THE ARTIFICIAL KIDNEY FOR ACUTE GLUTETHIMIDE (DORIDEN*) AND BARBITURATE POISONING

Report of Four Representative Cases

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THE artificial kidney has been used successfully in acute poisoning in a number of patients.[1-5] Hemodialysis appears to be a rational and effective treatment of acute toxicity caused by ingestion of excessive amounts of barbiturate, glutethimide, salicylate, bromide, diphenylhydantoin sodium, bichloride of mercury, or mushroom poisons.

In treating poisoning from hypnotic drugs the goal of dialysis is twofold: to eliminate the poison and to shorten coma. Patients can be allowed to sleep out their barbiturate effects as long as respiration, blood pressure, and temperature are under control. In a light case of barbiturate poisoning, we let the patient sleep, but observe him closely so as to be able to ward off complications. The clinical intervention with hemodialysis is justified in two conditions: (1) when the amount of poison ingested or the initial concentration of poison in the blood is unquestionably in the fatal range, and (2) when the underlying physical state of the patient dangerously heightens the risk of prolonged sleep or coma. The time required to assemble a Kolff twin-coil artificial kidney[6,7] and the risk of hemodialysis to the patient are negligible when the procedure is performed by an experienced team. The reduction of morbidity is as legitimate an indication for the use of the artificial kidney as is the reduction of mortality.

Our report concerns four representative cases of acute poisoning from hypnotic drugs that do not cause much direct damage to the kidneys. Two of the patients had glutethimide poisoning and two of the patients had barbiturate poisoning. The four patients underwent a total of seven dialyses with the Kolff twin-coil kidney. The usual methods to maintain comatose patients were employed. A large amount of fluid was intravenously administered during and after dialysis in order to obtain the maximal urinary excretion of poison. The amount of fluid was adjusted from an hourly measurement of urinary output, and the amount of electrolytes in solution was estimated from a urinary electrolyte determination. In the patients who required tracheotomy for respiratory difficulty before dialysis, regional heparinization was applied to prevent excessive bleeding from the surgical wound.[8] By means of Goldbaum's technic[9,10] the blood or plasma concentrations of glutethimide or barbiturate were determined before and after each hemodialysis by Dr. Irving Sunshine, technical director and toxicologist in the Cuyahoga County Coroner's Office.

**Doriden (glutethimide N.N.R. Ciba), Ciba Pharmaceutical Products, Inc.*
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Case Reports

Case 1. *Glutethimide poisoning.* A 48-year-old housewife in a state of coma for approximately five hours was admitted to a local hospital. For the previous four years she had been under a psychiatrist's care. She had ingested approximately 15 tablets of glutethimide (Doriden, 0.5 gm. per tablet) and an unknown number of phenobarbital tablets (150 mg. per tablet). The lethal dose of glutethimide for human patients ranges from 10 to 20 gm.[4] Gastric lavage was performed in the emergency room. Deep-tendon reflexes were present but shortly disappeared. The respiration was maintained through an endotracheal tube. Levophed* was administered intravenously to maintain adequate blood pressure. Having been treated conservatively for approximately 24 hours without improvement in her condition, she was transferred to the Cleveland Clinic Hospital for treatment with the artificial kidney.

When we first examined the patient, her blood pressure was 120/68 mm. of Hg during the continuous infusion of Levophed. Respirations were slow and shallow. The pupils were equal and dilated. The patient appeared completely flaccid without deep-tendon reflexes. There was no response to painful stimuli. The initial concentration of glutethimide in the blood was reported as 3.9 mg. per 100 ml., and no barbiturate was detected. She immediately underwent treatment with the artificial kidney for eight hours. At the end of dialysis the amount of glutethimide in the blood was 1.9 mg. per 100 ml. She was able to move the extremities. *Figure 1* is a graph of

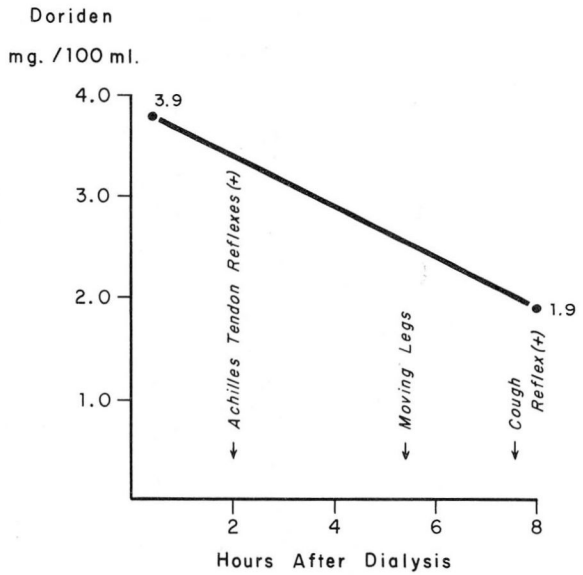

Fig. 1. Case 1. Clinical and chemical status of a 48-year-old woman with glutethimide (Doriden) poisoning after treatment with the artificial kidney.

**Levophed (levarterenol bitartrate), Winthrop Laboratories.*

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the clinical and chemical status during dialysis. The postdialytic course was uneventful and she was discharged on the twentieth hospital day.

Comment. This patient had severe glutethimide poisoning, having ingested approximately 7.5 gm. of Doriden and an unknown amount of phenobarbital. The possible synergism of barbiturate cannot be assessed. She underwent continuous clinical deterioration, manifested by coma, respiratory difficulty, and hypotension, athough she had a short period when deep-tendon reflexes were present. She recovered from acute poisoning by means of hemodialysis.

Case 2. *Glutethimide and barbiturate poisoning.* A 56-year-old housewife, known to have depressive psychosis for the past 12 months, was found in her home in a coma of about four hours' duration. Empty bottles of Doriden, Butiserpine* and Quiactin† were nearby on the floor. Evidence of crushed medicine was found around her mouth, in a glass, in the sink, and on the floor. The amount of ingested drugs was unknown. She was taken to a hospital and was given gastric lavage, amphetamine sulfate (Benzedrine‡), 40 mg. intravenously, as a stimulant, and intubation for respiratory difficulties. After these emergency treatments she was transferred to the Cleveland Clinic Hospital for treatment with the artificial kidney. When first examined the blood pressure was 90/50 mm. of Hg. Respirations were slow and shallow. The pupils were dilated and were fixed. She was completely flaccid and had some hyperactive deep-tendon reflexes. Hoffmann's sign was present bilaterally. The Babinski reflex was absent, but ankle clonus was present. In our emergency room the patient received a large amount of Megimide§ and Benzedrine without apparent response. Hypotension developed shortly after she was admitted, and Levophed was necessary to maintain the blood pressure. Respiration was maintained with a Bennett respirator. As the conservative treatment had failed, about three hours after admission she was treated with the artificial kidney for nine hours; there was slight clinical improvement. During hemodialysis she began to breathe spontaneously. The blood pressure was maintained without administering vasoconstrictors. The pupil reflexes were sluggish, but the corneal reflex remained absent. The next day a small amount of Levophed again was required to maintain blood pressure, and she underwent a second treatment with the artificial kidney for five hours, but without apparent improvement. The pupils did not react, and deep-tendon reflexes were sluggish. The cough reflex could be elicited after the second dialysis. The patient remained in deep coma, and areflexia persisted until the sixth day of hospitalization, when she underwent the third dialysis for six hours; there was no improvement. She underwent artificial hibernation for the last two days without success. She died about 10 hours after the termination of the third dialysis.

The barbiturate concentration in the blood was as follows: prior to the first dialysis, 1.6 mg. per 100 ml., at the end of dialysis, 0.9 mg.; prior to the second dialysis, 0.5 mg. per 100 ml.; no barbiturate was detected at the end of the second dialysis. Before the first dialysis Doriden was not found in the blood but was in the urine. At necropsy

**Butiserpine (butisol sodium, butabarbital sodium, reserpine), McNeil Laboratories, Inc.*

†Quiactin (oxanamide: 2-ethyl-3-propylglycidamide), The Wm. S. Merrell Company.

‡Benzedrine sulfate (amphetamine sulfate), Smith Kline & French Laboratories.

§Megimide (β-ethyl-β-methyglutarimide), Abbott Laboratories.

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there was no evidence of barbiturate in the blood. *Figure 2* is a chart showing the clinical and chemical status during and after dialysis. The coroner reported the cause of death as: (1) synergistic effect of glutethimide and barbiturate, (2) bilateral pneumonia, and (3) bilateral hydrothorax and hydropericardium.

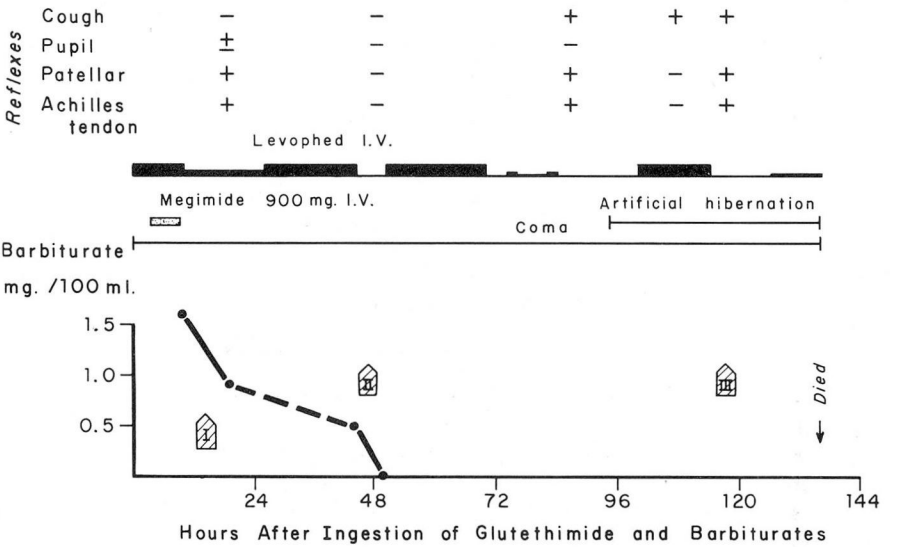

Fig. 2. Case 2. Clinical and chemical status of a 56-year-old woman with glutethimide and barbiturate poisoning after treatment with the artificial kidney and artificial hibernation, and to death. I, II, and III = dialyses.

Comment. This patient ingested unknown doses of several drugs, such as Doriden, and presumably Butiserpine and Quiactin; the role of Butiserpine and Quiactin cannot be assessed. Doriden was not found in the blood sample but in urine, which was collected during dialysis. The synergistic effect of a combination of drugs and secondary pneumonia may have led to the irreversible state, despite removal of toxic substances by three dialyses. In retrospect, perhaps the three dialyses should have been given in rapid succession.

Case 3. *Secobarbital poisoning.* A 75-year-old man known to have depressive psychosis for the past year was admitted to the Cleveland Clinic Hospital in a coma of six hours' duration. He had ingested about 40 tablets of secobarbital (Seconal,* 100 mg. per tablet). He appeared to be in shock with a blood pressure of 60/40 mm. of Hg. Respirations were rapid and shallow. He was completely flaccid with no deep-tendon reflexes. Pupils were dilated and were fixed. The corneal reflex was absent. Gastric lavage was performed immediately. For the next eight hours he was treated conservatively, and within four hours showed some clinical improvement by responding to

**Seconal (secobarbital), Eli Lilly and Company.*

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painful stimuli. Deep-tendon reflexes were present. He became hypotensive and required the administration of Levophed.

Because of no improvement with the conservative management, he was treated with the artificial kidney for seven hours. *Figure 3* is a chart showing the clinical and chemical status during and after hemodialysis. The next day a tracheotomy was performed.

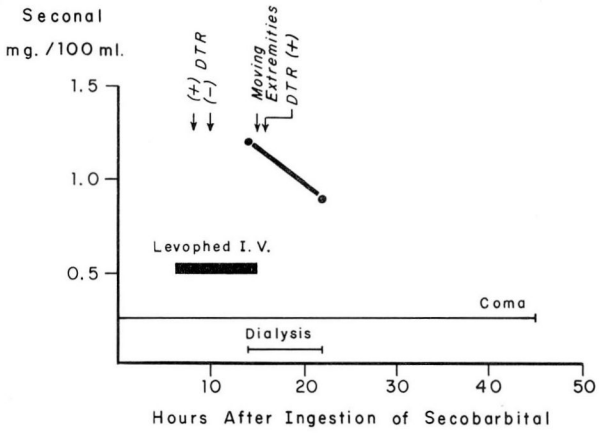

Fig. 3. Case 3. Clinical and chemical status of a 75-year-old man with secobarbital poisoning after treatment with the artificial kidney.

He began to respond and became relatively alert on the second day after dialysis; he remained oliguric for three days after dialysis. The remaining course was uneventful and the patient was discharged on his thirtieth hospital day.

Comment. This patient had severe secobarbital poisoning. He was treated conservatively for about eight hours after admission to the hospital but continued to deteriorate clinically. The slow recovery after seven hours of dialysis was probably due to generalized cerebral arteriosclerosis and to his age. There was no evidence of underlying complications in this patient. Hemodialysis relieved him of the severe toxicity.

Case 4. *Barbiturate poisoning.* A 46-year-old housewife with known systemic lupus erythematosus and recent mental depression was admitted to the Cleveland Clinic Hospital because of coma of about five hours' duration from possible barbiturate poisoning. No information was available as to what type of barbiturates had been ingested or the dosage. Respiration was gasping at first, then ceased entirely. Intubation was immediately applied. Blood pressure was 90/70 mm. of Hg. Pupils were dilated and were fixed. The patient was completely flaccid without deep-tendon reflexes and response to painful stimuli. In order to rule in or out a cerebral lesion, a spinal puncture was performed; the fluid specimen was reported as normal. A Bennett respirator was necessary to support the pulmonary ventilation. Shortly after admission, the artificial kidney was used for eight hours without apparent improvement. The respirator still was needed to maintain adequate air exchange, and the infusion of Levophed was needed

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to support the blood pressure. About nine hours after termination of the first dialysis a second treatment with the artificial kidney was given for nine hours. During the second dialysis, clinical improvement was evident; the patient began to maintain her own blood pressure as well as respiration. *Figure 4* is a chart showing the clinical and chemical status of the patient during and after dialysis. The remaining course was uneventful and she was discharged on her twenty-seventh hospital day.

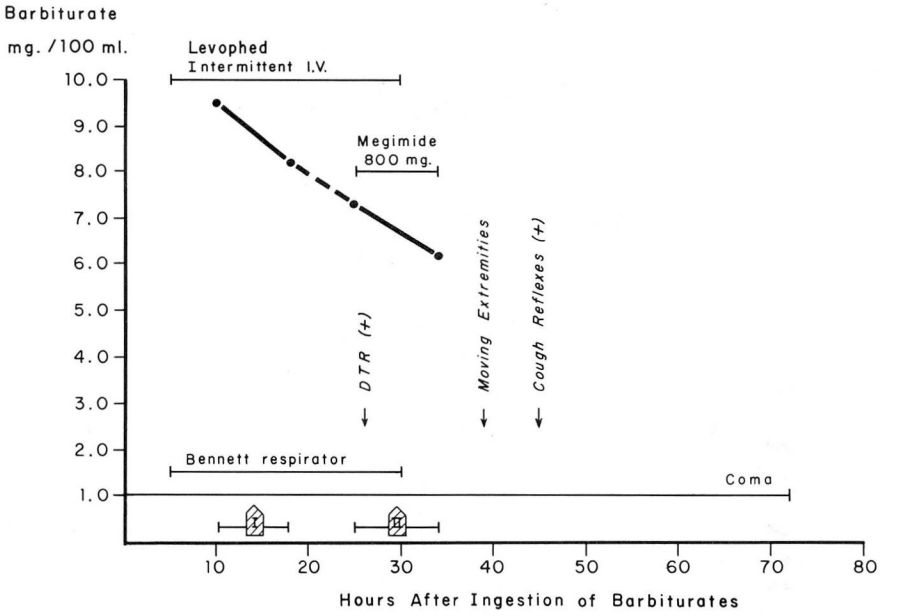

Fig. 4. Case 4. Clinical and chemical status of a 46-year-old woman with presumably barbiturate poisoning after treatment with the artificial kidney. I and II = dialyses.

Comment. This patient had severe barbiturate poisoning with a possible synergism of other drugs the role of which can neither be assessed nor be excluded from consideration. The first dialysis did not result in clinical improvement, and a second dialysis was necessary to obtain recovery from the acute poisoning.

Discussion

Each of our four patients with acute drug poisoning was first treated with the usual conservative supportive management, such as gastric lavage, correction of airway obstruction, artificial respiration through an endotracheal tube, and treatment of shock with intravenous infusion of drugs to restore an adequate blood pressure. In the absence of improvement with the conservative management the artificial kidney was used in the hope that hemodialysis would reverse the toxic

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state. A large amount of fluid was given intravenously to each patient during and after dialysis to promote excretion of the drugs through the patient's own kidneys. The amount of fluid and electrolyte intake was determined by hourly measurement of urinary output and urinalysis for electrolytes, such as sodium, chloride, and potassium. There was no evidence of postdialytic oliguria as seen in chronic renal failure,[11] except in one patient (case 3). That patient with secobarbital poisoning remained oliguric (urinary output was less than 500 ml. per day) for three days after dialysis.

When the patient's clinical condition rapidly deteriorates despite the conservative measures mentioned, along with well-maintained artificial respiration, hemodialysis must be done without delay. A patient whose condition is not rapidly deteriorating should be allowed to sleep off the sedative effects, and his circulation and respiration should be closely observed and supported to prevent decubitus. A sicker patient should undergo artificial hibernation in the hope of lessening permanent cerebral damage.[12] We believe that prolonged coma carries even more dangerous complications. Questions relating to minimal lethal doses, fatal concentrations of drugs in the blood, and effectiveness of therapy are uncertain. In acute poisoning, the uncertainty of factors such as: exact dosage, date of ingested or absorbed drugs, elapsed time before treatment, underlying physical state, and individual tolerance to drugs, makes it difficult if not impossible to foretell whether or not the patient will survive with or without a particular therapeutic procedure.

Megimide[13] is especially useful to unmask light cases of poisoning, but it is probably useless when massive doses of sedatives have been taken. Megimide stimulates respiratory and circulatory centers and restores reflexes and consciousness in light cases of sedative intoxication. However, an overdose of Megimide produces exaggerated reflexes, muscular twitching, tremor, clonus, and hyperventilation and epileptic potentials in the electroencephalogram. It is not a specific antidote against either barbiturate or glutethimide, such as Nalline hydrochloride* is against morphine. Megimide is given intravenously intermittently in doses of 50 mg. from every three to five minutes until muscle tone and pharyngeal and laryngeal reflexes have returned. An overdosage of Megimide may result in convulsions.

Some drugs are bound to proteins in the blood stream or even to proteins in the cells. It might be expected that the portion of drugs that is bound to plasma proteins cannot be removed by dialysis.[14] Berman, Jeghers, Schreiner, and Pallotta[1] observed no significant difference after dialysis in the concentration of pentobarbital sodium in plasma as compared with concentrations of the same drug in saline solution after dialysis. Even if the amount of a drug removed by hemodialysis is small, it may critically reduce the concentration of sedative from a fatal amount.

**Nalline hydrochloride (nalorphine hydrochloride: N-allyl-normorphine hydrochloride), Merck Sharp & Dohme.*

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In one of our patients (case 2), no drugs were detected in the blood at the end of the second dialysis. Death probably was indirectly caused by drug poisoning, in that initial anoxic cerebral damage and complicating bronchopneumonia made the condition irreversible.

A patient with glutethimide poisoning may undergo remarkable alternation of presence and absence of symptoms within short intervals. He may be completely comatose and areflexic at one moment and at the next moment respond to painful stimuli. This alternation has been thought to be due to resorption from the small intestine of the glutethimide that is intermittently excreted in the bile.[2]

Summary

Four patients with severe glutethimide or barbiturate poisoning were treated with hemodialysis by the twin-coil artificial kidney. Three of the four patients survived: one died perhaps because the initial deep coma led to anoxic cerebral damage and was later complicated by bronchopneumonia.

Early dialysis may prevent clinical deterioration to an irreversible state, and may prevent the occurrence of complications. Dialysis can remove critical amounts of toxic substances from the blood, and reduce fatal concentrations in the blood to within the range of normal sedative concentration.

Addendum

Since we submitted this paper, we have successfully treated two more patients with acute barbiturate poisoning, using the artificial kidney.

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