

# Metabolic consequences of drug misuse

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*Br J Anaesth* 2000; **85**: 136–42

**Keywords:** metabolism; drug misuse

Metabolic consequences of drug misuse are uncommon, but are increasing as illicit drug use becomes more widespread. Although the range of medical problems produced is very wide, metabolic problems most commonly occur with heroin, cocaine and the ecstasy group of drugs, which are therefore the main theme of this review.

## Diamorphine (heroin)

Apart from cannabis, diamorphine is the most widely used illicit substance in Britain. Its respiratory depressant effects are well known, and the slowing of respiration caused by the drug can lead to an acute respiratory acidosis. Following an overdose, the patient may be cyanosed, comatose, miotic and bradycardic. Respiratory support may be needed urgently; reversal with naloxone is usually effective. The risk–benefit balance lies strongly in favour of naloxone administration, which has a diagnostic role as well as a useful therapeutic effect. There is a risk of precipitating agitation as a result of opioid withdrawal in an opioid-dependent individual, but this should not prevent its urgent administration. Adverse effects of naloxone are unusual. One publication has reviewed 453 cases in which naloxone was administered to heroin-dependent patients, and found a low incidence of complications (1.3%). These included immediate violence, pulmonary oedema, convulsions and asystole.<sup>32</sup> Anaphylactoid reactions can occur with some opioids, particularly codeine, and anaphylaxis may also occur as a result of contaminants in illicit heroin. One report has suggested that many heroin fatalities are caused by an anaphylactoid reaction, so that a significant number of deaths in heroin users may result from this cause.<sup>12</sup> One of the most serious consequences of non-fatal heroin overdose is the development of rhabdomyolysis, which may lead to renal failure. Alcohol, as well as being perhaps the most important precipitant of non-traumatic rhabdomyolysis, is also a cofactor in many cases of heroin-induced rhabdomyolysis.<sup>8 14</sup>

Other opioids, such as codeine and methadone, are implicated less commonly.<sup>18 35</sup> In general, rhabdomyolysis is a result of the heavy sedation produced as the patient lies

comatose and motionless for a number of hours after an overdose of diamorphine. In most cases, lack of muscle tone and immobility appear to be sufficient to lead to rhabdomyolysis as a result of direct compression of skeletal muscle tissue. This mechanism is aggravated by hypoxaemia, acidosis, hypovolaemia and hypothermia, which often coexist in the deeply unconscious patient. However, it is also possible that a direct toxic effect is responsible, as rhabdomyolysis associated with heroin abuse has been linked to myocardial cell damage.<sup>41</sup> Cardiac damage and non-Q-wave myocardial infarction may also be caused by myocardial hypoperfusion.<sup>29</sup>

Rhabdomyolysis has also been reported in patients who have not experienced periods of unconsciousness.<sup>14</sup> In some cases, the damage may be severe enough to lead to renal failure requiring haemodialysis. Rarely, heroin-induced rhabdomyolysis can be complicated by other consequences of coma and pressure, leading to prolonged and incomplete recovery, as case reports have shown: myelitis, neuropathies and compartment syndromes can complicate the picture.<sup>7 26</sup> Compartment syndromes are not uncommon. Intracompartmental pressures should be measured when necessary, and fasciotomy may need to be performed.<sup>24</sup>

Once suspected, the diagnosis of heroin-induced rhabdomyolysis is usually straightforward. Occasionally there may be no symptoms in the conscious patient and, in a significant number of cases, there are no signs over the muscles indicating that damage has occurred.<sup>14</sup> Ultrasound may be helpful in confirming the diagnosis and location of the lesion by revealing hyperechoic areas within the muscles.<sup>43</sup> More commonly, muscle swelling and tenderness occur. If there is any significant degree of rhabdomyolysis, plasma aspartate transferase, alanine transferase, creatine kinase and lactate dehydrogenase concentrations increase markedly. The most serious biochemical complications are hyperkalaemia and hypocalcaemia.<sup>45</sup> Even at an early stage, large amounts of haem and myoglobin may be found in urine. Increasing plasma urea and creatinine concentrations indicate the onset of renal failure. Management consists of fluid replacement and early estab-

lishment of adequate urine flow. Hyperkalaemia needs to be managed attentively, but excessive amounts of calcium should not be given during the hypocalcaemic phase in order to prevent later exacerbation of hypercalcaemia. If acute renal failure occurs, it should be managed conventionally.

### Opioid withdrawal syndrome

After a few weeks of regular use, sudden withdrawal of diamorphine produces an influenza-like syndrome which begins 8–24 h after the last dose, reaches a peak by 36–72 h and resolves within 7–10 days. Symptoms include hypersecretion, sleeplessness, muscle aches, tremor, anxiety, nausea, vomiting, diarrhoea and abdominal cramps. Apart from reintroduction of an opioid, these symptoms respond to administration of drugs such as clonidine or lofexidine. However, in acute medical situations there may be a variety of reasons why an opioid drug should not be reintroduced. It is important for medical staff to be aware that opioid withdrawal can also be dealt with symptomatically, by administration of drugs such as diazepam or thioridazine for anxiety and agitation, beta blockade for tachycardia and hypertension, and loperamide for diarrhoea.

### Heroin leucoencephalopathy

While most of the complications of heroin use tend to result from direct toxicity following intravenous use, a rare but dramatic complication occurs only after inhalation of heroin vapour ('chasing the dragon'): heroin is placed on aluminium foil, which is heated from beneath, and the resulting vapour is inhaled through a tube. A series of 47 patients was reported from the Netherlands in 1982,<sup>49</sup> 11 of whom died. Epidemiological studies showed that all had been using heroin in this way. All developed a severe illness, usually some days or even longer after the last heroin consumption, characterized by a cerebellar syndrome. Many had rigidity and hyperthermia. The pathological diagnosis was spongiform demyelination; the only other consistent abnormality was brown pigmentation of the alveolar macrophages in the lungs, probably related to the inhalation of hot vaporized heroin. A contaminant or pyrolysis product was suspected, but none was identified; several neurotoxic agents known to cause similar leucoencephalopathies were ruled out.

### MDMA (ecstasy)

During the 1970s and early 1980s, 3,4-methylenedioxy-methamphetamine (MDMA; ecstasy) became increasingly popular as a 'recreational' drug in the USA. In at least one university, as many as 30–40% of students had tried it.<sup>33</sup> However, several MDMA-associated deaths were reported, mainly from cardiac arrhythmias,<sup>10 44</sup> though hyperthermia was also reported.<sup>3</sup> During the mid-1980s, MDMA use spread to Britain and, from there, to the rest of Europe, and

**Table 1** Reasons for hyperthermic collapse after MDMA ingestion

Prolonged exertion with minimal fluid replacement	Drug effects
Warm environment	Crowded clubs
Mood-enhancing effects of MDMA	Feeling of empathy; facilitates dancing
Amphetamine-like effects of MDMA	Euphoria, alertness; energy from sympathetic stimulation; disregard for body signals (thirst, tiredness, exhaustion)
Serotonergic effect of MDMA	Increased muscle tone leads to heat production

also to Australia, being promoted mainly through clubs. In the UK, a remarkable development occurred. Ecstasy was introduced to the dance scene, and its use rapidly became epidemic. The main reason for this seems to lie in the pharmacological profile of the drug.<sup>36</sup> It is related to mescaline and lysergic acid diethylamide (LSD), which are hallucinogenic, but it does not produce the perceptual distortions associated with other hallucinogenic drugs. At the same time, the amphetamine-like effects of ecstasy provide an increase in physical and mental energy and minimize any feelings of tiredness, thus enabling the user to continue dancing for longer than may be safe for body systems.

Two case reports of fatal hyperthermia following MDMA ingestion appeared in the British literature<sup>5 6</sup> and, in 1992, a series of seven fatal cases was reported.<sup>16</sup> A subsequent collation of literature reports<sup>31</sup> drew attention to the importance of a high body temperature as a predictor of a fatal outcome. The mean recorded temperature in fatalities was 41.6°C, compared with 40.5°C in the hyperthermic survivors. It seems apparent that cases of severe hyperthermia and deaths from heat stroke were mainly the result of prolonged dancing without rest and without taking enough liquid to enable normal temperature control by sweating<sup>15</sup> (Table 1). Collapse occurred, sometimes with convulsions. When examined in hospital, these patients tended to have a very high heart rate and a low arterial pressure, and had body temperatures as high as 43°C. Deaths have resulted, usually because the body cannot sustain the massive stress of high body temperature. As well as its amphetamine-like properties, the role of the serotonergic effect of the drug may be important in some cases, and may explain some fatalities where physical exercise was only minimal.

Convulsions, cardiovascular collapse, disseminated intravascular coagulation, rhabdomyolysis and acute renal failure are all complications of the gross thermal stress (see Table 2). Once disseminated intravascular coagulation has become established, management is difficult. This complication is the commonest reason for death in the hyperthermic patient who has taken MDMA. It is possible that an effect of MDMA on platelet function may also be responsible.

**Table 2** Seven fatal cases of MDMA toxicity reported in 1992; DIC=disseminated intravascular coagulation

Case	Age and gender	Circumstances and amount	Clinical course	Outcome
1	18 M	Three tablets taken at club	Collapse, hyperthermia (41.8°C), tachycardia, hypotension, asystole	Died 2.5 h after admission
2	17 M	Two tablets taken at party	Coma, convulsions, hyperthermia (41°C) tachycardia, hypotension, DIC	Died 14 h after ingestion (11 h after admission)
3	18 M	Five tablets taken at party	Collapse, hyperthermia (42.1°C), gastrointestinal haemorrhage	Died 36 h after admission
4	16 F	One tablet taken at club	Hallucinating, hyperthermia (40°C), tachycardia, hypotension, metabolic acidosis, DIC	Died 36 h after admission
5	21 F	Two tablets taken at party	Convulsions, hyperthermia (41°C), tachycardia, hypertension, DIC	Liver transplant after 4 days; death from graft rejection after 18 days
6	20 M	Found collapsed in street after party; haemophilia	Convulsions, hyperthermia (40°C), tachycardia, hypertension, DIC, rhabdomyolysis, acute renal failure	Died 60 h after admission
7	18 M	Took three tablets at pop concert	Convulsions, hyperthermia (43°C), tachycardia, hypotension, rhabdomyolysis, acute renal failure	Died 6.5 h after admission

## Management of the hyperthermic patient

The main objectives are to facilitate thermoregulation and to prevent the development of disseminated intravascular coagulation. Full supportive care should be provided. An anticonvulsant, such as intravenous diazepam, may be needed if the patient is having convulsions. The most urgent priority is to restore intravascular volume, since extracellular fluid volume tends to be grossly depleted by prolonged sweating. A rapid 1 litre intravenous fluid challenge should reduce the pulse rate and increase arterial pressure. If the patient has a temperature of  $\geq 40^{\circ}\text{C}$ , or is not sweating, and has established heat stroke, the use of dantrolene may be indicated.<sup>16</sup> Management of the other acute complications follows standard medical practice.

## Hepatic damage

In 1992, seven cases of hepatic damage associated with MDMA use were reported.<sup>16</sup> Several isolated cases have also been reported, including two cases of acute hepatitis<sup>9 11</sup> and one of accelerated hepatic fibrosis.<sup>23</sup> A series of 12 cases of hepatic damage has been reported from the Institute of Liver Studies at King's College Hospital,<sup>13</sup> where it was suggested that the incidence of ecstasy-induced hepatitis is increasing. A spectrum of severity seems to exist, with histological changes varying from a mild to moderate lobular hepatitis to features of massive hepatic parenchymal collapse with areas of nodular regeneration. An immunological mechanism appears to be the most likely cause of the sporadic cases of hepatitis which have occurred in ecstasy users. It is possible that, with the current degree of ecstasy use leading to repeated re-exposure, the incidence of cases of liver damage may increase with time.

## Hyponatraemia

Once it became apparent that hyperthermia was a danger for ecstasy users, fluid replacement was advised. Some early harm-limitation messages indicated that ecstasy users should drink large amounts of fluids (but without specifying that the fluids were to replace fluid losses caused by prolonged exertion). Some people have become acutely ill and a small number have died from acute water intoxication. The causation can be largely explained by the popular misconception that water drinking is good for those taking ecstasy, together with the pharmacological properties of the drug.

Hyponatraemia is an uncommon complication of MDMA ingestion. Only a few cases have been reported.<sup>19 22 27 28</sup> The death of Leah Betts achieved wide publicity in the popular press, and it became clear that fatal water intoxication can be precipitated by excessive water drinking in ecstasy users. Fifteen cases were identified between August 1994 and December 1995 by the National Poisons Information Service (London), with serum  $\text{Na}^+$  concentrations of  $<130$

mmol litre<sup>-1</sup>. The clinical pattern was remarkably uniform, with initial vomiting and disturbed behaviour, followed by drowsiness and agitation and, in seven cases, epileptiform convulsions. Drowsiness, a mute state and disorientation were observed for up to 3 days (Hartung TK, Schofield E, Short AI, Parr MJA, Henry JA, unpublished).

The neurological dysfunction is caused by haemodilution, with a rapid decrease in serum Na<sup>+</sup> concentration, leading to intracellular movement of water and, subsequently, to cerebral oedema. The patients developed severe illness within 12 h of ingesting ecstasy, suggesting that there is an acute drop in serum Na<sup>+</sup> concentration secondary to unrestricted fluid ingestion. The hyponatraemia appears to involve inappropriate secretion of antidiuretic hormone. One case of MDMA-induced hyponatraemia has been documented in which antidiuretic hormone concentrations were measured, and it was confirmed that concentrations of antidiuretic hormone were in fact inappropriately increased, the plasma arginine vasopressin concentration being 4.5 pmol litre<sup>-1</sup>.<sup>19</sup> It has been shown more recently that secretion of antidiuretic hormone is markedly increased following administration of 40 mg MDMA in healthy volunteers.<sup>15</sup> It thus appears that this phenomenon is not an idiosyncratic effect of the drug, but is a predictable pharmacological effect. Thus, anyone taking MDMA who drinks large amounts of water without exercising and sweating is risking hyponatraemia with its attendant complications. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a well recognized phenomenon which may occur postoperatively<sup>2</sup> or after the administration of psychoactive drugs.<sup>42</sup> However, in most drug- or illness-induced cases, it arises gradually as a result of normal intake of fluid with restriction of output by antidiuretic hormone, whereas in ecstasy-associated cases, there has been an excessive intake of fluid within a short space of time. This results in an acute onset of symptoms, and it can occur with Na<sup>+</sup> concentrations which might not otherwise appear to be dangerously low. Most patients seem to make a steady recovery without neurological sequelae once they reach medical care. Fluid restriction is usually sufficient and any administration of fluids should be avoided if there is any suspicion of hyponatraemia, but the use of intravenous mannitol, loop diuretics or hypertonic saline may be considered.

## Cocaine

Although historically well known as a topical anaesthetic for intranasal surgery, cocaine is now widely abused for its euphoriant effects. However, users pay the penalty of the challenge presented to body systems, and may suffer from headaches, sexual dysfunction, chronic cough (related to crack cocaine smoking), convulsions and cerebrovascular accidents. Cardiovascular complications include chest pain (the commonest mode of hospital presentation), cardiac arrhythmias, myocardial infarction (caused by the

immediate effects on blood vessels and platelets as well as the result of accelerated atheroma),<sup>20</sup> myocarditis, dissecting aneurysm and sudden death. Prolonged recreational use may also lead to paranoia and violent, antisocial behaviour, including homicide and suicide. Because of its powerful vasoconstrictor effect, snorting cocaine hydrochloride causes damage to nasal membranes and the nasal septal cartilage. Crack cocaine causes thermal damage to the airways, over and above its systemic effects.

In most cases, the effects of cocaine are relatively short-lived because its elimination half-life is 30–60 min, and the patient is usually asymptomatic within 2 h. However, heavy cocaine use may be associated with more prolonged symptoms and may lead to rhabdomyolysis or hyperthermia. Its unwanted metabolic effects derive from central nervous system stimulation resulting from blockade of dopamine re-uptake, so that the patient may be agitated, violent, hallucinating or convulsing. The exertion involved can generate heat, leading to hyperthermia and contributing to rhabdomyolysis. In addition, blockade of norepinephrine re-uptake leads to marked sympathomimetic effects as a result of alpha-1 and beta-1 stimulation. These include tachycardia and hypertension, but may also be responsible for the development of hyperthermia and rhabdomyolysis. The mode of use may be relevant: intravenous use is a risk factor for complications, as is the use of free base 'crack' cocaine, which is smoked and rapidly enters the circulation through the pulmonary vasculature. Crack cocaine may also be swallowed, with serious consequences.<sup>30</sup>

Seizures, hyperactivity, hypokalaemia, severe muscle contraction and hyperthermia may be important causes of rhabdomyolysis in cocaine intoxication. These may interact with ischaemia secondary to hypotension or vasoconstriction. The incidence of cocaine-associated rhabdomyolysis has not yet been defined, but there have been numerous case reports, and more cases are being seen with growing use of the drug.<sup>47</sup> One study found that 24% of patients attending an emergency department with cocaine toxicity had evidence of rhabdomyolysis, but most had no associated symptoms. A survey in Miami of 39 patients presenting with rhabdomyolysis after cocaine use, found a mean creatine kinase concentration of 12 187 u litre<sup>-1</sup>. Thirteen had renal failure, seven of whom developed disseminated intravascular coagulation; six patients died.<sup>38</sup> The development of renal failure is not uncommon as a consequence of cocaine-induced rhabdomyolysis.<sup>34</sup> In occasional cases, renal failure may occur in the absence of rhabdomyolysis. Cocaine may also hasten progression to uraemia in patients with underlying renal insufficiency.

The amount of cocaine used does not predict the likelihood of a fatal outcome. Fatal blood concentrations in cocaine users who die from other causes, such as road traffic accidents, are similar to those who have died of cocaine toxicity.<sup>21</sup> Another factor whose relevance is not widely appreciated is the formation of cocaethylene, an ethyl homologue of cocaine which is formed in the liver

**Table 3** Features of excited delirium

Phase	Clinical	Behavioural
1. Hyperthermia	Increased body temperature, profuse sweating	Attempts to cool body, removes clothes; goes into the open
2. Delirium	Paranoid behaviour, dilated pupils	Shouting, thrashing, violence, unexpected strength
3. Respiratory arrest	Collapse, cessation of breathing	Loss of strength
4. Death	Cardiorespiratory arrest	

only in the presence of ethanol. Cocaethylene has pharmacodynamically similar properties to cocaine; although it is metabolized along the same pathways as cocaine, its plasma elimination half-life is three to five times that of cocaine, so that the potential for accumulation to toxic levels is greater. This is probably why the risk of immediate death is 18- to 25-fold greater for ingestion of alcohol during use of cocaine than for use of cocaine alone.<sup>1-4</sup> Many binge users of cocaine drink relatively heavily during sessions because they are aware that this interaction prolongs the effects of cocaine use. Another factor which may influence the severity of symptoms in patients presenting with cocaine toxicity is the concentration of plasma cholinesterase (pseudocholinesterase). This enzyme is responsible for the detoxification of cocaine in the body, and it has been shown that patients with life-threatening cocaine toxicity had lower plasma cholinesterase activity than those who had non-life-threatening toxicity.<sup>17</sup> The low cholinesterase concentrations may be related to poorer nutritional status of regular cocaine users.

Early intervention with high-dose diazepam is probably the most effective first-line measure to prevent the progression of symptoms and ultimately to prevent rhabdomyolysis. Haloperidol or droperidol are not indicated as first-line drugs as they may increase the risk of seizures. Nitrates are appropriate for hypertension and, although beta-blockers may carry the risk of inducing alpha-adrenergic vasoconstriction, a short-acting beta-antagonist such as esmolol can be used. However, by the time the patient has presented, rhabdomyolysis may be established and conventional treatments will then be required to prevent the development of renal impairment or to manage established renal failure. Hyperpyrexia may be severe and the immediate management should include high-dose diazepam, urgent restoration of fluid balance and the administration of dantrolene.

### Cocaine excited delirium

Apart from the effects of cocaine described above, an important but unusual complication of cocaine use, termed agitated delirium or excited delirium, began to be apparent during the epidemic of cocaine use in the USA in the 1980s.<sup>48</sup> It may well be an extreme form of cocaine toxicity.<sup>40</sup> Although it may rarely complicate mental or physical illnesses, it is most commonly associated with cocaine use. Emergency physicians, anaesthetists and

intensive care staff should be aware of it, as cases are now occurring in Britain. It occurs in regular cocaine users who have used the drug within the last 24 h; there is no evidence that an overdose of cocaine has been taken and there is no readily apparent precipitating cause. Four elements occur in close succession: hyperthermia, agitated behaviour, collapse and death (Table 3). The number of self-limiting cases is unknown. The individual becomes aware of an increase in body temperature, sweats profusely and attempts to cool down by tearing off clothes and cooling himself with cold water. This stage merges into a phase of confusion and agitation. In many cases, the person wanders into the street shouting and behaving erratically. He may hide behind bushes or attack his image in mirrors or shop windows. After a period of time the individual becomes subdued and may die. Death frequently occurs after the police have been called and have been attempting to restrain the individual. When restraint is used, extreme strength is often apparent, and several people may be needed to maintain control. Body temperature, where it has been measured, is frequently  $>40^{\circ}\text{C}$ , so hypermetabolism is clearly a feature of the illness.

A report from Florida has compared people who died from accidental cocaine overdose with those who had died from excited delirium. Compared with controls, those who died from excited delirium were more likely to be black, male and younger. They were less likely to have a low body mass index and more likely to have died in police custody, to have received medical treatment immediately before death, to have survived for a longer period, to have developed hyperthermia and to have died during the summer months.<sup>39</sup> Post-mortem blood concentrations of cocaine and its metabolites were similar to those in cocaine users who had died of other causes. The authors considered as a possible cause of excited delirium that chronic cocaine use disrupts dopaminergic function and that, when this is coupled with recent cocaine use, it may be sufficient to precipitate agitation, delirium, aberrant thermoregulation, rhabdomyolysis and sudden death. The most characteristic finding at post-mortem is that the dopamine receptor density in the striatum is not increased as it is in cocaine overdose.

There are currently no medical management guidelines for excited delirium. Physical restraint is clearly counter-productive, and may contribute to a fatal outcome in a hyperthermic, agitated patient, but is usually necessary in the interest of public safety. Once the patient reaches

medical care, diazepam is the agent most likely to be of use, reducing neuronal excitability and acting as a pharmacological restraint. Urgent fluid replacement is probably of considerable importance, though there is, as yet, no evidence to support this.

## Other drugs

Amphetamine sulphate has long been known as an occasional cause of hyperthermia and rhabdomyolysis. More recently, MDMA has overtaken it in Britain, mainly because of its association with dancing, but toxicity and deaths still occur. In the western USA, methamphetamine is commonly abused and abusers can present with agitation, violence, rhabdomyolysis and renal failure. Creatine kinase concentrations tended to be twice as high as with rhabdomyolysis from other causes.<sup>37</sup>

Phencyclidine is an important cause of rhabdomyolysis, but is very rarely used outside the USA. In one series of 1000 cases, 22 had rhabdomyolysis.<sup>38</sup> Cannabis is very widely used and has powerful pharmacological effects. However, metabolic complications are unusual. There is a single case report of hyperthermia following cannabis use, in which an individual developed hyperthermia after jogging.<sup>46</sup> Volatile substance abuse (solvent misuse) is a common means of intoxication in young people. Heavy exposure can lead to neuropathic damage, but chronic toluene exposure can also produce metabolic consequences. Toluene-induced renal tubular acidosis can cause hypokalaemia, increasing the risk of cardiac dysrhythmias and leading to hypokalaemic paralysis, rhabdomyolysis and renal calculi.<sup>25</sup>

## Conclusion

Physicians, anaesthetists and intensive care staff need to be conversant with the clinical problems produced by illicit drugs. The metabolic problems are among the most taxing of these because they are usually associated with severe toxicity and because of the wide range of body systems involved. One of the key features of management is aggressive hydration for patients with hyperthermia and rhabdomyolysis.

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