DRUG-INDUCED EMERGENCIES IN ICU

ESSAY SUBMITTED FOR PARTIAL FULFILLMENT OF MASTER DEGREE (M.S.C.) IN ICU

BY

FADY AZIZ AZER

M.B.B. CH. (2003)

SUPERVISED BY

PROF DR. NAHED EFFAT YOUSSEF

PROFESSOR OF ANESTHESIA & ICU

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

DR. HANAN MAHMOUD FARAG

ASSISTANT PROFESSOR OF ANESTHESIA & ICU

AIN SHAMS UNIVERSITY

DR. ABDELAZIZ ABDALLAH ABDELAZIZ

LECTURER OF ANESTHESIA & ICU

AIN SHAMS UNIVERSITY

Ain Shams University

Faculty of Medicine

(2010-2012)

ACKNOWLEDGMENTS

I'm particularly thankful to **Prof. Dr. Nahed Effat Youssef,** *Professor of Anesthesia & ICU, Ain Shams University* for instilling in me a thirst of knowledge and commitment and providing me perspective and support throughout the progress of this work.

An overwhelming debt of gratitude to **Dr. Hanan Mahmoud Farag,** *Assistant professor of Anesthesia & ICU, Ain Shams University* due to her considerable encouragement for accomplishing this work.

I'm very grateful to **Dr. Abdelaziz Abdallah Abdelaziz,** *Lecturer of Anesthesia & ICU, Ain Shams University* in being helpful in the preparation of this work, reviewing it, suggesting additions, and giving his expert knowledge and experience.

LIST OF CONTENTS

LIST OF TABLES

LIST OF FIGURES:

LIST OF ABBREVIATIONS:

ABG	Arterial blood gases	**ACh**	Acetylcholine
AChE	Acetylcholinesterase	**AF**	Atrial fibrillation
AGMA	Anion gap metabolic acidosis	**ALT**	Alanine transaminase
AST	Aspartate transaminase	**AV**	Atrioventricular
BUN	Blood urea nitrogen		
CHF	Congestive heart failure	**ChE**	Cholinesterase
CHIPES	Calcium salts, Heavy metals,Iodinated compounds, Packet of drugs, Potassium salts, enteric-coated tablets, salicylates and sodium salts	**CPK**	Creatine phosphokinase
CNS	Central nervous system	**CT**	Computerized tomography
DTs	Delirium tremens	**ED**	Emergency department
ECG	Electrocardiography	**FDA**	Food and Drug Administration

GIT	Gastrointestinal tract	**GABA**	Gamma-aminobutyric acid
GHB	Gamma-hydroxybutyric acid	**INR**	International normalized ratio
ICU	Intensive care unit	**IM**	Intramuscular
IU	International unit	**IV**	Intravenous
LD	Lethal dose	**LSD**	Lysergic acid diethylamide
MDMA	3,4-methylenedioxy-N-methylamphetamine	**MI**	Myocardial infarction
NAC	N-acetyl cysteine	**OP**	Organophosphorus
PO	Per os	**PT**	Prothrombin time
PChE	Pseudocholinesterase	**PCo2**	Partial pressure of Co2
PO2	Partial pressure of O2	**SC**	Subcutaneous
SLUDGE	Salivation, Lacrimation, Urination, Defecation, GI cramps, Emesis	**Vd**	Volume of distribution
VF	Ventricular fibrillation	**VT**	Ventricular Tachycardia

GENERAL CONSIDERATIONS IN THE EVALUATION & TREATMENT OF DRUG POISONING & OVERDOSES

Introduction

Poisoning or intoxication is defined as the occurrence of harmful effects resulting from exposure to a foreign chemical. Such effects may be local or systemic and objective or subjective. In the absence of signs or symptoms, external or internal body contact with a potentially harmful amount of a chemical is merely considered an exposure ***(Dart, 2004).***

An overdose is an excessive exposure to a chemical that in specified therapeutic amounts is normally intended for human use. Whether an exposure or overdose results in poisoning depends more on the conditions of exposure-primarily the dose- than the identity of the agent involved. Ordinarily safe chemicals, even those essential for life such as oxygen and water, in excessive amounts or by an inappropriate route can result in harmful effects. Poisoning is distinguished from adverse allergic, intolerance, and idiosyncratic pharmacogenetic reactions in that effects are concentration or dose-related and, hence, predictable. As such, it includes adverse drug reactions due to unwanted secondary effects and pharmacokinetic and pharmacodynamic interactions ***(Sweetman, 2004).***

Poisonings, exposures, and overdoses may be characterized by the route, duration, and intent of exposure. Ingestion, dermal or ophthalmic contact, inhalation, and parenteral injection (including bites and stings) are the most common routes, but rectal, urethral, vaginal, bladder, peritoneal, intraocular, and intrathecal exposures can also occur. Events that occur once or during a short period of time are considered acute, whereas those that occur repeatedly or over a prolonged time interval are said to be chronic. Intentions can vary with respect to exposure and outcome, and the designation of a particular occurrence as unintentional or deliberate sometimes involves value judgments. Events due to unforeseeable circumstances (e.g., chemical spills, industrial accidents, environmental contamination), normal childhood behavior (e.g., environmental exploration by tasting), and mistaken chemical identification (e.g., product label missing, not read, or misread) are clearly unintentional. In contrast, exposures due to substance abuse, addiction, and failure to appreciate the consequences of exposure (e.g., uninformed vocational or avocational use of chemicals; self-medication) are intentional, but the induction of harmful effects is not. Hence, if poisoning ensues, it is generally considered unintentional. Overdoses and poisonings

due to therapeutic misadventures (e.g., dosing errors, failure to monitor routinely for adverse reactions or excessive drug concentrations) are usually considered unintentional, whereas those due to attempted or assisted suicide, Munchausen syndrome (a psychiatric factitious syndrome) or Munchausen syndrome by proxy, or for achieving a greater or more rapid therapeutic effect (i.e., misuse) are generally regarded as intentional. Chemically induced abortion, murder or attempted murder, child abuse, and product tampering can be considered unintentional or intentional depending on whether the perspective is that of the victim or the perpetrator ***(Watson et al, 2005).***

Epidemiology

Although comprehensive data regarding the true incidence of poisoning are not available, it is clearly a significant medical problem. Exposures and poisonings are responsible for more than 10% of all ambulance transports, and 14% of adult ICU admissions with an average length of stay of about 3 days. Nevertheless those figures increase dramatically in small cities, poor and rural areas where there is no much public awareness. In addition, 25% of routine medical admissions involve some form of drug-related adverse patient event ***(Bosch et al, 2000).***

Most exposures reported to poison centers are acute (99%), unintentional (84%), occur at home (90%), result from ingestion (75%). Agents most frequently involved are analgesics, sedative/hypnotic/antipsychotics, antidepressants, stimulants and street drugs, cardiovascular medications, alcohols and glycols, gases and fumes, anticonvulsants, muscle relaxants, chemicals, antihistamines, cleaning products, cosmetics, foreign bodies, plants, cough and cold preparations ***(Kearns et al, 2003).***

Mechanism of Action

Most chemicals are absorbed and cause systemic poisoning by selectively binding to and disrupting the function of specific targets (e.g., enzymes & proteins). Effects may be generalized or limited to a specific organ or tissue, depending on the distribution and location of target sites. In contrast, corrosives (e.g., acids, alkali, fixatives, oxidizing and reducing agents, and other highly reactive chemicals), because of their high reactivity, are nonselective, act primarily at surface sites, and undergo little if any absorption. Systemic effects, if they occur, are usually secondary to local toxicity (e.g., anoxia due to pulmonary injury, acidosis and shock secondary to surface tissue necrosis) ***(Golfrank et al, 2002).***

Poisoning is usually functional and reversible. Hence, if vital signs and organ function can be supported, complete recovery will occur on elimination of the offending agent. However, if normal activity of the target site is essential for cell viability, an exposure may result in necrosis. Agents that can cause potentially fatal cellular damage include acetaminophen, carbon monoxide, corrosives, ethylene glycol, heavy metals, methanol, and neurotoxic hydrocarbons ***(Brent et al, 2005).***

Absorption

Absorption involves the translocation of chemicals across the membranes of cells that make up mucosal surfaces, pulmonary epithelium, and skin, all of which function as biologic barriers to chemical movement. Translocation occurs by filtration or passive diffusion through gaps or pores in membranes (e.g., small molecules) by dissolving in and diffusing through the membrane itself (e.g., lipid-soluble chemicals), or by attaching to carrier molecules in the membrane, which actively or passively facilitate diffusion (e.g., water-soluble chemicals). The rate and extent of absorption depend on physical properties of the chemical and the route of exposure. In general, only chemicals that are small, have low molecular weight, and are soluble in both water and lipids at the pH of body fluids (in either neutral or ionized states) can readily cross membranes ***(Baselt, 2004).***

Absorption after IV injection is complete and almost instantaneous. Peak arterial and venous blood concentrations occur within 30 to 90 seconds. Pulmonary absorption is rapid but incomplete. The absorption of chemicals after IM or SC injection is slower but relatively complete. Peak blood levels generally occur within an hour of administration. The absorbed dose is proportional but not necessarily equal to the one administered. Regardless of route, absorption tends to follow first-order kinetics (i.e., the amount of chemical absorbed per unit of time is directly proportional to its concentration). Hence, threshold tissue concentrations are usually reached quicker and effects begin sooner after an overdose than after a therapeutic one ***(Sullivan et al, 2001).***

Distribution

It is influenced by biologic variables such as age, sex, weight, and disease states as they relate to body composition (e.g., water, fat, muscle content) and serum protein concentrations. Because distribution is also a translocation process, it is influenced by the same chemical characteristics as absorption and follows first-order kinetics. Distribution generally occurs much faster than absorption, as evidenced by the occurrence of peak effects within minutes of an IV drug injection. Slow distribution is partly responsible for the delayed onset of action of some agents (e.g., digitalis, heavy metals, lithium, and salicylates) ***(Niesink et al, 1996).***

Elimination

Elimination of chemicals from the body (detoxification) is accomplished by urinary, pulmonary, GI, and glandular (e.g., bile, milk, tears, saliva, sweat) excretion or metabolic inactivation. Hepatic metabolism and renal excretion are the major routes of elimination for most agents. Pulmonary excretion also plays a major role in the elimination of gases and volatile chemicals. Elimination generally follows first-order kinetics. When metabolism is saturable and the primary route of elimination follows

zero-order kinetics, a small increase in dose can result in a large increase in blood and tissue concentrations and potential poisoning. Chemicals exhibiting such metabolism include alcohols, phenytoin, salicylate, and theophylline. Renal excretion is accomplished by translocation processes (e.g., glomerular filtration, tubular secretion, and reabsorption) and is therefore influenced by the same factors as absorption and distribution. Any condition that impairs hepatic or renal blood flow or function can decrease chemical elimination. Hence, the duration of the effect tends to be longer after an overdose than after a therapeutic dose ***(Baselt, 2004).***

Clinical Considerations

The principal objectives in the diagnosis and evaluation of the poisoning are recognition of an exposure or poisoning, identification of the offending agent(s), prediction of potential toxicity, and assessment of the severity of clinical effects. Treatment objectives include provision of supportive care, prevention of chemical absorption, prevention or reversal of poisoning by the use of antidotes, enhancement of chemical elimination, safe disposition, and prevention of subsequent exposures. Accurate diagnostic evaluation is a prerequisite for optimal management ***(Goldberg et al, 1986).***

The priority of assessment and treatment objectives depends on the phase of poisoning during the preclinical phase; management priorities include chemical identification, prediction of toxicity, and prevention of absorption (i.e., decontamination). The sooner decontamination is accomplished, the greater its efficacy. ***(Golfrank et al, 2002).***

During the toxic phase, assessment of the severity of poisoning, provision of supportive care, administration of antidotes, prevention of further absorption, and enhancement of elimination are the primary objectives. If significant vital signs, cardiac rhythm, or mental status abnormalities are present, the history, physical, and diagnostic testing should be deferred or conducted concurrently with resuscitation and stabilization of vital signs ***(Kulig, 1992).***

During the resolution phase, continued supportive care, antidotal therapy, enhancement of elimination, and reassessment of severity (i.e., evaluation of the response to treatment) are the most important management considerations. Measures to prevent subsequent re-exposure should also be initiated before discharge ***(Kulig, 1992).***

Recognition of Poisoning

Making the diagnosis is easy when a history of exposure is available. However, patients may be unaware of an exposure, unwilling to admit to one, or unable to give a history at all, or patients may give a history that is vague, confusing, or intentionally disguised. Victims of attempted murder, child or elder abuse, therapeutic misadventure,

and chronic or insidious poisoning (e.g., that resulting from chemical exposure during hobby or vocational activities) may not relate an exposure to their symptoms. Children, nonverbal patients, and those who are confused or comatose may not be capable of giving a history. Patients who have taken a chemical for the purpose of self-harm (e.g., suicide, Munchausen syndrome), self-therapy (e.g., abortion, addiction, illness treatment with folk remedies or pharmaceuticals), or recreation may fear ridicule and deny or disguise an exposure ***(Hill, 1965).***

Poisoning should always be considered in patients with metabolic abnormalities (especially acid-base disturbances), gastroenteritis, or changes in behavior or mental status of unclear etiology. Drug intoxication is a risk factor for trauma and suicide and should also be considered in all injured patients ***(June et al, 2000).***

Identification of the Offending Agent

History

Even when a history is available, its accuracy and reliability must be assessed. The identity of the chemical involved is incorrectly reported by up to 50% of patients with intentional ingestions. Lay-person misidentification of acetaminophen as aspirin and vice versa is also relatively common. To avoid missing the correct diagnosis, the presence or absence of both drugs should be confirmed by laboratory analysis when an overdose of either one is reported or suspected ***(Wright, 1980).***

Clinical Manifestations

The etiology of poisoning can usually be narrowed to a few possibilities by the results of the physical examination and readily available ancillary tests such as the ECG, serum chemistries (e.g., electrolytes, BUN, creatinine, glucose, and osmolality), and urinalysis. With respect to the physical examination, the mental status and vital signs provide the most useful information for diagnostic purposes. Using these parameters, the physiologic state of the patient can usually be characterized as excited (i.e., CNS excitation with increased blood pressure, pulse, respirations, and temperature), depressed (i.e., decreased level of consciousness and decreased vital signs), discordant (i.e., inconsistent, mixed, or opposing CNS and vital sign abnormalities), or normal. The differential diagnosis can then be narrowed to the common or characteristic causes of these physiologic states ***(Ashton et al, 1989).***

The excited state is primarily caused by sympathomimetics, anticholinergics, hallucinogens, and withdrawal syndromes. The depressed state is primarily caused by sympatholytics, cholinergics, opioids, or sedative hypnotics. The discordant state is primarily due to asphyxiants, anion gap metabolic acidosis (AGMA) inducers (agents that cause increased AGMA in the absence of lactic acidemia due to hypoxia, liver failure, seizures, or shock), membrane active agents (those that block sodium channels or otherwise alter the activity of excitable cell membranes), and agents that cause a

variety of CNS syndromes due to interference with dopamine, GABA, glycine, or serotonin synthesis, metabolism, or function. A normal physiologic state may be due to a nontoxic exposure, psychogenic illness, or presentation during the preclinical phase of poisoning. Agents that have a long preclinical phase (i.e., delayed onset of toxicity) are known as toxic time bombs. Delayed onset of toxicity may result from slow absorption or distribution, metabolic activation, or a mechanism of action that involves the disruption of metabolic or synthetic pathways. Psychogenic illness should be considered when symptoms are inconsistent with the reported exposure and cannot be substantiated by objective physical findings, laboratory abnormalities, and toxicologic testing and other etiologies have been excluded ***(Bosse et al, 1999)***.

The severity of mental status and vital sign abnormalities and the nature of associated autonomic findings can be used to narrow the differential diagnosis of physiological stimulation and depression to one of four subcategories. In the excited patient, marked vital sign abnormalities (e.g., severe hypertension with end-organ ischemia, tachyarrhythmias, hyperthermia, cardiovascular collapse) with minor mental status changes (except for seizures) suggest an agent with peripheral sympathomimetic activity as the cause. Conversely, marked mental status abnormalities with nearly normal vital signs suggest a centrally acting hallucinogen. Anticholinergic poisoning can be differentiated from sympathomimetic, hallucinogen, and withdrawal syndromes by the presence of dry, flushed, and hot skin; decreased or absent bowel sounds; and urinary retention. Other causes of excitation are usually accompanied by pallor, diaphoresis, and increased bowel or bladder activity ***(Jones et al, 2000).***

In the patient with physiological depression, marked cardiovascular abnormalities (e.g., hypotension and bradycardia) with relatively clear sensorium suggest a peripherally acting sympatholytic, whereas marked CNS and respiratory depression with minimal pulse and blood pressure abnormalities suggest a centrally acting agent (opioid or sedative hypnotic). Cholinergic poisoning can be distinguished from other causes of physiologic depression by the presence of characteristic autonomic findings: Salivation, lacrimation, urination, defecation, GI cramps, and emesis (SLUDGE syndrome). In addition, cholinergic poisoning causes pallor and diaphoresis, whereas the skin is usually warm and dry with opioid and sedative-hypnotic poisoning ***(Greenberg et al, 1996).***

Table 1. Differential Diagnosis of Poisoning Based on Physiologic Assessment and Underlying Mechanisms ***(Irwin et al, 2008).***

Excited (CNS Stimulation with Increased Vital Signs)	***Depressed (CNS Depression with Decreased Vital Signs)***	***Discordant (Mixed CNS and Vital Sign Abnormalities)***	***Normal***
Sympathomimetics	**Sympatholytics**	**Asphyxiants**	**Nontoxic exposure**
Amphetamines	Alpha-adrenergic	Carbon monoxide	**Psychogenic illness**
Bronchodilators (Beta 2	antagonists	Cyanide	**Toxic time bombs**
agonists)	Angiotensin-converting	Hydrogen sulfide	Acetaminophen
Catecholamine analogues	enzyme inhibitors	Inert (simple) gases	Agents that form
Cocaine	Beta 2-adrenergic	Irritant gases	concretions
Decongestants	blockers	Methemoglobinemia	*Amanita phalloides* and
Ergot alkaloids	Calcium channel	Oxidative phosphorylation	related mushrooms
Methylxanthines	blockers	inhibitors	Anticholinergics
Monoamine oxidase	Clonidine gestants	Herbicides (nitrophenols)	Cancer therapeutics
inhibitors	Cyclic antidepressants	**AGMA inducers**	Carbamazepine
Thyroid hormones	Decongestants	Alcoholic ketoacidosis	Chloramphenicol
Anticholinergics	(imidazolones)	Ethylene glycol	Chlorinated
Antihistamines	Digitalis	Iron	hydrocarbons
Antispasmotics (GI-GU)	Neuroleptics	Methanol (formaldehyde)	Colchicine
Atropine and other	**Cholinergics**	Paraldehyde	Digitalis preparations
belladonna alkaloids	Bethanechol	Metformin/Phenformin (chronic)	Dilantin kapseals
Cyclic antidepressants	Carbamate insecticides	Salicylate	Disulfiram
Cyclobenzaprine	Echothiophate	Toluene	Enteric-coated pills
Mydriatics (topical)	Myasthenia gravis	Valproic acid	Ethylene glycol
Nonprescription sleep	therapeutics	**CNS syndromes**	Heavy metals
aids	Nicotine	Disulfiram	Fluoride
Orphenadrine	Organophosphate	Extrapyramidal reactions	Immunosuppressive
Parkinsonian therapeutics	insecticides	Isoniazid (GABA lytic)	agents
Phenothiazines	Physostigmine	Neuroleptic malignant syndrome	Lithium
Plants/mushrooms	Pilocarpine	Serotonin syndrome	Lomotil (atropine and
Hallucinogens	Urecholine	Solvents (hydrocarbons)	diphenoxylate)
LSD and tryptamine	**Opioids**	Strychnine (glycinergic)	Methanol
derivatives	Analgesics	**Membrane active agents**	Methemoglobin inducers
Marijuana	Antidiarrheal drugs	Amantadine	(some)
Mescaline and	Fentanyl and	Antiarrhythmics	Monoamine oxidase
amphetamine derivatives	derivatives	Beta-blockers	inhibitors
Psilocybin mushrooms	Heroin	Cyclic antidepressants	Paraquat
Phencyclidine	Opium	Fluoride	Opioids
Withdrawal syndromes	**Sedative-hypnotics**	Heavy metals	Organophosphate
Baclofen	Alcohols	Lithium	insecticides (some)
Beta 2-adrenergic	Anticonvulsants	Local anesthetics	Podophyllin
blockers	Barbiturates	Meperidine/propoxyphene	Salicylates
Clonidine	Benzodiazepines	Neuroleptics	Sustained-release
Cyclic antidepressants	Bromide	Quinine (antimalarials)	formulations
Ethanol	Ethchlorvynol		Thyroid hormone
Opioids	GHB		synthesis inhibitors
Sedative hypnotics	Glutethimide		Throxine valproic acid
	Methyprylon		Viral antimicrobials

The odor of a chemical or of the patient's breath or vomitus may suggest the etiology of poisoning. Chemicals with characteristic odors include acetone, ammonia, arsenic (garlic), camphor, chloral hydrate, cyanide (bitter almond), ethanol, ethchlorvynol, hydrogen sulfide (rotten egg), isopropyl alcohol, marijuana, methyl salicylate (oil of wintergreen), naphthalene and paradichlorobenzene (mothballs), organophosphate insecticides (garlic), paraldehyde, petroleum distillates, phenol, phosphine (fishy), and thallium (garlic) ***(Goldfrank et al, 1982).***

Eye findings can sometimes help to narrow the diagnostic possibilities. Mydriasis can be caused by any agent or condition that results in physiologic excitation, but it is most pronounced in anticholinergic poisoning, in which it is associated with minimal pupil response to light and accommodation. Similarly, although miosis is a nonspecific manifestation of physiologic depression, it is usually most pronounced in opioid poisoning. Visual disturbances suggest anticholinergic, cholinergic, digitalis, hallucinogen, methanol, and quinine poisoning ***(Thompson et al, 1971).***

Table 2. Criteria for a Nontoxic Exposure
(Thompson et al, 1971).

1. Patient is asymptomatic by both history and physical examination
2. Amount and identity of all chemicals and time of exposure are known with high degree of certainty
3. Exposure dose is less than the smallest dose known or predicted to cause toxicity
4. Time elapsed since exposure is greater than the longest known or predicted interval between exposure and peak toxicity

Dermatologic abnormalities may also be helpful. Flushed skin can be caused by anticholinergics, boric acid, a disulfiramethanol reaction, monosodium glutamate, niacin, scombroid (fish poisoning), and rapid infusion of vancomycin (red man syndrome). The skin is hot and dry in anticholinergic poisoning but normal or moist with other etiologies. Flushing should not be confused with the orange skin discoloration caused by rifampin. Pallor and diaphoresis may be due to cholinergics, hallucinogens, hypoglycemics, sympathomimetics, and drug withdrawal. Cyanosis may be due to agents that cause cardiovascular or respiratory depression, methemoglobinemia, pneumonitis, or simple asphyxia. Cyanosis should not be confused with the blue discoloration of the skin caused by amiodarone or by topical exposure to blue dyes. Hair loss, mucosal pigmentation, and nail abnormalities are suggestive of heavy metal poisoning ***(Ford et al, 2001).***

Finally, the presence of neuromuscular abnormalities may suggest certain etiologies. Seizures and tremors can be caused by cholinergics, hypoglycemic agents, lithium, membrane-active agents, some narcotics (e.g., meperidine, propoxyphene), and most physiologic stimulants. They can also occur in patients poisoned by agents that