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Clinical Effects and Treatment of Imipramine and Amitriptyline Poisoning in Children

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Imipramine and amitriptyline are tricyclic antidepressant compounds whose chemical structure, dosage, pharmacology, and toxicity are so similar that they are commonly considered together (Klerman and Cole, 1965 ; Giarman, 1965 ; Rasmussen, 1965, 1966).

The danger to children of accidental ingestion of these drugs has become increasingly recognized in recent years (Noack, 1960 ; Giles, 1963 ; Sunshine and Yaffe, 1963), and at least 21 such accidents, including five deaths, have been reported. The main features of these reports are summarized in the accompanying Table.

Annual number of N.H.S. prescriptions of imipramine + amitriptyline in Great Britain 1962-6. The 1966 figure is predicted from data for the first six months.

During 1966 seven children were admitted to the medical wards of the Royal Hospital for Sick Children, Edinburgh, with a diagnosis of imipramine or amitriptyline overdosage. Over the preceding two-year period five similar cases were seen, but none was recorded before 1964. This suggests a trend which is entirely in keeping with the prescription rates for these two compounds in Great Britain as shown in the Chart (data supplied by the Ministry of Health). There is therefore reason to believe that from being an alarming but rare event, poisoning

of children by these two drugs may become an increasingly common problem.

The purpose of this paper is to record the characteristic features of both mild and severe imipramine or amitriptyline poisoning and to derive a rational scheme of management based on a consideration of the pharmacology of these drugs, on a review of the literature, and on our own experience in practice.

Clinical Features of Mild Poisoning

Ten of our patients (all except Cases 26 and 31) and four of those previously reported (Cases 7, 8, 9, and 10) showed the symptoms of mild poisoning only. Some depression of consciousness was almost invariably seen, while six showed ataxia or a disturbance of posture out of proportion to their drowsiness. A striking feature in five of the children was the extreme agitation with which they responded to any stimulus, or which appeared spontaneously, alternating with periods of drowsiness.

Tachycardia, persisting during sleep, was present in 10 of these children, but none developed arrhythmia or hypotension, and electrocardiograms recorded in Cases 32 and 33 showed sinus tachycardia, with normal complexes. Some degree of pupillary dilatation was noted in four of the patients, while thirst, dizziness, nystagmus, or vomiting was occasionally apparent.

These symptoms tended to develop gradually within one to four hours of ingestion of the drug. Paraldehyde was given to control restlessness in one (Case 8), but all the others recovered spontaneously and completely within 24 hours.

One patient (Case 28) did not develop symptoms of poisoning, and may not in fact have swallowed any drug, though he was found with several tablets in his mouth and surrounded by many more from which he had sucked the sugar coating.

Clinical Features of Severe Poisoning

Severe poisoning is characterized by the development of convulsions and coma ; in addition, severe respiratory depression, cardiac arrhythmias, E.C.G. changes, and profound hypotension may occur. The detailed clinical features are best described by a case report.

Case 31

A previously healthy boy of 5 years 4 months was observed to become grossly ataxic over a period of a few minutes. He seemed to be unaware of his surroundings, and within 15 minutes lapsed into coma and had a generalized tonic-clonic seizure. During the journey to hospital of 45 minutes, almost continuous twitching of the limbs

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was observed and on arrival he was deeply unconscious. Any form of stimulus, such as the aspiration of pharyngeal secretions, provoked a generalized convulsion lasting some 30 seconds.

On examination there were no localizing signs. Tone and deep tendon reflexes were normal and the plantar responses were flexor. The pupils were dilated equally and responded sluggishly to light (within one hour they became widely dilated and fixed); the fundi appeared normal and there was no meningism. The boy's temperature was normal, his colour good, and respirations were 24/min., regular but shallow. The apex rate was 148/min. and regular. Peripheral pulses were of good volume and the arm blood pressure was 115/70 mm. Hg.

Estimates of blood glucose, plasma calcium, urea, and electrolytes gave normal values, and lumbar puncture yielded clear cerebrospinal fluid under normal pressure with normal glucose and protein concentrations.

After passage of a cuffed endotracheal tube, gastric lavage was performed and the stomach content (which contained no visibly identifiable remnant of tablets) kept for examination.

Paraldehyde (5 ml. intramuscularly) was given to control convulsions, and thereafter he became completely unresponsive even to painful stimuli.

The parents at first insisted that the child could have had access only to a salicylate preparation (Palaprin), but on persistent questioning they recalled that a bottle of grandmother's "nerve tablets" were kept on top of the wardrobe. These were said to be Triptafen tablets, each containing amitriptyline (25 mg.) and perphenazine (2 mg.).

The presence of amitriptyline (though not of perphenazine) in the gastric aspirate was quickly established and a conservative policy of management adopted. Slow intravenous infusion of 5% dextrose in half-strength Ringer's lactate was started. Pulse rate, blood pressure, respiratory rate, pupil size, and conscious level were recorded every 15 minutes and rectal temperature every two hours. Over the next 24 hours the blood pressure fluctuated between 110/70 and 90/60 mm. Hg. Tachycardia persisted, the apex rate reaching 160/min., but no irregularity was detected and the peripheral pulses remained easily palpable.

The level of consciousness rose steadily. Sixteen hours after the estimated time of ingestion of the tablets the endotracheal tube was removed because of gagging, and shortly afterwards the child opened his eyes. His reactions to stimuli then became more vigorous, and by 24 hours he responded to any interference with grossly exaggerated movements of the limbs and signs of great agitation. This was controlled by intramuscular chlorpromazine (25 mg.), a total of four doses being required at intervals of 4, 6, and 13 hours.

No urine was passed spontaneously for the first 24 hours though the bladder became readily palpable above the pubic symphysis. The child's rectal temperature rose to 38.3° C. (101° F.) at 36 hours, but by then there was evidence of a basal pneumonia, which complicated his recovery.

Forty-eight hours from the time of ingestion he recognized his parents and was able to drink from a cup. By 60 hours he was entirely rational with no evidence of neurological deficits, and after a course of antibiotics and physiotherapy he left hospital on the eighth day.

TABLE

Case No.	Author	Age in Years	Drug(s)	Dose (mg.)	Dose (mg./kg. Body Weight)*	Levels (µg./100 g.)	Symptoms and Signs	Treatment	Outcome
1	Noack	2 6/12	Imipramine	2,500	(192)	Liver, 2,700	Coma, continuous convulsions, cyanosis, dilated pupils, cardiac and respiratory arrest	Gastric lavage, artificial respiration, cardiac massage	Died
2	Somuncuoglu	3 4/12	"	375	21.6	—	Vomited, coma, twitching, respiratory depression, cyanosis, tachycardia, sweating, fixed dilated pupils, urine retention, skin rash	Gastric lavage, I.V. calcium	Recovered
2	Arneson	1 7/12	"	1,250	(112)	—	Vomited, coma, continuous convulsions, hypotension, ataxia and atetosis, arrhythmia, E.C.G. changes	Gastric lavage, I.V. barbiturate, artificial respiration, blood and fluids I.V.	"
4	Connelly and Venables	2	"	375	(31)	—	Coma, continuous convulsions, arrhythmia, E.C.G. changes	Paraldehyde	"
5	Alajem <i>et al.</i>	1 6/12	"	375	37.5	—	Coma, convulsions, tachycardia, congestive failure, hypotension, small fixed pupils, ataxia, E.C.G. changes	Gastric lavage, barbiturate I.V. and P.R.	"
6	Garrison and Moffitt	1 10/12	"	500	(42)	—	Excitement, coma, convulsions, fixed dilated pupils, hypotension, arrhythmia, E.C.G. changes	Gastric lavage, I.V. barbiturate, forced diuresis, vasopressor agents, assisted ventilation, lanatoside C	"
7	Fendrick	4 6/12	Amitriptyline	75	4.2	—	Ataxia, alternating drowsiness and excitement, propulsive gait, disorientated	Oral fluids and observation	"
8	Giles	2 9/12	Imipramine	?	?	—	Disorientated, vomited, opisthotonos and bizarre movements	Paraldehyde	"
9	"	1 7/12	"	75	(7)	—	Vomited, drowsy, disorientated	Observation	"
10	"	5	Imipramine, ? Thioridazine	75 ?	(4.2)	—	Dizzy, ataxic, semicomatose, hyper-reactive to stimuli, tachycardia		"
11	"	1 3/12	Imipramine	100	(9.6)	—	Coma, convulsions, fixed dilated pupils, pyrexia, nystagmus, cyanosis, tachycardia, arrhythmia, hypotension	Oxygen, paraldehyde	"
12	"	1 6/12	"	350	(32)	—	Vomited, excitable, coma, convulsions, tachycardia, hypotension, E.C.G. changes	Paraldehyde	Died
13	Mazur	2 6/12	"	?	?	—	Ataxia, coma, convulsions, cyanosis, fixed dilated pupils, tachycardia, hypotension, agitation, urinary retention	Gastric lavage, oxygen, rectal chloral hydrate, barbiturate I.M., vit. C I.V., I.V. fluids, caffeine, analeptics, adrenaline	Recovered
14	Sunshine and Yaffe	1 3/12	Amitriptyline	1,000	(95)	Serum, 250 Liver, 7,800	Coma, convulsions, cyanosis, fixed dilated pupils, tachycardia, pyrexia, hypotension, E.C.G. changes	Gastric lavage, barbiturate I.V. and I.M., assisted ventilation, vasopressor agents, peritoneal dialysis	Died
15	Jacobziner and Raybin	4	Imipramine	1,000	(63)		Coma, convulsions, respiratory distress, ventricular tachycardia	Gastric lavage, oxygen, barbiturate I.V., paraldehyde, procainamide	Recovered

* Figures in parentheses indicate that calculation is based on average weight for age, where actual weight was not recorded.

(Continued on next page)

When discharged from follow-up two months later he was well in all respects, and had resumed normal school activities. He was indeed able to give a full account of having found the tablets, swallowed them all (between 55 and 60), and discarded the empty bottle. His first symptoms had developed some 45 minutes later.

Toxicology

The suggestion of salicylate poisoning in the above case was discounted both on clinical grounds and in view of the fact that side-room testing for plasma salicylate (Brown *et al.*, 1967) yielded negative results. In formally excluding this possibility by spectrophotofluorometric assay of the blood, evidence suggesting the presence of a phenothiazine derivative or a tricyclic antidepressant was found. Concurrently, the appropriate history was obtained. Amitriptyline was then identified and assayed in the gastric aspirate by extraction at alkaline pH with heptane, back extraction into acid, and ultraviolet spectroscopy. While the recovery was only 30 mg., it should be emphasized that, in general, gastric washings represent the most suitable clinical material from which to make positive identification of an ingested drug, since metabolic change is minimal and the actual concentration may be higher than in any other available body fluid, particularly if aspiration has been carried out within a short time of ingestion.

The estimation of plasma amitriptyline by a fluorometric method analogous to that used by McBay and Algeri (1963) for imipramine gave a level of 700 µg./100 ml. for the blood sample drawn five hours after ingestion, when absorption would have

been virtually complete. This represents a level of about 20 times that obtained in adults on therapeutic doses, and considerably exceeds levels found in the fatal cases of Sunshine and Yaffe (Case 14) and Dingell *et al.* (1964) (Case 18). It is unfortunate that such determinations have been made so rarely in these cases, since the peak blood level represents a valuable measure of the degree of overdosage, in addition to providing confirmation of the identity of the drug in question.

Only 13 mg. of amitriptyline was recovered from the urine passed during the first 48 hours after ingestion. Attempts to establish the presence of perphenazine in this specimen or in gastric aspirate or blood were unsuccessful even when the sensitive and specific method of Ragland *et al.* (1965) was used.

Discussion

From the data in the Table some quantitative assessment of the toxicity of imipramine and amitriptyline to children can be made. The severe symptoms described may be precipitated by the ingestion of less than 10 mg./kg. (Cases 11 and 19), and seem inevitable when the dose exceeds 20 mg./kg. In practical terms the latter figure means, for a 2-year-old, 10 standard tablets of either drug, or one bottle of amitriptyline paediatric elixir (usually prescribed for the treatment of functional nocturnal enuresis).

The smallest fatal dose in a child was 32 mg./kg. (Case 12) and the largest amount taken by one who survived was 112 mg./kg. (Case 3). This variation in susceptibility parallels experi-

TABLE—continued

Case No.	Author	Age in Years	Drug(s)	Dose (mg.)	Dose (mg./kg. Body Weight)*	Levels (µg./100 g.)	Symptoms and Signs	Treatment	Outcome
16	Fruthaler and Snyder	?	"	?			Coma, convulsions, pyrexia, respiratory failure, cardiac arrest	Barbiturate, artificial respiration, open cardiac massage	"
17	" "	?	"	?			" "	?	Died
18	Dingell <i>et al.</i>	2 6/12	"	750	53.5	Serum, 110 Liver, 2,300	?	Vomiting induced	"
19	Braun <i>et al.</i>	2 6/12	"	125	8		Coma, convulsions, cyanosis, respiratory depression, dilated pupils, urinary retention, ataxia, restlessness, hypotension, tachycardia, congestive failure, arrhythmia, E.C.G. changes	Oxygen, forced diuresis, barbiturate I.V., chloral hydrate	Recovered
20	" "	1 9/12		300	25		Ataxia, restlessness, coma, convulsions, respiratory depression, dilated pupils, tachycardia, arrhythmia, hypotension, E.C.G. changes	"	"
21	Prout <i>et al.</i>	1 11/12		600	(50)		Coma, convulsions, cyanosis, respiratory depression, fixed dilated pupils, hypotension, arrhythmia, E.C.G. changes	Gastric lavage, paraldehyde, forced diuresis	"
22	Present series	1 11/12	Amitriptyline	150	13.6		Ataxia, drowsy, hyperexcitable when roused, dilated pupils, tachycardia	Gastric lavage, observation	"
23	" "	4	Imipramine	200	(12.6)		Very drowsy, dilated pupils, tachycardia	Vomiting induced, gastric lavage, observation	"
24	" "	1 10/12	Amitriptyline	?	?		Ataxia, drowsiness, tachycardia	Gastric lavage, observation	"
25	" "	2 4/12	Imipramine	100	6.4		Drowsy, tremor, agitation, tachycardia	" " "	"
26	" "	4 8/12	Imipramine Promazine	750 1,500	40 80		Agitation, coma, convulsions, tachycardia, hypothermia, pupils fixed, not dilated	Gastric lavage, I.V. fluids, observation	"
27	" "	2 4/12	Imipramine	100	8	—	Drowsy, tachycardia, nystagmus	Gastric lavage, observation	"
28	" "	1 6/12	Amitriptyline Perphenazine	?	?	—	Nil	" " "	"
29	" "	3	Amitriptyline	80	5.7	—	Drowsy, tachycardia	" " "	"
30	" "	4 3/12	"	80	4.5	—	Drowsy	" " "	"
31	" "	5 4/12	Amitriptyline Perphenazine	1,400 112	82 6.5	Serum, 700	Ataxia, coma, convulsion, fixed dilated pupils, respiratory depression, tachycardia, agitation, urinary retention	Gastric lavage, paraldehyde I.M., I.V. fluids, chlorpromazine I.M.	"
32	" "	2 4/12	Imipramine	100	8.3	Serum, 20	Agitation, tachycardia, thirst, dilated pupils	Gastric lavage, observation	"
33	" "	3 5/12	"	100	6.8	Serum, 10	Tachycardia, thirst, dilated pupils	" " "	"

* Figures in parentheses indicate that calculation is based on average weight for age, where actual weight was not recorded.

ence in adults, death having been recorded after ingestion of only 625 mg. (9 mg./kg) (Edwards, 1966), but survival after as much as 5.5 g. (80 mg./kg.) (Harthorne *et al.*, 1963).

Of the five deaths among these children, one patient (Case 1) who had ingested 192 mg./kg., was moribund within one hour and failed to respond to vigorous resuscitation. One (Case 18) died three days after ingestion, but no further details are recorded, while the timing of death from cardiac arrest in Case 17 is not reported. Cases 12 and 14 are noteworthy in that both had shown progressive clinical improvement, in terms of conscious level and circulatory status, before sudden collapse and death 12 and 60 hours respectively from the time of ingestion of the drug.

Treatment

On the wide variety of measures which have been used in the management of children or adults poisoned by tricyclic antidepressants, only a minority stand out as being both clinically effective and pharmacologically sound.

Active Therapy

Since there is often some delay in confirming the identity of the drug involved, gastric lavage should be carried out as soon as the child reaches hospital; the general recommendations of Matthew *et al.* (1966) in relation to gastric lavage in adults are applicable also to paediatric practice. In Case 31 little over 2% of the estimated ingested dose was recovered from the stomach, but when the procedure is carried out very soon after ingestion recovery of some 15% may be achieved (Rasmussen, 1966). If the accident is detected within minutes, induction of vomiting by the parents or the general practitioner may be a useful measure, provided that transfer of the child to hospital is not thereby delayed.

Both peritoneal and extracorporeal dialysis have proved ineffective in the treatment of this type of poisoning (Sunshine and Yaffe, 1963; Harthorne *et al.*, 1963). Moreover, our own measurements confirm previous indications that renal excretion of the free drug is so low that forced diuresis is not indicated (Hucker and Porter, 1961; Sunshine and Baumler, 1963), though this procedure has been advocated by Prout *et al.* (1965) on the strength of a positive result from a sensitive screening test for the detection of imipramine metabolites in the urine (Forrest *et al.*, 1960). The pharmacological activity of such metabolites is, however, unknown, whereas the *N*-desmethyl derivatives of both imipramine and amitriptyline, which are known to be active, are firmly tissue-bound (Dingell *et al.*, 1964). Beighton and Hardingham (1966) recovered at most 10% of the ingested dose of amitriptyline from the urine of their patient, measurement again being based upon a relatively non-specific test.

Supportive Therapy

Both barbiturates and paraldehyde are effective for controlling convulsions in severe antidepressant poisoning, and the former in particular are recommended by Rasmussen (1965). However, the respiratory depression induced by barbiturates may be potentiated in this situation (Luby and Domino, 1961; Arneson, 1960; Garrison and Moffitt, 1962; Merck, Sharp and Dohme, 1963). This disadvantage does not seem to apply to paraldehyde; for example, the most severely poisoned of the present series (Case 31), who had a respiratory minute volume of 2.2 litres by direct spirometry on admission—that is, 20% below the ideal basal level, on the criteria of Radford (1955)—required no oxygen or assisted ventilation after 5 ml. of intramuscular paraldehyde.

Circulatory collapse is potentially the most dangerous consequence of imipramine or amitriptyline poisoning. Cairncross and Gershon (1962) and Boissier *et al.* (1965) have shown, in animal experiments, that whereas the initial tachycardia is mediated by an atropine-like vagal blockade larger doses of either drug have direct toxic effects upon the myocardium and conducting tissue. This can result in profound hypotension and a variety of bizarre E.C.G. changes, including A-V block, multifocal extrasystoles, and ventricular tachycardia, together with broadening and distortion of the QRS complex. Corresponding E.C.G. patterns in poisoned children have been described and discussed by Giles (1963) and by Braun *et al.* (1965).

The two unconscious patients in the present series (Cases 26 and 31) developed neither severe hypotension nor any arrhythmia, and electrocardiograms were not recorded; however, we may have overlooked prolonged ventricular tachycardia (Jacobziner and Raybin, 1963). E.C.G. monitoring should therefore form part of the management of all severely affected patients.

The findings by Cairncross and Gershon (1962) that these severe manifestations of toxicity can be precipitated by an increase in cardiac work load has three important practical implications: (1) That complete control of convulsions is imperative and that sedation and bed rest should be continued for as long as E.C.G. changes are liable to be detected—that is, for three days or more. (2) That the use of hypertensive agents is to be deprecated. In the presence of a healthy vasculature and parasympathetic blockade, vital organs are unlikely to suffer ischaemic damage until the systolic blood pressure has been well below 80 mm. Hg for several hours (Bloch *et al.*, 1966). (3) That large intravenous infusions are dangerous; this constitutes a further argument against forced diuresis in the treatment of this type of poisoning.

The parasympathomimetic agent pyridostigmine has been shown, both experimentally and clinically, to be of some value in preventing or reversing the cardiotoxic actions of the tricyclic antidepressants (Rasmussen, 1965, 1966), and the same author recommends the use of propranolol for the control of arrhythmias arising in this situation. Cardiac failure in association with ventricular tachycardia was partially relieved by procainamide in Case 15 (Jacobziner and Raybin, 1963), but an analogue, xylocaine, has been shown to have less depressant effect on the myocardium (Harrison *et al.*, 1963) and has become the drug of choice for the suppression of arrhythmias after myocardial infarction (Lown *et al.*, 1967). The adult dose is 25–50 mg. intravenously, followed by continuous intravenous infusion of 1–2 mg./min.

Attempts to stimulate the myocardium with calcium (Somuncuoglu, 1960) or lanatoside C (Garrison and Moffitt, 1962) have not met with demonstrable success, and in the presence of A-V block with ventricular extrasystoles the use of cardiac glycosides would be contraindicated.

The possible influence of the phenothiazines which were alleged to have been taken in combination with imipramine or amitriptyline in Cases 26 and 31 cannot be assessed at present, but the value of phenothiazines in the management of tricyclic antidepressant poisoning warrants further study. There is a complex pharmacological relation between the two classes of compound (Klerman and Cole, 1965), and they have some toxic actions in common (Gordon and McCandless, 1959; Irwin and Burlew, 1959). Chlorpromazine has, however, been used in the management of psychotic behaviour occurring as a side-effect of imipramine therapy in adults (Boardman and Fullerton, 1959) and in the treatment of the syndrome associated with the simultaneous ingestion of imipramine and a monoamine oxidase inhibitor (Saunders, 1965). It proved effective in controlling the agitated behaviour in our patient (Case 31), but no superiority has been demonstrated over the paraldehyde or chloral used by others.

Conclusions

A scheme for the management of the severe case of imipramine or amitriptyline poisoning, as derived from the above discussion, may be summarized as follows:

- (1) Gastric aspiration and lavage should be carried out as soon as the patient reaches hospital.
- (2) Intramuscular paraldehyde should be given as soon as convulsive movements appear.
- (3) The patient should be carefully observed, with E.C.G. monitoring, and nursed in surroundings as free as possible from extraneous stimuli.
- (4) Oxygen and/or assisted ventilation should be provided as indicated by the clinical state and by blood-gas analysis.
- (5) A slow intravenous drip of an isotonic solution, such as dextrose with half-strength Ringer's lactate, should be established.
- (6) If arrhythmias or circulatory failure supervene, xylocaine and pyridostigmine (but not hypertensive agents) should be added to the drip.
- (7) In the event of cardiac arrest there should be no hesitation in applying full resuscitative measures (see Case 16 of Fruthaler and Snyder, 1963).
- (8) While consciousness is being regained, sedation in the form of chlorpromazine, chloral, or paraldehyde should be given.
- (9) Relaxation of strict bed rest should be allowed only after a minimum of three days, provided that the E.C.G. is then normal.

Summary

Attention is drawn to the increasing incidence of poisoning due to the ingestion of imipramine and amitriptyline by young children. Twelve non-fatal cases are reported, and compared with 21 others in the literature, including five deaths.

Mildly affected children exhibit drowsiness—sometimes alternating with excitement—tachycardia, ataxia, and sometimes dilated pupils. In more severe cases convulsions and coma rapidly supervene. Arrhythmias and circulatory failure may occur and can prove fatal. These severe symptoms always appear when the ingested dose exceeds 20 mg./kg., though much smaller doses may suffice.

Early gastric lavage is indicated. Peritoneal or extracorporeal dialysis is ineffective and forced diuresis is contraindicated. Treatment of the severe case is symptomatic. Paraldehyde is preferred to barbiturates in controlling convulsions. Xylocaine and pyridostigmine may have a place in the management of arrhythmias, but hypertensive agents are contraindicated.

Careful observation should include E.C.G. monitoring. Sedation is required during recovery, and bed rest should continue for a minimum of three days.

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