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DRUG AND ADDICTIVE SUBSTANCE POISONING WITH MEDICAL PHARMACOLOGIST ASSESSMENT

[*1]Mahluga Jafarova DEMİRKAPU

[*1]Department of Pharmacology, Faculty of Medicine, Tekirdağ Namık Kemal University, Tekirdağ, Turkey

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*Corresponding author: mjdemirkapu@nku.edu.tr

Abstract

Poisoning is a medical emergency that represent a major health problem all over the world. The rate of poisoning with prescription and non-prescription drugs, and addictive substances are increasing day by day. This paper summarizes drugs and addictive substances that often cause poisoning in 2017 and their pharmacological properties. Among all the poisonings, drug poisonings were the first in adults and third in children age 5 years or less. Analgesics were the most common drug poisoning in both populations. Considering the etiology of drug poisoning, the ranking is as follows: sedative-hypnotics/ antipsychotics, opioids and other addictive substances, alcohols, calcium channel blockers and acetaminophen (paracetamol). Amphetamines were the most frequent poisoning substances in addictive substances. Analgesics are the cause of poisoning that results in death at age 5 or less. Although paracetamol, one of the analgesics, which is sold over the counter, ranks 6th among the fatal poisonings, it is in the first place among drug poisonings in all age groups, probably because of its easy access and cheapness.

Key Words: Acetaminophen, Amphetamine, Calcium channel blockers, Medication, Poisoning, Tricyclic antidepressants.

Özet

Zehirlenmeler, tüm dünyada önemli sağlık sorununu oluşturan acil tıbbi durumdur. Reçeteli ve reçetesiz ilaçlarla, bağımlılık yapan maddelerle zehirlenme oranı her geçen gün artmaktadır. Bu çalışmada 2017 yılında sıklıkla zehirlenmeye yol açan ilaç ve bağımlılık yapan maddeler ve onların farmakolojik özellikleri derlenmiştir. Tüm zehirlenmeler arasında ilaç zehirlenmeleri yetişkinlerde birinci, 5 yaş ve altı çocuklarda üçüncü sırada yer almaktadır. Her iki popülasyonda en yaygın ilaç zehirlenmesinin nedeni analjeziklerdir. İlaç zehirlenme etyolojisi göz önüne alındığında, sıralama aşağıdaki gibidir: sedatif-hipnotikler/antipsikotikler, opioidler ve diğer bağımlılık yapan maddeler, alkoller, kalsiyum kanal blokörleri ve asetaminofen (parasetamol). Amfetaminler bağımlılık yapan maddeler arasında en sık zehirlenmeye yol açanlardır. Analjezikler 5 yaş ve altı çocuklarda ölümle sonuçlanan zehirlenmenin nedenlerindendir. Reçetesiz satılan analjeziklerden biri olan parasetamol, muhtemelen kolay erişimi ve ucuzluğu nedeniyle tüm yaş gruplarında ilaç zehirlenmeleri arasında ilk sırada, ölümcül zehirlenmeler arasında altıncı sırada yer almaktadır.

Anahtar Kelimeler: Asetaminofen, Amfetamin, Kalsiyum kanal blokörleri, İlaç, Zehirlenme, Trisiklik antidepresanlar.

1. Introduction

Poisoning is an important health problem in the whole world (Thomas et al., 2007). Timely and accurate diagnosis (Table 1-3), timely appropriate treatment significantly reduces mortality due to intoxication, Poisonings occurs with poisons that enter the body in various ways and cause temporary or permanent damage. Examples include cleaning substances (household), cosmetics or personal care products, pesticides, heavy metals, poisonous plants and medicines used for therapeutic purposes. Poisoning can take place via oral, dermal, respiratory and/or injected routes. According to the purpose of poisoning can be unintentional and intentional exposures.

Table 1. Pupil changes in poisonings

Mydriasis	**Myosis**	**Variable-acting substances**
• Sympathomimetics - Cocaine - Caffeine - Ephedrine - Pseudoephedrine - Theophylline - Amphetamines - Synthetic cathinones	• Opioids - Morphine - Heroin - Codeine - Oxycodone - Methadone	• Sedative-hypnotics - Benzodiazepines - Alcohol - Barbiturates - Meprobamate • MAOİ - Alone - Combined: SSRI, Meperidine
• Anticholinergics - Atropine - Scopolamine -Tricyclic antidepressants - Antihistamines - Parkinson drugs - Antispasmodics	• Cholinergics - Organophosphates - Carbamates - Pilocarpine - Nicotine - Physostigmine - Bethanechol	
• Hallucinogens -Lysergic acid diethylamide -Phencyclidine - Mescaline - Psilocybin	• Sympatholytics - Clonidine - Antipsychotics	

Table 2. Skin signs in poisonings

Red and dry skin	**Pale and wet skin**	**Cyanotic skin**
Anticholinergics	• Sympathomimetics	- Methemoglobinemia - Sulfhemoglobinemia - Hypoxia
• Disulfiram-like reaction - Disulfiram / Ethanol - Cephalosporin / Ethanol	• Cholinergics	
• Monosodium glutamate	• Hallucinogens	
Rifampin	Arsenic	
Carbon monoxide		

Table 3. Important vital signs in poisonings

Signs	**Substance (Major Generic Category)**
Hyperthermia Tachycardia Hypertension Tachipnea	Sympathomimetics Anticholinergics Hallucinogens MAOİ
Bradypnea Apnea Hypothermia, Bradycardia, Hypotension (less seen)	Opioids
Bradycardia Hypotension / Hypertension Bradypnea / Tachipnea	Cholinergics

According to the 2018 Annual Report of the American Association of Poison Control Centers (AAPCC), almost half of the 2115186 poisoning cases recorded in 2017 were poisonings at the age of 5 and under (Gummin et al., 2018). The rate of male sex and unintentional poisoning in children and female sex and intentional poisoning in adults are higher. In addition, the poisoning route has often been achieved through oral intake. In drug poisoning, analgesics are most common in the entire population (Table 4-7). Drugs that cause poisoning include tricyclic antidepressants (TCAs), calcium channel blockers (CCBs) and amphetamines besides analgesics.

0.3-3.0 % of the applications made to emergency services in Turkey constitutes poisoning. Analgesic poisoning and antidepressant poisoning are the most common of all poisonings. Cases of oral poisoning, female sex and intentional poisoning are common. Intoxication due to pesticides in Diyarbakır and Adana, carbon monoxide in Bursa and animal bite / insect bites in Mersin come to the fore (Clinical Toxicology Course, 2018).

Table 4. Substance categories most frequently involved in human exposures (Top 10)

Substance (Major Generic Category)	**%**
Analgesics	11.08
Cleaning Substances (Household)	7.43
Cosmetics/Personal Care Products	6.76
Sedative/Hypnotics/Antipsychotics	5.74
Antidepressants	5.02
Antihistamines	4.34
Cardiovascular Drugs	4.24
Foreign Bodies/Toys/Miscellaneous	3.49
Pesticides	3.28
Alcohols	2.82

Table 5. Substance categories most frequently involved in pediatric (≤5 years) exposures (Top 10)

Substance (Major Generic Category)	**%**
Cosmetics/Personal Care Products	12.59
Cleaning Substances (Household)	10.96
Analgesics	9.18
Foreign Bodies/Toys/Miscellaneous	6.39
Topical Preparations	4.84
Antihistamines	4.70
Vitamins	4.26
Pesticides	3.43
Dietary Supplements/Herbals/Homeopathic	3.43
Plants	2.80

Tablo 6. Substance categories most frequently involved in adult (>20 years) exposures (Top 10)

Substance (Major Generic Category)	**%**
Analgesics	11.18
Sedative/Hypnotics/Antipsychotics	9.83
Antidepressants	7.21
Cardiovascular Drugs	6.40
Cleaning Substances (Household)	5.45
Alcohols	4.80
Anticonvulsants	4.24
Pesticides	3.60
Stimulants and Street Drugs	3.55
Antihistamines	3.29

Table 7. Categories associated with largest number of fatalities (Top 10)

Substance (Major Generic Category)	**%**
Miscellaneous Sedative/Hypnotics/Antipsychotics	12.38
Opioids	9.65
Miscellaneous Stimulants and Street Drugs	9.16
Miscellaneous Alcohols	6.19
Calcium Antagonist	5.21
Acetaminophen Combinations	4.35
Acetaminophen Alone	4.29
Beta Blockers	3.62
Miscellaneous Antidepressants	2.67
Miscellaneous Unknown Drug	2.67

Analgesics are opioid and non-opioid drugs used in acute and chronic pain control. The common poisoning drug is non-opioid analgesic drug paracetamol (acetaminophen; N-acetyl-p-aminophenol; APAP). Acetaminophen is often found combined with other drugs in more than 300 over the counter (OTC) allergy medications, cold medications, sleep medications, pain relievers, and other products in Turkey. When taken above the maximum daily dose, paracetamol causes fatal and non-fatal hepatic necrosis (Clark et al., 2012). TCAs commonly used between the late 1950s and late 1980s are still used in depression and other indications and cause life-threatening poisoning. Although poisonings due to CCBs used in the treatment of hypertension, angina pectoris, cardiac arrhythmias, etc. are not common, they are among life-threatening ones. Amphetamines, which were used as nasal decongestants for the first time, were later used to increase alertness and lose weight, but are currently abused worldwide. Cathinones are beta-ketone amphetamine analogs and are consumed for abuse.

In this study, it aimed to compile the pharmacological properties and poisoning of drugs that cause poisoning in 2017.

2. Material and Methods

We searched PubMed and Google scholar for 2017 poisoning data. All pharmacological and toxicological databases reviewed to access drug information.

3. Results and/or Discussion

3.1.Pharmacological properties and poisoning of Paracetamol

The therapeutic dose is 10 to 15 mg kg-1 per dose in children and 325 to 1000 mg per dose in adults, should be given every four to six hours. The maximum recommended daily dose is 80 mg kg-1 in children and 4000 mg in adults. The toxic dose may vary among individuals according to baseline glutathione levels and other factors (alcohol ingestion, chronic liver disease, concomitant use of drugs or herbal products that induce CYP2E1 enzymes etc.). Toxicity is likely to occur with single ingestions greater than 250 mg kg-1 or those greater than 12 g over a 24 hour period (Makin et al., 1995). Acetaminophen is rapidly and completely absorbed from the duodenum. Serum concentrations peak between one-half and two hours after an oral therapeutic dose. The presence of food may delay the timing of absorption. Therapeutic serum concentrations

range from 10 to 20 mcg mL-1 (65 to 130 micromol L-1). Elimination half-lives range from two to four hours for all acetaminophen preparations (Forrest et al., 1982; McGill and Jaeschke, 2013)

Metabolism of acetaminophen occurs within the hepatic microsomes. 90% of acetaminophen is metabolized to sulfate and glucuronide conjugates, and excreted in the urine (Forrest et al., 1982; McGill and Jaeschke, 2013). Approximately 2% is excreted in the urine unchanged. The remaining acetaminophen is metabolized into a toxic, N-acetyl-p-benzoquinoneimine (NAPQI) via cytochrome P450 enzymes (CYP2E1, CYP1A2, CYP3A4). With toxic doses of acetaminophen, the sulfation and glucuronidation pathways become saturated, and more acetaminophen is shunted to the cytochrome P450 enzymes and metabolized to NAPQI (Lee et al., 1996). NAPQI binds covalently to the mitochondrial proteins, leads to oxidative hepatocyte injury, and hepatocellular centrilobular necrosis (James et al., 2003; Lee, 2003) (Fig 1).

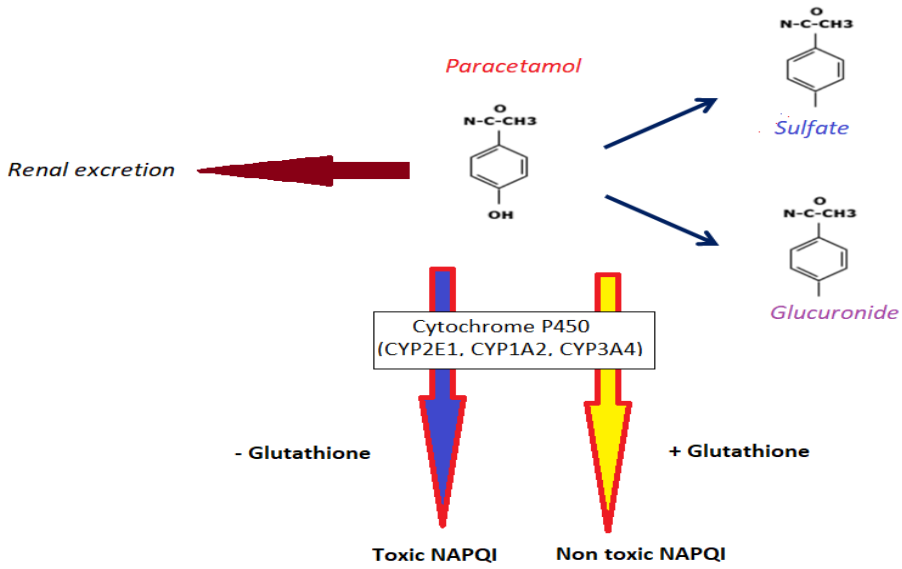

Figure 1. Metabolism of Paracetamol

Poisoning signsare often mild and nonspecific. The clinical course of poisoning is often divided in four sequential stages. *Stage I (0.5 to 24 hours):* Paracetamol poisoning signs are nausea, vomiting, diaphoresis, pallor, lethargy, and malaise in stage I or patients are

asymptomatic. Laboratory studies are typically normal. Hepatic aminotransferase (AST, ALT) concentrations are often normal, but may rise as early as 8 to 12 hours after ingestion in severely poisoned patients (Singer et al., 1995). *Stage II (24 to 72 hours)*: The laboratory evidence of hepatotoxicity, and occasionally nephrotoxicity, become evident. Initially, stage I symptoms resolve and patients appear to improve clinically while worsening subclinical elevations of hepatic aminotransferases develop. As stage II progresses, patients develop right upper quadrant pain, with liver enlargement and tenderness. Elevations of prothrombin time (PT) and total bilirubin, oliguria, and renal function abnormalities may become evident (Mazer and Perrone, 2008). *Stage III (72 to 96 hours):* The systemic symptoms of stage I reappear in conjunction with jaundice, hepatic encephalopathy, a marked elevation in hepatic enzymes, hyperammonemia, and a bleeding diathesis. Signs of severe hepatotoxicity include plasma ALT and AST levels that often exceed 10.000 IU L-1, prolongation of the PT/INR, hypoglycemia, lactic acidosis, and a total bilirubin concentration above 4.0 mg dL-1, or 68 micromol L-1. Death most commonly occurs in this stage, usually from multiorgan system failure (Jaeschke et al 2012). *Stage IV (four days* to two weeks): Patients who survive stage III enter a recovery phase that usually begins (Smilkstein, 1998). Recovery can be slower in severely ill patients; symptoms and laboratory values may not normalize for several weeks. Histologic recovery lags behind clinical recovery and may take up to three months.

Diagnosis and treatment of poisoning: The serum paracetamol concentration is the basis for diagnosing acute paracetamol poisoning and determining the need for treatment. In all patients with suspected paracetamol overdose, a history should be obtained to elicit the dose, intent of use (ie, intentional or not), pattern of use (eg, single or repeated doses), time of the ingestion, the presence of coingestants, and the existence of comorbid conditions that may predispose to the development of hepatic injury. Additional laboratory tests should include electrolytes, BUN and creatinine, serum total bilirubin level, prothrombin time with INR, AST, ALT, amylase, and urin alysis. In patients with intentional ingestions or unreliable histories, toxic screening of blood and urine for other ingested drugs should be performed. Treatment consists of supportive care, prevention of drug absorption, and, the antidotal treatment with N-acetylcysteine (NAC) and enhancement of drug elimination.

3.2. Pharmacological properties and poisoning of tricyclic antidepressants

In therapeutic use, TCAs are rapidly absorbed from the gastrointestinal tract, reaching maximal plasma concentrations within two to eight hours. TCAs are lipophilic and thus have a large volume of distribution (Vd). The fraction of the drug found in the plasma is usually highly bound to alpha-1 acid glycoprotein. TCAs are primarily metabolized by the liver, undergoing phase one metabolism primarily via CYP 2D6 and phase 2 glucuronidation. Many phase one metabolites are pharmacologically active and may persist in the plasma for 12 to 24 hours. Depending upon the TCA, the half-life of the parent compound can range from 7 to 58 hours. Approximately 70% of the total dose is renally excreted as inactive metabolites; the remainder is eliminated primarily via the biliary system, with a small amount excreted unchanged in the urine. Enterohepatic recirculation can delay final elimination of a large fraction of the drug (Kerr et al., 2001).

Toxicity is caused by blockade of cardiac fast sodium channels, central and peripheral muscarinic acetylcholine receptors, peripheral alpha-1 adrenergic receptors, histamine (H1) receptors, and CNS gamma-aminobutyric acid (GABA) A receptors.

Poisoning signs include sedation, but may also include confusion, delirium, or hallucinations. Cardiac conduction delays, arrhythmias, hypotension, and anticholinergic toxicity (eg, hyperthermia, flushing, dilated pupils) are also common. The clinical course of patients with TCA poisoning can be unpredictable, and patients who present immediately after ingestion may initially be well-appearing, only to deteriorate rapidly, due to the variable absorption kinetics described above. In most cases, acute TCA ingestions of 10 to 20 mg kg-1 lead to significant cardiovascular and central nervous system (CNS) toxicity (Liebelt et al., 2011).

Diagnosis and treatment of poisoning: The diagnosis is made based on the history of ingestion of the drug included in the relevant group, characteristic symptoms and ECG findings. Patients with TCA poisoning can appear stable but deteriorate rapidly, and significant toxicity can occur despite falsely reassuring ECG findings. ECG findings suggestive of cardiotoxicity include: prolongation of the QRS >100 msec; abnormal morphology of the QRS (eg, deep, slurred S wave in leads I and AVL); and, abnormal size and ratio of the R and S waves in lead AVR (R wave in AVR >3 mm; R to S ratio in AVR >0.7), or possibly a Brugada pattern. Treatment consists of supportive care, prevention of drug absorption, and, and enhancement of drug elimination. Sodium bicarbonate should be used to treat cardiac toxicity; benzodiazepines should be used for agitation control. Despite prominent anticholinergic toxicity in some patients with TCA poisoning,

physostigmine is contraindicated as it is associated with cardiac arrest (Pentel and Peterson, 1980).

3.3. Pharmacological properties and poisoning of calcium channel blockers

CCBs are used both as immediate-release and extended-release preparations (Eisenberg et al., 2004). Extended-release preparations are more important in poisoning CCBs. Pathophysiology of CCBs is shown in Fig 2.CCBs are highly protein bound, have a large Vd, and are metabolized in the liver. As the dose is increased, the rate of CCB clearance decreases, prolonging the half-life (McAllister et al., 1985).

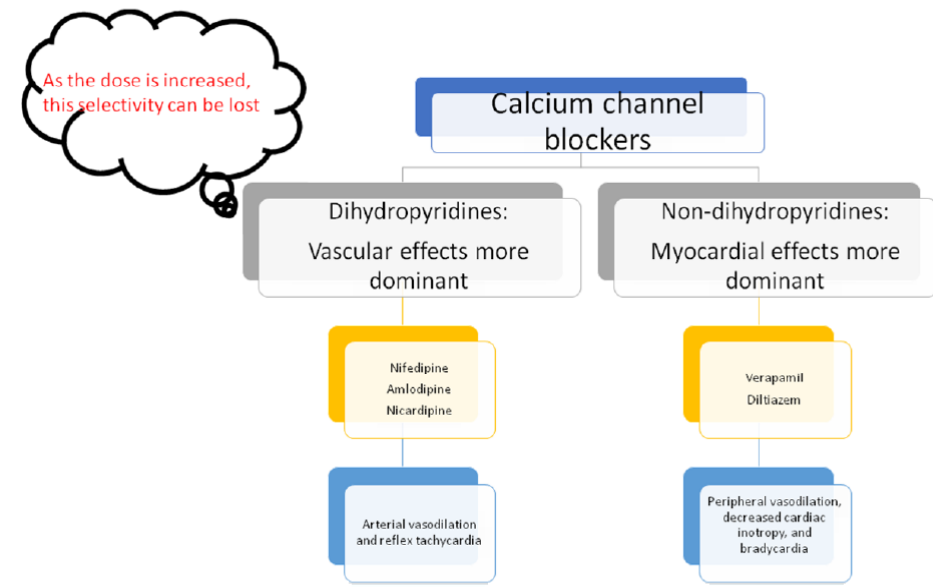

Figure 2. Pathophysiology of CCBs

Signs of CCBs poisoning include hypotension and bradycardia, which usually is seen in non dihydropyridine CCB overdose. However, bradycardia may also be seen with severe dihydropyridine CCB poisoning.

Diagnosis and treatment of poisoning: The diagnosis of CCB poisoning is made clinically on the basis of the history and clinical findings. Over dose with dihydropyridine CCBs causes

hypotension coupled with reflex tachycardia, although severe toxicity may result in hypotension and bradycardia. Overdose with non dihydropyridine CCBs causes the dangerous combination of hypotension and bradycardia.CCB poisoned patients may maintain a surprisingly clear mental status in the setting of hypotension. Electrocardiogram changes associated with CCB poisoning include PR interval prolongation and any bradydysrhythmia. The presence of hyperglycemia in a nondiabetic patient may help to distinguish CCB from beta blocker poisoning. Treatment consists of supportive care, prevention of drug absorption, and, and enhancement of drug elimination. Norepinephrine is the initial vasopressor of choice (Levine et al., 2013). Atropine should be used for symptomatic bradycardia.

3.4. *Acute amphetamine and synthetic cathinone ("bath salt") intoxication*

Our knowledge of many of the synthetic cathinones is limited. Amphetamines are lipophilic compounds that readily cross the blood-brain barrier (Baselt, 2004). This property results in rapid onset of effects when injected, inhaled, or insufflated. Oral ingestion yields peak concentrations in about two hours. Cathinone peaks after oral ingestion in about one hour. Amphetamines have large Vd, approximately 3 to 6 L kg-1. Half-lives vary widely by drug, ranging from 3 to 24 hours, but may extend beyond 30 hours, as urinary elimination is extremely pH dependent. The metabolism of amphetamines occurs by several hepatic pathways and elimination is primarily renal (Chiang, 2011). Metabolism of cathinones generally occurs by demethylation followed by glucuronidation and sulfation, with metabolites eliminated primarily in the urine and bile (Prosser and Nelson, 2012). Phenylethylamines, including traditional amphetamines and the newer synthetic compounds, cause the release of neurotransmitters, such as dopamine, serotonin, and norepinephrine and may also inhibit their reuptake. Some cause the release of serotonin from central axons, and some are serotonin receptor agonists (Prosser and Nelson, 2012).

Poisoning with amphetamines causes tachycardia, hypertension, and hyperthermia. Poisoning with synthetic cathinones produces a prominent neuropsychiatric syndrome whose signs can include agitation, combativeness, hallucinations, paranoia, confusion, myoclonus, and in rare cases seizures (Wood et al., 2010).

Diagnosis and treatment of poisoning: The diagnosisof amphetamine poisoning is usually made on the basis of a history of abuse and clinical features consistent with an overdose of these substances, primarily symptoms and signs of a sympathomimetic syndrome. Treatment consists

of supportive care, prevention of drug absorption, and, and enhancement of drug elimination. First line therapy for treating psychomotor agitation consists of intravenous administration of benzodiazepines.

4. Conclusion

Unintentional and intentional exposures continue to be a significant cause of morbidity and mortality all over the world. Taking paracetamol from analgesics above the maximum daily dose may cause fatal hepatotoxicity. CCBs can cause fatal consequences by making cardiovascular system toxicity, TCAs, amphetamine, and synthetic cathinone cardiovascular toxicity as well as central nervous system toxicity.

5.Acknowledgement

"All things are poison and nothing is without poison; only the dose makes a thing not a poison." Paracelsus

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