Poisoning with delayed-release tablets

Treatment of Debendox poisoning with purgation and dialysis

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Meadow, S. R., and Leeson, G. A. (1974). *Archives of Disease in Childhood*, 49, 310. **Poisoning with delayed-release tablets: treatment of Debendox poisoning with purgation and dialysis.** Accidental poisoning with delayed-release tablets causes symptoms at a time when the tablets can no longer be retrieved from the stomach. A child died from eating 23 tablets of Debendox, which is a delayed-release tablet containing dicyclomine and doxylamine. A second child survived a similar overdose, having been subjected to vigorous purgation and peritoneal dialysis.

Accidental poisoning with delayed-release tablets poses certain problems that are different from those of most childhood poisoning. Books on the management of poisoning do not deal with these specific problems.

Delayed-release (timed release) tablets have a special coating which delays the release of the active ingredients. A major problem is that when they are accidentally ingested symptoms may not arise until several hours later, by which time the tablets have passed beyond the stomach and cannot be retrieved by either forced emesis or gastric lavage.

Debendox is a delayed-release tablet which is widely advertised as, 'The only timed release tablet specifically for the prevention of morning sickness. She takes it before she goes to bed and the unique Debendox tablet doesn't start working till she needs it—in the morning'.

The active ingredients are released 6 to 8 hours after ingestion. One tablet of Debendox contains 10 mg dicyclomine hydrochloride (Merbentyl), which has a parasympathetic depressant activity similar to atropine; 10 mg doxylamine succinate (Decapryn), which is an ethanolamine closely related to diphenhydramine and has antihistamine activity; 10 mg pyridoxine hydrochloride, which is relatively nontoxic.

Recent experience at Leeds Children's Poisons Centre with a child who died after accidental ingestion of Debendox led to formulation of a policy to deal with such situations, the policy proving

successful a few months later when a second child was admitted after ingestion of Debendox.

Case reports

Case 1. A male, aged 18 months. At 10.00 a.m. he ate 'a bottle full' of Debendox tablets. The parents discovered this 2 hours later but were not unduly worried because he seemed to be suffering no ill effects. During the late afternoon he became restless, disorientated, and ataxic. He was admitted to the Children's Poisons Unit at 7.00 p.m. He appeared flushed with pyrexia and was extremely agitated, showing occasional myoclonic jerks. His pupils were dilated, his eyes rolling, and there was coarse nystagmus. At the time of admission he was vomiting, but the vomitus contained no tablets. Despite supportive therapy his condition deteriorated; major fits began at 9.00 p.m. and continued intermittently despite a total of 4 mg diazepam and 1 ml paraldehyde. At 11.00 p.m. a further 2 mg diazepam was followed by respiratory and cardiac arrest. Prompt resuscitation and ventilation which was continued for 2 hours failed to restore cardiac activity. Necropsy examination revealed 23 tablets of Debendox just proximal to the ileocaecal valve; the shells of the tablets still contained some of the ingredients.

Comment. The clinical picture was similar to that of atropine poisoning, and the course of his illness could be explained by the dicyclomine component in the tablet. However, antihistamine poisoning can also cause children to have excitation agitation and fits, and can lead to cardiorespiratory arrest (Reyes-Jacang and Wenzl, 1969), so that the relative importance of the dicyclomine and the antihistamine doxylamine in this child's death is uncertain. The necropsy findings suggested that the drugs were still being absorbed when he died 13 hours after eating the tablets.

Case 2. A male, aged 15 months. At 8.30 a.m. he swallowed an unknown number—possibly as many as 30—of Debendox tablets. 2 hours later he vomited; neither tablets nor sediment were seen in the vomit. He became drowsy and was admitted to the poisons unit at 11.00 a.m. Gastric lavage yielded no tablets. At that time he looked flushed and was drowsy. Serum electrolytes showed a mild acidosis; an intravenous infusion was set up. During the next 4 hours determined efforts were made to clear his bowels of Debendox. He was given a series of purges, magnesium sulphate orally, soap and water enemas, and saline colonic wash outs.

At 1.00 p.m. myoclonic jerks developed, he became very confused, and his level of consciousness fell. He still appeared to be absorbing the poisons, which it was assumed must have been far down the small intestine. Peritoneal dialysis was set up using Dialaflex 61 isotonic solution and was continued for 11 hours. He was semiconscious and continued to have frequent myoclonic jerks. At 3.00 p.m. half-digested tablets began to appear in the fluid returned from the colonic wash outs. From 8.00 p.m. his condition began to improve, and there was marked improvement by midnight. The next morning he appeared normal.

Chemical analysis of body fluids and effluent

The samples were analysed for doxylamine and dicyclomine by gas chromatography, and verified by gas chromatograph-mass spectrometry techniques.

Aliquots of collected biological fluid samples (frozen until assayed) were made basic with 1 mol/l. glycine-NaOH buffer, pH 10, and extracted 3 times with 10 volumes of benzene. The extracts were dried under a stream of anhydrous nitrogen and redissolved in 100 μ l chloroform. Extraction efficiency for dicyclomine and doxylamine was 92.6 and 93.4%, respectively. Analysis was performed with a gas chromatograph (Packard Instrument Co.) model 7300, equipped with a flame ionization detector. Detector and inlet temperature was 200 °C and column temperature was 180 °C. A 1.8 m $\times$ 4 mm glass column was packed with 5.0% S.E. 30 on Chromosorb AW-DMCS, 80–100 mesh, and before use the column was base loaded with 50 μ l of 10% tetraethylene pentamine in ethanol. The internal standard was 4-[α -methyl- α -(2-dimethylaminoethoxy)-benzyl]-pyridine acid succinate. Peak area ratios were determined and standard curves constructed. The presence of dicyclomine and doxylamine was confirmed by gas chromatograph-mass spectrometry techniques.

Rectal effluent. Both substances were present in high concentration.

Urine (Table). Doxylamine was present in the urine passed 7 hours after ingestion. The maximum concentration was at 10 hours. By 25 hours excretion was minimal.

Dialysate. Doxylamine was present in the fluid returned from peritoneal dialysis, reaching a maximum

TABLE
Urinary excretion of doxylamine in Case 2

Time after ingestion (hr)	Urinary doxylamine (μ g/ml)
7	192
10	509
13½	51
19	30
24½	1

concentration of 15.9 μ g/ml 7 hours after ingestion. Dialysate excretion at that time was 15,900 μ g/1000 ml exchange.

Plasma. The assay method was not sufficiently sensitive to measure doxylamine in plasma. Dicyclomine is rapidly broken down after absorption and could not be identified in the plasma, urine, or dialysate.

Discussion

Most children who have accidentally eaten tablets are subjected to forced emesis or gastric lavage. The problem with delayed-release tablets is that if the mother waits until symptoms develop before seeking help it is likely that the tablets will have passed beyond the stomach and cannot be retrieved easily. The first boy became ill 6 hours after ingestion, and gradually deteriorated, dying 13 hours after ingestion.

In the light of this sad experience a more aggressive policy was prepared should the situation be repeated. The policy was successful with the second child. In addition to routine supportive measures (intravenous infusion, expert nursing, and maintenance of an airway), treatment was organized with 3 additional aims.

(1) Removal of tablets from small intestine.

Previous discussions with surgical colleagues suggested that laparotomy would only be successful if the tablets were extremely hard; it was feared that a soft mass of semidigested tablets would be difficult to find and remove. Therefore, a combination of oral purges, enemas, and colonic wash outs was used, and these retrieved a considerable proportion of the tablets before they were completely absorbed. Half-digested tablets appeared in the rectal effluent 4 hours after purging began, that is, 6½ hours after the tablets were eaten. It seems likely that the vigorous and successful purgation was the main factor in saving the boy's life.

(2) **Peritoneal dialysis.** This was set up to increase drug excretion. Analysis of the dialysate

and urine suggested that more doxylamine was excreted in the dialysate than in the urine because of the very large dialysate volume (3000 ml/hour) compared with the urine volume. It is also possible that peritoneal dialysis has particular advantages when a drug is in the small intestine in that some of the drug may permeate directly across into the dialysate from the bowel.

Dialysis has a small but important role in the treatment of poisoning. It is neither generally recommended nor required, but if the patient's condition is deteriorating, if a fatal outcome is likely, or if severe organ damage is likely, then dialysis may be indicated. Before it is used one must be confident that dialysis will accelerate the body's elimination of the poison, and that the poison is dialysable. A useful review of dialysis of poisons and drugs is compiled regularly by Schreiner (1970). There are reports of certain antihistamines being removed by dialysis, but no previous report of its use for doxylamine. Dicyclomine is metabolized so rapidly, and so little is usually excreted in the urine, that dialysis is unlikely to be helpful in its elimination.

(3) Caution in use of any other drugs. The first child died immediately after being given diazepam. It would be wrong to suggest that the diazepam caused his death, for he had been deteriorating for several hours, was extremely ill, and was still absorbing the poisons. However, intravenous diazepam does cause respiratory arrest in comparatively healthy children, and it may be that this is more likely in a poisoned person. There has been a previous report of arrest occurring when a patient recovering from an overdose was given diazepam (Doughty, 1970), and a suggestion that diazepam may potentiate nondepolarizing muscle relaxants (Feldman and Crawley, 1970). We had decided that any future child poisoned with Debendox or any drug likely to affect respiration should not receive diazepam and that severe fits would be treated cautiously with paraldehyde. The difference in the onset of symptoms is curious. Case 1 developed symptoms 6 hours, and Case 2 2 hours, after ingestion. This may be an example of the variability and unpredictability in the action of

enteric coated tablets. Their action varies from person to person and within the same individual on different occasions (Leonards and Levy, 1965), probably as a result of the differences in gastric emptying and intestinal absorption (Clark and Lasagna, 1965). Delayed-release drugs prepared as coated microspherules may be more predictable (Gotoff, McCue, and Wendell, 1968), though even more delayed in their action. One child accidentally poisoned with aspirin in microspherule form developed neither symptoms nor raised serum salicylate level until 16 hours after ingestion (Kaufman and Dubansky, 1972).

Delayed-release forms of many different drugs are now available, and new ones are introduced regularly. The recent announcement of a sustained-release form of amitriptyline must fill paediatricians with foreboding. Therefore, the doctor who deals with a patient suffering from drug overdose must find out the exact presentation of the drug, and must not assume that the danger is over simply because of the absence of symptoms 6 hours after ingestion.

We thank Professor R. W. Smithells, under whose care the second child was admitted, and Dr. Cyril Maxwell, Medical Director of Merrell Division of Richardson Merrell in London.

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