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Adverse reactions to acetylcysteine and effects of overdose

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Abstract

Since the introduction in 1979 of intravenous acetylcysteine (Parvolex) as an antidote for overdosage of paracetamol the National Poisons Information Service and the manufacturer have been notified of 38 adverse reactions that were anaphylactoid in nature and 19 accidental overdoses. The most common feature of the anaphylactoid reaction to normal dosage was rash; other features reported included angioedema, hypotension, and bronchospasm; all the patients recovered. The features associated with an overdose of acetylcysteine were similar but more severe; two patients died, but the extent to which the overdose of acetylcysteine may have been implicated was not clear in either case.

Introduction

Intravenous acetylcysteine (Parvolex) is an effective antidote for the treatment of overdosage of paracetamol.[1 2] In the course of surveying the morbidity and mortality of paracetamol overdosage in adults the National Poisons Information Service encountered problems associated with the use of acetylcysteine—namely, adverse reactions and accidental overdosage.

Method

From July 1978 to December 1980 every doctor who consulted the National Poisons Information Service about an overdose of paracetamol in an adult was sent a follow up questionnaire. This was designed primarily to study the efficacy of the available antidotes in preventing damage to the liver but also asked if there were any problems arising from the use of an antidote. From January 1981 to November 1983 the same questionnaire was sent only if the patient had presented to hospital more than eight hours after ingestion of paracetamol as the relative efficacy of the antidotes at this stage was still in question. Additionally, throughout both of these periods the National Poisons Information Service followed up all inquiries concerned directly with adverse reactions to and overdoses of intravenous acetylcysteine. The manufacturer and user of the trademark Parvolex (Duncan Flockhart & Co Ltd) was contacted via the Drug Surveillance Department, Glaxo Group Research Ltd, and the Committee on Safety of Medicines was also approached.

Results

Most adverse reactions reported with acetylcysteine were anaphylactoid; other reactions appeared to be rare. For the purpose of this paper we defined an anaphylactoid reaction as consisting of one or more of the following features: flushing, urticaria, bronchospasm, hypotension, or angioedema occurring during infusion of acetylcysteine.

During the study adequate follow up data were received in answer to 12 of 17 inquiries directly concerned with probable anaphylactoid reactions to acetylcysteine. The National Poisons Information Service also received 127 completed questionnaires concerning overdosage of paracetamol that described adults who had been treated with acetylcysteine. These showed four more cases of anaphylactoid reactions to acetylcysteine, making a total of 16 reactions. Over the same time the manufacturer received 23 notifications of anaphylactoid reactions associated with the use of acetylcysteine in adults in the United Kingdom. Taking into account the overlap of reports, a total of 38 anaphylactoid reactions were reported. In addition, the National Poisons Information Service received reports of 16 overdoses of acetylcysteine. Two were identified from the questionnaires on overdosage of paracetamol and 14 were direct requests for advice after administration of the overdose. The manufacturer was independently notified of seven overdoses in the United Kingdom, making a total of 19 allowing for overlap. Table I shows a breakdown of the incidence each year of anaphylactoid reactions and overdoses reported to the National Poisons Information Service and the manufacturer of Parvolex.

Table II summarises the clinical features of the anaphylactoid reactions occurring with correct doses of acetylcysteine notified to the National Poisons Information Service and the manufacturer. The most common clinical feature was a rash or pruritus (29 cases); in 17 cases this was described as urticarial. Most of the reactions were noted 20 minutes after the start of infusion. A few, however, were not noted until up to one hour after although precise timings were not always

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available. All the reactions subsided quickly after the infusion had been stopped, but in some cases symptomatic drug treatment, such as hydrocortisone, antihistamines, aminophylline, or adrenaline, was also administered. Of five patients who developed bronchospasm, one had a history of asthma and two did not have any previous history of atopy. There was not enough information about the remaining two patients with bronchospasm. Six patients became hypotensive, including one who had bronchospasm. None was given specific pressor treatment, and all recovered.

TABLE I—*Annual incidence of anaphylactoid reactions to and overdoses of acetylcysteine as reported to the National Poisons Information Service (NPIS) and the manufacturers Duncan Flockhart, 1979 to November 1983*

	Anaphylactoid reaction			Overdose		
Year	NPIS	Manufacturer	Total*	NPIS	Manufacturer	Total*
1979	1	2	3			
1980	2	6	8			
1981	2	6	8	1		1
1982	7	5	12	6	3	9
1983	4	4	7	9	4	9
Total	16	23	38	16	7	19

*These take into account the overlap between the two sets of findings.

TABLE II—*Number of patients in whom particular clinical features of anaphylactoid reactions occurred after receiving a normal dose of acetylcysteine. (Most patients exhibited more than one clinical feature)*

Clinical features	Number of patients (n = 38)
Flushing	3
Rash/pruritus	29
Nausea/vomiting	8
Angioedema*	8
Tachycardia	3
Bronchospasm	5
Hypotension	6

*No life threatening laryngeal involvement reported.

Of the 19 cases of overdose, adequate clinical details were obtained for 15. The features (table III) associated with overdose were similar to the anaphylactoid reactions reported after correct dosage but more severe. The size of the overdose varied, but 10 times the recommended dose was most often given (five cases). In 11 of the 15 patients the overdose was given as the initial infusion. In two patients (cases 10 and 12) the initial infusion was given correctly but 10 times the recommended dose was given as the second infusion. In another two patients (cases 4 and 14) the total dose of the drug given was correct but it was administered too quickly; in one (case 4) the second infusion was given over 15 minutes instead of four hours and in the other (case 14) the third infusion was given over two instead of 16 hours.

Six patients developed hypotension after overdosage of acetylcysteine. Of these, two were given positive inotropic agents. One patient (case 5) developed haemolysis four days after overdose. This was successfully treated with blood transfusion. She was later found to be deficient in glucose-6-phosphate dehydrogenase. Three patients (including case 5) developed renal failure. They had high plasma paracetamol concentrations, ranging from 145 mg/l 12 hours after ingestion (case 11) to 318 mg/l four hours after ingestion (case 15). This patient (case 15) also sustained damage to the liver indicated by a transient rise in liver enzyme activities. She made a full recovery.

Two patients died after being given overdoses of acetylcysteine. One (case 11) was a 32 year old woman who was admitted roughly 12 hours after taking an overdose of paracetamol. Her plasma paracetamol concentration on admission was 145 mg/l; this concentration would be expected to be associated with severe hepatic toxicity. An infusion of 10 times the correct dose of acetylcysteine was started and then stopped after she had been given between two and a half and six times the correct starting dose as she developed flushing and hypotension. She was resuscitated but subsequently developed disseminated intravascular coagulation. As a result she bled extensively and was severely hypotensive for about 12 hours. She died 10 days after admission; throughout this time in hospital she had been completely anuric. Postmortem examination showed hepatorenal failure to have been the principal cause of death. The other patient to die (case 13) was found unconscious at home and was admitted to hospital two hours later. An overdose of prochlorperazine and paracetamol was diagnosed. The paracetamol concentration was 230 mg/l (time of ingestion not certain), and she was given 10 times the loading dose of the antidote over the first one and three quarter hours. Eight hours after admission she had a cardiac arrest and died.

Discussion

Intravenous acetylcysteine is widely regarded as a safe antidote. Since its introduction in 1979 there have been 12 adverse reactions recorded in published reports.[3-7] Three of these reactions occurred in Australia.[5,6] The National Poisons Information Service and the manufacturer subsequently collected from the United Kingdom information about 38 cases of anaphylactoid reaction to acetylcysteine; nine of these had previously been reported.[3,4,7] All the patients who experienced reactions after receiving the recommended dose responded promptly to the stopping of infusion and symptomatic drug treatment.

The exact proportion of patients showing an anaphylactoid reaction after receiving intravenous acetylcysteine is not known. Our own figures, from completed questionnaires about overdoses of paracetamol, showed four reactions in 127 courses of the antidote, implying an incidence of 3%. This figure is not,

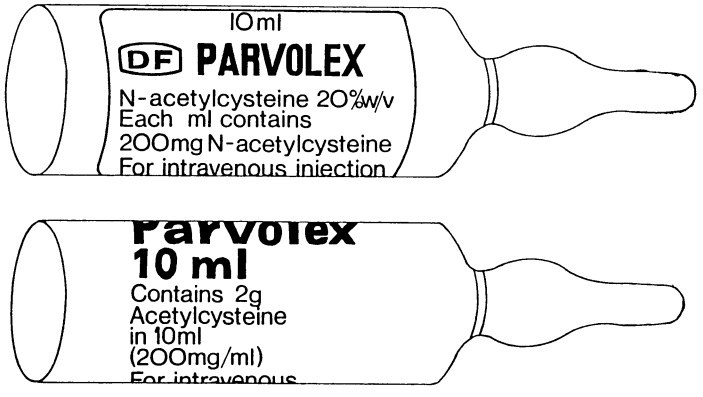
TABLE III—*Details of 15 patients who accidentally received overdoses of acetylcysteine*

Case No	Size of overdose	Clinical features												Other drugs taken
		Flushing	Rash	Nausea/vomiting	Oedema	Tachycardia	Bronchospasm	Hypotension	Respiratory depression	Haemolysis	Disseminated intravascular coagulation	Renal failure	Death	
1	×3	+							+					
2	×6			+			+	+						
3	×6													
4	×1·5		+		+	+		+						
5	×6		+		+	+		+		+		+		Temazepam
6	×2													
7	×10	+												
8	×10			+										
9	×2			+				+						
10	×10			+										
11	×2-6·5	+						+			+	+	+	
12	×10		+											
13	×10						+	+					+	Prochlorperazine
14	×8													
15	×2·5											+		
Total		3	3	4	2	2	2	6	1	1	1	3	2	

however, taken from a random sample of patients given acetylcysteine as the National Poisons Information Service is usually contacted about problem cases and questionnaires were not always returned. Also the National Poisons Information Service generally recommends oral methionine for patients with uncomplicated overdosage of paracetamol who present within 12 hours after ingestion. A calculation on the basis of sales figures for Parvolex in the United Kingdom, however, gives an estimated incidence of about one in 500 courses of treatment (0·2%). As all anaphylactoid reactions are unlikely to have been reported the actual incidence is probably somewhere between these two extremes.

The National Poisons Information Service and the manufacturers have now collected 19 reports of overdoses of acetylcysteine. One of these cases has been mentioned briefly before.[8 9] The reactions were similar in pattern to those occurring after the correct dose of acetylcysteine but tended to be more severe. In two patients given 10 times the intended initial dose over 15 minutes there was no reaction at all.

Most cases of overdose appear to have occurred as a result of misreading the label on the ampoule. The figure (top) shows the earlier labelling of the 10 ml ampoule, which used conventional ways of expressing the concentration. The commonest error was



Old (top) and new (bottom) labelling of ampoules, showing change to clearer indication of total content of acetylcysteine.

to assume that the ampoule contained 200 mg in total and not 200 mg/ml. Consequently, a person of average body weight would receive 30 to 40 ampoules in the initial infusion rather than three or four. The regimen itself, although relatively complicated and requiring three different rates of infusion, tended to be calculated correctly. The manufacturer has since changed the labelling of the ampoule so that it now expresses the concentration in two quite different ways (figure (bottom)). Existing stocks of ampoules with the old labelling are still held by some hospital pharmacies, but stickers expressing the total dosage per ampoule have been applied to the cartons and ampoules. The data sheet, pack leaflet, pocket guide, and wall chart produced by Duncan Flockhart have also been correspondingly revised. The data sheet has also been amended to include a caution about the use of acetylcysteine in asthmatic patients and has noted the time to onset of anaphylactoid reactions.

Two deaths occurred after overdosage of acetylcysteine, but in neither case was the extent to which acetylcysteine was implicated clear. Disseminated intravascular coagulation, hepatorenal failure,[10 11] and renal failure in the absence of significant hepatic damage[12 13] are all recognised complications of severe paracetamol overdose. Overdosage of prochlorperazine (case 13) rarely results in death. The National Poisons Information Service has no fatal cases on record that could unequivocably be ascribed to overdose of prochlorperazine alone. We have also failed to find any published reports of fatal cases.

Whether the reactions occurring with acetylcysteine both at the correct dose and in overdose are related to an allergic response or a direct effect cannot currently be confirmed. The urticarial nature of the rashes and the bronchospasm, however, implies histamine release. Such anaphylactoid or pseudoallergic reactions have often been reported after intravenous administration of other drugs, particularly muscle relaxants. In most cases no immunological basis for such reactions has been shown.[14]

The National Poisons Information Service suggests that oral methionine should be the treatment of choice in overdosage of paracetamol in those who present within 12 hours after ingestion. We have received no reports of adverse reactions other than vomiting after administration of methionine, and the incidence of that is low.[15] If an anaphylactoid reaction occurs after infusion of acetylcysteine methionine can, apparently, be substituted safely. The National Poisons Information Service regards intravenous acetylcysteine as the treatment of choice only if: (1) the patient has been given activated charcoal by mouth; (2) the patient is vomiting before or after receiving methionine; or (3) the patient is unconscious. A course of acetylcysteine typically costs around £29, whereas a course of methionine costs 62p.

The reactions associated with acetylcysteine after correct dosage usually consist of skin manifestations alone and occasionally bronchospasm and hypotension. We suspect they are anaphylactoid in nature. These reactions usually occur between 20 minutes and one hour after the start of the infusion and are easily controlled by stopping the infusion and symptomatic treatment. The reactions associated with accidental overdose are similar but more serious. We hope that further cases of overdose will be avoided by publicity of the problem and the change in the labelling of the ampoule and in product information.

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ADDENDUM—Since this paper was written the National Poisons Information Service has been consulted about three further cases of accidental overdosage of acetylcysteine. Full details are not yet available, but two of the patients received 10 times the correct initial dose. They both developed hypotension and disseminated intravascular coagulation and one developed renal failure, adult respiratory distress syndrome, and gastrointestinal haemorrhage but no renal damage. The third received three times the correct initial dose and her clinical features included facial oedema, bronchospasm, hypotension, disseminated intravascular coagulation, and renal failure. All three patients recovered completely.

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