BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2011.03950.x

Methaemoglobinaemia associated with the use of cocaine and volatile nitrites as recreational drugs: a review

Laura Hunter,[1] Laura Gordge,[2] Paul I. Dargan[3,4] & David M. Wood[3,4]

[1]Guy's and St Thomas' NHS Foundation Trust, [2]School of Medicine, King's College London, [3]Guy's and St Thomas' NHS Foundation Trust and King's Health Partners, and [4]King's College London

Correspondence
Dr David Wood, Medical Toxicology Office, 2nd Floor, Bermondsey Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK.
Tel.: +44 020 7188 5848
Fax: +44 020 7188 1289
E-mail: David.Wood@gstt.nhs.uk

Keywords
adulterants, cocaine, methaemoglobinaemia, volatile nitrites

Received
1 December 2010

Accepted
7 February 2011

Accepted Article
25 February 2011

Methaemoglobinaemia can cause significant tissue hypoxia, leading to severe, potentially life-threatening clinical features and/or death. Over recent years there have been increasing reports of methaemoglobinaemia related to recreational drug use. There have been 25 articles describing methaemoglobinaemia related to recreational use of volatile nitrites (poppers) and more recently, four reports of methaemoglobinaemia in association with recreational cocaine use. In this article we discuss the mechanisms by which methaemoglobinaemia occurs in relation to the use of both volatile nitrites and cocaine, and summarize the published cases of recreational drug-related methaemoglobinaemia. The volatile nitrites can cause methaemoglobinaemia directly through their activity as oxidizing agents. However, with cocaine, methaemoglobinaemia is related to adulterants such as local anaesthetics or phenacetin, rather than to the cocaine itself. Clinicians managing patients with acute recreational drug toxicity should be aware of the potential for methaemoglobinaemia in these patients, particularly in patients with cyanosis or unexplained low oxygen saturations on pulse oximetry, and ensure that appropriate and timely management is provided, including, where appropriate, the use of methylthioninium chloride (methylene blue).

Introduction

Recreational drug use is common worldwide and regularly results in presentation to the emergency department with acute toxicity. Classical 'toxidromes' associated with various classes of recreational drugs are recognized, but frequently patients will present with symptoms and signs that do not correlate with the direct action of the drug allegedly ingested. One example of this is methaemoglobinaemia, which has been recognized as a consequence of recreational use of volatile nitrites since the late 1970s [1–24], and more recently there have been case reports of methaemoglobinaemia in individuals recreationally using cocaine [25–28]. Unlike the case with nitrites, where the methaemoglobinaemia is directly because of the oxidizing effect of the nitrites, with cocaine, methaemoglobinaemia is because of the adulterants, rather than the cocaine itself.

Methaemoglobin is formed by oxidation of the haem molecule, from its reduced Fe^{2+} (ferrous) state to an oxidized Fe^{3+} (ferric) state. Erythrocyte cytochrome b5-MetHb reductase and nicotinamide adenine dinucleotide phosphate (NADPH)-MetHb reductase are involved in maintaining normal physiological concentrations of methaemoglobin at approximately 1–2% [29]. Methaemoglobinaemia refers to the presence of elevated circulating methaemoglobin within erythrocytes, which results in reduced tissue oxygen via two mechanisms. Primarily, methaemoglobin cannot bind oxygen resulting in a reduction in oxygen-carrying ability. Secondly, the presence of methaemoglobin in the erythrocyte structurally alters haemoglobin such that unaffected haem molecules available for oxygen transportation have an increased affinity for oxygen which impairs oxygen off-loading to the tissues [14].

Methaemoglobinaemia can either be congenital or acquired. Congenital methaemoglobinaemia may be because of structural abnormalities in the haemoglobin molecule (haemoglobin M), or to metabolic problems such

Table 1

Clinical findings in patients with methaemoglobinaemia

Methaemoglobin concentration	Clinical findings
1–3%	None
3–15%	Possibly none; pulse oximeter will read low oxygen saturations
15–20%	Cyanosis (central and peripheral); not improving with oxygen administration
20–50%	Dyspnoea, headache, fatigue, dizziness, syncope, weakness
50–70%	Tachypnoea, metabolic acidosis, dysrhythmias, seizures, central nervous system depression, coma
>70%	Grave hypoxic symptoms, death

as erythrocyte methaemoglobin reductase, pyruvate kinase or glucose-6-phosphate dehydrogenase (G6PD) deficiency [29]. Individuals with G6PD deficiency are at increased risk of developing methaemoglobinaemia on exposure to an oxidizing agent, due low levels of NADPH. G6PD deficiency is more common in individuals of African, Asian or Mediterranean descent. In these patients, antidotal therapy with methylthioninium chloride is less effective and it may precipitate haemolysis [14].

More commonly, methaemoglobinaemia is an acquired phenomenon, secondary to the oxidizing effects of exogenous substances [29]. Of particular relevance, to this article, is the association of methaemoglobinaemia with local anaesthetic agents and phenacetin [30–34].

The clinical effects of methaemoglobinaemia can be predicted from the methaemoglobin concentration (Table 1). However, patients with co-morbidities which decrease oxygen transport or delivery (respiratory and/or cardiovascular disease or anaemia) will develop significant symptoms at lower methaemoglobin concentrations.

Pulse oximetry is inaccurate in patients with methaemoglobinaemia, as the pulse oximeter reading is based on the assumption that the only two varieties of haemoglobin present are oxyhaemoglobin and deoxyhaemoglobin. Generally, the pulse oximeter will transmit readings in the region of 85%. Co-oximetry gives accurate concentrations because of the ability to identify the absorptive characteristics of several haemoglobin species at different wavelengths including methaemoglobin [35]. It is important that blood samples are analysed promptly, as methaemoglobin concentrations decrease with time.

Mild cases of methaemoglobinaemia are unlikely to require any treatment other than administration of oxygen and removal from exposure to the causative agent. Reduction back to the ferrous state will occur via the normal physiological mechanisms present in the erythrocyte [29]. Methylthioninium chloride (methylene blue) is the treatment of choice for patients with symptomatic methaemoglobinaemia. It acts as a substrate for NADPH-MetHb reductase, resulting in the formation of reduced methylthioninium chloride which acts as an electron donor to reduce Fe^{3+} back to Fe^{2+}. The recommended dose is 1–2 mg kg^{-1}, which may be repeated if necessary. More detailed information on the treatment of methaemoglobinaemia can be found in recent review articles by Bradberry *et al*. [36] and do Nascimento *et al*. [37].

This review article will focus on acquired methaemoglobinaemia related to recreational drug use. We will summarize the published cases of recreational drug-related methaemoglobinaemia, both as a direct consequence of the drugs used and from the adulterants in recreational drugs.

Search strategy

Medline, EMBASE, CINAHL and Psychinfo were searched utilizing the search terms methaemoglobinaemia OR methemoglobinemia AND nitrites OR isobutyl nitrite OR butyl nitrite OR amyl nitrite OR cocaine OR recreational drugs. Twenty-nine articles were identified detailing methaemoglobinaemia as a result of recreational drug use. Full-text was not available for two of these papers [12, 20]. It appears that one of the nitrite fatalities has been reported both as a single-case report [22] and in a series of isobutyl nitrite methaemoglobinaemias [8].

Volatile nitrite-related methaemoglobinaemia

The volatile nitrites are aliphatic esters of nitrous acid. They are highly volatile, sweet-smelling liquids normally administered by nasal inhalation. Their vasodilatory effects were first described in 1859 and subsequently, they were used in the treatment of angina from 1867. During the 1960s nitrates replaced their use in the treatment of angina and abuse of nitrites became widespread. They were legally marketed as 'room odorizers' and attained their colloquial name of 'poppers' from the noise made when the glass vials were crushed inside a tissue, prior to inhalation. They remain widely available and are often sold in men who have sex with men (gay) clubs, sex shops and in head shops. They are sold in small glass bottles containing 10–30 ml, under a variety of trade names including 'Rush', 'Liquid Gold' and 'TNT' [38]. Volatile nitrites are not classified under the UK Misuse of Drugs Act (1971). However, amyl nitrite is classified as a 'prescription only medicine' and as isobutyl nitrite is recognized as a Class 2 carcinogen, it is controlled under the UK Dangerous Substances and Preparations (Safety) Regulations 2006 [39].

Recent surveys suggest that nitrites are also popular among young adults and teenagers who participate in the dance scene. The 2009 Mixmag Drug Survey reported that

68.7% of readers had reported having ever used poppers [40]. The British Crime Survey 2009/2010 reported that lifetime use of poppers in the general population was significantly lower at 9.5% [41]. Similarly, recent use rates (within the last month) were significantly higher in clubbers (15.1%) compared with the general population (0.4%). In addition, the use of nitrites is popular among men who have sex with men, due their aphrodisiac and vasodilatory properties. They are inhaled either during foreplay to obtain a high and produce relaxation of the anal sphincter, or just preceding orgasm to prolong climax. Poppers have also been inhaled by dipping cigarettes into the liquid. Because of the high flammability of nitrites, inadvertent lighting of these cigarettes at a later time, risks severe burns.

Oral ingestion of nitrites is associated with a higher risk of toxicity, particularly the development of methaemoglobinaemia. Other commonly reported unwanted effects include palpitations, headache, visual disturbance, flushing, dizziness, nausea and syncope, which are thought to be related to vasodilatation and reflex tachycardia. In addition to acting as vasodilators, the volatile nitrites are recognized to cause oxidation of haemoglobin to methaemoglobin, and following prolonged exposure individuals may develop clinically significant methaemoglobinaemia.

The first published case of methaemoglobinaemia, as a result of recreational use of nitrites was published in 1979. Horne *et al*. [1] described the case of a 25-year-old man who presented to the emergency department, complaining of 'greyish complexion' which had developed following inhalation of butyl nitrite. He was found to have a methaemoglobin concentration of 18%.

Subsequent to this, there have been 25 reports of methaemoglobinaemia secondary to inhalation and/or ingestion of volatile nitrites, with methaemoglobin concentrations of between 17.8% and 94% [2–21]. The majority of these cases survived, and a proportion were treated with methylthioninium chloride. The cases where the individual survived are summarized in Table 2 [1–21] and the three reported deaths are discussed in more detail later in this article [22–24]. For the interest of the reader, we have discussed three of the non-fatal cases in more detail below.

The highest recorded methaemoglobin concentration (94%) in nitrite-related methaemoglobinaemia occurred in a 44-year-old man who was found unconscious and cyanosed in the steam room of a bath house [3]. There was a history of ingestion of 'large' amounts of amyl nitrite and an empty bottle was found adjacent to the patient. On arrival of the paramedics, the patient was hypoventilating, hypotensive and unresponsive to pain. The patient was intubated by paramedics and ventilated with 100% oxygen. Despite supplemental high-flow oxygen and a normal chest examination, the patient remained profoundly cyanosed. Twelve minutes following arrival in the emergency department, the patient suffered a bradycardic cardiorespiratory arrest. This responded to 2 mg of epinephrine and 30 s of cardiopulmonary resuscitation. Arterial blood gas analysis showed a methaemoglobin concentration of 94%, and metabolic acidosis (pH 7.17, $pC0_2$ 39 mmHg, bicarbonate 14 mmol l^{-1}, base excess −14 mmol l^{-1}). He was administered 80 mg (1 mg kg^{-1}) of methylthioninium chloride i.v. over 10 min. Within 20 min, the patient's colour had improved and there was evidence of spontaneous respiration. A repeat methaemoglobin concentration was 26%. A second dose of methylthioninium chloride was administered (100 mg i.v.) with 50 ml of 8.4% sodium bicarbonate for persistent metabolic acidosis. Despite the extremely high methaemoglobin concentration, there was a good outcome in this case. The patient was extubated within 24 h of admission, and left hospital with no sequelae.

In a further report in 1992, a 29-year-old man presented to the emergency department, following inhalation of amyl nitrite [4]. He was normotensive, tachycardic (112 beats min^{-1}) with a normal respiratory rate but was noted to have circumoral cyanosis and a pulse oximeter reading of 56%. Methaemoglobin concentration was 61%. Methylthioninium chloride (100 mg) was administered i.v. Within 45 min of methylthioninium chloride administration, the patient's non-invasive oxygen saturation had increased to 98%. The patient survived and was discharged uneventfully. This case is unusual with respect to the pulse oximetry reading of 61%. Generally, it is recognized that patients with methaemoglobinaemia will have pulse oximetry readings in the region of 80–85%.

In a further report, a 35-year-old woman presented to the emergency department, following ingestion of alcohol and inhalation of isobutyl nitrite [5]. On arrival, she had a GCS 4/15, BP of 86/37 mmHg, heart rate of 66 beats min^{-1} and was 'deeply cyanosed'. She was intubated and ventilated with 100% oxygen. Arterial blood co-oximetry yielded a methaemoglobin concentration of 75.2% and she was administered 3 mg kg^{-1} of i.v. methylthioninium chloride, leading to an improvement in conscious level and cyanosis. Methaemoglobin concentration repeated at 30 min after methylthioninium chloride administration was 34.3%. Subsequently, the patient received hyperbaric oxygen treatment for 1 h, following which the methaemoglobin concentration reduced to 2.2%. There are several reports [7, 42, 43] in the literature of the successful use of hyperbaric oxygen in the treatment of methaemoglobinaemia, either used alone or used in conjunction with methythioninium chloride. Hyperbaric oxygen will reduce the methahaemoglobin concentration at a rate of approximately 8% per hour. There are limitations to using hyperbaric oxygen in the UK, because of limited availability. The success of methylthioninium chloride in treating the majority of cases, coupled with widespread availability and ease of administration, means that it currently remains the treatment of choice. However, hyperbaric oxygen remains a possible treatment modality, particular in patients who do not respond to therapeutic doses of methylthioninium chloride.

Table 2

Summary of history of exposure, clinical features on presentation, methaemoglobin concentration and treatment of the reported cases of acute methaemoglobinaemia related to the recreational use of volatile nitrites

Author	Demographics	Used	Observations	Methaemoglobin concentration	Treatment
Horne *et al.* [1]	25-year-old male	Butyl nitrite (inhaled)	None documented	18%	None
Wason *et al.* [2]	36-year-old male	Isobutyl nitrite (inhaled)	BP = 120/80 mmHg (postural syncope), HR = 120 beats min^{-1}, peripheral and central cyanosis	48%	20 ml 1% methylthioninium chloride
Wason *et al.* [2]	39-yearold male	Butyl nitrite (inhaled)	BP = 90/60 mmHg, HR = 140 beats min^{-1}, RR = 24 min^{-1}, peripheral and central cyanosis	Not analysed until 7 days post collection (4%)	None
Shesser *et al.* [8]	16-year-old male	Isobutyl nitrite (inhaled)	BP = 120/70 mmHg, HR = 124 beats min^{-1}, RR = 18 min^{-1}	Diagnosed clinically	70 mg methylthioninium chloride
Guss *et al.* [9]	21-year-old male	Isobutyl nitrite (inhaled), concurrent cocaine/ methaqualone	BP = 150/70 mmHg, HR = 100 beats min^{-1}, pulse oximetry = 85%, peripheral and central cyanosis	37%	1 mg kg^{-1} methylthioninium chloride
Forsyth & Moulden [10]	2-year-old female	Liquid gold (oral)	Hypotensive, HR = 130 beats min^{-1}, RR = 26 min^{-1}, clinical cyanosis	43%	Methylthioninium chloride 1 mg kg^{-1}
Sobey & Campbell [11]	37-year-old male	Amyl nitrite (inhaled)	BP = 128/84 mmHg, HR = 60 beats min^{-1}, RR = 16 min^{-1}, peripheral and central cyanosis	17.8%	80 mg methylthioninium chloride (1 mg Kg^{-1})
Sutton & Jeffrey [4]	29-year-old male	Amyl nitrite (linhaled)	BP = 100/60 mmHg, HR = 112 beats min^{-1}, RR = 16 min^{-1}, pulse oximetry = 56%	61%	100 mg methylthioninium chloride
Dudley & Solomon [13]	20-year-old female	Amyl nitrite (route unknown)	BP = 80/40 mmHg, GCS = 14, peripheral and central cyanosis	30%	i.v. methylthioninium chloride (dose not stated)
Edwards & Ujma [3]	44-year-old man	Amyl nitrite (route unknown)	Hypotensive, hypoventilating, unresponsive to pain	94%	Intubated and ventilated. Methylthioninium chloride 1 mg kg^{-1}
Stambach *et al.* [14]	Unknown female early 20s	Amyl nitrite (oral)	BP = 80/30 mmHg, HR = 130 beats min^{-1}, GCS 15, pulse oximetry = 85%	83%	Methylthioninium chloride 2 mg kg^{-1}
Modarai *et al.* [15]	32-year-old female	Amyl nitrite (inhaled)	BP = 100/50 mmHg, HR = 130 beats min^{-1}, GCS = 15, RR = 22 min^{-1}, pulse oximetry = 82%	59.9%	Methylthioninium chloride 1.5 mg kg^{-1}
Modarai *et al.* [15]	28-year-old male	Amyl nitrite (inhaled)	BP = 80/40 mmHg, HR = 140 beats min^{-1}, RR = 30 min^{-1}, pulse oximetry = 74%	63.3%	Methylthioninium chloride 2 mg kg^{-1}
Jansen *et al.* [7]	18 –year-old male	Isobutyl nitrite (oral)	BP = 130/70 mmHg, HR = 100 beats min^{-1}, pulse oximetry = 85%, peripheral and central cyanosis	85%	Methylthioninium chloride (dose not stated), hyperbaric oxygen
Machabert *et al.* [16]	21-year-old male	Amyl nitrite (inhaled)	BP 130/80 mmHg, HR = 90 beats min^{-1}, peripheral and central cyanosis	41.6%	Methylthioninium chloride 50 mg
Lin *et al.* [17]	31-year-old man	Amyl nitrite (inhaled + aerosolized)	BP = 90/50 mmHg, HR = 130 beats min^{-1}, RR = 20 min^{-1}, pulse oximetry = 82%, peripheral and central cyanosis	52.2%	2 mg kg^{-1} methylthioninium chloride
Beneteau-Burnat *et al.* [18]	44-year-old male	Inhaled and ingested 'poppers'	BP = 130/80 mmHg, HR = 73 beats min^{-1}, GCS 15, peripheral and central cyanosis	38.7%	2 mg kg^{-1} methylthioninium chloride
Lindenmann *et al.* [5]	35-year-old female	Isobutyl nitrite (inhaled)	BP = 86/37 mmHg, HR = 96 beats min^{-1}, GCS = 4, professoround cyanosis	75%	Methylthioninium chloride (dose not stated) and hyperbaric oxygen
Ranchon *et al.* [19]	48-year-old male	Inhaled 'poppers'	Normal cardio-respiratory exam, pulse oximetry = 80%	34%	100 mg methylthioninium chloride
Gentry Wilkerson [21]	19-year-old female	Amyl nitrite (oral)	BP = 127/78, HR = 121 beats min^{-1}, pulse oximetry = 88%, peripheral and central cyanosis	72%	1.5 mg kg^{-1} methylthioninium chloride

Fatalities occurring in patients with nitrite-related methaemoglobinaemia

Three case reports were identified of fatalities in individuals believed to have been using volatile nitrites recreationally [22–24].

The first of these was a 30-year-old Black man who was brought to the emergency department by police having been found collapsed outside a discotheque [22]. The only history available was that he had been seen earlier in the evening by an employee, in the toilet, with a brown bottle. On arrival he was combative and speaking incoherently. He was hypotensive (78/50 mmHg), tachycardic (126 beats min^{-1}) and profoundly cyanosed but peripherally warm. In the hour following admission he deteriorated, and developed a sinus bradycardia followed by an asystolic cardiac arrest, unresponsive to treatment with atropine, calcium chloride and a vasopressor infusion. During resuscitation the diagnosis of methaemoglobinaemia was suspected, because of the dark colour of his blood samples, and he was administered 20 mg of i.v. methylthioninium chloride. Resuscitation attempts were unsuccessful. Toxicological studies at post-mortem showed a blood methaemoglobin concentration of 38% and gastric contents with a nitrite concentration of 90%, consistent with oral ingestion of isobutyl nitrite. It appears from the case report that the diagnosis of methaemoglobinaemia was only entertained postcardiac arrest. Methylthioninium chloride was administered, but at a sub-therapeutic dose. A dose of 2 mg kg^{-1} of methylthioninium would be required initially, with repeat doses administered, based on therapeutic reponse, if measurement of methaemoglobin concentrations was not possible.

The second case involved a 23-year-old Black man who was brought by police officers to an emergency department having allegedly inhaled isobutyl nitrite on the morning he was due to appear in court [23]. On arrival at hospital the patient was unconscious. The emergency department physician noted an odour like 'antifreeze'. Documentation of resuscitation attempts were not included in the report. Methaemoglobinaemia was not considered and methylthioninium chloride was not administered. The patient died 2 h after presentation. Post-mortem analysis of blood showed a methaemoglobin concentration of 95%. This case is unusual as the patient developed severe methaemoglobinaemia after suspected inhalation of a volatile nitrite and this appeared to be of delayed onset.

Because of the ethnicity of the patients detailed above, glucose-6-phosphate dehydrogenase (G6PD) deficiency is a possibility that would result in greater susceptibility to the oxidizing effects of a volatile nitrite. Neither patient was tested for G6PD deficiency.

The final fatality was a 69-year-old man who died following approximately 20 min of inhalation of isobutyl nitrite, during a sexual act [24]. He was noted to have sudden difficulty in breathing, followed by cardiac arrest and died within minutes. Post-mortem concentrations of methaemoglobin, were found to be 23%. The authors believed that the patient died as a result of hypoxia, secondary to isobutyl nitrite-induced methaemoglobinaemia. The case report acknowledges that the deceased had a significant cardiac history. At post-mortem the deceased was found to have severe triple vessel coronary disease. There was no evidence of recent myocardial event, stroke or other cause of death elicited at post-mortem. The presence of cardiac disease would significantly increase the risk of cardiac arrhythmia in response to high concentrations of methaemoglobinaemia and associated hypoxia. In view of the rapidity with which symptoms presented, it is more likely that the cause of death was a result of cardiac arrhythmia. It is also recognized that recreational users of volatile nitrites, frequently use other recreational drugs, which may in themselves increase the risk of arrhythmias.

Cocaine-associated methaemoglobinaemia

Cocaine itself and its metabolites are not recognized to cause methaemoglobinaemia. However, there are reports, discussed below in more detail, of adulterants added to cocaine that are associated with methaemoglobinaemia [25–28]. An adulterant is a pharmacologically active substance added to a recreational drug. These are sometimes chosen to mimic some of the effects of the drug and give the impression of high quality and purity but in other instances there appears to be no obvious reason for their use. They are distinguishable from diluents or cutting agents, such as sugar, mannitol or lactose, which are typically inert [44]. Local anaesthetics are commonly used as adulterants in cocaine, as they share the 'numbing properties' that people associate with 'good-quality cocaine' and therefore it is less easy for users to suspect their presence. There is often no apparent reason for the use of other adulterant substances, such as phenacetin, which do not mimic the effects of cocaine and potentially are expensive. Both adulterants and dilutents/cutting agents are added to cocaine and other recreational drugs to increase artificially the weight of powder being sold and so increase the profit margin for dealers.

Data from United Nations Office on Drugs and Crime, published in 2009, reported a reduction in cocaine production of 15% from the previous year, to 845 metric tonnes [45]. Cocaine at the time of exportation from the growing/production areas tends to be of high purity (>95%); however, 'street-level' purity is generally significantly lower than this. The average purity of cocaine at street level in the UK is estimated to be approximately 33% by European Monitoring Centre for Drugs and Drug Addiction and typically lower than 20% by the Serious Organized Crime Agency. In some areas seizures of cocaine in the UK have had purity as low as 5% [46–47]. The potential effect of the reduced purity levels of cocaine is that individuals are repeatedly re-dosing or using greater amounts to achieve the desired 'high', which will increase their exposure to the adulterants within the 'cocaine'.

Toxicological analysis of seized drugs provides qualitative information on the adulterants present in the 'cocaine'; quantitative analysis to determine the proportion of cocaine and the adulterants present is not typically undertaken. Information on the frequency of different adulterants found in cocaine is available from a number of different sources. Analysis of seizures from law enforcement agencies can provide information on the frequency of adulterants in cocaine entering a country and/or before it reaches street level. A study in Italy found that the commonest adulterant in cocaine seized by police in Rome in both 1996 and 1997 was lidocaine (present in 16.5% and 12.3% of seizures respectively) [48]. Similarly, analysis of seized cocaine in the UK in 1995 demonstrated that the local anaesthetics lidocaine, procaine and benzocaine were among the most common adulterants detected [49]. In the Italian cocaine analysis, phenacetin was not detected in any seizures in 1996, but was present in 6.1% of seizures in 1997 [48]. There is no information in this study on the relative concentration of phenacetin or lidocaine in the seizures. In one case report of a fatality in a body packer with acute cocaine toxicity secondary to rupture of a cocaine-containing package, toxicological analysis of the packages post-mortem demonstrated the presence of phenacetin at a concentration of 30% [50]. The analysis of 'street-level' drugs provides an indication of the frequency of adulterants in drugs actually being used recreationally. In the UK analysis of drugs, discarded by individuals or seized by club security staff and collected in amnesty bins within nightclubs in London and Manchester in 2008, showed the presence of phenacetin in 29% and 8% of cocaine samples respectively [51]. In the Netherlands, individuals are able to have recreational drugs analysed anonymously through the Dutch Drugs Information Network (DIMS), which also provides information to public health services on the purity and range of adulterants in a number of recreational drugs, including cocaine. Through the DIMS project, it has been shown that the frequency of cocaine samples containing phenacetin has increased from 1.6% in 1997 to 40.6% in 2007 [52].

The local anaesthetics, particularly benzocaine, prilocaine and cetacaine (a combination of benzocaine, tetracaine and aminobenzoate), are well-recognized causes of methaemoglobinaemia [30–34]. Prilocaine is metabolized to ortho-toluidine which is an oxidizing agent. It is also likely that benzocaine metabolites are responsible for benzocaine-related methaemoglobinaemia as benzoic esters are hydrolyzed by a mechanism similar to anilides to form oxidizing metabolites [29].

The association between phenacetin and the development of methaemoglobinaemia appears to be related to the n-hydroxyphenacetin and p-phenetidine metabolites rather than phenacetin itself. There have been several reports in the medical literature of methaemoglobinaemia associated with the therapeutic use of phenacetin [53–56]. In the majority of these cases, there is limited clinical information to determine whether the development of methaemoglobin is solely because of the normal physiological production of phenacetin metabolites or whether it relates to their accumulation because of other underlying medical conditions such as renal failure. It appears that the degree of methaemoglobinaemia induced in those exposed to phenacetin varies. In those thought to be 'susceptible' because of altered phenacetin metabolism and/or reduced renal elimination of phenacetin and its major metabolites, a single dose of 30-mg kg^{-1} phenacetin lead to an increase of methaemoglobin concentration from 0.2% to 11.4%. In healthy controls the increase seen was from 0.7% to 1.8% [55].

There have been a few cases reported in the medical literature of recreational use of cocaine associated with the development of methaemoglobinaemia, which are likely to be related to either local anaesthetics or phenacetin being used as adulterants in the cocaine [25–28]. These cases are briefly summarized below, including, where available, the results of toxicological screening. It should be noted that often in these case reports, it is not possible to determine the extent of the toxicological screening that has been undertaken. It is possible that, where one adulterant is detected that is known to be associated with methaemoglobinaemia, the sample may not have been analysed further to determine if there were any other adulterants present that may also be associated with methaemoglobinaemia. Finally, the lack of numerous case reports in the published literature of methaemoglobinaemia associated with the recreational use of cocaine does not necessarily mean that this is an uncommon complication of cocaine use. There is the potential of publication bias as this is an already reported phenomenon, as well as the fact that treating clinicians may mis-attribute the methaemoglobinaemia to an already known adulterant or to the co-use of another agent such as 'poppers' (volatile nitrites) and therefore decide that there is no indication to undertake toxicological analysis with a view to publication.

The first case of cocaine-related methaemoglobinaemia reported in the medical literature was in 1992 [25]. A 27-year-old man presented to an emergency department with tonic–clonic seizures and severe cyanosis following use of a large quantity of street cocaine. Clinical parameters on admission were consistent with acute intoxication (blood pressure 220/130 mmHg, heart rate 130 beats min^{-1} and temperature 38.3°C). Following intubation for ongoing seizures unresponsive to benzodiazepines, an arterial blood gas demonstrated a metabolic acidosis and a methaemoglobin concentration of 37%. He was treated with i.v. methylthioninium chloride (1 mg kg^{-1}) and his methaemoglobin concentration had fallen to 15% 1 h following treatment. He made a full recovery and self-discharged from hospital 6 days later. Toxicological analysis by gas-chromatography mass-spectrometry of a urine sample confirmed the presented of benzocaine, norcocaine and cocaine. Additional analysis of the 'cutting powder' used confirmed that this was benzocaine. The authors did not report whether phenacetin was screened for in either the biological samples or the cutting powder.

A 34-year-old man with a history of epilepsy attended a UK emergency department, under police escort, having been witnessed to ingest orally a packet of white powder. One hour postingestion, the patient developed repeated generalized seizures, with a persistent 'blue skin discoloration' [26]. The patient was intubated and ventilated. Arterial blood gas analysis revealed PaO_2 65.1 kPa with a calculated oxygen saturation of 82.5%; on the basis of these results and the dark colour of the blood sample, a methaemoglobin concentration was measured at 13.8%. The patient did not receive treatment with methylthioninium chloride as the methaemoglobin concentration was below 20%. Subsequent urine toxicological screening identified cocaine, as well the adulterants lidocaine and benzocaine. Phenytoin was also detected, although this is probably from therapeutic use in the emergency department. The authors attributed the seizures to methaemoglobinaemia-related hypoxaemia reducing the seizure threshold in a patient with known epilepsy.

There is one published case where phenacetin, in addition to local anaesthetics, was detected in a patient presenting with acute cocaine toxicity and methaemoglobinaemia [28]. A 24-year-old woman suffered a pre-hospital cardiac arrest following the use of cocaine and ethanol. Return of spontaneous circulation was achieved in the pre-hospital environment. On arrival in the emergency department, an arterial blood gas demonstrated a profound metabolic acidosis and a methaemoglobin concentration of 24%. She received an i.v. bolus of 90 mg of methylthioninium chloride. Despite meticulous supportive care, she developed hyper-pyrexia and associated rhabdomyolysis and died 2 days following admission to hospital. Post-mortem toxicological analysis detected the presence of cocaine and benzoylecgnoine, as well as the presence of a number of adulterants (benzocaine, lidocaine, levamisole and phenacetin).

There is one final case of cocaine-related methaemoglobinaemia from Ireland, although there is no toxicological screening to confirm which, if any adulterants, may have been responsible for the development of the methaemoglobinaemia [27]. A 24-year-old man used 12 lines of cocaine over a 48-h period, and then presented to an emergency department in Dublin having awoken the following morning and noticing that his face was blue. Oxygen saturations on finger-probe pulse oximetry were 84% and co-oximeter analysis of a arterial blood gas sample showed a methaemoglobin concentration of 28% (pH 7.39, pCO_2 5.82 kPa, pO_2 28.7 kPa, bicarbonate 26 mmol l^{-1} and oxygen saturations of 97%). A diagnosis of cocaine-induced methaemoglobinaemia was made and treatment with i.v. methylthioninium chloride commenced. The patient made a full and uneventful recovery. Unfortunately as already noted, there was no confirmatory toxicological analysis undertaken to confirm whether this methaemoglobinaemia was related to use of local anaesthetics or phenacetin as adulterants in the cocaine.

Conclusion

Methaemoglobinaemia can result in severe, potentially life-threatening clinical features because of tissue hypoxia. Methaemoglobinaemia can occur in individuals using recreational drugs either directly because of the oxidizing effect of the drugs (e.g. volatile nitrites) or related to adulterants in recreational drugs (e.g. local anaesthetics or phenacetin in cocaine). Poly-drug use is common in recreational drug users and the use of two or more agents with the potential to cause methaemoglobinaemia may increase the risk of it developing in recreational drug users. This is particularly important in the context of cocaine use, as street cocaine in Europe and North America commonly contains both phenacetin and local anaesthetics as adulterants.

Clinicians managing patients with acute recreational drug toxicity should be aware of the potential for methaemoglobinaemia in these patients, particularly in patients with cyanosis or unexplained low oxygen saturations on pulse oximetry.

Competing Interests

There are no competing interests to declare.

REFERENCES

1 Horne MK, Waterman MR, Simon LM, Garriott JC, Foerster EH. Methemoglobinaemia from sniffing butyl nitrite. Ann Intern Med 1979; 91: 417–8.

2 Wason S, Detsky AS, Platt OS, Lovejoy FH. Isobutyl nitrite ingestion by ingestion. Ann Intern Med 1980; 92: 637–8.

3 Edwards RJ, Ujma J. Extreme methaemoglobinaemia secondary to recreational use of amyl nitrite. J Accid Emerg Med 1995; 12: 138–42.

4 Sutton M, Jeffrey B. Acquired acute methaemoglobinaemia from amyl nitrite inhalation. J Emerg Nurs 1992; 18: 8–9.

5 Lindenmann J, Matzi V, Kauffman P, Krisper P, Maier A, Porubsky C, Smolle-Jeuttner FM. Hyperbaric oxygenation in the treatment of life-threatening isobutyl nitrite-induced methemoglobinemia. Inhal Toxicol 2006; 18: 1047–9.

6 Goldstein GM, Doull J. Treatment of nitrite induced methemoglobinemia with hyperbaric oxygen and methylene blue. Proc Soc Exp Biol Med 1971; 138: 137–9.

7 Jansen T, Barnung S, Mortensen CR, Jansen EC. Isobutyl –nitrite- induced methemoglobinemia; treatment with an exchange blood transfusion during hyperbaric oxygenation. Acta Anaesthesiol Scand 2003; 47: 1300–1301.

8 Shesser R, Mitchell J, Edelstein S. Methemoglobinemia from isobutyl nitrite preparations. Ann Emerg Med 1981; 10: 262–4.

9 Guss DA, Normann SA, Manoguerra AS. Clinically significant methemoglobinaemia from inhalation of isobutyl nitrite. Am J Emerg Med 1985; 3: 46–7.

10 Forsyth RJ, Moulden A. Methaemoglobinaemia after ingestion of amyl nitrite. Arch Dis Child 1991; 66: 152.

11 Sobey RJ, Campbell C. A 37 years old with amyl nitrite-induced methemoglobinemia. J Emerg Nurs 1992; 18: 11–3.

12 Sarvesaran ER, Fysh R, Bowen DAL. Amyl nitrite related deaths. Med Sci Law 1992; 32: 267–9.

13 Dudley MJ, Solomon T. A case of methemoglobinemia. Arch Emerg Med 1993; 10: 117–9.

14 Stambach T, Haire K, Soni N, Booth J. Saturday night blue- a case of near fatal poisoning from the abuse of amyl nitrite. J Accid Emerg Med 1997; 14: 339–40.

15 Modarai B, Kapadia YK, Terris J. Methylene blue: a treatment for severe methaemoglobinaemia secondary to misuse of amyl nitrite. Emerg Med J 2002; 19: 270–1.

16 Machabert R, Testud F, Descotes J. Methaemoglobinaemia due to amyl nitrite inhalation: a case report. Hum Exp Toxicol 1994; 13: 313–4.

17 Lin CH, Fang CC, Lee CC, Ko PCI, Chen WJ. Near fatal methemoglobinemia after recreational inhalation of amyl nitrite aerosolized with a compressed gas blower. J Formos Med Assoc 2005; 104: 856–9.

18 Beneteau-Burnat B, Pernet P, Varbourdolle M, Peloux P, Casenove L. Hypermethemoglobinemia in a substance abuser. Am J Emerg Med 2005; 23: 816–7.

19 Ranchon G, Mollard F, Laine N, Malick P, Robert D. Poppers induced methemoglobinemia: an unusual cause of cyanosis. Eur J Emerg Med 2008; 15: 361–2.

20 Pruijm MT, de Meijer PH. Methemoglobinemia due to ingestion of isobutyl nitrite ('poppers'). Ned Tijdschr Geneeskd 2002; 46: 2370–3.

21 Gentry Wilkerson R. Getting the blues at a rock concert: a case of severe methaemoglobinaemia. Emerg Med Australas 2010; 22: 466–9.

22 Dixon DS, Reisch RF, Santinga PH. Fatal methemoglobinemia with ingestion of isobutyl nitrite, a 'room odorizer' widely used for recreational purposes. J Forensic Sci 1981; 26: 587–93.

23 O'Toole JB, Robbins GB, Dixon DS. Ingestion of isobutyl nitrite, a recreational chemical of abuse, causing fatal methaemoglobinaemia. J Forensic Sci 1987; 32: 1811–2.

24 Bradberry SM, Whittington RM, Parry DA, Vale JA. Fatal methemoglobinemia due to inhalation of isobutyl nitrite. Clin Toxicol 1994; 32: 179–84.

25 McKinney CD, Postiglione KF, Herold DA. Benzocaine-adulterated street cocaine in association with methaemoglobinaemia. Clin Chem 1992; 38: 596–7.

26 Chakladar A, Willers JW, Pereskokova E, Beaumont PO, Uncles DR. White powder, blue patient: methaemoglobinaemia associated with benzocaine-adulterated cocaine. Resuscitation 2010; 81: 138–9.

27 Conway R, Browne P, O'Connell P. An unusual cause of methaemoglobinaemia. Ir Med J 2009; 102: 184.

28 Matthews AR, Oladapo O, Morgan BW. A cocaine death with concomitant adulterant – induced toxicity. Clin Toxicol 2009; 47: 761.

29 Flomenbaum NE, Goldfrank LR, Hoffman RS, Howland MA, Lewin NA, Nelson LS, eds. Methemoglobin Inducers in Toxicologic Emergencies. New York: McGraw-Hill Publishers, 2006.

30 Guay J. Methemoglobinemia related to local anesthetics: a summary of 242 episodes. Anesth Analg 2009; 108: 837–45.

31 Wright RO, Lewander WJ, Woolf AD. Methemoglobinemia: etiology, pharmacology, and clinical management. Ann Emerg Med 1999; 34: 646–56.

32 Hegedus F, Herb K. Benzocaine induced methaemoglobinaemia. Anesth Prog 2005; 52: 136–9.

33 Vadgama S, Wallace J. Methemoglobinaemia as a complication of topical anaesthesia during bronchoscopy. J Bronchol 2005; 12: 111–3.

34 Falkenhahn M, Kannan S, O'Kane M. Unexplained acute severe methemoglobinemia in a young adult. Br J Anaesth 2001; 86: 278–80.

35 Ralston AC, Webb RK, Runciman WB. Potential errors in pulse oximetry. III: effects of interference dyes, dyshaemoglobins and other pigments. Anaesthesia 1991; 46: 291–4.

36 Bradberry SM. Occupational methaemoglobinemia. Mechanisms of production, features, diagnosis and management including the use of methylene blue. Toxicol Rev 2003; 22: 13–27.

37 do Nascimento TS, Pereira RO, de Mello HL, Costa J. Methemoglobinemia: from diagnosis to treatment. Rev Bras Anestesiol 2008; 58: 657–64.

38 TOXBASE. Alkyl nitrites. Available at http://www.toxbase.org/Poisons-Index-A-Z/P-Products/Poppers/ (last accessed 1 December 2010).

39 European Monitoring Centre for Drugs and Drugs Addiction. Volatile solvents. Available at http://www.emcdda.europa.eu/publications/drug-profiles/volatile#control (last accessed 1 December 2010).

40 Dick D, Torrance C. MixMag drugs survey. Mix Mag 2010; 225: 44–53.

41 Home Office Statistical Bulletin. Drug Misuse Declared: Findings from the 2009/10 British Crime Survey. Available at http://rds.homeoffice.gov.uk/rds/pdfs10/hosb1310.pdf (last accessed 1 December 2010).

42 Goldstein GM, Doull J. Treatment of nitrite-induced methaemoglobinaemia with hyperbaric oxygen. Proc Soc Exp Biol Med 1971; 138: 137–9.

43 Goulon M, Nouailhat F, Gajdos P. On a case of acquired methaemoglobinaemia with coma, treated with hyberbaric oxygen and methylene blue. Rev Neurol 1966; 114: 376–8.

44 Shannon M. Clinical toxicity of cocaine adulterants. Ann Emerg Med 1988; 11: 1243–7.

45 United National Office on Drugs and Crime. World Drug Report 2009. Available at http://www.unodc.org/documents/wdr/WDR_2009/WDR2009_eng_web.pdf (last accessed 1 December 2010).

46 Serious Organised Crime Agency. Annual Report 2008/2009. Available at http://www.soca.gov.uk/about-soca/library (last accessed 1 December 2010).

47 European Monitoring Centre for Drugs and Drug Addiction. Annual Report 2009. Available at http://www.emcdda.europa.eu/attachements.cfm/att_93236_EN_EMCDDA_AR2009_EN.pdf (last accessed 1 December 2010).

48 Fucci N, De Giovanni N. Adulterants encountered in the illicit cocaine market. Forensic Sci Int 1998; 95: 247–52.

49 King LA. Drug content of powders and other illicit preparations in the UK. Forensic Sci Int 1997; 85: 135–47.

50 Fucci N. Phenacetin and cocaine in a body packer. Forensic Sci Int 2004; 141: 59–61.

51 Kenyon SL, Ramsey JD, Lee T, Johnston A, Holt DW. Analysis for identification in amnesty bin samples from dance venues. Ther Drug Monit 2005; 27: 793–8.

52 Brunt TM, Rigter S, Hoek J, Vogels N, VanDijk P, Niensk RJM. An analysis of cocaine powder in the Netherlands: content and health hazards due to adulterants. Addiction 2009; 104: 798–805.

53 Nakayama N, Masuda Y. Suppression of phenacetin-induced methemoglobinemia by diethyldithiocarbamate and carbon disulfide and its relation to phenacetin metabolism in mice. J Pharmacobiodyn 1985; 8: 868–76.

54 Jensen CB, Jollow DJ. The role of N-hydroxyphenetidine in phenacetin-induced hemolytic anemia. Toxicol Appl Pharmacol 1991; 111: 1–12.

55 Shahidi NT. Acetophenetidin-induced methemoglobinemia. Ann N Y Acad Sci 1968; 151: 822–32.

56 Bláhová K, Feber J. Severe Vicedrin poisoning in a 17-month-old girl. Cesk Pediatr 1991; 46: 98–100.