusion column can only be used for a short time due to saturation problems (2 to 3 h). Therefore, the total amount of the drug removed during treatment episode may not be significant and two to three columns may be needed before obtaining satisfactory results. As a drug treatment device, the SSRD is a simple, self-contained system using a single needle blood access; it is portable and easy to operate. It is a relatively biocompatible device since the sorbent particles are not in direct contact with the blood. This eliminates the possibility of removing platelets, as well as other blood components. Since dialysis with the SSRD requires less heparinization than in haemoperfusion, the chances of encountering bleeding problems should be reduced. In addition to these properties, the SSRD has the advantage of being operable for long terms without attaining significant saturation. From the above results and discussion, it is envisioned that the SSRD will be an easier and less expensive device in the treatment of drug overdose (paracetamol or phenobarbitone) than the haemodialysis and haemoperfusion systems. It is suggested that the dialyser tested shows promise for eventual use in the treatment of phenobarbitone overdose. For paracetamol, the SSRD can be of value in the treatment of overdose cases, if a larger clearance is attained by using a larger dialyser and if the treatment time can be extended above the presently used periods.

In general the SSRD type of device will have limitations similar to those of standard haemoperfusion columns. It is almost as effective as the columns in removing drugs with moderate protein binding (such as phenobarbitone, 40–60%). For drugs of very large volume of distribution (such as digoxin or a drug of very high protein binding (propranolol) the system would not be indicated. Winchester (1983) lists the drugs suitable for removal by haemoperfusion. From this reference it is noted that not all drugs are indicated for removal only by haemoperfusion columns.

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