The features and management of poisoning with drugs used to treat Parkinson’s disease

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Introduction
Drugs used in the treatment of patients with Parkinson’s disease are occasionally taken in overdose. This review summarizes world-wide experience of poisoning with such drugs, and their features in overdosage, as no clinician will have seen a large number of cases, that the recognition and management of such rare cases may be optimized.

Benzhexol and benztropine
Benzhexol and benztropine are anticholinergic agents used as adjuncts in the treatment of Parkinson’s disease. Toxicity is due to both peripheral and central anticholinergic effects. The peripheral symptoms of overdose include nausea, dizziness, blurred vision, a dry mouth and urinary retention, and signs include hyperpyrexia, dilated pupils, dry mouth and skin, flushed faces, tachycardia and a distended bladder. Central nervous system manifestations include excitement, confusion, restlessness, paranoid ideation and euphoria. Vivid visual hallucinations and a feeling that time is ‘standing still’ are said to be especially prominent symptoms.¹² Tactile hallucinations and actions such as gathering, grasping or plucking imaginary objects from the air have also been described³⁴ as well as auditory hallucinations.⁵⁶ These features are sometimes referred to as the central anticholinergic syndrome, and not surprisingly bring the patient to public attention within a few hours of a large overdose.¹ Acute dystonia has been reported following benzhexol ingestion by a 20-month-old boy⁷ and after an overdose of benztropine and alcohol in an adult.⁶ A 30-year-old man took an overdose of benztropine mesylate and developed an anticholinergic syndrome which lasted nine days. Fluctuating serum benztropine concentrations over that time suggested that his lengthy intoxication may have been secondary to prolonged, intermittent absorption rather than from slow plasma clearance.⁸ One death has been reported due to benzhexol toxicity in a 48-year-old schizophrenic male, however death may have resulted from the underlying bronchopneumonia and empyema.⁹

The management of benzhexol and benztropine overdoses is supportive. Gastric lavage is indicated only if a substantial overdose has been ingested within 1–2 h of presentation. In view of the potent anticholinergic action of the drugs which delay gastric emptying, some toxicologists recommend extension of gastric lavage time up to 4 h. The anticholinergic effects can be reversed by slow intravenous injection of 2 mg physostigmine. However, increased bronchial secretions, bronchospasm and convulsions¹⁰ may be provoked by its use and as the duration of action of physostigmine averages 30 min to 2 h and benztropine and benzhexol have a considerably longer half-life, toxic manifestations may recur. For these reasons the use of physostigmine has been abandoned. Experience has shown that it is better to handle patients with reassurance, rather than drugs; if sedation is needed, diazepam is the drug of choice.

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Orphenadrine

Orphenadrine has been used as a skeletal muscle relaxant, in the treatment of Parkinson’s disease and to overcome the Parkinsonian side-effects of phenothiazines.\(^1\) Up to 1981, 271 cases of orphenadrine overdose (including 37 deaths) were described by Sangster.\(^2\) Both adults and children have died following poisoning.\(^3,4\)

The features of overdose are predominantly anticholinergic. Within 2 h of ingestion of an overdose, coma, mydriasis, loss of pupillary reactivity and tachycardia can develop.\(^5\) Urinary retention and hot dry skin are also anticholinergic features, but occur slightly later. Athetosis and hyperthermia have been described.\(^6\) More serious effects include convulsions, respiratory depression and cardiac arrhythmias, and death may ensue within 12–18 h of ingestion.\(^7,8\) Orphenadrine has a negative inotropic effect on the myocardium and can slow cardiac conduction.\(^9,10\) Arhythmias may be worsened by the presence of hypoxia and have been fatal 12–18 h after ingestion. Hypoglycaemia, prolongation of the prothrombin time, abnormal liver function tests resulting from hepatic necrosis, and disseminated intravascular coagulation have been reported occasionally after overdose. Post-mortem findings have included cerebral and pulmonary oedema.\(^11\)

Management is supportive, but as there can be marked cardiorespiratory depression, assisted ventilation may be required. Gastric lavage is indicated only if a substantial overdose has been ingested within 1–2 h of presentation. The value of activated charcoal, forced diuresis, haemodialysis, peritoneal dialysis or haemoperfusion has not been fully assessed and therefore none of these is recommended.\(^12\)

Apart from its adverse effects, arrhythmias are almost certainly the result of the direct cardiotoxicity of orphenadrine rather than its anticholinergic actions.\(^13\) They should be treated only when causing significant haemodynamic impairment. The role of physostigmine in the management of orphenadrine cardiotoxicity is very controversial. It was used in a 3-year-old boy with ventricular tachycardia which was unresponsive to cardioversion and was successful,\(^14\) but is not routinely recommended because of the adverse effects noted above. External cardiac pacing may be ineffective for treatment of arrhythmias because of the depressant action of orphenadrine on myocardial excitation. Orphenadrine concentrations can be measured using GLC or HPLC,\(^15,16\) but are of no help in management.

Amantadine

Amantadine is dopaminergic and weakly anticholinergic. It is an N-methyl-D-aspartate receptor antag- onist with neuroprotective properties.\(^17\) Ninety per cent of a therapeutic dose is excreted unchanged in the urine and intoxication has been reported in patients as a result of renal insufficiency.\(^18,19\)

The features of overdose are largely cardiovascular and neurological.\(^20\) Doses of 800 mg have been associated with convulsions in adults.\(^21\) An adult who took approximately 2.8 g amantadine developed an acute toxic psychosis with disorientation, visual hallucinations, aggression and urinary retention and dilated pupils.\(^22\) Another patient ingested 1.3 g and developed altered mental status and complex ventricular arrhythmias which responded to intravenous lignocaine.\(^23\)

Management of a patient with toxicity from amantadine is supportive. Gastric lavage is indicated if a potentially life-threatening amount has been ingested within the previous 1–2 h. Benzodiazepine therapy should be used for sedation or control of convulsions. Use of physostigmine reversed amantadine-induced confusion and myoclonus in one patient,\(^24\) but would not normally be expected to be used for the reasons discussed above. The large volume of distribution of amantadine would indicate that haemodialysis is unlikely to increase drug elimination effectively.

Levodopa

L-dopa is converted by dopa decarboxylase to dopamine, an active catecholamine with prominent alpha- and beta-adrenergic effects, and toxicity appears to be a direct effect and also receptor-mediated.\(^25\)

There are few reports of acute overdose in the literature. A 61-year-old man (on 7.5 g levodopa daily) ingested up to 100 g levodopa together with alcohol over a period of 12 h. Initial hypertension was followed by prolonged symptomatic hypoten- sion, sinus tachycardia, mental confusion, agitation, insomnia and anorexia.\(^26\) Nausea, vomiting, dyskinesia, arrhythmias and renal and hepatic damage were not encountered. Improvement began on the second day, but it was 7 days before features finally disappeared. Analyses of serum and urine for dopa and its metabolites confirmed the overdose. One patient died after the ingestion of 11 g levodopa, but there was no definite evidence that levodopa was the cause of death.\(^27\)

Supportive measures should be used, with gastric lavage if the patient presents within 1–2 h of ingestion of a large amount of levodopa. The cardiac rhythm should be monitored. Pyridoxine (vitamin B6) 50 mg tds acts as a co-factor for dopa-decarboxylase, and reverses the neurotoxicity of levodopa by increasing its peripheral decar- boxylation.\(^28\)
Levodopa with benserazide

Dopa decarboxylase, the enzyme responsible for peripheral metabolism of L-dopa, is inhibited by benserazide. No data on overdosage with levodopa/benserazide combinations are available. However, it would be expected that the presence of benserazide would enhance the central toxicity of levodopa, leading to postural hypotension and psychiatric disturbances. The peripheral effects of levodopa, such as nausea, vomiting and cardiac arrhythmias, would be expected to be less than with levodopa alone.

Overdosage of benserazide with levodopa should be managed with supportive measures, as for levodopa alone with the exception that pyridoxine (Vitamin B₆) has no benefit when benserazide has been taken in addition to L-dopa.

Levodopa with carbidopa

Carbidopa is also a dopa decarboxylase inhibitor. There are few reports of overdosage with the combination of L-dopa and carbidopa.

A 57-year-old woman ingested approximately 2.25 g carbidopa and 22.5 g levodopa in a combined formulation along with unknown amounts of ibuprofen, carisoprodol, hydrocodeine, and paracetamol. Choreiform movements developed and persisted despite impairment of consciousness. Paralysis with pancuronium was necessary for their control. Tachycardia was present for 5 days, but the blood pressure was not affected. The management of an acute combined overdose of levodopa with carbidopa is as for levodopa alone with the exception that pyridoxine (Vitamin B₆) has no benefit when carbidopa has been taken in addition to L-dopa.

Bromocriptine

Bromocriptine is a potent dopaminergic agonist. Features of overdose include nausea and vomiting, due to stimulation of the vomiting centre and to a local effect on the gastrointestinal tract. Other symptoms include drowsiness, dizziness, sweating and hallucinations. Tachycardia, pupillary dilatation, tachypnoea and hypotension may occur. The systemic hypotension is probably due to stimulation of peripheral dopamine receptors and pupillary dilatation is presumed to be a sympathomimetic effect.

Adults have taken 225 mg and babies up to 7.5 mg without dangerous effects. None of 18 accidental ingestions in children resulted in a fatality. Bromocriptine is rapidly and completely absorbed, peak blood levels occurring within 2–3 h after oral administration after a therapeutic dose.

Symptomatic management is all that is required. In view of the potent emetic effect of the drug, gastric lavage would not be expected to be useful unless an extremely large number of tablets have been ingested within 1–2 h. An antiemetic may be given if vomiting is recurrent and persistent. Postural hypotension is best treated with bed rest, elevation of the foot of the bed and intravenous fluids if necessary. Inotropic agents would not be expected to be required.

Conclusions

Patients who have taken overdoses of antiparkinsonian agents require meticulous supportive care. Such agents produce toxicity by either dopaminergic or anticholinergic actions or both. It is important to monitor patients for development of complications of poisoning, i.e. arrhythmias, convulsions and a distended bladder. Gastric lavage is indicated if a substantial overdose has been ingested within 1–2 h of presentation. Benzodiazepine agonists should be used to control convulsions or for sedation. Arrhythmias should only be treated if they cause haemodynamic disturbance. The anticholinergic effects can be reversed by physostigmine but bronchial secretions, bronchospasm and convulsions may be promoted and thus its use has been abandoned. The only antidote of any value appears to be vitamin B₆ for L-dopa overdose alone. Such an occurrence is however very rare, as most L-dopa is likely to be prescribed in combination with a dopa-decarboxylase inhibitor.

There is diversity in the toxicity of the various agents described in this review. Most deaths resulted from orphenadrine overdosage, but no large overdose with antiparkinsonian agents can be taken lightly. If in doubt about the management of a particular patient, please telephone your nearest centre of the National Poisons Information Service.

References

6. Humphreys A, Tanner AR. Acute dystonic drug reaction or