Evaluation of Common Non-pharmacological Chemical Substance Poisonings in Childhood

Çocuklarda Sık Gözlenen İlaç Dışı Kimyasal Madde Zehirlenmelerinin Değerlendirilmesi

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ABSTRACT

Acute intoxications in adolescents and adults are mostly associated with intentional or accidental ingestions. Intoxications are commonly seen in children aged between 1 and 5 years and most of the cases are associated with accidental intake. In most of the children, no clinical symptoms related to intoxication are observed or only mild effects can develop. The main route of drug elimination is through kidneys. Absolute clearance in children is often lower than in adults but weight-adjusted clearance is higher. Depending on more rapid elimination in children the plasma half-life of the drug might be shorter in children than in adults. A shorter elimination half-life means that plasma steady-state is achieved with repeated doses. It is important to prevent childhood intoxications, and the use of child-resistant packaging and adequate supervision together with the secure storage of household substances are the basis of prevention of accidental childhood intoxications. Intoxications represent one of the most common medical emergencies in children, and epidemiological characteristics vary in different countries. Therefore, special epidemiological surveillance is necessary for each country to determine the problem according to which preventive measures should be taken. Early awareness and taking appropriate therapeutic measures seems to be effective in the reduction of mortality rate. The major and most common non-pharmacological chemical intoxications in childhood have been reviewed here with the intent of helping health-care professionals, particularly pediatricians to recognize and reduce the risk of harmful childhood intoxications.

Keywords: Childhood, intoxication, child health, antidote

ÖZ

Ergen ve yetişkinlerdeki akut zehirlenmeler çoğunlukla kasıtlı veya kazara alımlar ile ilişkilidir. Bir ve beş yaş arasındaki çocuklarda zehirlenmeler yaygın görülmektedir ve olguların çoğu kazara alımlara bağlıdır. Çocukların çoğunda zehirlenmeye bağlı hiçbir klinik belirti gözlenmez veya sadece hafif etkiler gelişebilir. İlaç eliminasyonu esas olarak böbrekler aracılığı ile olur. Çocuklarda mutlak klerens yetişkinlere göre genellikle daha düşüktür, fakat vücut ağırlığına göre hesaplanan klerens daha yüksektir. Çocuklarda daha hızlı eliminasyona bağlı olarak, ilacın plazma yarı ömrü yetişkinlere kıyasla daha kısa olabilir. Eliminasyon yarı-ömrünün daha kısa olması, plazma kararlı durumuna tekrarlanan dozlarda ulaşıldığı anlamına gelir. Çocukluk çağı zehirlenmelerinin önlenmesi önemlidir, çocuk emniyeti olan ambalaj kullanılması ve evsel ürünlerin kontrollü olarak güvenli muhafaza edilmeleri, kazara oluşan çocukluk çağı zehirlenmelerinin önlenmesinin esasını oluşturur. Zehirlenmeler, çocukluk çağında en sık görülen acil tıbbi durumlardan biridir ve epidemiyolojik özellikleri ülkeden ülkeye farklılık göstermektedir. Bu nedenle, sorunu belirlemek için hangi önleyici tedbirlerin alınabileceği konusunda her ülke için özel epidemiyolojik takip gereklidir. Zehirlenmelerde erken farkındalık ve uygun terapötik önlemlerin alınması ölüm oranının düşmesinde etkili görünmektedir. Çocukluk çağındaki ciddi zehirlenmeler konusunda riski tanımak ve azaltmak için başta pediatristler olmak üzere sağlık çalışanlarına yardımcı olacağı düşüncesiyle, çocukluk çağında en önemli ve en sık görülen ilaç dışı kimyasallarla olan zehirlenmeler derlendi.

Anahtar Kelimeler: Çocukluk çağı, zehirlenme, çocuk sağlığı, antidot

Introduction

Besides toxicokinetic properties of the intoxicating agent, the response to it in children is different than in adults, and this fact should be taken into consideration when dealing with children. It should be kept in mind that intoxication symptoms in children can be similar to those of some diseases. Therefore, medical history, physical examination, and clinical symptoms of the patient should be evaluated, and the treatment of the patient with suspicion of intoxication should be performed as soon as possible.

In the present review, some common non-pharmacological intoxicating agents, and epidemiological and clinical features of intoxications and treatment approaches have been discussed.

1. Yellow Phosphorus

Yellow phosphorus is a waxy, yellow-colored inorganic material which has a transparent appearance (1). It is used in industry, mainly in making matches, pesticide, firework, watches, and explosive material. It is also present in the composition of ammunition, and agricultural fertilizers (1,2), and is used as rodenticide in agriculture. As the rodenticides containing 2-5% yellow phosphorus are often prepared as paste, intoxications due to accidental oral intake being mistaken for toothpaste by children is frequently observed (2,3). The strong garlic odor of yellow phosphorus can be definitive in the diagnosis of the patients with suspicion of intoxication (1,2).

Skin, epithelial, and mucous membranes of respiratory and gastrointestinal systems are among the contamination routes. After oral intake, it distributes to all tissues, mainly liver and reaches maximum blood concentration within 2-3 hours (2,4). The lethal dose of yellow phosphorus is 1 mg/kg. The main exposure in children is via oral route, and it is rapidly absorbed through intestines following oral intake and leads to many complications, hepatotoxicity being in the first place. It causes severe damage in various organs such as the heart, kidneys, spleen, and brain in addition to liver. Apart from oral intake, intoxications can be seen as a result of the inhalation of industrial particles, or dermal exposures (1,4,5).

When a firework-like substance containing yellow phosphorus (10%), silica, potassium chlorate, ferrous oxide, and magnesium carbonate, and known as "cracker" in Turkey is eaten by children, intoxication is frequently observed (1,5,6). The mortality rate is high (23%), and upper abdominal pain, vomiting, lethargy, respiratory distress, hepatotoxicity, and coagulation dysfunction are observed. Severe intoxications cause arrhythmia, coma, hypotension, and lead to death (5). The clinical signs of acute intoxications occur in mainly three stages. The first stage is gastrointestinal symptoms characterized with vomiting, nausea, diarrhea, and abdominal pain, which develop within 24 hours following oral intake. Although laboratory tests seem to be normal at this stage, sudden death can occur. It is thought that this situation is due to the consequence of cardiovascular arrhythmia, and collapse developing within the first 24 hours. Cardiac collapse can also develop as a result of fluid and electrolyte loss caused by vomiting or diarrhea. The second stage (1-4 days) is a latent period without any symptoms. However, hepatic enzyme and bilirubin levels increase and hepatotoxicity begins to progress at this stage. The third stage (4-7 days) is characterized by acute hepatic failure and acute renal failure together with metabolic disturbance, encephalopathy, coagulopathy, arrhythmia, cardiogenic shock, abnormal liver function tests, acute tubular necrosis, changes in mental status such as confusion, psychosis, hallucination; coma, hypotension, cardiac toxicity, and multiple organ failure (1,2). It is suggested that yellow phosphorus leads to transient proliferation in erythrocytes although it often causes no change in hematological parameters. Bone marrow pathology should be examined in critical patients (4).

There is a limited number of studies on its metabolism and the enzymatic destruction pathways are not known in details. It has been reported that yellow phosphorus, which is a protoplasmic toxin, disturbs glycogenesis, leads to lipid peroxidation, and disturbs the synthesis of plasma proteins regulating prothrombin time and coagulation (1,2).

There is no specific method for the diagnosis of intoxication, and the measurement of blood phosphorus levels is not found to be practical in clinics. The diagnosis is mostly provided with the medical history taken from the children or the parents. If the history is not clear, the garlic odor in breath or luminescence in stool/vomit can be beneficial in the diagnosis. The odor of the stool is named as "smoking stool syndrome". There is no specific antidote or treatment approach in yellow phosphorus intoxications. Unfortunately this makes the selection of correct treatment difficult. Laboratory findings can be helpful in determining the stage of the clinical picture. In biochemical tests, metabolic acidosis, hypoglycemia, hyperbilirubinemia, increased levels of aspartate aminotransferase and alanine aminotransferase are observed. Abnormal partial thromboplastin time and leukopenia are among the hematological abnormalities. Electrocardiography (ECG) findings show changes in T (ventricular repolarization) and QRS (ventricular depolarization) waves, arrhythmia and atrial fibrillation. All of these findings can be easily observed particularly in the third stage (1,6). The time interval between the ingestion of the intoxicating agent and the emerging of symptoms can vary. In addition to the cases in which the symptoms appear within a few minutes, there are also cases where symptoms appear after 24 hours. Gastric lavage and decontamination within 2-5 hours following the ingestion of the poison can be beneficial. The first treatment method is the prevention of the absorption of oxidized phosphorus. At the beginning of the treatment, isotonic serum physiological solution, vitamin K, and ranitidine are given, and oxygen support is supplied with face mask. Plasma transfusion is performed. While the mortality rate is 23% in patients with the symptoms of vomiting and abdominal pain, and who have been diagnosed

in the early period; the mortality rate is 73% in intoxications with the symptoms of anxiety, nervousness, somnolence or coma. For supportive treatment, the monitoring of electrolyte balance, acid-base status, liver and renal functions, and the determination of coagulation parameters is important (3,5). In the treatment of acute intoxications, gastric lavage is performed, or the oxidation of the toxin to less toxic phosphoric acid and phosphates is provided by using potassium permanganate (1:5000). Alternatively, the transformation of phosphorus to non-toxic copper phosphite can be done by gastric lavage with copper sulfate solution (0.2%). Use of fatty substances that increase the absorption of phosphorus or consumption of fatty nutrients should be avoided. However, the efficacy of all these treatment methods is not definite. Furthermore, it is suggested that the use of intravenous (i.v.) steroids and N-acetylcysteine for treatment is not practical. Hypotension, hypoglycemia, hypocalcemia, convulsions, coagulopathy, and arrhythmias should be corrected with supportive treatment. It has been reported that supportive treatment is partially effective in the first and second stages, but the only treatment method in the first stage is liver transplantation. In a study which has evaluated the survival rates in patients who had acute liver failure and living donor transplantation due to yellow phosphorus intoxication in Turkey, it has been reported that one out of 4 children who had medical treatment and three out of 6 children who had liver transplantation have survived (1).

Due to the development of resistance against rodenticides containing warfarin in rodents, the use of rodenticides with yellow phosphorus has become popular. As the commercial forms of rodenticides containing yellow phosphorus are produced as paste to be consumed by the rodents, their consumption by children has also become easy (2).

2. Ethylene Glycol

Apart from being used as anti-freeze in automobiles, ethylene glycol is also used in carpet washing shampoos in industry, as cooler in air conditioners, in the composition of cloth and metal cleaners, and pesticides, in fire extinguishers, and wood sheathing. Ethylene glycol is an odorless, colorless, sweetish liquid which has syrup consistency (7,8). Both accidental and suicidal intake of ethylene glycol is frequently observed owing to the sweet taste and easy access (9). Its intestinal absorption and tissue distribution is rapid as its water solubility is good. Its serum concentration reaches the maximum level within 30-60 minutes following oral intake. Before it is metabolized, it is relatively non-toxic. The main metabolites responsible for toxicity are glycolaldehyde, glycolic acid, glyoxylic acid, and oxalic acid (8). These metabolites cause accumulation of calcium oxalate crystals in the tissues leading to tissue damage, metabolic disorders, metabolic acidosis with anion gap, lactic acidosis, and hypoglycemia. Ethylene glycol intoxication occurs mainly in three stages. The symptoms in the first stage (first 12 hours)

is due to ethylene glycol (8,9). Its depressant effect on the central nervous system (CNS) is observed (8-10). Metabolic acidosis, which is seen between the first and second stages, can usually be misleading for the determination of the stage of the intoxication. In the second stage (12-24 hours), in addition to severe metabolic acidosis, multiple organ failure due to the metabolites of ethylene glycol can be observed. It has been reported that the most mortality is seen in this stage. The third stage (24-48 hours) is characterized by acute tubular necrosis and renal failure. Oliguria, anuria, hematuria, proteinuria, and crystalluria are also observed. Oliguric or anuric renal failure can sometimes develop even 45 days later (8,9). The history in ethylene glycol intoxications is very important for diagnosis, as in other intoxications. As drunkenness often attracts attention, it can be confused with ethanol induced drunkenness, so it can be misleading for diagnosis. However, the absence of ethanol odor can be beneficial for differential diagnosis (9,10).

Ethylene glycol toxicity is observed when exposure is above 1 g/kg or when serum level >20 mg/dL (9). In recent years, it has been reported that ethylene glycol intoxications are more common than methanol intoxication, which is one of the frequently seen intoxications (11). As formation of calcium oxalate crystals is observed in both of them, often ethylene glycol intoxications can be confused with methanol intoxications. General supportive treatment including respiratory and circulatory support is primarily performed (9). Gastric decontamination is not effective. In asymptomatic children, serum calcium levels, electrolytes and renal functions should be evaluated for the estimation of plasma ethylene glycol levels (7). It is rapidly absorbed, so gastric lavage and/or ipeca syrup is not beneficial in decontamination; and as high amounts of activated charcoal is required for small amounts of ethylene glycol, the use of activated charcoal in clinical settings is not practical (9). It is suggested that the main source of severe acidosis due to ethylene glycol is the circulating glycolic acid (11). The formation of calcium oxalate crystals also induces an acidic environment. Sodium bicarbonate should be given for the correction of acidosis (8). It is necessary to act quickly for the administration of sodium bicarbonate, particularly when pH is below 7.3 (10,11). Continuous infusion of bicarbonate can be performed together with i.v. thiamin (100 mg) and pyridoxine (vitamin B6, 100 mg) for urine alkalinization. Dialysis can be necessary for the inhibition of toxic metabolite formation and for removal of the main product and its metabolites. Hemodialysis should be performed, particularly when severe acidosis is observed, when renal function is diminished or when damage is observed in other organs. Serum magnesium levels should also be followed up. Together with thiamin, magnesium also functions as a co-factor in the alternative degradation pathway of ethylene glycol (9). Although there is limited data supporting the efficacy of pyridoxin in treatment, it is thought to be beneficial in diminishing the toxicity of glycolic acid (11). Calcium support is also recommended to prevent tetanus (9). Ethanol infusion

prevents toxic metabolite formation. In acute ethylene glycol intoxications, empiric treatment begins with 10% i.v. ethanol (7,9). Ethanol (40%) is given at a dose of 2 mL/kg for 30 minute as oral loading dose. Fomepizole (4 methyl pirazole), which is another antidote as an alternative to ethanol, is a competitive antagonist of alcohol dehydrogenase. I.v. fomepizole (15 mg/kg within 30 minutes) should be given to symptomatic children or to the children with plasma ethylene glycol levels above 200 mg/L (3.2 mmol/L). Fomepizole should be repeated every 12 hours (4 doses 10 mg/g, then 15 mg/kg) until plasma ethylene glycol level diminishes below 200 mg/L (7,10). It has been reported that the effectiveness of fomepizole is highest when it is given before the formation of toxic metabolites. When the fomepizole dose is arranged during treatment, it is recommended to arrange the dose according to the concentration of toxic metabolites instead of serum ethylene glycol concentration. In developed countries, fomepizole is preferred instead of ethanol. Fomepizole has been reported to have no side effects except rare allergic reactions. It has also been reported that it is not necessary to arrange the dose in patients with renal or hepatic diseases, and that it does not interact with other drugs (11). On the other hand, there are investigations which report that it has disadvantages such as CNS depression and hypoglycemia (7). Nevertheless, fomepizole is said to be effective in ethylene glycol intoxications in newborns (12,13). Hemodialysis can be necessary for patients with renal failure or resistant metabolic acidosis (7). Fomepizole administration and hemodialysis have been performed in a pediatric case at the age of 8 months to correct acidosis and oxalate crystaluria that developed due to the ingestion of more than 120 mL ethylene glycol. Following fomepizole and hemodialysis, acidosis was corrected by preventing the conversion of ethylene glycol to toxic metabolites, and the patient has been reported to have improved within 48 hours (12). However, there are reports that show that fomepizole administered at a dose of 10 mg/kg every 12 hours following a loading dose of 15 mg/kg was also successful without any need for hemodialysis in newborns (13).

3. Lead

Infants, pregnant women, and occupational groups that are in close contact with lead are more sensitive to its toxic effects. Lead exposure in children develops due to a high incidence of pica (earth eating), more exposure to street and home dusts, less clearance of lead from the body, and increased absorption in the presence of iron deficiency anemia. In children asymptomatic lead intoxication is observed most frequently. Chronic exposure to low dose lead can cause persistent mental dysfunction which can only be understood by screening methods (14).

Lead passes to placenta during pregnancy and causes premature birth and low birth weight in the fetus or death (15). 40-50% of lead exposure in children is due to the use of domestic dyes with lead content (16,17). Exposure to

dye powders through respiratory tract during grinding is also mentioned. Other sources of exposure are drinking the water contacting lead pipes, food in tin or ceramic containers, alternative treatment methods such as ayurveda (16).

Lead inactivates enzymes by binding sulfhydryl, phosphate and carboxyl groups on proteins. Furthermore, it interacts with calcium, zinc and iron, disturbs nerve conduction by affecting cell membrane, influences redox events, and causes multiple organ dysfunction by disturbing nucleotide metabolism (15).

When the lead level is above 400-600 µg/L, classical effects of lead intoxication such as colic, abdominal pain, lack of appetite, vomiting, and constipation are observed; and if blood lead concentration is >450 µg/L, microcytic anemia is seen. The neurological effects depend on the chronicity and severity of intoxication. If the lead level is above 750-1000 µg/L, encephalopathy, delirium, ataxia, coma, and convulsions occur. Chronic exposure to low doses of lead in children causes reduction in IQ levels of about 1-2 points. If lead intoxication is suspected in children, complete blood count and abdominal X-ray should be requested. I.v. ethylene diamine tetra acetic acid (EDTA) and oral dimercapto succinic acid (DMSA) (2,3) are used for chelation in treatment (16). At the present time, previous agents such as British anti-lewiste and penicillamine are rarely used (16). Although the efficacy of DMSA is similar to EDTA, due to the inadequacy of clinical experiences its use is approved only in children with blood lead levels between 45-69 µg/dL (18). It is necessary to be careful during chelation therapy in children. If there is encephalopathy in the child and if the blood lead level is above 750 µg/L, referral of the child to the intensive care unit might be needed. The bad odor and taste of DMSA makes its oral use in children difficult. Thus, it is recommended to give it by mixing with nutrients such as jam and jelly. In recent studies it is suggested that chelation treatment is not beneficial in children with blood lead level above 450 µg/L (16). The use of penicillamine in lead intoxication has not been approved by Food and Drug Administration. Also because the benefit of chelation treatment in patients with lead level below 25 µg/dL has not been approved, this level is a criteria for the discontinuation of the treatment. Centers for Disease Control and Prevention has decreased the limit for toxic blood level of lead in children from 40 µg/dL to 30 µg/dL in 1975, to 25 µg/dL in 1985, and to 10 µg/dL in 1991 (19). In Turkey, several studies evaluating lead levels in children have been conducted. In the study of Vural and Güvendik (20) which was conducted in 1987 with children living in Ankara, mean blood level of lead was found as 19.35 µg/dL; in the study of Bostancı et al. (21) which was conducted in 1995 to determine the lead level in umbilical cord samples of the newborns living in the center and villages of Ankara, it was found as 9.4-15.5 µg/dL. The study of Göker (22) conducted in İstanbul in 1995, found the lead level as 5.55 µg/dL, and the study of Can et al. (23) which was conducted in Tekirdağ in 1997 found it as 29.6 µg/dL. The lead level was found as 23.4 µg/dL in the study of Yapıcı et al. (24) conducted in Silivri in 1999.

Lead exposure at low doses can cause severe motor and cognitive dysfunction. These effects of lead exposure particularly in children younger than 6 years of age should not be ignored. As the prenatal and neonatal periods are durations of rapid growth, absorption of heavy metals in nutrients is higher compared to the adults. As a result, this group is at more severe risk. Although toys containing lead in their composition have been banned in many countries, lead intoxications due to toys contaminated with lead are still being reported all over the world (25).

Illegal employment in Turkey is common and most of these workers are children, and this makes lead exposure and lead toxicity unavoidable in children. Toxic levels of lead have been identified in blood samples in 8% of the lead workers aged below 18 years (18).

Controlling the children at risk at certain time intervals, regular monitoring of blood lead levels in occupational groups that are in close contact with lead, monitoring blood lead levels with more extended screening, and also developing protection and prevention strategies against lead exposure by conducting environmental analyses (soil, plant, water etc.) are necessary particularly for the protection of children from the toxic effects of lead (14).

4. Methanol

Methanol is found in the composition of several products which are used in daily life such as stain removers, cologne, and spirit, solvents such as anti-freeze, washing solutions and brake fluids (7,16). In children the ingestion of even a small amount of methanol can cause severe intoxication, similar to that of ethylene glycol (16). Methanol is metabolized to toxic metabolites by alcohol dehydrogenase. Severe abdominal pain, retina toxicity, acidosis, convulsions, and coma are among its toxic effects (7,26). Exposure to high doses of methanol leads to severe clinical effects such as metabolic acidosis, CNS depression, hypotension, acute renal failure, and methanol blindness (16,26). Although there are some differences in methanol intoxications, the treatment approach is similar to the one applied in ethylene glycol intoxication. The half-life of methanol is 43 hours and severe symptoms develop hours later (7). As hypoglycemia and hypothermia can develop due to ethanol particularly in young children, its use in treatment is not preferred. Fomepizole does not cause hypoglycemia and sedative side effects, and its tolerability is also more than ethanol. However, its higher cost compared to ethanol restricts its use in clinics (16,26-28).

In a study conducted in Turkey, it has been reported that 3.3% of the intoxication cases which were notified to the National Poisoning Research Center between 1993 and 2002 were alcohol intoxications, and 11.3% of the alcohol intoxications were due to methanol. The rate of methanol intoxication in children aged between 0 and 12 years was found as 55.7% (29). In a study conducted by Türkmen et al. (30) it was reported that when the medical history of a 4-year-old girl with complaints of nausea, vomiting, and abdominal

pain was taken, she had drunk washing solution 2 days before. Toxicological studies performed following autopsy have shown that blood level of methanol is 79 mg/dL. It has been stated that although the lethal dose of methanol is reported to be 1-2 mg/kg, exposure to even small doses such as 0.1 mg/kg can lead to blindness or death. According to the reports most of the methanol intoxication cases were children under 6 years of age (30).

5. Essential Oils

Although essential oils are used in perfumery, aromatherapy or massage, they are compounds with high toxicity potential (31,32). When they are topically applied, they demonstrate analgesic and anti-pyretic effects. Furthermore, they are also widely used in the treatment of common cold and coughing (33). Although the chemical structure and toxic effects of most of the essential oils are not exactly known, they are a mixture of esters, alcohols, aldehydes, and ketones (32,34). Resulting from the increased use of essential oils, the number of admissions to emergency departments due to intoxications with these substances has increased in recent years. In a study evaluating the toxic agents in intoxication cases admitted to the emergency services, poisonings due to essential oils was found to be at the 9th range among 35 agents. Most of the time there is no child safety latch in packagings, and this forms a basis for the intoxication events in children (34).

The initial signs of intoxication with essential oils are mucosal irritation, vomiting, epigastric pain, and diarrhea. Convulsions, CNS depression, hepatic and renal failure are the other signs. Asymptomatic children should be monitored for at least 6 hours after providing fluid support. Hospitalization can be necessary in symptomatic children. Presence of respiratory distress should remind us of the aspiration of essential oils. Supportive treatment is recommended, and blood glucose levels should also be monitored (31,32).

At the present time, turpentine oil is more commonly used than other essential oils due to its relatively low toxicity. Symptoms develop 24 hours after ingestion. In addition to chemical pneumonia, gastrointestinal system irritation, burning due to oral ingestion, metabolic acidosis, hepatic failure, and renal damage, mental changes can also be observed. Gastric decontamination is contraindicated in treatment. In all patients, oxygen saturation should be measured and presence of respiratory distress should be determined. Most of the patients with intoxications due to turpentine oil are asymptomatic. When hospitalization is not found to be necessary, the parents should be informed that they should again refer to a hospital when coughing, noisy or rapid respiration are observed (31). Camphor oil is a volatile oil which causes gastrointestinal irritation and CNS depression, and symptoms often develop within 5-10 minutes following ingestion. The lethal dose of camphor oil in children is 5 mL. Convulsions are observed 20-30 minutes after ingestion. The symptoms of intoxication due to eucalyptus oil are epigastric

pain, vomiting, burning sensation in mouth and throat, convulsions, respiratory difficulty, and CNS depression. While CNS symptoms can develop within 30 minutes, they can also develop 4 hours later. Oral ingestion of 3-5 mL of pure eucalyptus oil causes transient coma and convulsions. Mainly supportive treatment is recommended in the treatment of intoxications due to camphor oil and eucalyptus oil. However, as it may lead to sudden convulsions, the use of ipeca syrup is not recommended, and the efficacy of activated charcoal and hemoperfusion has not been approved yet (33).

6. Organophosphates

Organophosphates are irreversible inhibitors of acetylcholinesterases and they cause accumulation of acetylcholine in the cholinergic receptors. Exposure is mainly through oral route, skin, mucous membranes, conjunctiva or respiratory tract (35). The symptoms can be observed even 24 hours later in organophosphate intoxications. As a result of the excessive stimulation of the parasympathetic system, salivary and lacrimal gland secretions, bronchial and gastrointestinal secretions increase, peristaltic activity increases, bronchoconstriction, bradycardia, reduction in visual acuity, hypotension, headache, somnolence, convulsions, and miosis develop. Urine and fecal incontinence, loss of sphincter control are among the secondary findings. Paralysis is observed when taken at high doses. Hyperglycemia and glycosuria without ketonuria can also be observed. Symptoms related to the dermal absorption of organophosphates are rarely seen. The highest risk for acute toxicity is through oral ingestion. Asymptomatic children should be monitored for 24 hours, and symptomatic children need more careful monitoring (7,35,36). One of the antidotes used in specific treatment is atropine, which has anti-muscarinic effects, and the other antidote is pralidoxime, which is an enzyme reactivator. Atropine antagonizes the competitive effects of acetylcholine on muscarinic receptors. In general, its short-term and intermittent use is recommended. Data related to its long-term use as i.v. infusion is limited. Mild symptoms can be corrected with supportive treatment. The patients who gave no response to treatment with atropine should be treated with pralidoxime. Administration of pralidoxime within 24 hours following ingestion increases the effectiveness of treatment. Two children who had been admitted to the emergency department after eating peach with remnants of pesticide containing organophosphate, were elethargic, their pupils were miotic, they responded to stimulation with agitation, and had increased secretions, bradycardia, tachypnea, and dyspnea. Both of them were intubated and mechanically ventilated as they had excessive secretions in the respiratory tract alongside respiratory distress. I.v. atropine and pralidoxime were administered. But as the bronchial secretions increased and bronchospasms became more severe, i.v. infusion of atropine (0.02-0.08 mg/kg/hour) was started. Following this, a significant reduction in the secretions and bronchospasms was observed. In

organophosphate intoxications which give no response to short-term and intermittent atropine, long-term i.v. atropine is recommended (35). In another patient who had been admitted to hospital after exposure to pesticide containing organophosphate, acetylcholine esterase level was found to be low, and the initial treatment with activated charcoal and fluid administration which was begun in another center was continued. In intermediate syndrome which develops within 1-4 days following acute organophosphate intoxication, paralysis is observed in the flexor muscles of the neck, muscles innervated by cranial nerves, muscles of proximal extremities, and respiratory muscles; and the paralysis of the respiratory muscles can necessitate respiratory support. The symptoms and findings of cholinergic over-stimulation are not often observed in these patients. electromyography can be helpful in diagnosis. Early treatment with antidote, and supportive treatment can prevent the development of this syndrome or decrease its severity. The symptoms usually disappear within 5-18 days (37). Antidote administration for treatment is performed according to the degree of toxicity. In exposures through skin, washing the skin and clothes with water and soap is necessary to prevent further absorption of the substance. Gastric lavage and activated charcoal is necessary in oral exposures. The dose of atropine in children is 0.05 mg/kg in moderate intoxications. If no effect is observed, this dose should be repeated every 5-10 minutes until muscarinic symptoms disappear (35).

According to the 2008 data of National Poison Data System, 8% of the intoxications are due to pesticides (38). Intoxications usually happen accidentally at home or in people working in agriculture, industry (during the production and transport of these agents), and in insect control areas. As these compounds can be easily reached, accidental or suicidal intoxications are frequently observed particularly in developing countries. Early diagnosis and treatment is important in these severe and life-threatening intoxication cases. When the expected respiratory system complications emerge, mortality rates can be decreased by starting appropriate treatment without delay and by providing respiratory support when required. In severe intoxication cases, it should not be forgotten that long-term use of i.v. atropine in addition to short-term and intermittent atropine administration has vital importance (35).

7. Carbon Monoxide

Carbon monoxide (CO) is an important intoxicating agent which is lethal particularly in winter in Turkey. In normal conditions, it is found at a concentration of 0.001% in the atmosphere. It is formed at very low amounts (0-5%) endogenously from the breakdown of hemoglobin molecule. CO has been detected at a concentration of 3-7% in newborns. Its concentration is 5-10% in patients with hemolytic anemia and in smokers (39). Intoxications are most commonly encountered in winter and windy weathers as the carbon compounds in the structure of charcoal don't

burn completely and CO develops during burning. Another source of exposure is the exhaust fumes of cars (39,40). In a study consisting of 250 children diagnosed with acute CO intoxication, it has been reported that intoxications develop most commonly due to exhaust fumes and incompletely burned charcoal (41). CO intoxications have been reported as the most common cause (31%) of lethal intoxications in Turkey (42). The incidence of CO intoxications in children is quite high. It disturbs cellular metabolism by reacting with other heme-proteins just as the mitochondrial cytochromes. A level of 20% carboxyhemoglobin (COHb) causes headache and nausea, 20-40% causes convulsions, and above 40% it causes ataxia, collapse, and coma. Cardiac arrhythmia, cerebral edema, and acidosis can also be observed. Cherry-red color in lips and purplish color in nail folds are among the signs. Metabolic acidosis, cardiovascular and neurological signs are frequent symptoms (7). In intoxications, the risk of toxic effects is higher in tissues sensitive to hypoxia, mainly brain and heart. Although neurological symptoms are well-known, the knowledge related to cardiovascular system findings in children is limited. It has been reported that myocardial damage can develop without the development of clinical findings. CO intoxications often develop acutely in childhood and can occur with different and non-specific signs and symptoms (42). As non-specific findings such as headache, dizziness, nausea-vomiting are observed in mild CO intoxications, these patients may be easily misdiagnosed with non-specific viral infections that are particularly observed in winter, food intoxication, gastroenteritis, and even colic in infants (39). Therefore, particularly in winter, CO intoxication should be suspected in the presence of nausea, vomiting and headache with unknown etiology, and blood COHb level should be measured in these patients (42). If the exposure continues, tachycardia, tachypnea, exercise intolerance, findings related to myocardial ischemia, life threatening arrhythmias and cardiac arrest might develop. Difficulty in thinking, blurred vision, weakness, ataxia, syncope, convulsions, retinal hemorrhage, renal failure, non-cardiogenic pulmonary edema, and coma are observed. It is necessary to remove the patient from the environment with CO and to give oxygen support for treatment. After opening the airway, 100% inhalation of oxygen should be provided. While the half-life of CO is approximately 5 hours, this period can decrease to 1 hour (30-150 minutes) when 100% oxygen is administered. Hyperbaric oxygen therapy (HBOT) is another method which has been used in CO intoxications since 1962. HBOT can be performed in certain centers in various parts of the world, but the transfer of the patients to these centers may pose a problem. However, it is a preferred method as it decreases the mortality rates and has beneficial effects in the long term. In Turkey, HBOT is performed in 7 centers that are present in Ankara, İstanbul, Eskişehir, and Bodrum (39).

8. Cyanide

The pip and seed of some fruits such as apples, apricots, and peaches contain significant amounts of cyanide. The toxicity potential of the apricot pip is higher due to its cyanogen and hydrogen cyanide content (43). Cyanide and CO intoxication are often observed in combination. In a previous study it was found that 4% of the patients who had died in a house fire had lethal levels of cyanide. Cyanide mainly causes cellular hypoxia, anoxia, lactic acidosis, and metabolic acidosis. Metabolic acidosis is observed in 67% of acute intoxications. The clinical findings are observed immediately after ingestion. Headache, agitation, confusion, loss of consciousness, convulsions, and cardiac rhythm disturbances are among the symptoms. Following oral intake of cyanide, deep and rapid respiration, shortness of breath, acute dyspnea are observed. Exposure to high concentrations of cyanide leads to symptoms such as epileptic convulsions, apnea, cardiac arrest. The main cause of cyanide-induced death is the depression of the respiratory center (43). It is important to start the treatment early in cyanide intoxications (7). Oxygen support should be provided initially. Cyanide antidote kits containing amyl nitrite and sodium nitrite are used. They produce methemoglobin by interacting with the cyanide that is present in cyanomethemoglobin. The sodium thiosulfate in the content of the antidote kits transforms cyanomethemoglobin to thiocyanate which is a less toxic molecule. Another antidote that is used in treatment is hydroxycobalamin. It forms cyanocobalamin by reacting with cyanide. The use of activated charcoal is also suggested to be effective in cyanide intoxication (43).

9. Addictive Drugs

According to the results of the previous studies, although substance abuse among the students of primary and secondary education in Turkey is found to be lower than the other countries, tobacco use is found to be quite common. It has been reported that the most commonly used substances in developing countries are tobacco products, alcohol, marijuana, and volatile substances. This is also true for Turkey (44).

Ecstasy (3,4) methylenedioxymethamphetamine, is a derivative of amphetamine and it leads to locomotor stimulation, euphoria, excitement, and stereotypic behaviors. Ecstasy also has psychotomimetic effects which change perception and mood. Although the action mechanism of ecstasy is not exactly known, it is suggested that it increases free 5-hydroxytryptamine (5-HT) levels by decreasing re-uptake of 5-HT from nerve terminals. The addiction potential is low, but tolerance develops rapidly to its positive effects, and its negative effects become intensified in long-term exposure to high doses. Coma, convulsions, arrhythmia, malignant hyperthermia, rhabdomyolysis, hypertension, and multiple organ failure can be observed after intake. Activated charcoal shows its effect within 1 hour in asymptomatic

children. Monitoring blood pressure, body temperature and ECG are recommended. Blood levels should be measured to determine the degree of exposure. When the symptoms disappear, after a 24-hour follow-up, the children can be discharged under the control of their parents. The children in whom the symptoms are observed should be kept under observation for at least 48 hours. Hospitalization to intensive care may be necessary in patients with cardiac and CNS symptoms. Careful monitoring of hematological and biochemical parameters is recommended. Hyperthermia can be corrected with simple precautions. However, if it is not successful, i.v. dantrolene 1 mg/kg can be administered for approximately 10-15 minutes. In unresponsive patients, the dose can be repeated in 15-minute intervals without exceeding a total dose of 10 mg/kg within 24 hours. Hypertension can be corrected with labetolol. Convulsions and agitation should be treated with benzodiazepines. Chlorpromazine and haloperidol are among the initially preferred drugs to lower the seizure threshold (7).

Lysergic acid diethylamide (LSD), which has a strong hallucinogenic effect, is a 5-HT agonist. It is absorbed rapidly and its duration of action is very short. Dermal absorption of LSD is weak. In intoxications, hypertension, hyperthermia, and psychosis are observed. It is necessary to be careful particularly in symptomatic children. Gastric decontamination is not recommended. Sedation with phenothiazines should be avoided. In some situations, LSD may be associated with malignant hyperthermia (7,45).

Cocaine demonstrates its effect by inhibiting the re-uptake of dopamine, noradrenalin, and 5-HT. Agitation, hallucination, convulsions, hypertension, myocardial ischemia, and cranial infarction can be seen depending on its intake. In asymptomatic children, administration of activated charcoal within 1 hour following intake is beneficial. Blood pressure and ECG should be monitored. It is necessary to monitor symptomatic children more carefully. Agitation, hallucination, and convulsions can be controlled with benzodiazepines. It is necessary to correct acidosis as soon as possible as acidosis can intensify cardiac toxicity. Hypertension, arrhythmia, and angina can be treated with diazepam, nitrates, and calcium antagonists. Combined use of β-blockers and phenothiazines should be avoided due to the unpredictable interaction between these drugs. Coagulation and thrombosis should be kept in mind in terms of the probability of myocardial infarction development (7).

10. Nicotine

Nicotine is a toxic alkaloid which is found in the structure of many plants, mainly the tobacco. It demonstrates its effect by stimulating nicotinic acetylcholine receptors (7). When it is taken orally, nausea, vomiting, abdominal pain, increased salivation, confusion, agitation, clouding of consciousness, convulsions, coma, hypertension, tachycardia, and tachypnea are observed (15). In severe intoxications, arrhythmias and parasympathetic stimulation also accompany the symptoms.

Nicotine intoxication in children is often observed as a result of eating cigarette derivatives such as cigarette or cigar. Vomiting is frequently seen after eating cigarette, which is a good thing as it contributes to the reduction of the gastric absorption of nicotine (7). One cigarette contains approximately 13-30 mg nicotine. While it's lethal dose in adults is 40-60 mg, in children 1 mg (0.2 mg/kg) is lethal. Severe intoxications develop when nicotine is taken at a dose of 1.4-1.9 mg/kg (15). In intoxications due to oral intake of one or two cigarette ends, asymptomatic children should be kept under observation for 2 hours. No specific treatment is needed. However, activated charcoal and gastric lavage are recommended in exposure to large amounts in children (7). For convulsions, diazepam (i.v. 0.1-0.2 mg/kg, not exceeding 5 mg/kg) or midazolam (i.v. 0.05 mg/kg within 20-30 seconds, or intramuscular 0.1-0.2 mg/kg) are administered (15).

11. Isopropanol

Isopropanol is an alcohol derivative which is found in the composition of nail polish, hairspray, anti-freeze, and screen washers. It is rapidly absorbed by the stomach and causes gastric irritation, CNS depression, and hypotension. Isopropanol transforms into acetone via alcohol dehydrogenase enzyme and the acetone is excreted primarily through lungs and kidneys. Asymptomatic children should be kept under observation for at least 2 hours. Activated charcoal is not effective in the reduction of isopropanol absorption, and it is contraindicated in the presence of CNS depression. Gastric lavage and vomiting are effective only when performed within the first hour. Intensive supportive therapy is necessary in symptomatic patients. Treatment with i.v. fluid and inotropic agents might be needed in the case of hypotension and peripheral vasodilatation. Hemodialysis is recommended in patients with blood isopropanol concentration of 4 g/L. Peritoneal dialysis has also been reported to be effective in isopropanol intoxications. However, this method can be ineffective in some patients, as it may cause refractory hypotension (7).

Conclusion

In conclusion, due to the rapidly developing technological advancements, people are exposed to various natural and/or synthetic chemical agents in routine daily life, either consciously or unconsciously. In addition to drugs, exposure to natural toxins of herbal and animal origin, industrial pollutants, food additives and contaminants, environmental agents, and domestic products has become unavoidable. Incorrect preservation of domestic chemicals, parents not acting responsibly enough, and putting objects into mouth, which is a common behavior particularly in toddlers, are among the causes of intoxications in children. It is important to increase awareness of intoxications related to toxic agents, and unwanted effects among all individuals in the society, mainly the children, to take necessary precautions

and to follow appropriate treatment approaches. Although some drug packages have child safety latch, such packages are not used in many products on sale. The responsible attitude of the producing companies towards this subject can be effective in reducing intoxications in children. In addition to acute mild findings observed in intoxications in children, severe and irreversible damage and death are also observed. Therefore, it is necessary to inform foremost the parents, healthcare personnel, manufacturers, and children about intoxications. As early treatment is important making arrangements to reach National Poisoning Research Centers, and increasing the number of similar organizations would contribute to reducing the number of intoxication cases.

Ethics

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