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علم السموم التطبيقي والشرعي

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سموم تطبيقية سريرية . الأستاذة الدكتورة أمية حوة .

بحث . الهلوسات (15 صفحة)

Hallucinogenic Agents

- HISTORY AND DESCRIPTION
- The hallucinogens are a descriptive pharmacological class of synthetic and naturally occurring derivatives of the ergot alkaloids.
- These include the tryptamines, amphetamines,
- and related sympathomimetics.
- The feature that distinguishes these agents from the parent compounds is the production of hallucinations,1
- which are depicted as changes in perception, thought, and mood and the occurrence of dreamlike feelings.
- An individual who ingests hallucinogenic substances describes the effects as having a *spectator ego* , where a person experiences a bond with nature and society, a sense of overwhelming revelation and truth, and a vivid awareness of his or her surroundings.

- The use of hallucinogens was popularized in the 1960s by artists musicians, writers, poets, scientists, and other celebrities (such as Timothy Leary),who aimed to enlighten the world about the benefits of the substances.
- The compounds were purported to improve creative abilities, foster higher levels of thinking and consciousness, and enhance perception.
- The hallucinogens were thus labeled as *mind expanding* drugs. In addition, they claimed to have beneficial effects in the treatment of psychiatric disorders, cancer, and alcoholism — claims that have since been proven invalid.

ERGOT ALKALOIDS

- LYSERGIC ACID DIETHYLAMIDE (LSD)
- PHENETHYLAMINE DERIVATIVES
- MESCALINE
- PHENCYCLIDINE
- (1-PHENYLCYCLOHEXYL PIPERIDINE, PCP)
- MARIJUANA

MARIJUANA

- INCIDENCE AND OCCURRENCE
- Marijuana (Mexican cannabis, *pot*) is obtained from the dried flowering tops, seeds, and stems of the hemp plant variety of *Cannabis sativa* (Indian hemp).
- The plant is an annual herb indigenous to central and western Asia and is cultivated in India and other tropical and temperate regions for the fiber (manufacturing of rope) and hempseed.
- The oil of the hemp plant is expressed and used to make paints and soaps.*

CLINICAL USE AND EFFECTS

- **Dronabinol, a synthetic form of δ9-THC, is available in 5- and 10-mg capsules for the treatment of nausea and vomiting associated with cancer chemotherapy.**
- **It is also used as an appetite stimulant for anorexia associated with weight loss in AIDS patients.**
- **Other unlabelled uses include treatment of glaucoma and epilepsy.**
- **Nontherapeutic effects of dronabinol are identical to those of marijuana and other centrally active cannabinoids.**

- ***The amount of resin found in the pistil flowering tops markedly decreases as the plants are grown in more temperate regions, making the American crop of marijuana considerably less potent than the South American variety (a.k.a. sinsemilla, without seeds).***
- *** Cannabis, the ancient Greek name for hemp, was used in China and India (*charas*) and spread to Persia (*hashish*). It was introduced into European and American botanical formularies around the seventeenth century.**

- **Smoking marijuana or oral ingestion of cannabinoids has complex central sympathomimetic effects, mediated in part by the presence of neural cannabinoid receptors.**
- **Mood changes accompany marijuana use, ranging from euphoria, depression, paranoia, and anxiety** to detachment.**

- **MEDICINAL CHEMISTRY**
- **Cannabis yields between 0.5 and 20% of a resin containing the major active euphoric principle, delta-9-*trans* -tetrahydrocannabinol (δ 9-THC), along with other cannabinoid constituents.**

- Most prominent effects are relaxation and sedation.
- Behavioral effects appear as loss of goal-oriented drive and short-term memory, and a vague sense of time (*temporal disintegration*).
- The individual is prone to spontaneous laughter, hallucinations, and delusions, although the latter are usually seen with higher doses.

- Physiological symptoms involve:
- dry mouth, stimulation of appetite,
- muscular in-coordination,
- decrease of testosterone levels, urinary retention,
- increase in heart rate, and
- conjunctival injection. The last effect contributes to decreased intraocular pressure.

- TOXICOKINETICS
- An average cigarette contains about 500 to 1000 mg of the herb, each containing 1 to 2% δ 9-THC.
- Oral administration is almost completely absorbed (90%), while only 5 to 10% is absorbed through inhalation of marijuana smoke, primarily because of loss to pyrrolysis.
- Inhalation results in more rapid absorption (1 to 2 min vs. 0.5 to 1 h onset for oral), with a 2- to 4-h duration.
- Its high lipid solubility contributes to its large volume of distribution (Vd 10 l/kg) and long half-life (*t*1/2 7 days).

- This accounts for its leakage from lipid stores and detection in plasma and urine up to 8 weeks in chronic users.
- Dronabinol and δ 9-THC undergo extensive first-pass hepatic metabolism, yielding active and inactive principal metabolites,;
- 11-hydroxy- δ 9-THC and
- 8,11-dihydroxy- δ 9-THC, respectively.
- The δ 9THC-carboxy metabolite is found principally in urine.
- * *The herbicide paraquat was routinely sprayed on marijuana fields in northern Mexico and in the southern U.S., precipitating a syndrome of pulmonary fibrosis .*

- ACUTE TOXICITY AND CLINICAL MANAGEMENT
- Toxic effects are an extension of the pharmacological and clinical effects.
- Although serious toxicity is uncommon, psychosis and dangers related to poor judgment are complications.
- Usually the complications result from ingestion of high doses, excessive use, poor or contaminated street quality of the substance, or when taken in combination with other hallucinogens.

- Smoking of marijuana impairs motor skills, making driving a motor vehicle hazardous.
- In general, psychiatric reassurance and supportive care are adequate treatment modalities.
- Psychosis is transient and damageable with benzodiazepines.

- TOLERANCE, WITHDRAWAL, AND CHRONIC EFFECTS
- There is no apparent physical tolerance,
- and psychological tolerance is variable.
- The withdrawal syndrome manifests as sleep disturbances, irritability, nausea, weight loss, and restlessness.

- There is a higher incidence of mouth, throat, and lung cancer in young adults.
- There appears to be a decrease in sperm motility and number, and abnormal sperm morphology is associated with
- chronic marijuana smoking.
- Deleterious genetic effects, however, are debatable.

ERGOT ALKALOIDS

INCIDENCE AND OCCURRENCE

- **Ergot was originally derived from the dried sclerotium (resting body of fungus) of *Claviceps purpurea* (rye plant).**
- **Although preparations of the crude drug are seldom found in pharmaceutical formulas, the alkaloid derivatives are important medicinal agents derived primarily from parasitic and saprophytic alteration of the plant.**
- **Ergot produces a large number of alkaloids the most important of which are;**
- **the ergotamines, ergonovines, and ergotoxine.**

MEDICINAL CHEMISTRY

- **The ergotamines, natural or semisynthetic, are all derivatives of *d*-lysergic acid.**

PHARMACOLOGY & CLINICAL USE

- **Ergotamine, ergonovine, and ergotoxine compounds are readily soluble in water, although their absorption rate is erratic.**
- **The ergotamine derivatives have a variety of seemingly unrelated pharmacological properties.**
- **In general, ergotamine has partial agonist or antagonist activity against trypaminergic, dopaminergic, and adrenergic receptors.**
- **It constricts central and peripheral blood vessels, depresses central vasomotor centers, and induces uterine contractions.**

- **Other ergot derivatives, such as methylergonovine**
- **(Methergine®), act directly on uterine smooth muscle and induce sustained contractions.**
- **Clinically, the agents are used for their oxytocin-like effect in the routine management of postpartum uterine contractions and bleeding (methylergonovine), for the prevention of vascular headaches, such as migraine or cluster headaches (dihydroergotamine, Migranal® ; methysergide, Sansert®),**

- **SIGNS AND SYMPTOMS OF ACUTE TOXICITY**
- **Adverse reactions occur in patients with acute ingestion of less than 5 mg of ergotamine derivatives.**
- **The most important signs and symptoms include:**
- **nausea, vomiting, neuromuscular numbness and weakness, confusion, depression, drowsiness, and convulsions.**
- **Lightheadedness, disassociation, and hallucinatory experiences reflect CNS toxicity.**

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MECHANISM OF TOXICITY

- Within minutes of ingestion, an effective dose produces hallucinogenic sensations that last between 6 and 24 h.
- LSD produces significant pyramidal and extrapyramidal effects as a result of interaction with central 5-hydroxytryptamine (5-HT, serotonin) receptors.
- Specifically, the compound mimics 5-HT at 5-HT *A* autoreceptors on raphe nucleus cell bodies and acts as a partial or full agonist at 5-HT *A* and 5-HT *C* receptors.
- Selective binding to serotonin receptors accounts for the hallucinogenic and behavioral alterations associated with the substance.

- CLINICAL MANAGEMENT OF ACUTE OVERDOSE
- Treatment of acute overdose consists of withdrawal of the drug followed by symptomatic measures, including and not limited to, the ABCs of emergency treatment.
- LYSERGIC ACID DIETHYLAMIDE (LSD)
- INCIDENCE AND OCCURRENCE
- Lysergic acid diethylamide (LSD) does not occur naturally but is a semi-synthetic preparation of *d*-lysergic acid .
- Discovered by A. Hoffman in 1943 during the course of experiments directed toward the synthesis of stimulants (analeptics), LSD produces opposing actions of powerful central stimulation with slight depression .

- HALLUCINOGENIC EFFECTS
- The desirable effects, or in the least, the reason for intentional non therapeutic use of the substance, vary between euphoria and dysphoria.
- Swift mood swings, even after a single dose within the same time period, are easily produced.
- The LSD *Trip* is characterized predominantly by distortion in the realization of time and alteration of sensory perception, especially visual, auditory, tactile, olfactory, and gustatory.
- The individual experiences an intensified and altered perception of color.

- **Although it has no legitimate medical use today, the colorless, odorless, and tasteless compound is the most powerful psychotropic agent known, whose experimental value has proven it to be a model for psychosis.**
- **The substance is available "on the street" in liquid, powder, and microdot dosage forms, with 20 to 25 µ g as an effective oral dose.**

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TOXICOKINETICS

- Following oral ingestion of LSD, the effects are perceived within a few minutes and usually last for about 12 h.
- Although the cause is not clearly understood, the recurrence of *flashbacks* has been reported long after the detectable levels have disappeared.
- LSD is rapidly metabolized, and concentrations of the parent drug in the urine of a user do not exceed 1 to 2 ng/ml.

- Objects are surrounded by halos and may leave a trail of individual afterimages when moving across a visual field.
- Other distortions of reality include *synesthesias* , where an auditory stimulus is perceived "visually."
- Normal taste, smell and touch sensations are often strange, distorted, grotesque, or uninterpretable.
- The individual becomes depressed, anxious, and paranoid and may experience *ego fragmentation* or feelings of depersonalization.
- The latter reaction is pleasant, as the user experiences feelings of togetherness ("oneness") with the surroundings.

SIGNS AND SYMPTOMS OF ACUTE TOXICITY

- Common adverse reactions occur within minutes after ingestion.
- Sympathetic stimulation results in mydriasis, hyperthermia, piloerection, tachycardia, hyperglycemia, and hypertension.
- Although LSD has a high therapeutic index, first time users may experience panic reactions and loss of psychological control of the immediate environment.
- *Flashbacks* occur in 1 of 20 users. They are characterized as recurrence of the LSD experience in the absence of ingestion.

- Alternatively, the experience may be extremely uncomfortable, where the user feels a sense of loss of conscious control of thoughts and emotions and of being "out of touch" with the surroundings.
- In extreme cases, frightening perceptions and psychological distortions may lead to unanticipated behavior in an otherwise normal person.
- Such *bad trips* may be accompanied by delirium-induced self injury or suicide.

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- The full range of perceptual and psychological distortions recur, including somatic and emotional hallucinations.
- The lack of control over the experience often leads to the development of personality changes, prolonged psychosis, neurosis, and depression.
- The variety, intensity, and pattern of flashbacks are unpredictable and do not rely on dose or frequency of use.
- The flashbacks may be triggered in unsuspecting LSD users by administration of selective serotonin reuptake inhibitors (fluoxetine, paroxetine).

CLINICAL MANAGEMENT OF ACUTE OVERDOSE

- Reduction of anxiety and the reassurance that a *bad trip* is due to the effects of the drug and is not permanent are important in managing LSD toxicity.
- Benzodiazepines are beneficial for sedation.
- At one time, phenothiazines were frequently used to ameliorate the psychological manifestations and perceptual distortions.
- The antipsychotics drugs, however, are not recommended because of the lowering of seizure thresholds.
- Management of symptoms of sympathetic stimulation, especially tachycardia and hyperglycemia, is also warranted.

TOLERANCE AND WITHDRAWAL

- Chronic use of LSD is not associated with the physical and psychological tolerance or withdrawal seen with opioids or S/H, although cross-tolerance and sensitivity to mescaline and psilocybin have been reported .
- A return to normal functioning is common following a drug-free period.
- (sedatives-hypnotics)

METHODS OF DETECTION

- *Most published assays for LSD are intended for identification of the drug in illicit preparations. They do not offer the sensitivity and specificity required for detection in urine specimens.*
- *Radio immunoassays (RIAs) for LSD appear to offer an effective means for detecting very recent drug use.*
- *However, confirmation of the presence of LSD or its metabolites requires specific analysis.*
- *High-performance liquid chromatography (HPLC) combined with fluorescence detection, and capillary column gas chromatography with electron ionization mass spectrometry (GC-MS) can measure urinary concentrations as low as 0.5 ng/ml.*
- ***However, neither of these assays is useful for detection of LSD in urine for more than about 12 h after ingestion.***

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SIGNS AND SYMPTOMS OF ACUTE TOXICITY

- **The desirable pharmacological effects of psilocybin and its more active metabolite ,psilocin, mimic those of LSD.**
- **A 20-mg dose of psilocin is equivalent to 100μg of LSD. The effects, which last about 3 h, begin with anxiety and nausea, then proceed to dream-like trances and hallucinations.**
- ***Trailer* images, not unlike LSD, induce changes in color and shape perception.**

TRYPTAMINE DERIVATIVES

- **INCIDENCE AND OCCURRENCE**

the structure of tryptamine, psilocin (4-hydroxydimethyltryptamine) and serotonin (5-hydroxytryptamine),

- **all of which are pharmacologically**
- **and toxicologically similar.**

- **Few reports of acute intoxication are available.**
- **Symptoms present within 30 to 60 min after mushroom ingestion and include agitation, hyperthermia, and possible hypotension and convulsions.**
- **Anticholinergic symptoms, such as mydriasis, blurred vision, and dizziness accompany visual disturbances.**

MECHANISM OF TOXICITY

- **Ingestion of certain small mushrooms, not commonly used as food, results in hallucinations.**
- **The mushroom,*Psilocybe mexicana*(*food of the gods*) has been used for centuries by Mexican and Central American Indians in religious ceremonies.**
- **In 1958, A. Hoffman identified the active ingredient of the mushroom as psilocybin.**
- **As with LSD, the mechanism of toxicity is related to stimulation of sympathetic and serotonergic activity, although with less potency.**

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Phenethylamine Derivatives

- **Incidence And Occurrence**

- **The synthetic hallucinogenic amphetamines are widely used among high school and college students at *rave* parties, alcoholic bars, and at events requiring endurance and alertness, such as marathon dances.**

- **CLINICAL MANAGEMENT OF ACUTE OVERDOSE**
- **As with LSD, benzodiazepines and a cholinergic agent are useful in managing the undesirable effects of psilocybin mushroom poisoning.**

- **However, there are some special considerations surrounding the treatment of mushroom poisoning.**
- **For instance, depending on bioavailability, amount ingested, and individual susceptibility, not all persons ingesting the same meal will be symptomatic.**

- **Also, it is important to recognize that the anticholinergic effects are likely to mimic those from exposure to insecticides and may be delayed up to 6 h.**

- **MEDICINAL CHEMISTRY**

- **The b-phenethylamine derivatives are synthetic analogs of amphetamine .**
- **Since the compounds are amphetamine-like structures, their toxicity combines the properties of stimulants with those of the hallucinogens.**

- **Compounds, such as mescaline, with a long history of abuse, and comparatively newer drugs, such as DOM (STP) and MDMA (*ecstasy*), are discussed as prototypes for this class.**

- **TOLERANCE AND WITHDRAWAL**

- **As with LSD, chronic ingestion of psilocybin-containing mushrooms is not associated with physical and psychological tolerance or withdrawal symptoms, although**
- **cross-tolerance and sensitivity to other hallucinogens have been reported.**

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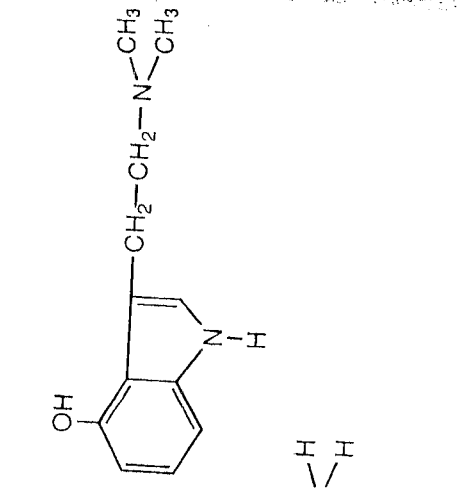
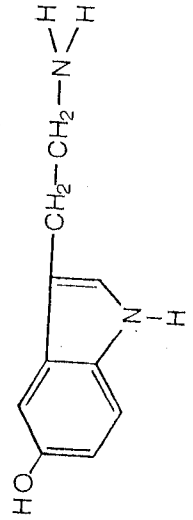
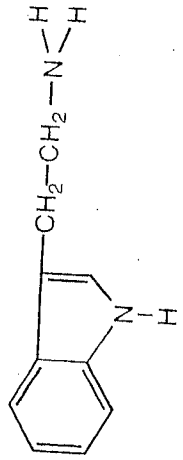


Psilocin



Serotonin



Tryptamine

FIGURE 14.2 Structures of tryptamine, serotonin (5-hydroxytryptamine), and psilocin (4-hydroxydimethyltryptamine).

MESCALINE

- **Mescaline is regarded as the first of a series of alkaloidal amine hallucinogens.**
- **The compound is derived from the dried tops of *Lophophora illiamsii* (peyote or mescal buttons), from the peyote cactus.**
- **The plant is indigenous to northern Mexico and the southern United States.**
- **The plant is associated with Native American religious ceremonies.**
- **Its chief effect is the production of euphoria and hallucinations with concomitant decrease in fatigue and hunger.**

- **Ingestion of mescal buttons that contain mescaline, the most active of the peyote constituents, produces mydriasis, accom-panied by unusual and bizarre color perception.***
- **Flashing lights and vivid configurations characterize the initial visions, followed by dimming of colors and sleep**
- **induction.**
- **Sensory alteration is 1000-fold less potent than LSD, but the production of tremors, hypertension, increased heart rate, and deep tendon reflexes are significant and similar to those of the sympathomimetic amines.**
- **Mescaline is rapidly absorbed; plasma concentrations peak at about 2 h and last about 12 h.**
- **Other than the risk of hypertensive crisis, toxicity with mescaline is rare.**

- Before it arrives on the streets, the crystalline form of the drug is diluted (*Cut*) with a diluent, such as lactose, mannitol, sucrose, procaine, or lidocaine.

- The substance is injected i.v. as a 10 to 20% solution, administered by intranasal insufflation (*snorted* as 50 to 75% powder), or burned and inhaled as the freebase (*crack* cocaine, 20% powder).

- COCAINE
- INCIDENCE & OCCURRENCE
- The sporadic use of cocaine during the last 50 years is a reflection of its cyclic popularity as well as availability, cost, and competition with other illicit drugs.
- The drug is derived from the dried leaves of the plant *Erythroxylon coca*, that appears to grow best at higher elevations (1500 to 6000 ft) in the South American countries of Peru, Bolivia, and Colombia. Historically, the ancient Incas of Peru chewed on the leaves of the plant to decrease fatigue and reduce appetite during long journeys, although it was still considered an inferior substitute for tea.
- Drug analysis of ancient Egyptian ruins detected the presence of cocaine and nicotine. And cocaine was sold medicinally as a brain tonic in the early 1900s (an ingredient of Coca-Cola®).

- MEDICINAL CHEMISTRY
- 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, the latter of which is related to the amino alcohol group found in atropine.

- The chemical structures of cocaine and related local anesthetics are illustrated in Figure

Today, the illicit form of the compound is transported to the United States principally in the same manner as described for opioids) — i.e., by *body packing* .

- * Cocaine drug carriers, or *body packers*, seal and conceal illicit drug packets in body compartments either by swallowing or inserting into body orifices. As with the opioids, the packets run the risk of leaking or bursting, making the overall clinical management of these individuals of immediate attention.

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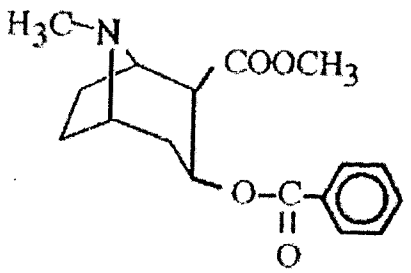

Structure 1. Cocaine

- PHARMACOLOGY & CLINICAL USE
- Although not generally regarded as a sympathomimetic, 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.

- SIGNS & SYMPTOMS OF ACUTE 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.

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- 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.

- 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.
- Effects on gastrointestinal smooth muscle are not dramatic.

- 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.

- 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 and, since succinylcholine risks hyperkalemia and hyperthermia, a nondepolarizing neuromuscular blocker, such as pancuronium bromide, should be used in the event of intractable seizures.*

- TOLERANCE & WITHDRAWAL
- Addiction to cocaine is essentially indistinguishable from amphetamine habituation.
- Because of its rapid metabolism, larger doses of cocaine are required to maintain the euphoric effects in a chronic user.
- The development of tolerance, however, is inconsistent, and users will succumb to the toxic effects at low doses in spite of the continuous use.
- There is generally no cross tolerance between cocaine and sympathetic stimulants.

- METHODS OF DETECTION
- Cocaine is extensively metabolized, primarily by liver and plasma esterases, and only 1% of a dose is excreted in the urine unchanged.
- Approximately 70% of a dose can be recovered in the urine over a period of 3 days.
- About 25 to 40% of cocaine is metabolized to benzoylecgonine, the major metabolite found in the urine.
- About 18 to 22% is excreted as ecgonine methyl ester and 2 to 3% as ecgonine.
- Lmmunochemical techniques such as EMIT and RIA are designed to detect benzoylecgonine.

- Unchanged cocaine is sometimes detected by chromatographic methods for up to 24 h after a given dose, while benzoylecgonine can generally be detected by immunoassays for 24 to 48 h.
- The presence of cocaine and its metabolites in urine is confirmed by GLC, HPLC, and GC/MS.
- Benzoylecgonine can generally be detected in urine up to 2 days after cocaine use using GLC, the most specific of the chromatographic techniques.

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