CNS STIMULANTS

COCAINE

The drug is derived from the dried leaves of the plant *Erythroxylon coca* , that appears to grow in the South American countries of Peru, Bolivia, and Colombia.

Coca leaves contain the alkaloids of ecgonine, tropine, and hygrine, of which only the derivatives of ecgonine are of commercial importance. Cocaine is an ester of benzoic acid and methylecgonine.

PHARMACOLOGY AND CLINICAL USE

cocaine has stimulant as well as anesthetic properties.

Cocaine displays reversible CNS and peripheral actions.

It blocks nerve conduction through its local anesthetic properties, primarily by inhibiting neuronal sodium permeability.

It possesses local vasoconstrictor actions secondary to inhibition of local norepinephrine reuptake at adrenergic neurons.

Unlike other local anesthetics, production of euphoria is due, in part, to inhibition of dopamine reuptake in central synapses. Because of its high toxicity and potential for abuse, its use is limited as a topical anesthetic / vasoconstrictor (1 to 10% solution) for surgical procedures involving the oral and nasal mucosal cavities.

TOXICOKINETICS

Cocaine is rapidly absorbed after i.v. or intranasal administration or by inhalation. Distribution depends largely on access to the systemic circulation, which is determined by protein binding and its vasoconstrictor effects, both of which limit systemic distribution.

Thus, distribution of the compound after local application is diminished by its vasoconstrictor activity. This effect, however, is obviated when exposure through inhalation or i.v. routes circumvents the local effects, resulting in significant potential for systemic toxicity.

Central, peripheral, and parasympathetic nervous systems, as well as cardiovascular and smooth muscle, display initial signs of stimulation, followed by depression. This characteristic is presumably due to selective depression of inhibitory neurons, as well as inhibition of general neuronal activity in these areas.

Initially, the stimulation mimics sympathetic activation exhibited by excitement, apprehension, nausea, vomiting, and tremors. Ensuing spasms and seizures are a result of high serum concentrations and overwhelming neuronal depression.

Its cardiovascular toxicity is evidenced by increased blood pressure and heart rate, resulting in an increase in myocardial work and oxygen demand. Thus, the drug has the potential for precipitating ventricular dysfunction and arrhythmias.

- **Simultaneously, it induces coronary artery vasospasm as a result of sympathetic stimulation. This dual mechanism precipitates myocardial ischemia or infarction .**

Smoking crack cocaine hastens episodes of asthma or chronic obstructive pulmonary disease (COPD). Mouth and pharyngeal pain, drooling, and hoarseness accompany the severe upper airway burn injury resulting from inhaling the heat from pipe smoking. In moderate toxicity, cyanosis, dyspnea, and rapid, irregular respirations ensue. Cardiogenic or noncardiogenic pulmonary edema and respiratory failure are progressive sequelae.

Other important toxic features of cocaine toxicity include the production of acute dyskinesia (crack dancing). This syndrome, characterized by episodes of choreoathetoid movements of the extremities, lip-smacking, and repetitive eye blinking, occurs soon after cocaine use and lasts several days.

Acute renal failure, increased risk of spontaneous abortions, elevation of maternal hypertension during pregnancy, and profound hyperthermia, are significant complications of cocaine toxicity.

CLINICAL MANAGEMENT OF ACUTE OVERDOSE

Maintenance of airway, breathing, and circulation (ABCs) is the priority in managing patients with cocaine toxicity. Cardiovascular, neurologic, and psychiatric complications are effectively controlled with benzodiazepine administration, particularly diazepam or lorazepam. Intravenous phenobarbital is used to control cocaine induced seizures if the benzodiazepines are inadequate. Phenytoin is not useful in cocaine-induced seizures because the risks of hyperkalemia and hyperthermia.

a nondepolarizing neuromuscular blocker, such as pancuronium bromide, should be used in the event of intractable seizures.

XANTHINE DERIVATIVES

caffeine, theophylline.

The compounds contain the purine nucleus and are naturally occurring xanthine derivatives.

Caffeine is the most active component of coffee. It is also found in Cola, tropical nuts of South America and Africa.

Both caffeine and theophylline are distributed throughout the tea leaves.

PHARMACOLOGY & CLINICAL USE

The xanthine derivatives, particularly caffeine, exert their pharmacological actions by increasing calcium permeability in sarcoplasmic reticulum, inhibiting phosphodiesterase-promoting accumulation of cyclic AMP, and acting as competitive, nonselective antagonists of adenosine A1and A2 receptors.

Theophylline inhibits the action of extracellular adenosine (bronchodilation effect) , stimulates endogenous catecholamines (central stimulant effect), and directly promotes mobilization of intracellular calcium and β -adrenergic agonist activity (airway smooth muscle relaxation).

Caffeine stimulates cerebral activity, skeletal and cardiac muscle contraction, and general basal metabolic rate, while theophylline has less central stimulation but significant bronchial smooth muscle relaxation properties.

Caffeine and theophylline enhance cardiac muscle contraction, induce coronary vasodilation, and promote diuresis. Caffeine is available in combination with ergotamine, belladonna alkaloids, or pentobarbital for the treatment of migraine headaches

In combination with sodium benzoate (injectable), caffeine is used in the treatment of drug-induced respiratory depression, and as caffeine citrate (injectable) for the short-term treatment of apnea in premature infants.

Theophylline is employed in the treatment of bronchial asthma and other respiratory related disorders.

CAFFEINE TOXICITY

The estimated LD of caffeine in humans is 5 to 10 g. Although fatalities are unlikely approaching this dose, individuals who ingest up to 10 mg/kg are at risk of developing dysrhythmias or strychnine-like seizures. More likely adverse effects of excessive caffeine intake are demonstrable as CNS stimulation, including insomnia, restlessness, sensory disturbances, and delirium.

increased skeletal muscle tension, tachycardia, premature ventricular contractions (PVCs), diarrhea, development of peptic ulcers and gastrointestinal bleeding.

Caffeine can neutralize the desired therapeutic effects of diuretics, antihypertensive agents, b-blockers, and sedative/hypnotics

. myocardial tachyarrhythmias and development of seizures should be monitored in patients after an acute ingestion of 1 g or more of caffeine.

THEOPHYLLINE TOXICITY

Theophylline shares similar properties with caffeine, although its toxicity is more acute and more common; chronic toxicity, however, is unlikely. Therapeutic blood levels are strictly regulated at 10 to 20 µg/ml

As with caffeine toxicity, rapid i.v. administration of theophylline is associated with headache, hypotension, dizziness, restlessness, agitation, and arrhythmias. In order to relieve the gastric irritation and nausea related with oral tablets, most theophylline preparations are available as controlled-release dosage forms.

STRYCHNINE

Originally labeled as an analeptic agent (stimulant), strychnine was introduced into Europe about the sixteenth century mainly for poisoning animals. Its use in medicine began about 1640, when it was found to possess CNS stimulant properties to combat depression and sleeplessness and improve respiration.

It was also used as an appetite stimulant and to increase muscle tone. Unfortunately, strychnine exhibits a narrow therapeutic index and consequently does not enjoy any favorable medicinal value. However, it is still used as a rodenticide.

Strychnine is an indole alkaloid obtained from the dried seeds of Nux vomica. It is extremely toxic as a central stimulant.

Fatal poisoning in adults, especially from the ingestion of tonic tablets, results from ingesting 30 to 100 mg and, in children, from accidental ingestion of rodenticide (15-mg can be a lethal dose).

Since the alkaloid is predominantly a lipophilic glycoside, it is well absorbed orally, and it is metabolized via the hepatic microsomal enzyme system.

Strychnine inhibits the postsynaptic receptor for glycine, an inhibitory neurotransmitter, allowing for the development of spinal convulsions of the tonic type (characterized as extensor thrusts).

Strychnine exerts its toxic abilities by blocking postsynaptic conduction in the inhibitory spinal Renshaw motor neurons, where it interferes with ascending and descending motor tracts, resulting in convulsions of spinal cord origin.

Signs and symptoms of toxicity

Signs and symptoms of toxicity are similar to those seen in experimental animals. Early stages are characterized by a grimacing stiffness of the neck and face, followed by increased reflex excitability that is precipitated by sensory stimulation. Tonic convulsions (traditionally demonstrated as arched back or opisthotonus) are followed by coordinated extensor thrusts

Convulsions occur as full contractions of all voluntary muscles, including thoracic, abdominal, and diaphragmatic, which ultimately suppress respiration.

Convulsive episodes are continuous or intermittent, with depression and sleep interspersed, depending on the depth of toxicity, and the patient is generally conscious and in pain.

After several full convulsions, medullary paralysis due to hypoxia is the cause of death.

Treatment must be instituted swiftly and is aimed at preventing convulsions, maintaining ventilation, and administration of an anticonvulsant/skeletal muscle relaxant, such as diazepam.

Successful treatment with diazepam (10 mg i.v., repeated as needed) depends on the following criteria:

(1) the dose of poison is below the lethal dose;

(2) if intervention is started soon after ingestion; and

(3) if convulsions have not ensued.

Gastric lavage is only indicated when the compound is suspected to be in the stomach contents and if convulsions have subsided.


Thank you