Medical Memorandum

Acute Primidone Poisoning in a Child

Primidone ("mysoline") has been used since 1950 in the treatment of epilepsy, and in 1952 Handley and Stewart published an account of the first clinical trial. Since then there have been many papers indicating the effectiveness and low toxicity of this drug. Animal experiments have shown that, although its anticonvulsant potency is twice as great as that of phenobarbitone, its toxicity is much less (Bogue and Carrington, 1953; Goodman *et al.*, 1953). Only three cases of overdosage with primidone have been recorded. The first case, reported by Arnold and Ceranke-Höfermayer (1953), was that of a 30-year-old man who attempted suicide by taking 120 tablets (30 g.) in two doses—70 tablets followed six hours later by another 50 tablets. He was found unconscious five hours later, and given analeptics. He remained unconscious until 24 hours after the first dose, and sleepy for another 24 hours. During the third day consciousness was still slightly impaired, with bulbar speech and motor incoordination, but by the end of the day he was normal, and had completely recovered seven days later. Examination of the blood, urine, and cerebrospinal fluid shortly after his admission to hospital showed nothing abnormal, and later blood tests and a sternal puncture revealed no evidence of bone-marrow damage. The second case, published by Sciarra *et al.* (1954), concerns another attempted suicide (no age or sex stated) in which 25 tablets of primidone (6.25 g.) were taken in a single dose. The only effect was a deep sleep of four to five hours' duration, no special resuscitative measures being required. In the third case, reported at an inquest held at Wigan on May 10, 1955, a woman of 48 years had taken a large number (estimated at from 80 to 120) of primidone tablets. This patient, who was seen apparently well at 1.20 p.m. on April 6, was found unconscious at 9.5 p.m. the same day and died the following morning at 10.30.

CASE REPORT

A boy of 4½ years had been treated for epilepsy and disturbed behaviour since he was 20 months old. For part of this period he had been treated with phenobarbitone, but for the last 2½ years he had been given 0.25 g. primidone twice daily. At 9.30 a.m. on January 1, 1956, the boy was seen playing with his box of primidone tablets. Later, it was clearly established that by this time he must have swallowed at least 50 tablets—that is, not less than 12.5 g.—of primidone. In the following account the times are reckoned from the time of ingestion of the drug.

30 Minutes.—His mother noticed he was sleepy, but thought this was due to a restless night and to a tablet of carbromal he had been given in the early hours of the morning. He went to sleep and was returned to bed.

4 Hours.—Found to be deeply asleep; the family doctor called in.

8 Hours.—Admitted to hospital. On examination found to be deeply unconscious; no reflexes elicited and no response to painful stimuli. Respirations 20 and pulse 120 per minute, blood pressure 80/65 mm. Hg, rectal temperature 97° F. (36.1° C.).

12 Hours.—Some improvement now apparent. There were occasional spontaneous movements, and painful stimuli produced slight stirring. Temperature had risen to 98.4° F. (36.9° C.) and pulse rate to 140 per minute; the blood pressure was 85/60 mm.

16 Hours.—Very little change in the condition, but the blood pressure had risen to 100/55 mm.

24 Hours.—Pulse rate now varying between 120 and 140 per minute and temperature 100° F. (37.8° C.). Lumbar puncture produced normal C.S.F. with 6 cells per c.mm.

and 25 mg. protein per 100 ml. Early dehydration noted, and some fine rales over small area of left lower lobe of lungs. Intravenous infusion of 4.1% glucose with N/5 saline started, and 1,200 ml. given over next 20 hours. He reacted strongly to the venepuncture, and during this procedure passed urine for the first time since taking the primidone. A small quantity (10.5 ml.) of this urine was saved for examination. Treatment with penicillin, 500,000 units 6-hourly, started.

27 Hours.—There was now definite improvement; left ankle and left triceps jerks were present, there were more spontaneous movements, pupillary reflexes were present though sluggish, and the patient reacted strongly to supraorbital pressure. In these circumstances bemegride ("megimide") and amiphenazole ("daptazole"), which were considered probably the best drugs to use in this condition, were withheld.

40 Hours.—Now fully awake but disoriented and very ataxic. The ataxia slowly diminished, and five days after taking the primidone the boy was again normal.

The urine collected 24 hours after the drug had been swallowed appeared to be clear at first, but as it cooled to room temperature shimmering white crystals began rapidly to form in it until a very heavy crystalline precipitate had collected. The crystals were filtered off, washed with water, and dried *in vacuo*. They had a melting-point of 280°–282° C., and chemical examination showed them to be pure primidone, as much as 21.5 mg. of the drug being obtained. No albumin, cells, or casts were present, and despite the marked crystalluria there was never any evidence of kidney damage. So far there has been nothing to suggest injury to the bone marrow, but neither the blood nor the marrow has been examined.

COMMENT

The results of acute primidone poisoning in this case, as in the cases reported by Arnold and Ceranke-Höfermayer and by Sciarra *et al.*, appear to confirm the opinion that this drug has a remarkably low toxicity. The heavy primidone crystalluria does not appear to have been observed in man before. Primidone is soluble in urine to the extent of 60 mg. per 100 ml. at 37° C. In the present case 21.5 mg. was filtered off from 10.5 ml. of urine—that is, more than three times the quantity of primidone which could normally be held in solution in that volume of urine at 37° C. Despite this there was no evidence of any effect on the kidneys.

We have been unable to find any references in the literature to specific antidotes against primidone poisoning. The commonly used analeptics could, of course, be tried, but we are of the opinion that the chemical structure of primidone is such that the new barbiturate antagonists bemegride and amiphenazole should be as effective in the treatment of acute poisoning with this drug as they are in acute barbiturate poisoning.

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REFERENCES

- Arnold, O. H., and Ceranke-Höfermayer, S. (1953). *Wien. med. Wschr.*, 103, 692.
Bogue, J. Y., and Carrington, H. C. (1953). *Brit. J. Pharmacol.*, 8, 230.
Goodman, L. S., Swinyard, E. A., Brown, W. C., Schiffman, D. O., Grewal, M. S., and Bliss, E. L. (1953). *J. Pharmacol.*, 108, 428.
Handley, R., and Stewart, A. S. R. (1952). *Lancet*, 1, 742.
Sciarra, D., Carter, S., Vicale, C. T., and Merritt, H. H. (1954). *J. Amer. med. Ass.*, 154, 827.