AN EVALUATION OF THE EFFECTIVENESS OF DIALYSIS FOR SEDATIVE AND ANALGESIC POISONING

JOHN F. MAHER and GEORGE E. SCHREINER

Department of Medicine, Georgetown University School of Medicine and Renal and Electrolyte Division, Georgetown University Hospital, Washington, D.C., U.S.A.

Since Doolan et al. (1951) first employed dialysis for the therapy of acute poisoning there has been widespread application of this technique for a growing list of dialysable poisons (Maher and Schreiner, 1968). Among 689 patients at Georgetown University Hospital whom we have treated by dialysis during the past eighteen years, 142 were treated for acute poisoning as shown in Table I.

| TABLE I |
| Dialysis for acute poisoning |
| Georgetown University Hospital (1950–1968) |
| Barbiturates | 77 |
| Glutethimide | 27 |
| Salicylates | 10 |
| Bichloride of mercury* | 7 |
| Ethchlorvynol | 3 |
| Uric acid | 3 |
| Methanol | 2 |
| Meprobamate | 2 |
| Ethylene glycol* | 2 |
| Bromide | 2 |
| Diphenylhydantoin | 1 |
| Kanamycin* | 1 |
| Aniline | 1 |
| Dextropropoxyphene | 1 |
| Carbon tetrachloride* | 1 |
| Phenytoin | 1 |
| Sodium fluoride | 1 |
| **142** |

* Dialysis performed within 48 hours of exposure for the removal of nephrotoxin rather than for treatment of uraemia.

The effectiveness of dialysis for the therapy of a given poison may be evaluated using the criteria outlined by Schreiner (1958). These may be summarized as follows: (1) dialysance or removal rate, (2) distribution, (3) time dose-cytotoxic relationship, (4) significance of additional removal by dialysis. The present study assays by these criteria the effectiveness of dialysis for sedative and analgesic poisoning including some less frequently encountered toxins.

Figure 1 shows data for phenobarbital in the upper half and secobarbital in the lower half. Dialysances of 110 and 65 ml per minute indicate that cellophane is not a significant diffusion
Fig. 1. The effectiveness of dialysis of a long acting (phenobarbital) and a short acting (secobarbital) barbiturate is judged by dialysance, distribution, dose-toxicity relationship, and comparative clearances.

Barrier for barbiturates. In the intoxicated patient a litre of serum contains an average of 2.1% of an ingested dose of phenobarbital or 1.2% of secobarbital ingested. The scatter is attributed to incomplete absorption and the difficulty in obtaining a reliable and precise ingestion history. About half of circulating secobarbital is bound to plasma protein and secobarbital is also distributed in body fat. An average of 0.9 hours of coma resulted from
J. F. MAHER AND G. E. SCHREINER

each milligram ingested per kilogram of body weight for both phenobarbital and secobarbital. The scatter is again attributed to the difficulty in obtaining a precise dosage history. The clearances are considerably higher by dialysis than by forced diuresis. That dialysis significantly adds to barbiturate removal is also indicated by the steeper decline in blood levels during dialysis when compared to forced diuresis, and the shorter duration of coma for a given blood level when dialysis therapy is used as we have previously shown (Setter et al., 1966). Barbiturates have thus fulfilled the criteria of dialysable poisons. In our experience, intoxication with short acting barbiturates causes deeper and more rapid onset of coma and more severe complications than phenobarbital poisoning. Ingestion of a smaller number of tablets of secobarbital than of phenobarbital causes coma and the short acting drugs are eliminated more slowly in intoxicated patients. For these reasons dialysis more often has been required for intoxication with short acting barbiturates.

![Dialysis of Glutethimide](image)

**Fig. 2.** Despite an adequate dialysance, a linear dose toxicity relationship and a high dialyzer clearance in relation to urinary excretion, effective dialysis is limited by the small quantity of glutethimide in circulating blood.

P = peritoneal dialysis. H = haemodialysis.

The same criteria for dialysis of glutethimide are evaluated in Figure 2. The dialysance is 90 ml per minute which is comparable to that of barbiturates. Each litre of serum, however, contains less than 0.5% of the dose of glutethimide ingested due in large part to sequestration in body fat. This is the major factor limiting the removal of glutethimide by dialysis. A linear relationship is seen between the dose ingested and the duration of coma. For each 200 milligrams per kilogram of body weight ingested there resulted a mean duration of coma of 72 hours. This is comparable to the relationship that was determined by The et al. (1961). The circled points represent patients who underwent dialysis and would have been expected because of their high blood levels to have a longer duration of coma. Dialysis does remove a much greater quantity than appears in urine despite forced diuresis. Since glutethimide is metabolized by the liver the spontaneous decline in blood levels is largely due to this mechanism. Blood levels decline more rapidly, however, during dialysis as we have previously shown (Maher et al., 1962). In severe glutethimide intoxication dialysis has been shown to be clinically effective.

Westervelt (1966) showed a beneficial effect of dialysis in ethchlorvynol poisoning. The
DIALYSIS FOR SEDATIVE AND ANALGESIC POISONING

dialysance varied from 50 to 105 ml/min., the blood ethchlorvynol level was reduced by
dialysis and clinical improvement occurred, but coma was often prolonged. Our results are
in agreement with those of Westervelt. There is a significant amount of ethchlorvynol in
circulating blood, the clearance is in the range of that achieved for barbiturates and the
severity of coma may be related to the blood level. Coma may last for several days, however.
Figure 3 shows that the serum half-life is shorter with haemodialysis or peritoneal dialysis
than with diuresis and the clearance by haemodialysis is much greater than occurs with
diuresis. Although coma is prolonged, ethchlorvynol is definitely removed by dialysis which
should be considered in the therapy of severe poisoning.

DIALYSIS OF ETHCHLORVYNOL

![Diagram showing dialysis of ethchlorvynol with different methods and their clearance rates.]

Fig. 3. With haemodialysis the serum half life of ethchlorvynol and its clearance are higher than with
diuresis. Peritoneal dialysis values are intermediate.

Maddock and Bloomer (1967) have reported an in vitro dialysance of 100 ml/min. for
meprobamate, a distribution space equal to 75% of body weight, 20% binding by plasma
proteins, and a direct correlation between blood meprobamate levels and the duration of
coma. They determined that 8.5% of remaining meprobamate is eliminated per hour and
calculated that haemodialysis would more than double the elimination rate. Mouton et al.
(1967) also correlated blood meprobamate levels with the severity of coma and demonstrated
significant removal by dialysis. Our studies indicate a distribution space equal to 40% of
body weight, usually mild coma of brief duration attributed to rapid metabolism and a rapid
decline in blood levels with haemodialysis. We judge that dialysis can be valuable for the
therapy of meprobamate poisoning but usually is not necessary.

Bromide is the poison most rapidly removed by dialysis (Fig. 4). The dialysance in vivo
exceeds 150 ml/min. Since ingestion is usually chronic, the distribution cannot be determined
by dividing the blood level by the quantity ingested. A virtual distribution space has been
calculated, however, by dividing the amount removed by dialysis by the delta blood level.
Using this technique, bromide space in the intoxicated patient also approximates extra-
cellular fluid volume. The blood level can be correlated with the clinical status of the patient except that dialysis can lower blood levels faster than equilibration occurs with body fluid compartments that reflect the clinical status more accurately (Schreiner, 1958; Schmitt et al., 1966). The serum half life is reduced to below 100 minutes by haemodialysis and the mean in vivo clearance with haemodialysis in our patients was 76 ml/min. A similar half life was reported by Jorgensen and Wieth (1963). With maximal diuresis the clearance was 14 ml/min., however, and the serum half life 310 minutes which would suffice for most patients with bromide intoxication.

Our studies with salicylate poisoning indicate a dialysance of 100 ml/min., a distribution space that approximates extracellular fluid volume and a direct correlation between severity of intoxication and blood levels. A significant quantity of salicylate appears in dialysate and blood levels decline more rapidly with dialysis than spontaneously. Since many cases of salicylate poisoning are mild, dialysis is required for only a small percentage of intoxicated patients.

We have recently studied a patient who became deeply intoxicated after ingestion of propoxyphene (Gary et al., 1968). The maximal blood level was 3 µg/ml which indicated a distribution space in excess of total body water that was not explained by unabsorbed poison. Two haemodialyses removed 124 mg. Calculation of the distribution space by dividing the delta blood level into the amount removed during dialysis gave values of 37 and 166 l. The lower value may have reflected poor equilibration because of hypotension. The larger calculated spaces are consistent with concentration of propoxyphene outside the circulating plasma. Haemodialysis removed propoxyphene at a clearance of 138 ml/min., while the renal clearance was 28 ml/min. Clinical improvement was slight.

Summary and conclusions

These studies indicate that dialysis can be useful for treatment of intoxication due to a variety of sedatives and analgesics. For phenobarbital, bromide and salicylate poisoning,
dialysis fulfills the criteria of Schreiner (1958), but intoxication is often mild and forced diuresis should suffice for the majority. Meprobamate, also rapidly removed by dialysis, usually causes mild coma of short duration due to rapid metabolism. Thus dialysis is rarely needed for therapy of this toxin. Prolonged coma results from ethchlorvynol intoxication despite significant removal by dialysis. Spontaneous removal of short acting barbiturates, glutethimide and propoxyphene is hampered by low blood levels with concentration of the drugs outside the circulation. Removal by dialysis is limited by the same factor, but represents a significant addition to the body's own mechanisms for elimination of the drugs. Explanations for a poor clinical response to dialysis despite high clearances include a large distribution space of the intoxicant, removal of inactive metabolites, persistence of blood levels above those associated with coma and irreversible neurological damage due to delay in therapy.

REFERENCES


