The Management of Imipramine (Tofranil) Intoxication in Children*


SUMMARY

Two cases of near-fatal imipramine intoxication in children have been documented. The cardiovascular complications and ECG changes are described in detail. The efficacy of neostigmine in the treatment of arrhythmias is emphasized. A general scheme of the emergency treatment for this form of poisoning is outlined.


Although several reports of imipramine intoxication have appeared in the literature, there is still no full agreement as to which anti-arrhythmic agent is the drug of choice to be employed in the emergency treatment. It is the purpose of this article to discuss the management of 2 cases of imipramine intoxication, to emphasize the bizarre ECG changes and to demonstrate the possible place for neostigmine and for pyridostigmine in the treatment of supervening arrhythmias.

CASE REPORTS

Patient 1

A 20-month-old White female was admitted to hospital about 5 hours after she had ingested an unknown number of her mother's imipramine (Tofranil) tablets. Nothing unusual had been noted until an hour before admission. She was unable to walk and her movements seemed jerky. Half an hour later she started 'going into spasms'.

On admission she was cyanosed both centrally and peripherally. A slow heartbeat could be heard, but the blood pressure was unrecordable. A nasotracheal tube was passed and she was ventilated with 100% oxygen. Her colour returned to normal, the blood pressure was recorded at 110 mmHg systolic and the pulse rate was 140/minute.

Five minutes later her whole body stiffened and her respiration and pulse slowed. It became necessary to respire her by means of intermittent positive pressure respiration. The heart rate was observed on a cardiac monitor. Intravenous fluid therapy was commenced and sodium bicarbonate was added to the infusion upon discovery of a metabolic acidosis. Despite this, she had 3 episodes during which she became stiff, the heart rate slowed and cardiac arrest occurred. This necessitated external cardiac massage on each occasion.

An electrocardiogram taken one hour after admission showed a rate of 184/minute with bizarre, broadened QRS complexes resembling a ventricular tachycardia (Fig. 1).

The patient was given 50 mg phenytoin (Epanutin) intravenously, but the exact amount administered was not

Fig. 1. Patient 1. ECG taken 1 hour after admission demonstrating bizarre, broadened QRS complexes resembling a ventricular tachycardia.
known because the drip was found to be blocked. Her convulsions were controlled with phenobarbitone 30 mg intramuscularly every 8 hours and phenytoin 50 mg intramuscularly every 12 hours. The ECG still showed a supraventricular tachycardia with considerably widened QRS complexes (0.20 sec) and depressed ST segments. Three hours after admission she began fighting the respirator, so she was weaned off it. The acid-base status and serum potassium level were now normal. Her blood pressure was maintained at 100 mmHg systolic. The ECG remained abnormal and there was no significant change in serial records obtained for one hour after the administration of 0.25 mg neostigmine by intramuscular injection. Subsequent to this there was improvement in the ECG picture. P waves could be identified with a prolonged PR interval. The QRS was prolonged to 0.12 sec at 4½ hours and 0.10 sec at 11 hours.

However her clinical state continued to improve and she became lucid 21 hours after admission. An ECG taken at 48 hours (Fig. 2) showed a sinus tachycardia, a mean frontal plane QRS axis of +60° and almost normal ST segments and T waves.

![ECG recordings from standard leads 1, 2 and 3. Left: Before neostigmine—QRS complexes show prolonged intraventricular conduction and ventricular extrasystoles. Right: After neostigmine—the rhythm has regularized to an atrial tachycardia with a prolonged PR interval and prolonged intraventricular conduction.](image)

Fig. 3. Patient 2. ECG recordings from standard leads 1, 2 and 3. Left: Before neostigmine—QRS complexes show prolonged intraventricular conduction and ventricular extrasystoles. Right: After neostigmine—the rhythm has regularized to an atrial tachycardia with a prolonged PR interval and prolonged intraventricular conduction.

Other investigations which were carried out were as follows: serum bilirubin level normal; total cholesterol 136 mg/100 ml; serum protein electrophoresis total 5.4 g; albumin 2.71 g; alpha-globulin 0.84 g and gamma globulin 0.84 g/100 ml. The SGOT and LDH enzymes were raised during the acute episode (Table I). The urine had a peculiar green colour the day after admission and the presence of imipramine was confirmed on analysis. Urinary output had been adequate throughout her stay. She was discharged well, on the fifth hospital day.

Patient 2

This case was seen 5 months after the first child. A White male, aged 1½ years who weighed 12 kg was admitted to an outlying hospital after ingesting an unknown quantity of two different drugs, one of which was phenytoin. A stomach washout was performed, intravenous fluid therapy initiated and diazepam (Valium) administered because of convulsions. Cardiac monitoring showed a changing ECG pattern varying from ventricular tachycardia to atrial fibrillation and flutter. He was transferred to the Intensive Care Unit at the Transvaal Memorial Hospital for Children the same day.

On admission the patient was semicomatose, responding only to painful stimuli. The pupils were dilated and the peripheral pulses were impalpable. The blood pressure was 40 mmHg systolic and the respirations were slow and shallow. Only occasional heart sounds were audible on auscultation. The ECG recordings obtained from the cardiac monitor showed a supraventricular tachycardia with prolonged intraventricular conduction and ventricular extrasystoles (Fig. 3, left). One of the authors (S.E.L.) noticed the similarity between the ECG recordings in this patient and those of the first patient. He suggested that the other drug ingested must have been imipramine. This was subsequently confirmed.

Neostigmine was immediately administered slowly by intravenous injection. While injecting this compound, the patient became more conscious, the respiration deepened and increased in rate. The blood pressure rose to 70 mmHg systolic and the peripheral pulses became palpable. The heart sounds were then audible—a quadruple changing to a more regular rhythm. An atrial tachycardia with prolonged PR interval was noted on the ECG (Fig. 3, right). A total dose of 1 mg neostigmine had been administered.

The clinical condition of the patient regressed 1 hour later. The cardiac monitor again demonstrated the previous
bizarre patterns. Neostigmine was again administered—in a dose of 0.5 mg—with the same dramatic improvement as noted previously. Three hours later the patient’s condition deteriorated once more and 0.25 mg intravenous neostigmine was required to effect improvement. Pyridostigmine (Mestinon) 1 mg was also administered intramuscularly. A metabolic acidosis (pH—7.26, pCO₂—35 mmHg and std bicarb. 16 mEq/litre) was corrected with sodium bicarbonate (20 mEq) by intravenous injection.

Thereafter the patient’s general condition gradually improved. By the following morning he was fully conscious, though his gait was unsteady. The blood pressure was 90/50 mmHg and the heart rate regular at 120/minute. The ECG had returned to normal (Figs. 4 and 5).

**DISCUSSION**

Severe symptoms of imipramine toxicity inevitably appear if the ingested dose exceeds 20 mg/kg. These comprise coma, convulsions, respiratory depression, cardiac arrhythmias and hypotension. The ECG changes that have been reported include complete or partial atrioventricular block, multifocal extrasystoles, supraventricular tachycardia, atrial flutter, ventricular tachycardia, widened QRS complexes, depressed ST segments and abnormal T waves. Ventricular fibrillation with cardiac arrest may occur and in adults myocardial infarction and heart failure. The most common disturbances have been (a) supraventricular tachycardia; (b) widening of QRS complexes; (c) depression of ST segments; and (d) abnormal T waves. A number of publications have records of ECG tracings identical to those obtained in our patients.

The pharmacological basis of the cardiac changes still appear to be unclear. Cairncross and Gershon showed that the development of the tachycardia was due to an anticholinergic block of vagal endings in the heart. This followed the administration of small doses of the drug. The effect of large doses of imipramine may represent a direct toxic effect of the drug on the myocardium and its conducting tissue, resulting in hypotension and the bizarre ECG changes. Reid et al. have evidence for an intraneuronal site of action of the tricyclic antidepressants. Other workers have suggested that sympatholytic activity may contribute to the hypotension. The dibenzazepine compounds (imipramine and amitriptyline) have also been shown to reduce the uptake of exogenous H⁻norepinephrine by several tissues (heart, spleen and adrenal) and elevate the plasma concentration of catecholamines. The increased levels of circulating catecholamines may result in a shift toward adrenergic dominance, with a consequent serious disturbance in autonomic balance. This could be responsible for the ECG changes, cardiac arrest and death.

There appears to be little dispute in the general and supportive care required in the emergency treatment of imipramine intoxication. These include the following:

1. Gastric aspiration and lavage to be carried out on arrival at the hospital.
2. Convulsions to be controlled by diazepam (or other suitable anticonvulsants, e.g. phenobarbitone, paraldehyde).
3. The patient should be attached to a cardiac monitor to establish the cardiac rhythm by ECG.
4. Oxygen and/or assisted ventilation should be provided, depending on the clinical state of the patient and the results of blood gas analysis.
5. Intravenous fluid therapy should be commenced as soon as possible, e.g. half concentrated Darrow’s solution in 2.5% dextrose. Additional sodium bicarbonate may be required for the correction of a severe metabolic acidosis. The serum potassium level should also be carefully monitored.

6. Ideally, the patient should be transferred to an intensive care unit.

7. Full resuscitative measures may have to be applied in the event of a cardiac arrest.

It should be emphasized that haemodialysis or forced diuresis is of no benefit, as the tricyclic depressants are rapidly absorbed and their active metabolites are firmly protein-bound in the tissues. Plasma levels are only transiently raised. After demethylation and glucuronidation in the liver, imipramine is then excreted in the urine.

Hypotensive agents are contra-indicated, because the plasma concentration of catecholamine has already been elevated by imipramine. Commenting on the use of isoproterenol in one patient, Teitelbaum felt that it would be dangerous for the above reason.

Controversy still exists with regard to the choice of antiarrhythmic agents. Rasmussen and Alexander and Nino have suggested that neostigmine and pyridostigmine are the best drugs, and have experimental evidence in support of this contention. More recently, Young and Galloway recommended the use of lignocaine for the ventricular and neostigmine for the supraventricular arrhythmias. Claims have been made that propranolol might be effective in blocking beta catecholamines. The problem is that both imipramine and propranolol have hypotensive effects and this can result in a severe hypotension. Brown et al. found practolol to be effective in controlling a supraventricular tachycardia in one case without fall in blood pressure. The hypotensive effect of practolol seems to be less than that of propranolol.

In the first patient, an unknown quantity of intravenous phenytoin followed by an intramuscular injection of 0.25 mg neostigmine did not reverse the ECG changes. However, in the second case, the administration of neostigmine intravenously and in greater dosage (1 mg) proved to be rapidly effective. There was immediate improvement in the respiration and ECG recordings with a rise in blood pressure. The duration of action was short, so that repeated administration was required as well as supplementation with intramuscular pyridostigmine.

We feel, as do other workers, that intravenous neostigmine and intramuscular pyridostigmine are the drugs of choice in the most common situation of supraventricular tachycardia, although lignocaine has certainly been found to be effective for the ventricular arrhythmias.

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REFERENCES