Cocaine Toxicity

Cocaine is a naturally occurring alkaloid with unique local anesthetic and sympathomimetic activity, which served as the prototype for the synthesis of local anesthetics.

Cocaine is contained in the leaves of Erythroxylum coca, a shrub that grows abundantly in Colombia, Peru, Bolivia, the West Indies, and Indonesia.

The alkaloid form of cocaine (benzoylmethylecgonine) is extracted from the leaf by mechanical degradation in the presence of a hydrocarbon.

The resulting product is converted into a hydrochloride salt to yield a white powder (cocaine hydrochloride).

Cocaine hydrochloride can be insufflated, applied topically to mucous membranes, dissolved in water and injected, or ingested; however, it degrades rapidly when pyrolyzed.

Smokeable cocaine (crack) is formed by dissolving cocaine hydrochloride in water and adding a strong base. A hydrocarbon solvent is added, the cocaine base is extracted into the organic phase, and then evaporated. The term free-base refers to the use of cocaine base in solution.

Cocaine is usually abused by either chewing coca leaves, smoking coca paste, or "snorting" cocaine hydrochloride. The last mentioned is the most popular form of cocaine intake, i.e. the drug is inhaled in powder form through the nostrils . Occasionally, cocaine hydrochloride is injected intravenously.

Today, a smokable form of cocaine ("crack" or "rock") has virtually become a rage in the West.
Pure alkaloidal cocaine ("free-base" or "baseball") can also be smoked.

Cocaine freebase is prepared from cocaine hydrochloride by extracting the cocaine with an alkaline solution (buffered ammonia) and adding a solvent such as ether or acetone. The mixture separates into two layers, the top solvent layer containing the dissolved cocaine. The solvent is then evaporated leaving almost pure cocaine crystals. Free-base is a colourless, odourless, transparent, crystalline substance that makes a popping or cracking sound when heated (hence the term "crack").

Both free-base and crack are more stable to pyrolysis than the hydrochloride salt, and therefore can be smoked either using a "coke pipe" or mixed into a cigarette ("joint").
A solution of cocaine hydrochloride can also be heated in a pan with baking soda added until a solid "rock" is formed, pieces of which can be smoked directly.

Street cocaine is often impure. The content of pure cocaine ranges from 10 to 50 percent (most commonly 15 to 20 percent).

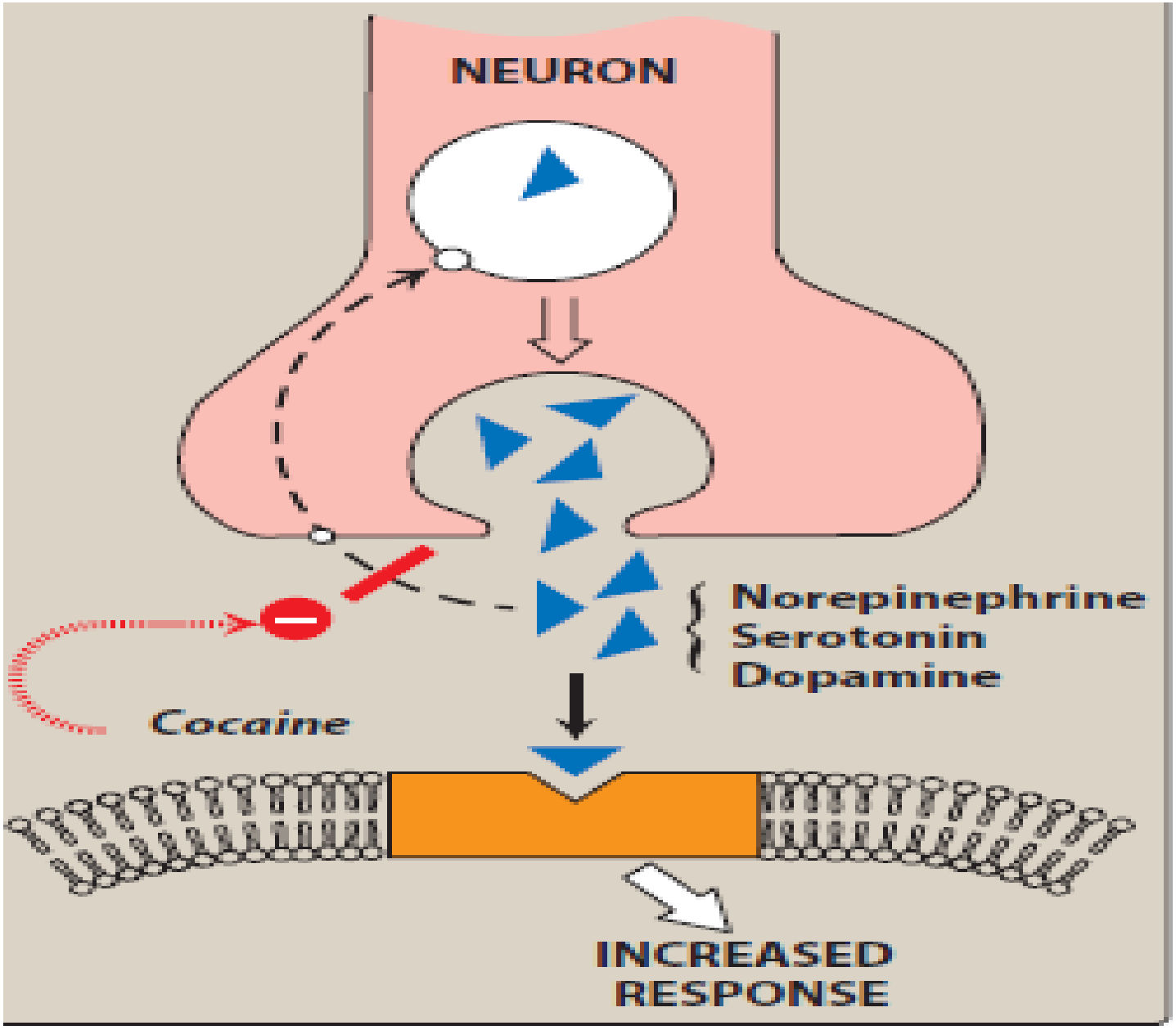
Cocaine, which is available on the street, is often adulterated with one or more of the following compounds: talc, lactose, sucrose, glucose, mannitol, inositol, caffeine, procaine, phencyclidine, lignocaine, strychnine, amphetamine, or heroin (“speed ball”).

NEUROTRANSMITTER EFFECTS

Cocaine blocks the reuptake of biogenic amines. Specifically, these effects are described on serotonin and the catecholamines dopamine, norepinephrine, and epinephrine.

The CNS stimulant effects of cocaine are mediated through inhibition of dopamine reuptake in the nucleus accumbens. The dopamine-reuptake trans- porter controls the levels of dopamine in the synapse by rapidly carrying the neurotransmitter back into nerve terminals after its release.

Cocaine, which binds strongly to the dopamine-reuptake transporter, is a classic blocker of such reuptake after normal neuronal activity. Because of this blocking effect, dopamine remains at high concentrations in the synapse and continues to affect adjacent neurons producing the characteristic cocaine "high".


NEURON
Norepinephrine
Serotonin
Dopamine
Cocaine
INCREASED
RESPONSE

Cocaine also increases the concentrations of the excitatory amino acids, aspartate and glutamate. These excitatory amino acids increase the extracellular concentrations of dopamine. Excitatory amino acid antagonists attenuate the effects of cocaine induced convulsions and death. Dopamine2 (D2) receptor agonists accentuate cocaine craving, while dopamine1 (D1) agonists diminish such craving. Cocaine also inhibits reuptake of noradrenaline and serotonin. Increase in the concentrations of the former plays an important role in the toxic effects of cocaine.

Concerning Peripheral nerves, through direct blockade of fast sodium channels, cocaine stabilize the axonal membrane, producing a local anaesthetic effect.

Cocaine is the only local anaesthetic that interferes with the uptake of neurotransmitter by the nerve terminals and simultaneously functions as a vasoconstrictor.

CARDIOVASCULAR EFFECTS

Initial effect of cocaine on the CVS is bradycardia, secondary to stimulation of vagal nuclei. However, the bradycardia is too transient to be clinically evident, and tachycardia becomes the prominent effect resulting from central sympathetic stimulation.

The cardiostimulatory effect of cocaine is due in large part to sensitisation to adrenaline and noradrenaline, preventing neuronal reuptake of these catecholamines, as well as due to increased release of noradrenaline from adrenergic nerve terminals.

The increased concentrations and persistence of catecholamines near the receptors of the effecter organ lead to exaggerated sympathetic effects. The sympathomimetic effects of cocaine increase myocardial oxygen demand and the alpha-adrenergic mediated coronary vasoconstriction limits coronary artery blood flow.

Cocaine inhibits endogenous fibrinolysis, increases thrombogenicity, and enhances platelet aggregation.

Toxicokinetics

- Absorption:

Ingestion and insufflation: Cocaine is well-absorbed from oral, nasal, and pulmonary routes. Onset of action on insufflation is within 1 to 3 minutes, and peak effects are seen in 20 to 30 minutes.

Intravenous injection: Onset of action is within seconds, and peak action occurs in 3 to 5 minutes.

Inhalation: Smoking produces effects as rapidly as IV injection.

Table1 lists the typical onsets and durations of action for various uses of cocaine.

- Metabolism:

Cocaine is metabolised by liver esterases and plasma cholinesterase to ecgonine methylester (EME), one of the major metabolites, while non-enzymatic hydrolysis results in the formation of the other major metabolite, benzoylecgonine (BE).

Patients with lower plasma cholinesterase levels may be predisposed to more severe cocaine toxicity. Since children have lower plasma cholinesterase levels, they may be affected by smaller amounts of cocaine. In addition, the metabolic half-life of cocaine may be increased by lower plasma cholinesterase concentrations.

Route of Exposure	Onset of Action (min)	Peak Action (min)	Duration of Action (min)
Intravenous	<1	3–5	30–60
Nasal insufflation	1–5	20–30	60–120
Smoking	<1	3–5	30–60
Gastrointestinal	30–60	60–90	Unknown

Clinical Features

Acute Poisoning:

a. Hyperthermia—This results from:

- Augmentation of heat production due to increased psychomotor activity.
- Diminution of heat dissipation due to vasoconstriction.
- Direct pyrogenic effect due to action on thermoregulatory centers in the hypothalamus.
- Stimulation of calorigenic activity of liver.

Body temperature often soars to 42.2 to 44.4°C, and does not respond to conventional antipyretics. It is often associated with rhabdomyolysis, seizures, and renal failure.

b. CNS effects—

Headache, Anxiety, agitation. Hyperactivity, restlessness, Tremor, hyperreflexia and Convulsions (Generalised tonic-clonic, partial motor, and partial complex seizure have all been reported).

Seizures may be recurrent and status epilepticus has been reported, particularly in children.

Sometimes there is lethargy and decreased level of consciousness which can persist up to 24 hours (“cocaine washed out syndrome”).

Cerebrovascular accidents are not uncommon, and include subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction, transient ischaemic attacks, migraine-type headache syndrome, cerebral vasculitis, and anterior spinal artery syndrome. Infarction of the brainstem/spinal cord has also occurred.

c. Ophthalmologic effects:

-Mydriasis and/or loss of eyebrow and eyelash hair from smoking crack cocaine may occur.
-Corneal abrasions/ulcerations due to particulate matter in smoke (“crack eye”).
-Central retinal artery occlusion and bilateral blindness due to diffuse vasospasm. Retinal foreign body granuloma may occur with IV abuse.

d. CVS effects:
-Tachycardia.
-Systemic arterial hypertension.
-Coronary artery vasoconstriction with myocardial ischaemia and infarction.
-Tachyarrhythmias.
-Chronic dilated cardiomyopathy has been reported.
-Aortic dissection and rupture.
-Coronary artery dissection.
-Sudden cardiac death can occur.

e.Pulmonary effects:

-Thermal injuries to the upper airway leading to epiglottitis, laryngeal injury, and mucosal necrosis have been reported after smoking “crack” or free base cocaine.
-Exacerbation of asthma.
-Non-cardiogenic pulmonary edema.
-Diffuse alveolar hemorrhage.

f.Musculoskeletal effects:
- Rhabdomyolysis with hyperthermia, massive elevation of creatine phosphokinase, and acute renal failure: Although the mechanism of cocaine-associated rhabdomyolysis is unclear, it is postulated that it may result from ischaemia due to vasoconstriction, direct toxicity, hyperpyrexia, and increased muscle activity from agitation or seizure activity.

DIAGNOSTIC TESTING

Cocaine and benzoylecgonine, its principle metabolite, can be detected in blood, urine, saliva, hair, and meconium.

Routine drug-of-abuse testing relies on urine testing using a variety of immunologic techniques. Although cocaine is rapidly eliminated within just a few hours of use, benzoylecgonine is easily detected in the urine for 2–3 days following last use. When more sophisticated testing methodology is applied to chronic users, cocaine metabolites can be identified for several weeks following last use.

Urine testing, even using rapid point-of-care assays, offers little to clinicians managing patients with presumed cocaine toxicity because it cannot distinguish recent from remote cocaine use. In addition, false-negative testing can result when there is a large quantity of urine in the bladder with very recent cocaine use or when the urine is intentionally diluted by increased fluid intake leading to a urine cocaine concentration below the cut-off value and interpretation of the test as negative. Under these circumstances, repeat testing is almost always positive.

While false-positive tests do occur, they are more common with hair testing than urine or blood because of the increased risk of external contamination. Because of the very low rate of false-positive results, confirmation of positive urine is unnecessary for medical indications.

There may be some usefulness for urine testing of body packers, especially when the concealed xenobiotic is unknown. While many body packers will have negative urine throughout their hospitalization, a positive urine test is suggestive of the concealed drug but obviously not confirmatory.
More importantly, a conversion from a negative study on admission to a positive study not only confirms the substance ingested, but also suggests packet leakage, which could be a harbinger of life-threatening toxicity. Another indication for urine testing for cocaine occurs in young patients with chest pain syndromes where the history of drug uses, specifically cocaine, is not forthcoming.

Routine diagnostic tests such as a bedside rapid reagent glucose, electrolytes, renal function tests, and markers of muscle and cardiac muscle injury are more likely to be useful than urine drug screening. An ECG may show signs of ischemia or infarction, or dysrhythmias that require specific therapy. Unfortunately, in the setting of cocaine-associated chest pain, the ECG has neither the sensitivity nor the specificity necessary to permit exclusion or confirmation of cardiac injury. Cardiac markers are therefore always-required adjuncts when considering myocardial ischemia or infarction.

Because cocaine use is associated with diffuse muscle injury, assays for troponin are preferred over myoglobin or myocardial band enzymes of creatine phosphokinase (CPK-MB).

MANAGEMENT

■ GENERAL SUPPORTIVE CARE

As in the case of all poisoned patients, the initial emphasis must be on stabilization and control of the patient's airway, breathing, and circulation.

If tracheal intubation is required, it is important to recognize that cocaine toxicity may be a relative contraindication to the use of succinylcholine. Specifically, in the setting of rhabdomyolysis, hyperkalemia may be exacerbated by succinylcholine administration, and life-threatening dysrhythmias may result.

If hypotension is present, the initial approach should be infusion of intravenous 0.9% sodium chloride solution as many patients are volume depleted as a result of poor oral intake and excessive fluid losses from uncontrolled agitation, diaphoresis, and hyperthermia.

In the setting of cocaine toxicity it is important to recognize that both animal and human experience suggests that elevated temperature represents the most critical vital sign abnormality.

Determination of the core temperature is an essential element of the initial evaluation, even when patients are severely agitated. When hyperthermia is present, preferably rapid cooling with ice water immersion, or the combined use of mist and fanning, is required to achieve a rapid return to normal core body temperature.

Sedation or paralysis and intubation may be necessary to facilitate the rapid cooling process.

Pharmacotherapy including antipyretics, drugs that prevent shivering (chlorpromazine or meperidine), and dantrolene are not indicated as they are ineffective and have the potential for adverse drug interactions such as serotonin syndrome (meperidine) or seizures (chloropromazine).

Sedation remains the mainstay of therapy in patients with cocaine- associated agitation. It is important to remember that cocaine use is associated with hypoglycemia and that many of the peripheral findings of hypoglycemia are the result of a catecholamine discharge. Consequently, a rapid reagent glucose test should be obtained, or hypertonic dextrose should be empirically administered if indicated, prior to or while simultaneously achieving sedation. Both animal models and extensive clinical experience in humans support the central role of benzodiazepines. Although the choice among individual benzodiazepines is not well studied, an understanding of the pharmacology of these drugs allows for rational decision-making.

The goal is to use parenteral therapy with a drug that has a rapid onset and a rapid peak of action, making titration easy. Using this rationale, midazolam and diazepam are preferable to lorazepam, because significant delay to peak effect for lorazepam often results in oversedation when it is dosed rapidly, or in prolonged agitation when the appropriate dosing interval is used. Drugs should be administered in initial doses that are consistent with routine practices and increased incrementally based on an appropriate understanding of their pharmacology. For example, if using diazepam, the starting dose might be 5–10 mg, which can be repeated every 3–5 minutes and increased if necessary. Large doses of benzodiazepines may be necessary (on the order of 1 mg/kg of diazepam). This may result from cocaine-induced alterations in benzodiazepine receptor function.

On the rare occasion when benzodiazepines fail to achieve an adequate level of sedation, either a rapidly acting barbiturate or propofol should be administered.

The use of phenothiazines or butyrophenones is contraindicated. In animal models, these drugs enhance toxicity (seizures), lethality, or both. Additional concerns about these drugs include interference with heat dissipation, exacerbation of tachycardia, prolongation of the QT interval, induction of torsade de pointes, and precipitation of dystonic reactions.

Once sedation is accomplished, often no additional therapy is required. Specifically, hypertension and tachycardia usually respond to sedation and volume resuscitation.

In the uncommon event that hypertension and/or tachycardia persists, the use of a β-adrenergic antagonist or a mixed α- and β-adrenergic antagonist is contraindicated. Again, in both animal models and human reports, these drugs increase lethality and fail to treat the underlying problem. The resultant unopposed α-adrenergic effect may produce severe and life-threatening hypertension or vasospasm.

A direct-acting vasodilator like nitroglycerin, nitroprusside or possibly nicardipine or a α-adrenergic antagonist (such as phentolamine) may be considered. Other nonspecific therapies for rhabdomyolysis such as intravenous fluid should also be considered.

DECONTAMINATION

The majority of patients who present to the hospital following cocaine use will not require gastrointestinal decontamination as the most popular methods of cocaine use are smoking, intravenous and intranasal administration.

If the nares contain residual white powder presumed to be cocaine, gentle irrigation with 0.9% sodium chloride solution will help remove adherent material.

Less commonly, patients may ingest cocaine unintentionally or in an attempt to conceal evidence during an arrest (body stuffing) or transport large quantities of drug across international borders (body packing). These patients may require intensive decontamination and possibly surgical removal.

SPECIFIC MANAGEMENT

End-organ manifestations of vasospasm that do not resolve with sedation, cooling, and volume resuscitation should be treated with vasodilatory agents (such as phentolamine).

When possible, direct delivery via intra-arterial administration to the affected vascular bed is prefer- able. Because this approach is not always feasible, systemic therapy is typically indicated. Phentolamine can be dosed intravenously in increments of 1–2.5 mg, and repeated as necessary until symptoms resolve or systemic hypotension develops.

Acute Coronary Syndrome

A significant amount of animal, in vitro, and in vivo human experimentation has been directed at defining the appropriate approach to a patient with presumed cardiac ischemia or infarction. In some instances an approach that is similar to the treatment of coronary artery disease (CAD) is indicated, although there are certain notable exceptions. An overall approach to care is available in the American Heart Association guidelines and a number of reviews.

High-flow oxygen therapy is clearly indicated as it may help overcome some of the supply–demand mismatch that occurs with coronary insufficiency.

Aspirin is safe in patients with cocaine-associated chest pain and is recommended for routine use.

In addition, **administration of morphine is likely to be effective as it relieves cocaine-induced vasoconstriction**. H.W

Morphine also offers the same theoretical benefits of preload reduction and reduction of catecholamine release in response to pain that is thought to be responsible for its usefulness in patients with CAD.

Nitroglycerin is clearly beneficial as it reduces cocaine-associated coronary constriction of both normal and diseased vessels and relieves chest pain and associated symptoms.

Interestingly, in several clinical trials of cocaine-associated chest pain, benzodiazepines are at least as effective or superior to nitroglycerin. Although the reasons for this are unclear, possible etiologies include blunting of central catecholamines or direct effects on cardiac benzodiazepine receptors. Either or both drugs can be used in standard dosing.

Over the last decade, the benefits of β-adrenergic antagonism have been demonstrated in patients with CAD.

In contrast, β-adrenergic antagonism increases lethality in cocaine-toxic animals and in humans, exacerbates cocaine-induced coronary vasoconstriction, and produces severe paradoxical hypertension.

Similarly, with regard to treatment of coronary constriction, labetalol is no better than placebo Thus, in the setting of cocaine use, β-adrenergic antagonism is absolutely contraindicated. The 2008 American Heart Association Guidelines for the treatment of cocaine-associated chest pain and MI state that use of β-adrenergic antagonists should be avoided in the acute setting. If, after the measures mentioned previously have been initiated, hypertension or vasospasm is still present and treatment is indicated, phentolamine is preferred based on its demonstrable experimental and clinical results.

If tachycardia does not respond to accepted therapies above, then diltiazem can be administered and titrated to effect.

Prior to the administation of any negative inotrope, it is essential to confirm that the tachycardia is not compensatory for a low cardiac output resulting from global myocardial dysfunction. Noninvasive methods of assessment of cardiac function have been used successfully in patients with cocaine-associated acute coronary syndromes.

There are no data on the use of either unfractionated or low-molecular-weight heparins, glycoprotein IIb/IIIa inhibitors, or clopidogrel.

The recent AHA guidelines recommend the administration of unfractionated heparin or low-molecular-weight heparin in patients with cocaine-associated MI.
The decision to use any of these medications should be based on a risk-to-benefit analysis.

Cocaine abuse is well-known for its propensity to cause sudden death not only due to its deleterious effects on health (cerebrovascular accidents, myocardial infarction, malignant hyperthermia, renal failure), but also due to its capacity to provoke the user to commit acts of aggression and violence.

Deaths due to massive overdose are especially common among those who smuggle the drug within their bodies (“cocaine packers”).

Bodypacker Syndrome:

The practice of swallowing balloons, condoms, or plastic packets filled with illegal drugs for the purpose of smuggling is called “body packing”, and the individual who does this is referred to as a “mule”. This must be differentiated from “body stuffing” in which an individual who is on the verge of being arrested for possession of illegal drugs, swallows his illicit contraband to conceal the evidence. Leaking from these poorly wrapped packets can produce cocaine toxicity.

Sudden death due to massive overdose can occur in either a bodypacker or a bodystuffer, if one or more of the ingested packages burst within the gastrointestinal tract.

Treatment:

- Emesis, lavage, charcoal, as applicable.
- Cathartic/whole bowel irrigation to flush the packages out of the intestines.- Symptomatic patients should be considered a medical emergency, and be evaluated for surgical removal of the packets.

- Asymptomatic patients should be monitored in an intensive care unit until the cocaine packs have been eliminated. This must be confirmed by follow-up plain radiography and barium swallows.
- Bowel obstruction in asymptomatic patients may necessitate surgery. Endoscopic removal has been successful in some cases.

Drugs to be avoided in the Treatment of Cocaine Poisoning

Drug	*Adverse Effects*
Beta blockers (especially propranolol)	Coronary artery spasm (Paradoxical hypertension)
Lignocaine, procainamide, quinidine	Convulsions Arrhythmias
Haloperidol, droperidol, phenothiazines	Hyperpyrexia Convulsions
Dantrolene	Cardiac insufficiency
Bromocriptine	Coronary artery constriction