Primidone Intoxication in a Child

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Primidone has been a valuable drug in the treatment of epilepsy since the early 1950's. It is akin to phenobarbitone (see Fig.) in which the carbon atom at the 'two' position in the pyrimidine ring has two hydrogens instead of a carbonyl oxygen. Bogue and Carrington developed the drug in 1949, and reported on its effectiveness in experimental animals (Bogue and Carrington, 1953). Clinical trials were conducted in England from 1950 to 1952, and were reported by Handley and Stewart (1952). Primidone was found to be safe and effective in the treatment of recurrent *grand mal* seizures, and later by Whitty (1953) and many others in the treatment of focal motor and psychomotor epilepsy.

FIG. Structural relations between primidone and phenobarbitone.

The majority of reports of primidone toxicity (Ayerst Laboratories, 1966; Goldin, 1954; Goodman and Gilman, 1965; Millichap and Aymat, 1968) have dealt with relatively minor and reversible or transient side-effects, such as rash, nausea, dizziness, listlessness, and mild ataxia and dysarthria. In addition, a number of reports of a folic acid responsive megaloblastic anaemia due to primidone have appeared (American Medical Association, 1965; Baker *et al.*, 1962; Berlyne, Levene, and McGlashan, 1955; Klipstein, 1964), as well as a lupus-like state (Ahuja and Schumacher, 1966; Benton *et al.*, 1962), and a 'pseudolymphomatous'

condition (Saltzstein and Ackerman, 1959), both of which disappear when the drug is discontinued. The rarity of these last two conditions suggests that they may be idiosyncratic in nature. Lastly, there is a report of three patients who developed moderately severe ataxia and dysarthria on maintenance doses of primidone and other anticonvulsants (Plaa, Fujimoto, and Hine, 1958).

Serious acute intoxication with primidone has been reported in 7 adults attempting suicide (Arnold and Ceranke-Höfermayer, 1953; Bogan, Rentoul, and Smith, 1965; Del Greco and Arieff, 1962; Dotevall and Herner, 1957; Fazekas and Renger, 1960; Morley and Wynne, 1957; Sciarra *et al.*, 1954), 3 of whom succeeded (Bogan *et al.*, 1965; Fazekas and Renger, 1960; Morley and Wynne, 1957). The lethal dose in each case was 20-30 g.; but 2 of the 4 survivors had also ingested 25-30 g. Accidental intoxication with primidone has been reported once in adults (Ajax, 1966), and twice in children (Gellman, 1965; Morley and Wynne, 1957). One of the children (Morley and Wynne, 1957), a 4½-year-old boy, ingested 12.5 g. primidone and lapsed into a 12-hour coma. This was followed by 3 to 4 days of disorientation and then complete recovery. The present case report describes the clinical course of acute primidone intoxication in a 2½-year-old girl, and discusses the patient's serum barbiturate levels in the light of the controversy as to the extent to which primidone is converted to phenobarbitone in man.

Case Report

A 2½-year-old epileptic girl ingested 90 50 mg. tablets of primidone, a total of 4.5 g. (or about 400 mg./kg. body weight). This was 13 times her daily dose, and about three hours later her mother found her 'unconscious and breathing slowly'.

She was taken to a local hospital where an intravenous drip was started. Her serum barbiturate level at that time was 8.5 mg./100 ml. She was then transferred to the University of Colorado Medical Center, where initial examination revealed a semicomatose child who responded to painful stimuli by withdrawal. Her pulse rate was 108/min., respirations 28/min., systolic blood pressure 80 mm. Hg, and body temperature 37.0 °C.

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TABLE
Serum Barbiturate Levels* after
Primidone Ingestion

Hours after Ingestion	Serum Barbiturate Level (mg./100 ml.)
3½	8.5
6	9.6
10	6.0
28	5.6

* Levels were determined using the UV spectrophotometric method of Broughton (1956), which gave no detectable reading for unaltered primidone.

rectally. There was marked flaccidity of all extremities to passive movements, and deep tendon reflexes were absent. Gag and cough reflexes were present, but corneal reflexes were diminished. The remainder of the physical examination was normal. A complete blood count was within normal limits; however, the urine contained 2-plus protein, 40-60 red blood cells per h.p.f., and crystals reported as triple phosphate. Analysis of her arterial blood gases showed her to be in a partially compensated metabolic acidosis, with a base deficit of 6 mEq/l. Serum chemistry was otherwise normal. Her serum barbiturate level on admission was 9.6 mg./100 ml. Barbiturate levels were determined at various times thereafter and are presented in the Table.

Conservative management was decided upon. During the first 12 hours after admission the patient's condition improved, and was marked by the gradual return of deep tendon and corneal reflexes, and response to less painful stimuli. Her vital signs remained stable. Her urine output was adequate, and alkalization of the urine, which is known to increase barbiturate excretion, was maintained by the addition of sodium bicarbonate to the intravenous fluids. About 13 hours after ingestion she developed a mild horizontal nystagmus on lateral gaze. By 24 hours she was talking to her mother, but there was mild slurring of speech, and some unsteadiness when crawling in her crib. Over the next two days she became fully alert, but remained moderately ataxic for another two days. Thus she had fully recovered from the intoxication five days after ingestion, though she developed serologically-proven mumps on the fourth day. A urinalysis done on the third day showed disappearance of the previously noted protein, red blood cells, and crystals.

Discussion

The patient showed many of the signs of sublethal primidone intoxication that have been reported in the past, namely a period of coma with loss of deep tendon reflexes, and a recovery period characterized by gradually lessening disorientation, dysarthria, nystagmus, and ataxia. These signs usually disappear over a 2 to 4 day

period, with complete recovery 5 to 7 days after the ingestion.

A similar clinical picture is common to intoxication with phenobarbitone and most barbiturate derivatives, and it has been suggested (Del Greco and Arief, 1962; Plaa *et al.*, 1958) that the clinical picture seen in primidone intoxication may be due to its conversion to phenobarbitone in the body. Butler and Waddell (1956) estimated the conversion to be 5% in dogs and 15% in humans, whereas Olesen and Dam (1967) estimated the value in man to be 24.5%. Most recently, Bogan and Smith (1968) measured the barbiturate levels in the serum of patients three hours after a dose of phenobarbitone or primidone. They calculated serum levels of 0.52 and 0.111 mg./100 ml. for each mg./kg. of phenobarbitone or primidone given, respectively. If these figures were valid for large doses of primidone, a barbiturate level of 44.4 mg./100 ml. would have been expected in our patient instead of 8.5 mg./100 ml. three hours after ingestion (see Table), which would have been fatal. Similarly, the child reported by Morley and Wynne (1957) ingested an estimated dose of 500 mg./kg., and this should have resulted in barbiturate levels of more than 50 mg./100 ml., with resultant death. Our findings, and those of Morley and Wynne (1957) do not support the reported high value of 25% for the conversion of primidone to phenobarbitone, when high doses of primidone are ingested, though it might be true for small doses.

Our patient's course illustrates that primidone is a relatively non-toxic drug. Over a period of five days she recovered completely from a single dose of primidone equal to 13 times the recommended daily dose for children her age. A comparable overdose of phenobarbitone would almost certainly have been fatal.

We did not use analeptic drugs in treating our patient. Though they have reportedly been used successfully in two cases of primidone intoxication (Arnold and Ceranke-Höfermayer, 1953; Dotevall and Herner, 1957), they were used without success in another (Fazekas and Renger, 1960). Because of their own toxicity, these drugs have not been generally accepted in the treatment of barbiturate intoxication (Henderson and Merrill, 1966).

Since primidone is bound to serum proteins less than phenobarbitone (Spinks and Waring, 1963), the use of forced diuresis should be even more effective in the immediate treatment of severe primidone intoxication than in severe phenobarbitone intoxication. In addition, haemodialysis with or without exchange transfusion could probably

be reserved for those patients in whom a brief trial of forced fluids results in no evidence of clinical improvement.

Summary

A case report is presented of a 2½-year-old epileptic girl who accidentally ingested 4.5 g. primidone (approximately 400 mg./kg.). She became semicomatose and areflexic, but her respirations remained stable. She was treated conservatively with generous amounts of intravenous fluids, which contained bicarbonate, to maintain a large amount of alkaline urine. Over a five-day period she recovered completely, after progressing through a period of nystagmus, incoordination, dysarthria, and ataxia. Since the ingested dose was 13 times the recommended daily dose, her course illustrates the wide margin of safety between the therapeutic and toxic doses of this drug.

We failed to observe very large or increasing levels of barbiturate in our patient's serum, and suggest that the reportedly high values for the conversion of primidone to phenobarbitone in man are not valid for large doses of primidone.

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