Acute diphenylhydantoin and primidone poisoning treated by peritoneal dialysis

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Since diphenylhydantoin (Phenytoin) was introduced in 1938 for the treatment of epilepsy it has become one of the most widely used anticonvulsant drugs and retains a reputation for considerable therapeutic safety. However, knowledge of its toxicity is increasing and an extensive and diverse literature now exists on the subject. The occurrence of blood dyscrasias and other serious complications of treatment with diphenylhydantoin have been reviewed by Sparberg (1963) and the use of this drug together with other anticonvulsants has also been causally related to megaloblastosis with associated folate deficiency (Reynolds, Milner, Matthews, and Chanarin, 1966) in an important proportion of patients receiving these drugs for lengthy periods.

Commonly encountered signs of neurotoxicity are nystagmus, ataxia, and dysarthria, which are likely to be present with blood levels of diphenylhydantoin exceeding 20 µg/ml. (Kutt, Winters, Kokenge, and McDowell, 1964). A number of patients are now known to have developed permanent cerebellar damage following both acute (Theil, Richter, Powell, and Doolan, 1961) and chronic (Utterback, 1958) diphenylhydantoin intoxication. The disturbances of cerebellar function were sometimes severe and the histological evidence in both man and animals that diphenylhydantoin produces Purkinje cell damage has been discussed by Kokenge, Kutt, and McDowell (1965).

The features of primidone (Mysoline) overdose have been attributed to the metabolic conversion of primidone to phenobarbitone, and high body fluid barbiturate levels are found in cases of primidone poisoning (Plaa, Fujimoto, and Hine, 1958; Bogan, Rentoul, and Smith, 1965). In contrast with diphenylhydantoin, permanent damage to the nervous system has not been reported after primidone intoxication and complete recovery is the rule with withdrawal of the drug.

There are therefore grounds for believing that an

early and rapid reduction in the blood and tissue concentrations of diphenylhydantoin after large overdoses are of greater urgency than had been realized until recently. We report here and discuss the outcome of peritoneal dialysis in a patient whose pre-dialysis blood diphenylhydantoin level, following a deliberate overdose of both this drug and primidone, considerably exceeded those previously reported.

METHODS

Diphenylhydantoin in serum, urine, and peritoneal dialysate was estimated by the ultraviolet spectrophotometric method of Wallace, Biggs, and Dahl (1965). This has the advantage over previously described methods of specificity and of high recovery values. Following a simple extraction procedure hydrolysis of the hydantoin ring in strong alkali is followed by a Hofmann degradation of the resulting amide to yield a steam-distillable product which has a high molar absorptivity with a maximum at 257 mµ. *In vitro* observations failed to show any effects of primidone on the diphenylhydantoin determinations by this method. Caeruloplasmin was estimated by the method of Houchin (1958) and the investigation into primidone crystalluria was kindly undertaken by Imperial Chemical Industries Ltd., using an AEI MS 9 mass spectrometer.

CASE REPORT

A male telephonist, aged 20, was admitted to East Ham Memorial Hospital, under the care of Dr. H. W. Salmon, in June 1967 having collapsed in a nearby cinema an hour after taking a large quantity of anticonvulsant drugs amounting to approximately 12 g diphenylhydantoin and 15 g primidone. He had suffered from idiopathic epilepsy since the age of 16 and in previous months had been instructed to take 400 mg diphenylhydantoin (Epanutin) and 500 mg primidone daily. A history of two previous suicide attempts was ultimately obtained; he also had a poor school and work record and was estranged from his parents. On the day following the overdose he was transferred to the National Hospital (N.H. A36766) under the care of Dr. Michael Kremer.

Examination then showed him to be a muscular young man (weight 70 kg) and apparently well nourished. He

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was disorientated but occasional lucid answers to questions were obtained and essential details of his suicide attempt could be established. Rocking movements of his head were frequent and jerking of the limbs required restraint. There was a coarse head and arm ataxia when he tried to sit up. He had a divergent strabismus with gross deficiency in reflex and voluntary conjugate eye movements. No spontaneous nystagmus was observed. Pupillary responses were present and he was able to swallow. Power in the limbs was good, tendon reflexes were present and plantar responses flexor. There was little response to pin prick or other painful stimuli. Blood pressure was 125/90; respiratory and pulse rates were normal, together with the remaining physical examination.

The results of investigations on admission to the National Hospital on 16 June 1967 were: proteinuria with a crystalline urinary deposit; haemoglobin 17.3 g/100 ml., PCV 50%, white cells and platelets normal and ESR 1 mm/1 hr; plasma sodium, 146 and potassium 4.1 m-equiv/l. Blood urea 21 mg/100 ml. Alkaline phosphatase 57 i.u./l., serum proteins, electrophoresis, and flocculation tests of liver function normal. Serum barbiturate (expressed as diethyl-barbituric acid) 7.1 mg/100 ml. The results of 131 iodine-triiodothyronine resin uptake, caeruloplasmin and protein bound iodine estimations are shown in the Table and compared with the results obtained at a later date. Radiographs of the skull and chest were normal. The cerebrospinal fluid contained 45 mg protein/100 ml. and 6 lymphocytes/cmm.

On the day after admission to the National Hospital his level of consciousness deteriorated with continuing extreme restlessness. The serum barbiturate had fallen to 2.1 mg/100 ml., and with the finding of a diphenylhydantoin blood level of 60 μ g/ml. (see Fig. 1) for 16 June he was transferred to the Middlesex Hospital (G. 81995) for peritoneal dialysis.

The results of dialysis, which was started at 0100 on 18 June and continued for 35 hours, are shown graphically. Twenty-one volumes of dialysing fluid (sodium lactate 5 g, sodium chloride 5.6 g, calcium chloride 0.38 g, magnesium chloride 0.15 g, dextrose 15 g, and water to 11) were employed in hourly cycles with addition of potassium at intervals. Intravenous fluids were regulated with reference to urinary output, PCV, and plasma electrolyte changes during dialysis. He was sedated with intramuscular paraldehyde and received vitamin B₁₂ 1.0 mg intramuscularly daily and folic acid 15 mg intramuscularly daily. Blood samples and aliquots of urine and dialysate were collected for diphenylhydantoin estimations.

Towards the end of dialysis there was clinical improvement with a return of swallowing and urinary continence. The fall in blood diphenylhydantoin and loss of the drug in dialysate and urine which occurred at this time are shown in the graph. He remained unco-operative and features of marked truncal and limb ataxia were noted together with nystagmus on lateral gaze. But by 20 June he was rational and able to converse.

On readmission to the National Hospital (23 June) he was able to give a full account of events leading up to the suicide attempt but remained amnesic for the four days

FIG. 1. Dialysis chart.

after this. There was nystagmus but ocular movements were full. Evidence of moderate cerebellar dysfunction was present but disability was slight. Tendon reflexes could be elicited with reinforcement and the plantar responses remained flexor. Sensation was intact.

Liver function tests were again normal and the BSP retention at 45 min was 3.5%; serum B₁₂ 690 μ g/ml. and serum folic acid 13.6 μ g/ml.; serum calcium 9.4 mg/100 ml. In a standard D-xylose absorption test the 5 hr urinary excretion was 4.5 g and the 90-min serum level was 37 mg/100 ml. The first part of a Schilling test was normal (20.9% excretion of the tracer dose in 24 hr). The creatine clearance was 114 ml/min. Further values for 131 iodine-triiodothyronine-resin uptake, caeruloplasmin and protein bound iodine (Table I) were obtained and will be discussed.

TABLE I

131 IODINE-TRIIODOTHYRONINE-RESIN UPTAKE, CAERULOPLASMIN AND PROTEIN BOUND IODINE IN BLOOD DURING (A) AND SIX WEEKS AFTER (B) PERIOD OF ACUTE DIPHENYLHYDANTOIN INTOXICATION

Investigation	A	B	Normal range
131 Iodine-triiodothyronine resin uptake	40.3% 41.3%	26.3%	25-35%
Caeruloplasmin mg/100 ml.	20.5	25.6	23-44 mg/100 ml.
Protein bound iodine μ g/100 ml.	2.9	5.4	4-8 μ g/100 ml.

The results of nerve conduction studies (Dr. R. S. Kocen) carried out 10 days after dialysis showed a motor-conduction velocity in the right lateral popliteal nerve of 51 m/sec (normal range 39 to 52 m/sec). Sensory nerve action potentials recorded with a needle electrode from the right lateral popliteal nerve at the knee in response to stimulation of the anterior tibial nerve at the ankle were normal. Caloric, optokinetic responses, and pure tone audiograms (Dr. M. R. Dix) were also normal at this time.

On discharge from hospital, five weeks after the overdose, he was symptom free and without evidence of cerebellar or other neurological deficiency. Psychiatric advice had been sought and attempts to achieve social rehabilitation were made. Anticonvulsant medication was restricted to 120 mg phenobarbitone/day.

DISCUSSION

Cases of poisoning with diphenylhydantoin in which death was related to central nervous system damage have been described by Tichner and Enselberg (1951), Schmeiser (1952), Krause (1959) and Laubscher (1966). In these, in cases where recovery occurred, and in the present case restless and at times violent behaviour were important features of the clinical state during the period of acute intoxication. Although nystagmus and defective convergence are common, external ophthalmoplegia is rarely seen in diphenylhydantoin intoxication alone and it is of interest, in this respect, that in three of the four cases of external ophthalmoplegia associated with diphenylhydantoin or primidone intoxication described by Orth, Almeida, Walsh, and Honda (1967) overdoses of both these drugs occurred.

The value of dialysis in treating diphenylhydantoin poisoning was suggested by Schreiner (1958) in his report of the case of a 2 year-old Negro boy whose complete recovery from a stage of deep stupor with periodic respirations seemed clearly related to haemodialysis, although biochemical data on blood and dialysate diphenylhydantoin levels were not obtained. Theil *et al.* (1961) have reported in detail the results of haemodialysis carried out in an 18 year-old woman 138 hours after a large overdose of diphenylhydantoin and phenobarbitone. The pre-dialysis diphenylhydantoin blood level was 50 $\mu\text{g/ml}$. (three times the upper limit of normal for patients on diphenylhydantoin therapy in their laboratory) and the immediate post-dialysis figure was 4 $\mu\text{g/ml}$. Clinical improvement in this case was slow with intellectual deficit persisting after several weeks. In the present case dialysis was started some 55 hours after the overdose and clinical improvement was obvious after 48 hours. Within two weeks he was without neurological abnormality. Paraldehyde proved a safe and effective sedative during the dialysis procedure.

Primidone was not thought to have been a major factor in producing the clinical state on the day following admission to the National Hospital. By this time the serum barbiturate had fallen from the initial value of 7.1 mg/100 ml. to a level unlikely to be seriously toxic at a time when the patient's condition was worsening. Specific identification of primidone crystals in the urine at this time by mass spectrometry supports the previous inference of Morley and Wynne (1957) in respect of the crystalluria they observed in a child with acute primidone poisoning.

On the basis of the findings of Reynolds *et al.* (1966) and Reynolds, Hallpike, Phillips, and Matthews (1965) concerning the effect of diphenylhydantoin together with certain other anticonvulsants in producing folate and vitamin B₁₂ deficiency associated with reversible impairment in intestinal absorption large doses of folate and vitamin B₁₂ were administered parenterally during and after dialysis. D-xylose and Schilling tests carried out subsequently were normal.

The finding of a low protein-bound iodine during the acute phase of intoxication is in line with the observations of Oppenheimer, Fisher, Nelson, and Jailer (1961) and those of Cantu and Schwab (1966). Although the change in caeruloplasmin between the time of admission and the recovery period was not significant the alteration in the *in-vitro* T₃ value during the same period was marked and could be attributed to competitive binding to protein by the drug.

It can be concluded that dialysis has a part to play in the management of acute diphenylhydantoin poisoning, and the extreme restlessness of most patients during severe intoxication should not result in this procedure being delayed—particularly if laboratory confirmation of seriously toxic blood levels of diphenylhydantoin be obtained.

SUMMARY

The case is reported of the successful treatment by peritoneal dialysis of a 20-year-old man after attempted suicide with diphenylhydantoin and primidone. The risks of damage to the central nervous system by exposure to toxic levels of diphenylhydantoin are considered and the importance of early dialysis in severe acute poisoning is emphasized.

We are grateful to Dr. Michael Kremer, Dr. H. W. Salmon, and the Medical Committee of the National Hospital, Queen Square, for permission to publish this case. We also wish to thank ICI for their co-operation in the identification of primidone and Mr. S. G. Pophalé for the diphenylhydantoin assays in Professor Cumings's laboratory. The illustrations were prepared by the National Hospital Department of Medical Photography.

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