ACUTE ACETONE POISONING DUE TO A SYNTHETIC PLASTER CAST

WITH A DISCUSSION OF ACETONE METABOLISM

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Poisoning with acetone appears to be extremely rare. In spite of the extensive use of this substance in industry hardly any cases of poisoning, presenting with more than slight drowsiness and nausea, were described before 1944. Since then there have been 8 recorded cases,[2,5-9,15,17,20] each one associated with the application of a synthetic plaster substitute consisting of glass and textile bandages, set by means of a fluid composed chiefly of acetone.

The clinical presentation of these cases has always followed a similar pattern, and the present case again shows all the leading features of acetone poisoning from this source.

CASE REPORT

An Indian boy, aged 7, was admitted to King Edward VIII Hospital on 9 February 1960 with a week's history of pain in his right thigh. He was found to be suffering from osteomyelitis, and the femur was drilled and pus evacuated. Culture revealed the presence of *Staphylococcus aureus*. In spite of treatment with penicillin and streptomycin the patient developed meningitis 3 days later, which responded rapidly to oxytetracycline and sulphonamides systemically, and penicillin intrathecally. After 1 week all signs had disappeared and the cerebrospinal fluid was normal.

His fever remained high, however, and on 26 February he developed the typical signs of purulent pericarditis. Treatment was changed to erythromycin in large doses, but he remained desperately ill for over 2 weeks, recovering shortly after the administration of kanamycin. Fever still persisted and he was found to have a purulent effusion in the right knee. This was aspirated and a plaster of Paris hip spica was applied, kanamycin and tetracycline being continued meanwhile. The fever then subsided slowly, the pulse rate ranged from 80 - 100 per minute and the boy appeared well and happy. On 16 May the haemoglobin was 14·3 g. per 100 ml., and the basal sedimentation rate 40 mm. per hour (Wintrobe). There were no abnormal findings in the urine.

The plaster had become badly soiled and a hip spica of a commercial preparation consisting of material lighter than plaster of Paris, together with pure acetone (solvent-evaporating agent) was applied over stockinette at 2.30 p.m. that day. An electric fan was blown over the cast for 45 minutes to ensure adequate ventilation and evaporation. As the weather was cold the patient curled up with his head under the blankets.

After 6 hours the nurses noticed that he was quiet and withdrawn, but he seemed to go to sleep normally.

After 18 hours he was still very drowsy, restless and fretful, sweating profusely and complaining of abdominal pain. He then began to vomit repeatedly with altered blood in the vomitus. The pulse rate was 160 per minute.

After 22 hours he was found to be drowsy and irritable but able to answer questions intelligently. He complained bitterly of thirst and greedily sipped water, even though drinking repeatedly caused further vomiting of coffee-ground material. The pulse was regular, rate 160 per minute, and of good volume. The temperature was normal. The patient was tender in the epigastrium and suprapubically. Breathing was deep and sighing, but irregular in rate. There was a smell of acetone in his breath, much more pronounced than we have ever noticed in any patient in diabetic coma. The tongue was dry and furred, but he did not otherwise appear dehydrated. There was no neck stiffness, but the movements of his hands seemed clumsy and badly coordinated. There was marked nystagmus. The pupils were normal in size, but reacted poorly when illuminated from the left, briskly when the light came from the right. Perimetry could not be carried out.

Lumbar puncture revealed a normal fluid except for a sugar content of 114 mg. per 100 ml. The urine gave a green reaction with Benedict's solution and contained much acetone. Serum electrolytes were as follows (in milli-equivalents per litre): alkali reserve 23·1, sodium 133, potassium 4·9, and chlorides 89. The blood sugar (after 20 hours' fasting) was 170 mg. per 100 ml.

It was decided to leave the cast undisturbed and to administer nothing but water by mouth.

After 28 hours the patient was vomiting less frequently and there was no more blood in the vomitus. Drowsiness, irritability and thirst continued, the pulse rate was still 150 per minute, and the temperature 100°F. His breath still reeked of acetone.

During the period 40 - 52 hours after application of the cast, the boy gradually became less drowsy. There was no

TABLE I. URINARY FINDINGS THROUGHOUT THE EPISODE OF ACUTE ACETONE POISONING

Time and date	*pH*	*Albumin*	*Sugar*	*Rothera test*	*Gerhardt test*	*Deposit*
17 May:						
1 p.m.		trace	+	− + −		triple phosphate, urate
6 p.m.	5·5	trace	nil	− + +		
8 p.m.	7	nil	nil	− + +		
10 p.m.	6	nil	nil	− + +		
18 May:						
6 a.m.	6·5	nil	nil	+ + +	pos.	
12 noon	6·5	trace	nil	+ + −		
2 p.m.	5·5	nil	nil	+ + −	pos.	epithelial cells
6 p.m.		nil	nil	+ + +		
10 p.m.		trace	nil	trace (??)		
19 May:						
6 a.m.	4	+	nil	− + −		epithelial cells
10 a.m.	6	nil	nil	+ + +	pos.	epithelial cells
12 noon		nil	nil	+ + +	pos.	
2 p.m.	6	nil	nil	+ + +	pos.	
6 p.m.	5·5	nil	nil	+ +	neg.	
10 p.m.	5·5	nil	nil	+ +	neg.	
20 May:						
6 a.m.	6	nil	nil	trace		

pos. = positive, neg. = negative.

TABLE II. COMPARISON OF PRESENT CASE WITH OTHER REPORTED CASES

	Cases								
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
Author	Strong[20]	Chatterton[5]	Pomerantz[15]	B.M.J.[2]	Cossman[6]	Harris[8]	Renshaw[17]	Fitzpatrick[7]	Present case
Age (yrs.); Sex	42; M	10; F	32; F	3; M	12; M	10; M	1½; F	21; F	7; M
Blower used	Yes	Yes	No—ambulant	No	No	No	No	No	Yes
Onset (hours)	10	10	12	1	?	9	12	? 1	? 6
Vomiting	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes
Haematemesis	Yes	Yes	No	No		Yes	Yes		Yes
Abdominal pain	Yes					Tightness			Yes
Bladder pain	Yes								Yes
Thirst						++			++
Respiration	Kussmaul	Kussmaul		Shallow	Deep, slow	Rapid, irregular, later apnoea	Slow, quiet		Deep, sighing
Hiccoughs	Yes					Yes			
Acetone in breath	++++	++++	++++	++++	++++	++++	++++		++++
Pulse (per min.)	100 - 120 irreg.	120	120	Rapid	Rapid, feeble	132	120		160
Blood pressure (mm. Hg)	130/90	Normal				80/60	90/65		
Pallor			Yes			Yes			
Drowsiness	+	+	+	+	+	+	+	+	+
Eyes					Mydriasis		Meiosis. Hippus		Nystagmus. ? Hemianopia
Tendon jerks						Brisk	Absent		Brisk
Dysarthria	Yes					Yes			
Urine: acetone	++++	++++	++++	++++	++++	++++	++++		++++
sugar	++	+++	+++			+	+		+
diacetic acid						++			++
albumin	+++	Trace	Nil				Nil		Trace
Dysuria	Yes		Yes						Yes
Blood sugar	306 mg.								170 mg.
Allergy	Wheals	Nil				Nil			Nil
Treated with glucose	Yes	Yes	Yes	No	No	Yes	No	Yes	No
Treated with insulin	Yes	No	No	No	No	No	No	No	No
End of episode (days)	5	3	1½	? 2		4	1	? 1	3½

B.M.J.=*British Medical Journal.*

more vomiting. The pulse rate slowly subsided from 140 to 100 per minute, and nystagmus disappeared, but the pupillary signs remained.

After 66 hours the patient was alert and cheerful. Acetone was still present in his breath, but less noticeably so. There were no abnormal physical signs. Serum cholesterol was 210 mg. per 100 ml., blood sugar 112 mg. per 100 ml. and serum lipids 710 mg. per 100 ml.

After 90 hours acetone was barely perceptible in the breath, the pulse rate was 90 per minute, haemoglobin 12·8 g. per 100 ml., and the sedimentation rate 36 mm. per hour (Wintrobe).

The urinary findings during the whole episode are shown in Table I.

A glucose-tolerance test was performed 13 days after application of the cast. As the patient tended to vomit any glucose given orally, 25 g. were given intravenously and blood sugar was estimated before and at half-hourly intervals after injection. The results (in mg. per 100 ml.) were: 49, 225, 105, 49, 31, and 40. Sugar was found in the urine after 1 hour.

The test was repeated 2 months later, this time injecting only 12·5 g. glucose. The results then were (in mg. per 100 ml.): 84, 184, 115, 76, 84, and 100. Sugar again appeared in the urine after 1 hour.

COMPARISON WITH OTHER CASES

Table II compares our main findings with those in previously reported cases. It will be seen that cases 4 and 8 came on rapidly, but in these the narcotic features alone were present. In the others drowsiness came on after varying periods of time.

Vomiting, however, began fairly regularly after 10 - 12 hours. It was present in 7 of these cases and blood was reported in the vomitus of 5 of them. Acetone was found in the vomitus in case 7. In case 1 the evacuated gastric contents caused burns on the lips and cheeks. The presence of a gastric tube appeared to aggravate the mucosal irritation, leading to increased haemorrhage and mucosal sloughing.

Pain. Case 6 complained of tightness of the epigastrium, while in case 9 (the present case) pain over the stomach and bladder were marked features. In case 9, as well as in cases 1 and 3, dysuria was noticed.

Thirst was extremely marked in cases 6 and 9, quite out of proportion to any mild dehydration that may have been present.

Respiration was deep, slow and sighing in 5 cases, usually described as 'Kussmaul' or 'acidotic' in type. In case 2 it became very shallow. Case 6 breathed rapidly and irregularly at first, but later became apnoeic. Hiccoughs were also observed in cases 1 and 6.

Cardiovascular effects. Tachycardia was present in all cases. It was most marked in case 9 and the preceding pericarditis may have been a factor in this. The blood pressure remained unaltered in 7 cases, but in 2 there was peripheral vascular collapse. In 2 cases pallor was specially commented on, suggesting peripheral vascular constriction.

Effects on central nervous system. Drowsiness was the first symptom in each case. This led in some instances to an irritable torpor with unimpaired intelligence, in others to deep sleep or coma. Pupil size was variable as were the tendon reflexes. Dysarthria was common and incoordination was seen in case 9. Focal signs were few: hippus and independent eye movements in case 7, nystagmus and a doubtful hemianopia in case 9. In case 9 meningitis had been present 2 months previously, but these signs had not been noticed before the episode of poisoning and disappeared rapidly afterwards.

Urinary effects. Rothera's test invariably showed a very strong reaction outlasting all clinical signs. In the 2 cases where it was tested for there was also a positive reaction with Gerhardt's reagent on some occasions. Neither of these patients had been taking salicylates or any other drugs known to produce a positive reaction. Albuminuria was present at some stage in 3 cases, particularly in case 1 where it was reported as +++. Formed elements in the urine were inconspicuous. Sugar was found whenever the blood sugar was above threshold level. Dysuria and pain over the bladder occurred in cases 1, 3 and 9.

Glucose-tolerance tests were unfortunately not performed during the acute episode; after recovery in cases 1 and 9, they ruled out the possibility of diabetes in these patients, as did the normal fasting blood sugar in case 3. We can offer no explanation for the hypoglycaemic levels in the first glucose-tolerance test in case 9.

DISCUSSION

Absorption

The question whether acetone is absorbed through the skin or the lungs in these cases has repeatedly been discussed. In cases 1, 2 and 9 (the present case) an airblower was used continuously to dissipate the fumes, while case 3 walked about the streets for hours after application of the cast. In those cases it seems unlikely that the concentration of acetone vapour was sufficient for undue respiratory absorption to have occurred and direct absorption through the skin must be held responsible. The only experimental work on this aspect appears to have been done by Caesaro and Pinerolo[4] who claimed that acetone was not absorbed through intact skin. However, contact in their experiments was far less prolonged than in our clinical cases.

On the other hand case 6 had stayed in a heavily laden atmosphere for a considerable time and cases 6 and 9 had kept their heads under the bedclothes, thus gaining ample opportunity for the inhalation of acetone vapour. In case 7 the synthetic cast was applied over an existing plaster, so that there was no direct contact with the skin at all. In cases 6 and 9, therefore, acetone may have, and in case 7 must have, entered through the lungs. Browning[3] quotes Sack describing a case of acetone poisoning in a workman cleaning a large tank which had contained the substance. Here again, inhalation seems the only possible method of entry.

It would seem to us that acetone may, therefore, enter the body through either lungs or skin, or both.

Fate of Absorbed Acetone

Koehler *et al.*[5] injected 10 g. of acetone intravenously into human volunteers. They observed drowsiness as the only constant toxic effect and did not detect any increase in β-hydroxybutyric acid or glucose in the blood. The blood level of acetone remained practically constant for the first 4 hours. From this one might conclude that acetone is not metabolized to any appreciable extent.

On the other hand Price and Rittenberg[1,6] have shown that in rats the proportion of acetone excreted in the breath and the urine rises with an increase in the administered dose, suggesting that a small amount is removed by some other pathway and only the remainder is excreted. Work-

ing with C^{14}-labelled acetone they later showed that some, at least, of this removal is by way of oxidation to carbon dioxide.

Mourkides *et al.*,[13] also working with rats, confirmed this work and found that this oxidative removal accounted for part only of the metabolized acetone, the proportion falling with increasing dosage. Hence there must be still other pathways for the removal of acetone.

Some of these pathways have been elucidated. Borek and Rittenberg[3] showed that rats can carboxylate acetone to aceto-acetic acid and Plaut and Lardy,[14] working with liver slices, found that a much larger proportion of acetone is metabolized this way if the tricarboxylic-acid cycle is inhibited with malonate. The finding of a positive Gerhardt test in our cases 6 and 9 is fully in keeping with this and proves the importance of this pathway in man.

Sakami and Lafaye,[19] and after them Rudney,[18] again working with rats, proved the conversion of acetone partly to formate and partly to a 3-carbon compound, probably propane diol, which is known to be capable of entering the tricarboxylic-acid cycle, being metabolized to hexose and perhaps pentose as well. Again our finding of a raised blood-sugar level in cases 1 and 9 seems to support the occurrence of this mechanism in man.

Borek and Rittenberg[3] suggested that a further metabolic pathway of acetone was to cholesterol and other lipids. Kronfeld *et al.*,[20] on the other hand, found that in ketotic cows lipogenesis was inhibited. The finding of normal cholesterol and lipid levels in our case 9 does not provide any evidence for the existence of this pathway in man.

The demonstration of acetone in the vomitus of case 5 shows that after the absorption of large quantities some of the ketone is excreted by the gastric mucosa.

Fig. 1 represents schematically these various methods of disposal of acetone.

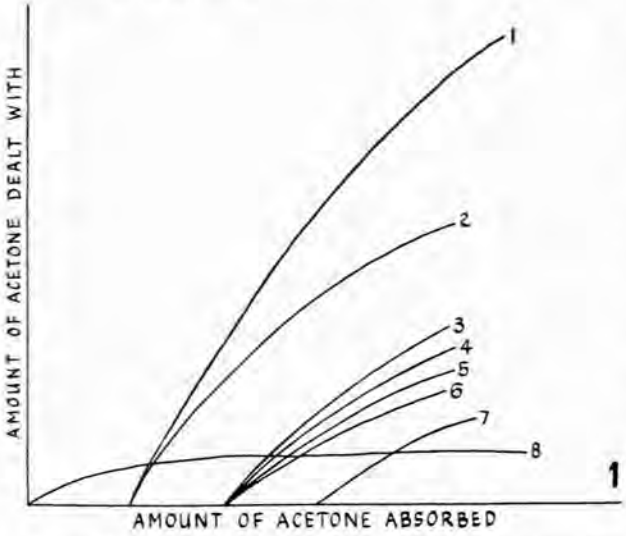

Fig. 1. Schematic representation of different pathways concerned with the removal of absorbed acetone: (1) excreted in breath, (2) excreted in urine, (3) metabolized to aceto-acetate, (4) metabolized to saccharides, (5) ?metabolized to lipids, (6) ?metabolized to other substances, (7) excreted in gastric mucosa, and (8) oxidized to CO_2.

Toxic Effects

Gastro-intestinal. Lewin[12] showed that acetone poisoning in rats produces hyperaemia of the mucous membranes of stomach and intestine. This fits in well with the frequent occurrence in the present cases of vomiting, haematemesis and occasional abdominal pain. The marked sloughing of the oesophageal mucosa in case 1 following upon the use of a rubber tube is also in keeping with this.

Thirst. The extreme thirst in cases 6 and 9, out of proportion to any dehydration present, suggests a direct effect on the thirst mechanism. It is not likely that the dryness of the mouth due to the deep respiration was the cause, for we have not found any comparable complaint in pneumonia.

Respiratory system. Landgren *et al.*[11] demonstrated a stimulating effect of acetone on the carotid body and sinus in cats, which they attributed to an anticholinesterase effect of the ketones. The present series of 9 cases suggests that in man an early stimulating effect is succeeded by a later inhibitory one. In case 6, in particular, rapid irregular respiration was later succeeded by slow, deep respiration, which gradually became shallower and eventually ended in complete apnoea. The fact that the deep, sighing respiration, usually described as 'Kussmaul' in type, is not due to acidosis is proved by the normal alkali-reserve levels in cases 1 and 9. It may be that the deep and rapid respiration is due to carotid sinus stimulation, the later shallow respiration being due to interference with the medullary respiratory centre. Irritation of the respiratory epithelium does not seem to be a feature of acetone intoxication.

Cardiovascular system. The carotid-sinus effect of Landgren *et al.*[11] may similarly be invoked to explain the marked tachycardia which was a leading sign in all cases. The fall in blood pressure and the pallor, suggesting peripheral vascular constriction, may also be attributed to such a mechanism. Here again, however, these signs are perhaps more likely to be due to a direct effect of acetone (or its metabolites) on the medullary vasomotor centres. It is interesting to note that the 2 cases (6 and 7), in which the blood pressure fell, also showed the shallow rather than the deep type of respiration.

Urinary system. The occurrence of dysuria in 3 cases is most easily explained as an irritative effect of the ketones on the bladder wall. Whether albuminuria should be attributed to the same cause is a moot point. It might equally well be due to kidney damage. Previous investigators have differed greatly in their views on the occurrence of renal damage in acetone poisoning.[8]

Central nervous system. The effects of acetone on the nervous system appear to resemble those of alcohol closely. Drowsiness is followed by an irritable torpor and later coma. Incoordination and dysarthria are common. Pupillary signs, tendon jerks and other focal manifestations appear to be variable.

Relation to Diabetic Coma

From the foregoing it will be apparent how closely acetone poisoning can mimic diabetic coma. Drowsiness, variable nervous signs, thirst, ketones in breath and urine, raised urinary- and blood-sugar levels are common in both. Abdominal pain and peripheral vascular collapse may also

be a feature of either. Small wonder that several of the 9 cases under review were at one stage diagnosed as suffering from diabetic coma.

It is tempting to doubt whether the resemblance is a purely fortuitous one or whether these signs and symptoms, as they occur in diabetic coma, may not be, in part at least, due to endogenously formed acetone. Is diabetic coma in fact acute acetone poisoning?

Sensitivity

The question of hypersensitivity to acetone has been raised. This finds slight support in the discovery of wheals under the synthetic cast in case 1. No such marks were found in cases 2, 6 and 9 and patch tests in cases 7 and 9 were negative.

Treatment

We can see no theoretical reason why treatment with glucose should be effective in pure acetone poisoning. It was applied in 5 cases, presumably on the analogy of diabetic coma, but these patients fared no better than the 4 treated without it. In fact, case 1, which was treated intensively with both glucose and insulin, had the stormiest passage of all and took longest to recover. Koehler *et al.*[9] could not demonstrate any effect of glucose or insulin on the removal of acetone.

In our opinion the synthetic plaster should be removed to minimize skin absorption and plentiful fluids should be administered to ensure a good urinary output. A stomach tube should not be used for this purpose. Apart from this, symptoms should be treated as they arise.

Final Comment

This report is not intended to condemn, in any way, the use of synthetic light-weight casts, since the complication of acetone poisoning appears to be very rare. It should, however, make the medical attendant aware of the possibility of this complication and obviate the troubles resulting from a diagnosis of diabetic coma which is so easily made in these cases.

SUMMARY

A case of acetone poisoning due to the application of a synthetic plaster substitute is described.

The clinical and biochemical findings are compared with those in previously reported cases.

The metabolism and pharmacological action of acetone are discussed.

Absorption can occur through either skin or lungs. Excess acetone is either excreted in breath and urine or metabolized by several different pathways. The amount of acetone present determines the relative importance of these mechanisms. Some of the major end-products of metabolism are carbon dioxide, aceto-acetic acid, saccharides and possibly lipids.

The major toxic effects are drowsiness going on to coma, vomiting, haematemesis, thirst, and cardio-respiratory irregularities.

The close resemblance of acetone poisoning to diabetic coma is pointed out.

Symptomatic treatment alone is advised.

There is little evidence of a hypersensitivity reaction in acetone poisoning.

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