Phenmetrazine hydrochloride

14. AUTHOR(S), REVIEWER(S), DATE(S) (INCLUDING UPDATES), COMPLETE ADDRESS(ES)

Phenmetrazine hydrochloride

International Programme on Chemical Safety
Poison Information Monograph 942
Pharmaceutical

1. NAME

1.1 Substance

Phenmetrazine hydrochloride

1.2 Group

ATC Classification

Antiobesity preparations, excl., diet products (A08A)
Centrally acting antiobesity products (A08A A)

1.3 Synonyms

A 66 hydrochloride; Marsin;
Neo-zine; Preludin hydrochloride;
Probese-P hydrochloride;
Psychamine A 66 hydrochloride;
USAF GE-1

1.4 Identification numbers

1.4.1 CAS numbers

Phenmetrazine hydrochloride 1707-14-8

1.4.2 Other numbers

Phenmetrazine CAS 134-49-6
Phenmetrazine theoclate CAS 13931-75-4

Phenmetrazine hydrochloride NIOSH/RTECS QE6650000

1.5 Main brand names, main trade names

1.6 Main manufacturers, main importers

2. SUMMARY

2.1 Main risks and target organs

Acute central nervous system stimulation, cardiotoxicity causing tachycardia, arrhythmias, hypertension and cardiovascular collapse. High risk of dependency and abuse.

2.2 Summary of clinical effects

Cardiovascular - Palpitation, chest pain, tachycardia, arrhythmias and hypertension are common; cardiovascular

collapse can occur in severe poisoning. Myocardial ischaemia, infarction and ventricular dysfunction are described.

Central Nervous System (CNS) - Stimulation of CNS, tremor, restlessness, agitation, insomnia, increased motor activity, headache, convulsions, coma and hyperreflexia are described. Stroke and cerebral vasculitis have been observed.

Gastrointestinal - Vomiting, diarrhoea and cramps may occur. Acute transient ischaemic colitis has occurred with chronic methamphetamine abuse.

Genitourinary - Increased bladder sphincter tone may cause dysuria, hesitancy and acute urinary retention. Renal failure can occur secondary to dehydration or rhabdomyolysis. Renal ischaemia may be noted.

Dermatologic - Skin is usually pale and diaphoretic, but mucous membranes appear dry.

Endocrine - Transient hyperthyroxinaemia may be noted.

Metabolism - Increased metabolic and muscular activity may result in hyperventilation and hyperthermia. Weight loss is common with chronic use.

Fluid/Electrolyte - Hypo- and hyperkalaemia have been reported. Dehydration is common.

Musculoskeletal - Fasciculations and rigidity may be noted. Rhabdomyolysis is an important consequence of severe amphetamine poisoning.

Psychiatric - Agitation, confusion, mood elevation, increased wakefulness, talkativeness, irritability and panic attacks are typical. Chronic abuse can cause delusions and paranoia. A withdrawal syndrome occurs after abrupt cessation following chronic use.

2.3 Diagnosis

The diagnosis of acute amphetamine poisoning is made on the history of exposure or abuse, and the characteristic features of CNS and cardiovascular stimulation. The presence of amphetamines in urine or blood can support the diagnosis but is not helpful in management. Whilst some patients show signs of toxicity at blood concentrations of 20 µg/L, chronic abusers of amphetamine have been known to have blood concentration of up to 3000 µg/L.

2.4 First aid measures and management principles

Management of amphetamine and its complications is essentially supportive.
The initial priority is stabilisation of the airway, breathing and circulation. Monitoring of pulse, blood pressure, oxygenation, core temperature and cardiac rhythm should instituted. Supplemental oxygen should be administered. Specific supportive care measures that may be necessary include: maintenance of hydration, control of seizures, relief of agitation, control of hyperthermia,

control of hypertension, management of rhabdomyolysis.

Decontamination with oral activated charcoal is appropriate if the patient is conscious.

There are no suitable methods of enhancing elimination of amphetamine and no specific antidotes.

3. PHYSICO-CHEMICAL PROPERTIES

3.1 Origin of the substance

Synthetic

3.2 Chemical structure

Phenmetrazine hydrochloride

Chemical name:
3-Methyl-2-phenylmorpholine hydrochloride

Other chemical names:
2-Phenyl-3-methyltetrahydro-1,4-oxazine hydrochloride
3-Methyl-2-phenyltetrahydro-2H-1,4-oxazine hydrochloride

Molecular formula: $C_{11}H_{15}NO,HCl$
Molecular weight: 213.7

3.3 Physical properties

3.3.1 Colour

3.3.2 State/Form

3.3.3 Description

3.4 Other characteristics

3.4.1 Shelf-life of the substance

3.4.2 Storage conditions

Store in airtight containers. Refrigeration unnecessary.

4. USES

4.1 Indications

4.1.1 Indications

Antiobesity preparation (not diet product)
Centrally acting antiobesity product

4.1.2 Description

Indications

Appetite suppressant (anorectic) for benzphetamine, diethypropion, phendimetrazine, phenmetrazine and phenteramine.

Misuse:

Performance enhancement
Relief of fatigue

Abuse:

Abuse either orally or by injection is extremely common.

(Dollery, 1991; Reynolds, 1996)

4.2 Therapeutic dosage

4.2.1 Adults

4.2.2 Children

4.3 Contraindications

Anorexia, insomnia, psychopathic personality disorders, suicidal tendencies, Gilles de la Tourette syndrome and other disorders, hyperthyroidism, narrow angle glaucoma, diabetes mellitis and cardiovascular diseases such as angina, hypertension and arrythmias (Dollery, 1991; Reynolds, 1996).

Amphetamine interacts with several other drugs (see 7.6).

5. ROUTES OF EXPOSURE

5.1 Oral

Readily absorbed from the gastro-intestinal tract and buccal mucosa. It Is resistant to metabolism by monoamine oxidase.

5.2 Inhalation

Amphetamine is rapidly absorbed by inhalation and is abused by this route (Brust, 1993).

5.3 Dermal

No data available.

5.4 Eye

No data available.

5.5 Parenteral

Frequent route of entry in abuse situations.

5.6 Other

No data available.

6. KINETICS

6.1 Absorption by route of exposure

Amphetamine is rapidly absorbed after oral ingestion. Peak plasma levels occur within 1 to 3 hours, varying with the degree of physical activity and the amount of food in the stomach. Absorption is usually complete by 4 to 6 hours. Sustained release preparations are available as resin-bound, rather than soluble, salts. These compounds display reduced peak blood levels compared with standard amphetamine preparations, but total amount absorbed and time to peak levels remain similar (Dollery, 1991).

6.2 Distribution by route of exposure

Amphetamines are concentrated in the kidney, lungs, cerebrospinal fluid and brain. They are highly lipid soluble and readily cross the blood-brain barrier. Protein binding and volume of distribution varies widely, but the average volume of distribution is 5 L/kg body weight (Dollery, 1991).

6.3 Biological half-life by route of exposure

Under normal conditions, about 30% of amphetamine is excreted unchanged in the urine but this excretion is highly variable and is dependent on urinary pH. When the urinary pH is acidic (pH 5.5 to 6.0), elimination is predominantly by urinary excretion with approximately 60% of a dose of amphetamine being excreted unchanged by the kidney within 48 hours. When the urinary pH is alkaline (pH 7.5 to 8.0), elimination is predominantly by deamination (less than 7% excreted unchanged in the urine); the half-life ranging from 16 to 31 hours (Ellenhorn, 1997).

6.4 Metabolism

The major metabolic pathway for amphetamine involves deamination by cytochrome P_{450} to para-hydroxyamphetamine and phenylacetone; this latter compound is subsequently oxidised to benzoic acid and excreted as glucuronide or glycine (hippuric acid) conjugate. Smaller amounts of amphetamine are converted to norephedrine by oxidation. Hydroxylation produces an active metabolite, O-hyroxynorephedrine, which acts as a false neurotransmitter and may account for some drug effect, especially in chronic users (Dollery, 1991).

6.5 Elimination and excretion

Normally 5 to 30% of a therapeutic dose of amphetamine is excreted unchanged in the urine by 24 hours, but the actual amount of urinary excretion and metabolism is highly pH dependent (Dollery, 1991).

7. PHARMACOLOGY AND TOXICOLOGY

7.1 Mode of action

Amphetamine appears to exert most or all of its effect in the CNS by causing release of biogenic amines, especialy norepinephrine and dopamine, from storage sites in nerve terminals. It may also slow down catecholamine metabolism by inhibiting monoamine oxidase (Hardman, et al., 1997).

7.2 Toxicity

7.2.1 Human data

7.2.1.1 Adults

The toxic dose varies considerably due to individual variations and the development of tolerance. Fatalities have been reported following ingestion of doses as low as 1.3 mg/kg, while tolerance has been

developed to 1,000 mg at a time and up to 5 g in a day.

7.2.1.2 Children

Children appear to be more susceptible than adults and are less likely to have developed tolerance.

7.2.2 Relevant animal data

Adult monkeys have an LD_{50} of 15 to 20 mg/kg, whereas for young monkeys the LD_{50} is only 5 mg/kg.

7.2.3 Relevant in vitro data

Not relevant

7.3 Carcinogenicity

To be completed

7.4 Teratogenicity

The use of amphetamine for medical indications does not pose a significant risk to the fetus for congenital anomalies (Briggs, 1990). Amphetamines generally do not appear to be human teratogens. Mild withdrawal symptoms may be observed in the newborn, but the few studies of infant follow-up have not shown long-term sequelae, although more studies of this nature are needed.

Illicit maternal use or abuse of amphetamine presents a significant risk to the foetus and newborn, including intrauterine growth retardation, premature delivery and the potential for increased maternal, fetal and neonatal morbidity.

These poor outcomes are probably multifactorial in origin, involving multiple drug use, life-styles and poor maternal health. However, cerebral injuries occurring in newborns exposed in utero appear to be directly related to the vasoconstrictive properties of amphetamines. Ericksson et al. (1989) followed 65 children whose mothers were addicted to amphetamine during pregnancy, at least during the first trimester. Intelligence, psychological function, growth, and physical health were all within the normal range at eight years, but those children exposed throughout pregnancy tended to be more aggressive.

7.5 Mutagenicity

No relevant data

7.6 Interactions

Acetazolamide - administration may increase serum concentration of amphetamine.

Alcohol - may increase serum concentration of amphetamine.

Ascorbic acid -lowering urinary pH, may enhance amphetamine excretion

Furazolidone - amphetamines may induce a hypertensive response in patients taking furazolidone.

Guanethidine - amphetamine inhibits the antihypertensive response to guanethidine.

Haloperidol - limited evidence indicates that haloperidol may inhibit the effects of amphetamine but the clinical importance of this interaction is not established.

Lithium carbonate - isolated case reports indicate that lithium may inhibit the effects of amphetamine.

Monoamine oxidase inhibitor - severe hypertensive reactions have followed the administration of amphetamines to patients taking monoamine oxidase inhibitors.

Noradrenaline - amphetamine abuse may enhance the pressor response to noradrenaline.

Phenothiazines - amphetamine may inhibit the antipsychotic effect of phenothiazines, and phenothiazines may inhibit the anorectic effect of amphetamines.

Sodium bicarbonate - large doses of sodium bicarbonate inhibit the elimination of amphetamine, thus increasing the amphetamine effect.

Tobacco smoking - amphetamine appears to induce dose-related increases in cigarette smoking.

Tricyclic antidepressants - theoretically increases the effect of amphetamine, but clinical evidence is lacking.

(Stockley, 1994; Dollery, 1991)

8. TOXICOLOGICAL ANALYSES AND BIOMEDICAL INVESTIGATIONS

8.1 Material sampling plan

8.1.1 Sampling and specimen collection

8.1.1.1 Toxicological analyses

8.1.1.2 Biomedical analyses

8.3.1.1.1 Basic analyses

8.3.1.1.2 Dedicated analyses

8.3.1.1.3 Optional analyses

8.3.1.2 Urine

8.3.1.2.1 Basic analyses

8.3.1.2.2 Dedicated analyses

8.3.1.2.3 Optional analyses

8.3.1.3 Other fluids

8.3.2 Arterial blood gas analyses

8.3.3 Haematological analyses

8.3.3.1.1 Basic analyses

8.3.3.1.2 Dedicated analyses

8.3.3.1.3 Optional analyses

8.3.4 Interpretation of biomedical investigations

8.4 Other biomedical (diagnostic) investigations and their interpretation

8.5 Overall interpretation of all toxicological analyses and toxicological investigations

Sample collection

Creatinine, urea, and electrolyte measurement are important to establish whether renal impairment or hyperkalaemia is present. Measurements of serum creatine kinase, aspartate transaminase and myoglobin can help to establish if there is rhabdomyolysis, and myoglobin can be detected in urine.

Liver function tests are relevant, since hepatitis can occur.

A full blood count and coagulation studies can be helpful, with measurement of fibrinogen and of fibrin degradation products, in establishing a diagnosis of disseminated intravascular coagulation.

Biomedical analysis

Temperature, blood pressure, and pulse rate should be monitored frequently. A temperature above 40°C, and marked hypertension and tachycardia are seen in severe poisoning.

An electrocardiogram can be useful in detecting myocardial ischaemia or arrhythmia. Electrocardiographic monitoring can be helpful in patients with arrhythmia.

Toxicological analysis

Urine or serum analysis for amphetamine can help to confirm exposure, but cannot be used to establish poisoning, because of difference in individual tolerance to amphetamines.

8.6 References

9. CLINICAL EFFECTS

9.1 Acute poisoning

9.1.1 Ingestion

Effects are most marked on the central nervous system, cardiovascular system, and muscles. The triad of hyperactivity, hyperpyrexia, and hypertension is characteristic of acute amphetamine overdosage.

Agitation, confusion, headache, delirium, and hallucination, can be followed by coma, intracranial haemorrhage, stroke, and death.

Chest pain, palpitation, hypertension, tachycardia, atrial and ventricular arrhythmia, and myocardial infarction can occur.

Muscle contraction, bruxism (jaw-grinding), trismus (jaw clenching), fasciculation, rhabdomyolysis, are seen leading to renal failure; and flushing, sweating, and hyperpyrexia can all occur. Hyperpyrexia can cause disseminated intravascular coagulation.

(Brust, 1993; Derlet et al., 1989)

9.1.2 Inhalation

The clinical effects are similar to those after ingestion, but occur more rapidly (Brust, 1993).

9.1.3 Skin exposure

No data available

9.1.4 Eye contact

No data available

9.1.5 Parenteral exposure

Intravenous injection is a common mode of administration of amphetamine by abusers. The euphoria produced is more intense, leading to a "rush" or "flash" which is compared to sexual orgasm (Brust, 1993). Other clinical effects are similar to those observed after ingestion, but occur more rapidly.

9.1.6 Other

No data available

9.2 Chronic poisoning

9.2.1 Ingestion

Tolerance to the euphoric effects and CNS stimulation induced by amphetamine develops rapidly, leading abusers to use larger and larger amounts to attain and sustain the desired affect.

Habitual use or chronic abuse usually results in toxic psychosis classically characterised by paranoia, delusions and hallucinations, which are usually visual, tactile or olfactory in nature, in contrast to the typical auditory hallucinations of schizophrenia. The individual may act on the delusions, resulting in

bizarre violent behaviour, hostility and aggression, sometimes leading to suicidal or homicidal actions. Dyskinesia, compulsive behaviour and impaired performance are common in chronic abusers. The chronic abuser presents as a restless, garrulous, tremulous individual who is suspicious and anxious.

9.2.2 Inhalation

As for 9.2.1.

9.2.3 Skin exposure

No relevant data.

9.2.4 Eye contact

No relevant data.

9.2.5 Parenteral exposure

As for 9.2.1.

9.2.6 Other

Vaginal exposure, as for 9.2.1.

9.3 Course, prognosis, cause of death

Symptoms and signs give a clinical guide to the severity of intoxication as follows (Espelin and Done, 1968):

Mild toxicity - restlessness, irritability, insomnia, tremor, hyperreflexia, sweating, dilated pupils, flushing;

Moderate toxicity - hyperactivity, confusion, hypertension, tachypnoea, tachycardia, mild fever, sweating;

Severe toxicity - delirium, mania, self-injury, marked hypertension, tachycardia, arrhythmia, hyperpyrexia, convulsion, coma, circulatory collapse.

Death can be due to intracranial haemorrhage, acute heart failure or arrhythmia, hyperpyrexia, rhabdomyolysis and consequent hyperkalaemia or renal failure, and to violence related to the psychiatric effects (Kalant & Kalant, 1975).

9.4 Systematic description of clinical effects

9.4.1 Cardiovascular

Cardiovascular symptoms of acute poisoning include palpitation and chest pain. Tachycardia and hypertension are common. One third of patients

reported by Derlet et al. (1989) had a blood pressure greater than 140/90 mmHg, and nearly two-thirds had a pulse rate above 100 beats per minute.

Severe poisoning can cause acute myocardial ischaemia, myocardial infarction (Carson et al., 1987; Packe et al., 1990), and left ventricular failure (Kalant & Kalant, 1975). These probably result from vasospasm, perhaps at sites of existing atherosclerosis. In at least one case, thrombus was demonstrated initially (Bashour, 1994).

Chronic oral amphetamine abuse can cause a chronic cardiomyopathy; an acute cardiomyopathy has also been described (Call et al., 1982).

Hypertensive stroke is a well-recognised complication of amphetamine poisoning (see 9.4.3).

Intra-arterial injection of amphetamine can cause severe burning pain, vasospasm, and gangrene (Birkhahn & Heifetz, 1973).

9.4.2 Respiratory

Pulmonary fibrosis, right ventricular hypertrophy and pulmonary hypertension are frequently found at post-mortem examination.

Pulmonary function tests usually are normal except for the carbon monoxide diffusing capacity. Respiratory complications are sometimes caused by fillers or adulterants used in injections by chronic users. These can cause multiple microemboli to the lung, which can lead to restrictive lung disease.

Pneumomediastinum has been reported after amphetamine inhalation (Brust, 1993).

9.4.3 Neurological

9.4.3.1 Central nervous system (CNS)

Main symptoms include agitation, confusion, delirium, hallucinations, dizziness, dyskinesia, hyperactivity, muscle fasciculation and rigidity, rigors, tics, tremors, seizures and coma.

Both occlusive and haemorrhagic strokes have been reported after abuse of amphetamines. Twenty-one of 73 drug-using young persons with stroke had taken amphetamine (Kaku &

Lowenstein, 1990), of whom six had documented intracerebral haemorrhage and two had subarachnoid haemorrhage. Patients with underlying arteriovenous malformations may be at particular risk (Selmi et al., 1995).

Stroke can occur after oral, intravenous, or nasal administration. Severe headache beginning within minutes of ingestion of amphetamine is usually the first symptom. In more than half the cases, hypertension which is sometimes extreme, accompanies other symptoms. A Cerebral vasculitis has also been observed (Brust, 1993).

Dystonia and dyskinesia can occur, even with therapeutic dosages (Mattson & Calverley, 1968).

Psychiatric effects, particularly euphoria and excitement, are the motives for abuse. Paranoia and a psychiatric syndrome indistinguishable from schizophrenia are sequelae of chronic use (Hall et al., 1988; Flaum & Schultz, 1996; Johnson & Milner, 1966).

9.4.3.2 Peripheral nervous system

No relevant data

9.4.3.3 Autonomic nervous system

Stimulation of alpha-adrenergic receptors produces mydriasis, increased metabolic rate, diaphoresis, increased sphincter tone, peripheral vasoconstriction and decreased gastrointestinal motility.

Stimulation of β-adrenergic receptors produces increased heart rate and contractility, increased automaticity and dilatation of bronchioles.

9.4.3.4 Skeletal and smooth muscle

Myalgia, muscle tenderness, muscle contractions, and rhabdomyolysis, leading to fever, circulatory collapse, and myoglobinuric renal failure, can occur with amphetamines (Kendrick et al., 1977).

9.4.4 Gastrointestinal

Most common symptoms are nausea, vomiting, diarrhoea, and abdominal cramps. Anorexia may be severe. Epigastric pain and haematemesis have been described after intravenous amphetamine use. A case of ischaemic colitis with normal mesenteric arteriography in a patient taking dexamphetamine has been described

(Beyer et al., 1991).

9.4.5 Hepatic

Hepatitis and fatal acute hepatic necrosis have been described
(Kalant & Kalant, 1975).

9.4.6 Urinary

9.4.6.1 Renal

Renal failure, secondary to dehydration or rhabdomyolysis may be observed.

9.4.6.2 Other

Increased bladder sphincter tone may cause dysuria, hesitancy and acute urinary retention. This effect may be a direct result of peripheral alpha-agonist activity.

Spontaneous rupture of the bladder has been described in a young woman who took alcohol and an amphetamine-containing diet tablet (Schwartz, 1981).

9.4.7 Endocrine and reproductive systems

Transient hyperthyroxinaemia may result from heavy amphetamine use (Morley et al., 1980).

9.4.8 Dermatological

Skin is usually pale and diaphoretic, but mucous membranes appear dry. Chronic users may display skin lesion, abscesses, ulcers, cellulitis or necrotising angiitis due to physical insult to skin, or dermatologic signs of dietary deficiencies, e.g. cheilosis, purpura.

9.4.9 Eye, ear, nose, throat: local effects

Mydriasis may be noted.
Diffuse hair loss may be noted.
Chronic users may display signs of dietary deficiencies.

9.4.10 Haematological

Disseminated intravascular coagulation is an important consequence of severe poisoning (Kendrick et al., 1980).
Idiopathic thrombocytopenic purpura may occur.

9.4.11 Immunological

No relevant data.

9.4.12 Metabolic

9.4.12.1 Acid-base disturbance

No relevant data

9.4.12.2 Fluid and electrolyte disturbance

Increase metabolic and muscular activity may result in dehydration.

9.4.12.3 Others

No data available

9.4.13 Allergic reactions

No relevant data

9.4.14 Other clinical effects

No relevant data

9.4.15 Special risks

Pregnancy: Eriksson et al. (1989) followed 65 children whose mother were addicted to amphetamine during pregnancy, at least during the first trimester. Intelligence, psychological function, growth, and physical health were all within the normal range at eight years, but those exposed throughout pregnancy tended to be more aggressive.

A case report describes a normal female infant born to mother who took up to 180 mg/day of dexamphetamine for narcolepsy throughout pregnancy (Briggs et al., 1975).

Breast-feeding: Amphetamine is passed into breast milk and measurable amounts can be detected in breast-fed infant's urine. Therefore lactating mothers are advised not to take or use amphetamine.

9.5 Other

Amphetamine withdrawal syndrome: Abrupt discontinuance following chronic use is characterised by apathy, depression, lethargy, anxiety and sleep disturbances. Myalgias, abdominal pain, voracious appetite and a profound depression with suicidal tendencies may complicate the immediate post-withdrawal period and peak in 2 to 3 days. To relieve these symptoms, the user will often return to use more amphetamine, often at increasing doses due to the tolerance which is readily established. Thus a cycle of use-withdrawal-use is established (Kramer et al., 1967; Hart & Wallace, 1975). Physical effects are not life threatening but can lead to a stuporose state (Tuma, 1993); the associated depression can lead to suicide. It may take up to eight weeks for suppressed REM (rapid eye movement) sleep to return to normal (Brust 1993).

"Overamped": When the intravenous dosage is increased too

rapidly the individual develops a peculiar condition referred to as "overamped: in which he or she is conscious but unable to speak or move. Elevated blood pressure, temperature and pulse as well as chest distress occurs in this setting. Death from overdose in tolerant individuals is infrequent.

9.6 Summary

10. MANAGEMENT

10.1 General principles

General supportive measures should be used. These should include stabilisation of the airway, breathing, and circulation; relief of agitation, adequate hydration, and control of core temperature. Convulsions, hyperthermia, and rhabdomyolysis may require specific treatment. Activated charcoal may be helpful for decontamination after oral ingestion. Ipecacuanha is contra-indicated because of its stimulant properties. There are no effective methods of enhancing elimination and no antidote.

Agitation and convulsion can be treated with diazepam. If agitation is severe, then chlorpromazine may have specific advantages over other major tranquillisers (Espelin & Done, 1968; Klawans, 1968). Parenteral dosages of 0.5 to 2 milligrams per kilogram have been used in Infants (Espelin & Done, 1968).

Severe hyperthermia (core temperature greater than 40°C) requires forced cooling by fans, tepid sponging or other means, and may also require the administration of diazepam or dantrolene or both agents in order to eliminate muscle activity.

Rhabdomyolysis associated with muscle overactivity can cause hyperkalaemia or renal failure, and should be treated conventionally. Dialysis may be needed if renal failure supervenes.

Acute severe hypertension (diastolic blood pressure greater than 100 mmHg) can be controlled by infusion of sodium nitroprusside by continuous intravenous infusion at an initial rate of 3 mcg/kg/min, titrated to achieve the desired response.

Patients who are addicted to amphetamines may develop the withdrawal syndrome described in 9.5.

10.2 Life supportive procedures and symptomatic/specific treatment

Treatment is supportive. Administration of supplemental oxygen, establishment of intravenous access and monitoring of vital signs including core temperature, and cardiac rhythm are recommended. The following may be necessary according to clinical indication:

-Maintenance adequate airway and ventilation
-Rehydration with intravenous fluids
-Control of seizures

-Control of agitation with benzodiazepines
-Control of severe hypertension (diastolic blood pressure greater than 110 mmHg)
-Control of hyperthermia
-Treatment of hyperkalaemia
-Cardiac intensive care for ischaemia or arrhythmia

10.3 Decontamination

No regime of oral decontamination has been demonstrated to improve outcome. Ipecacuanha is contra-indicated. Oral activated charcoal may be helpful following oral overdosage.

10.4 Enhanced elimination

No regime of decontamination has been demonstrated to improve outcome. Forced acid diuresis has been abandoned as a decontamination procedure. Neither haemodialysis nor charcoal haemoperfusion is likely to be of benefit.

10.5 Antidote treatment

10.5.1 Adults

There is no antidote to amphetamine poisoning.

10.5.2 Children

There is no antidote to amphetamine poisoning.

10.6 Management discussion

There are differences between dexamphetamine and related compounds such as 3,4-methylenedeoxymetamphetamine ("ecstacy"); for example, hyperthermia appears to be more of a problem with the latter, and this may be because of the association between use and frenetic physical activity ("rave" dancing) (Henry et al., 1992).

In the past, energetic gastric decontamination procedures were suggested (Espelin & Done, 1968). There is no evidence that such procedures improve outcome in amphetamine poisoning, and they are potentially hazardous.

Oral activated charcoal is probably the safest option for decontamination, but is only likely to bind drug in the stomach if a substantial oral dose of amphetamine has been taken, and the charcoal is given within an hour or two of ingestion. If should only administered to patients in whom swallowing and gag reflexes are intact. In drug smugglers who have swallowed supposedly inert packages of amphetamines ("stuffers" or "packers"), and who develop symptoms because of leakage from the packages, then repeated doses of oral activated charcoal with a cathartic are likely to be worthwhile.

Forced acid diuresis has now been abandoned as an elimination treatment, because it is intrinsically difficult and potentially dangerous.

Treatment of agitation in amphetamine poisoning is required

when a patient is a danger to himself or herself, or to others. Because poisoning is associated with sympathetic overactivity, and chlorpromazine has alpha-adrenoreceptor antagonist actions, chlorpromazine has been recommended as the sedative treatment of choice (see 10.1). There is no

study to demonstrate that chlorpromazine is in fact superior to benzodiazepine.

11. ILLUSTRATIVE CASES

11.1 Case reports from literature

Ingestion of 2.2g (28mg/kg) in a 21 year old man resulted in severe toxicity (Ginsberg et.al., 1970).

An 18 month old male infant ingested an unknown amount of amphetamine, subsequently detected in the urine. He had a history of restlessness and vomiting for 10 hours and was admitted to hospital with mild fever (38°C), pulse rate of 140 per minute and respiratory rate of 34 per minute. He looked acutely unwell, hyperactive and combative and had normal pupils with a bi-lateral light reflex. Some irregular flushing was found over the skin of the trunk. He was given diazepam 10mg intravenously, 10% chloral hydrate 10ml rectally and haloperidol 20mg intravenously. After a sleep of 20 hours normal activity resumed and the patient was clinically well and discharged (Soong et.al., 1991).

A 20-month-old male infant was admitted to hospital with a history of being too restless, hyperactive and agitated to be manageable for several hours, and had not responded to 10mg diazepam given intravenously in a local medical clinic. He had dilated pupils, doll's eyes and normal discs. Generalised hypperreflexia and a mild clonus were noted, but no focal neurological abnormalities could be found. His vital signs were - blood pressure 130/90 mmHg, pulse rate 150/min, respiratory rate 46/min and normal temperature. The clinical status remained unchanged for a further 18 hours and the patient then calmed down to sleep for 20 hours. Subsequently the parents found amphetamine powder spread near the infant's bed (Soong, et.al., 1991).

12. ADDITIONAL INFORMATION

12.1 Specific preventive measures

When prescribing amphetamines, due regard must be given to its potential for misuse and addiction.

12.2 Other

No data available.

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See Also:
Toxicological Abbreviations