

POSSIBLE BIOLOGICAL MECHANISMS OF SUDDEN SNIFFING DEATH SYNDROME DUE TO TOLUENE EXPOSURE

Toluen Maruziyeti Sonucu Gelişen Uçucu Madde Koklamaya Bağlı Ani Ölüm Sendromunun Muhtemel Biyolojik Mekanizmaları

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ABSTRACT

Sudden sniffing death syndrome due to toluene exposure is an outcome of the progressive social problem of intentional substance inhalation abuse. There is limited evidence about the biological mechanisms of toluene-induced sudden death, although toluene exposure is prevalent as a volatile solvent used in industrial settings. Toluene is known to possess toxic effects on many organs, most dramatically on the heart. Sudden death may result directly from ventricular tachyarrhythmias and severe bradycardia due to the cardiac toxicities of toluene. Toluene may also result in cardiomyopathy, myocarditis, and myocardial infarction, all of which are known to be associated with sudden death. In addition to its toxicity on the heart, this solvent is also toxic to the lungs, kidneys, nervous system, and bone marrow, which may contribute to the mechanism of sudden sniffing death due to toluene exposure. For these reasons, toluene-induced sudden death is discussed in this paper as a complex combination of the toxicities of toluene to the heart and other organs.

Key words: Sudden death, toluene.

ÖZET

Toluene bağlı ani koklama ölüm sendromu; toluen solunmasının ölümcül bir sonucudur ki bu durum giderek büyüyen bir sosyal sorundur. Toluen'e maruziyet stimulan ajan olarak ya da endüstride kullanımı şeklinde yaygın olsa da toluene bağlı ani ölümün biyolojik mekanizmaları hakkında sınırlı bilgi vardır. En dramatiği kalp üzerine olmak üzere toluenin birçok organ üzerine toksik etkisinin olduğu bilinmektedir. Ani ölüm toluenin kalp üzerine doğrudan toksik etkileri sonucu gelişen ventriküler taşiaritmi ya da ciddi bradikardi neticesinde doğrudan gelişebilir. Bu madde aynı zamanda kardiyomyopati, miyokardit ve miyokard infarktüsü gibi ani ölümle yakından ilişkili hastalıklara neden olabilir. Toluenin akciğerler, böbrekler, sinir sistemi ve kemik iliği gibi toluene bağlı ani ölüm mekanizmasına katkıda bulunabilecek organlar üzerine toksik etkileri vardır. Sonuç olarak, bu derlemede toluene bağlı ani ölümün maddenin kalp ve birçok organ üzerine toksik etkilerin karmaşık bir kombinasyonu sonucu geliştiği tartışılmıştır.

Anahtar kelimeler: Ani ölüm, toluen.

INTRODUCTION

Industrial exposure is a common pathway of toluene toxicity in many sectors. Since the 1960s, volatile inhalants have also become increasingly popular as drugs of abuse among children and young adults. Because volatile inhalants are relatively inexpensive and often included in common household products, paint thinner and adhesives are now among the most widely used stimulants in Turkey and many developing countries. In a recent study, the prevalence of paint thinner and adhesive abuse was 73% among homeless children and 5% among second-grade students in high schools in Istanbul, the largest metropolitan area of Turkey. This recent data has shown an increase in the number of volatile agent addicts. In the Western World (e.g., Britain or the United States), 5-20% of children have experimented with inhalants, pointing to volatile agent abuse as a worldwide problem (4,5).

Sudden sniffing death syndrome is the most dramatic outcome of volatile agent inhalation. As many as 50% of inhalant-related deaths are associated with sudden sniffing death syndrome, which occurs due to the cardiac toxicity of volatile agents (6-8). There has been a steady increase in the number of deaths per year occurring from volatile substance abuse (9). We discuss possible biological mechanisms of sudden death associated with toluene exposure in this review article.

DISCUSSION

In victims of sudden sniffing death syndrome, no pathologic findings were generally detected at autopsy (7). Therefore, sudden death is regarded as a prompt event that is mainly related to ventricular tachyarrhythmias and severe bradycardia due to the cardiac toxicity of volatile agents. Aerosols are more frequently associated with sudden death. Solvents are known as a relatively weak agent for inducing sudden sniffing death syndrome. It is suggested that sudden sniffing death syndrome due to toluene exposure is a rare phenomenon.

Different types of paint thinners and adhesives sold in Turkey contain 50-70% and 35-40% toluene, respectively. Toluene affects many organs in the body, especially the central nervous system and heart. Small doses of toluene can rapidly lead to euphoria and other disturbances of behaviour. Moderate doses of the agent may also induce delusions and hallucinations. Higher doses may produce life-threatening effects, such as convulsions and coma. Death may occur due to its direct cardiac or central nervous system toxicity or indirectly from, for example, inhalation of vomit, accidental trauma, and asphyxia (10).

Toluene exposure has resulted in chronic damage to the heart, lungs, kidneys, liver, peripheral nerves, and brain. (11,12). Toluene is oxidized gradually by cytochrome P450-dependent monooxygenase after its systemic absorption through the lungs and skin. Consequently, reactive oxygen species (ROS) are

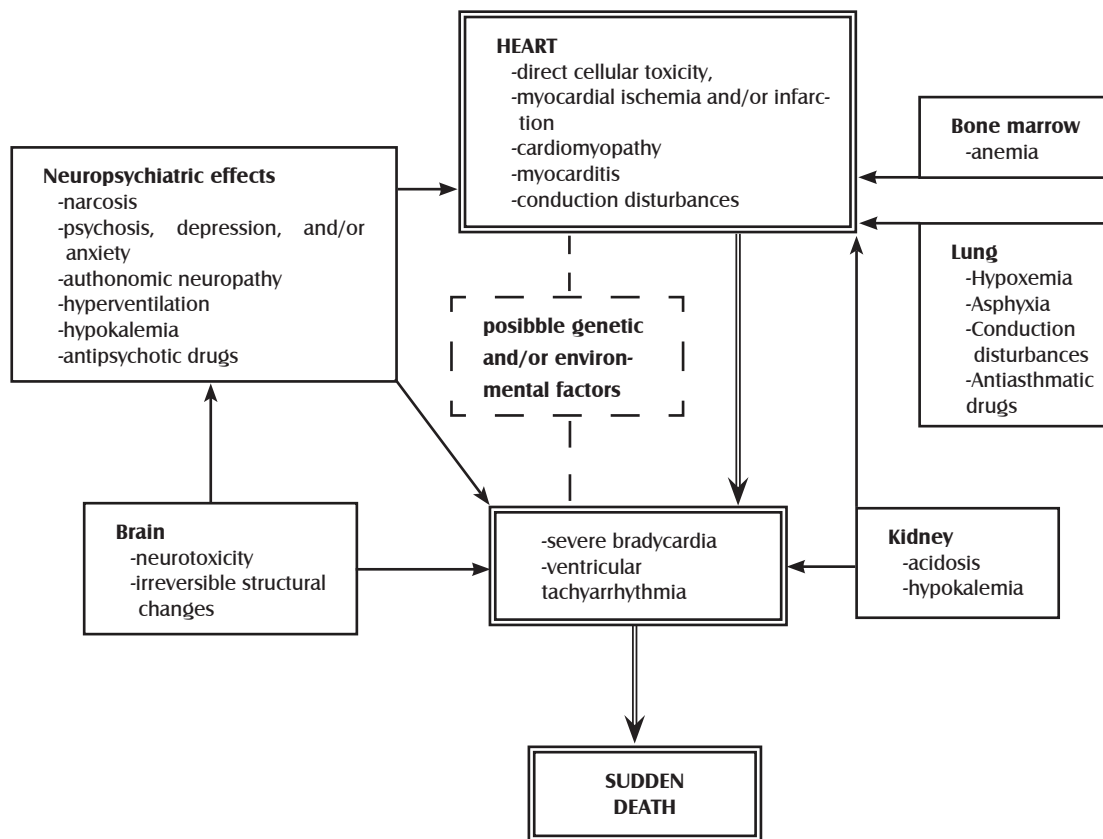
produced. ROS result in cellular toxicity to many organs (13). Paint thinner inhalation is known to increase lipid peroxidation and induction of antioxidant enzymes. Hool (14) noted that a common source of solvent-inducible oxidants may be located in mitochondria where the respiratory chain operates. Garbe et al. (15) discussed that ROS have been considered deleterious to cell function and there is good evidence to suggest that they play a role in the pathophysiology of a number of cardiac disease states, such as atherosclerosis, ischaemia, cardiac hypertrophy, and hypertension. Akar et al. (16) related collapse and instability of the mitochondrial inner membrane potential to mitochondrial ROS-induced ROS release and highlight the mitochondrial membrane as a new therapeutic target for prevention of arrhythmia. Toluene as a lipophilic solvent disturbs cellular membrane integrity, electrophysiology of the cellular membrane and inner membrane of mitochondria, and leads to reversible or irreversible cellular damage.

At higher doses (for example, 200 ml of paint thinner ingestion), tissue damage that affects many organs may be prompt and fatal (17). Moderate- or low-dose exposure of toluene may result in ventricular extrasystoles, bundle branch block, sinus bradycardia and A-V block (18-20), myocardial ischemia or infarction (21-24), cardiomyopathy (20,25), acute myocarditis (26), and ventricular tachyarrhythmias that are often ignored. These toxicities are closely related to sudden death. Coincidental allergic asthma, bronchitis, nephropathy, encephalopathy, neuropsychiatric diseases, and anemia contribute to the fatal outcome (Figure 1).

Toluene renders the heart susceptible to endogenous catecholamines, such that sudden alarm or exercise may precipitate sudden death (9). It also induces evident ischemia due to vasospasm, which may play an important role in the development of serious cardiac rhythm problems. In the case of myocardial infarction related to toluene exposure, recurrent ventricular fibrillation attacks resistant to defibrillation and antiarrhythmic treatment were often reported. Coexisting electrolyte abnormalities caused by renal toxicity of this substance may also contribute to the development of fatal arrhythmias (27).

In two cases of toluene-induced cardiomyopathy, left ventricular systolic function largely or completely returned to normal after the substance abuse ended (20). It could be argued that the toxic effects of toluene on the heart muscle may be reversible. In the literature, the damage or segmental wall motion abnormalities of the myocardium were usually reversible among the cases of toluene-induced myocardial infarction. Toluene is suggested to result in coronary vasospasm and functions of the myocardium returned to patently normal when the spasm was over. Recurrent non-Q-wave infarction associated with toluene inhalation obviously resulted in permanent cardiomyopathy (23). Anemia due to toluene-induced bone marrow toxicity may also contribute to induction of myocardial ischemia.

Figure 1: Basic Schematic Representation of Possible Biological Mechanisms of Sudden Death Sniffing Death Syndrome Associated with Toluene Exposure.



Note: Double-line boxes and arrows show the main mechanism of toluene-induced sudden death. The dotted-line box is a possible contributor; but needs further investigations. Other boxes and single-line arrows explain possible cardiovascular effects of other organ damage due to toluene exposure, which are suggested as other contributors to the main mechanism of toluene-induced sudden death.

The lungs are another organ effected by toluene, both directly during sniffing of toluene vapour and indirectly after systemic absorption of the agent. Isocyanates such as toluene diisocyanate are regarded as the most common cause of occupational asthma, with more than 100,000 workers in the U.S. exposed annually and 5-10% of these developing asthma (28). An 18-year-old student with a history of asthma accidentally inhaled organic solvent during a class and complained of immediate cough and dyspnea that worsened over the course of several hours (29). This case presented with severe respiratory distress, hypoxemia, and marked pulmonary hyperinflation as a result of mucus plugging, regarded as a complication of acute inhalation injury or acute severe asthma. In another study, a 43-year-old car painter who died within 1 hour after exposure to a polyurethane paint in the workplace is reported (30). Histologic examination showed diffuse mucus plugging and intense inflammation of the bronchioles. There are also distinct pathologic findings in the conduction system of young adults with a history of bronchial asthma who die suddenly. It is hypothesized that bronchial asthma affects the conduction system in some patients (31). The significant findings include

the appearance of a markedly fragmented bundle and changes in the sinoatrial node that are not found in normal healthy young adults. We do not know whether toluene-induced asthma has similar effects to the conduction system, but toluene-induced lung toxicity may predispose the individual to serious arrhythmias and sudden death due to mucus plugging of bronchioles, severe respiratory distress, hypoxemia, antiasthmatic drugs, and changes in the conduction system of the heart.

Renal toxicity of toluene may also contribute to sudden death. Toluene may cause acid-base imbalances, acute renal failure, Fanconi's syndrome, and renal tubular acidosis. In an experimental study involving toluene-treated rats, the weights of the kidneys diminished by 13%. Gupta et al. (32) described a 38-year-old male who developed acute oliguric renal failure following repeated glue sniffing for about 8 hours. Clinical and laboratory findings of this case supported the diagnosis of acute toxic tubular necrosis causing acute renal failure. Battle et al. (33) documented the occurrence of hypokalemia and hyperchloremic metabolic acidosis due to the distal form of renal tubular acidosis in five individuals addicted to toluene sniffing.

Toluene induces structural changes in the brain in solvent abusers. MR images revealed white matter lesions in 46%, atrophic dilatation of ventricles and sulci in 27%, and thalamic hypointensity in 20% of the patients who had abused toluene-containing solvents for longer than 4 years (34). The deposition of iron due to demyelination and axonal loss is the most probable mechanism for the thalamic hypointensity found in solvent abusers. The brain partially controls the functions of many organs such as the heart and adrenal glands. The malfunction of the brain in toluene addicts may possibly contribute to the mechanism of sudden death (35,36). Neuropsychiatric side effects of toluene may also increase the risk for sudden death. Some psychiatric conditions such as anxiety, depression, delirium, or psychosis are regarded as transient risk factors for sudden cardiac death (37). Chronic inhalation of toluene-based adhesives can produce permanent paranoid psychosis (38,39). Dementia and depression are some of the other neuropsychiatric adverse effects of toluene. Anxiety and depression are well-known risk factors for myocardial infarction and sudden death. Clinical depression may be associated with a higher risk of cardiac arrest independently of established coronary heart disease risk factors (40). Psychosis may result in hypokalemia due to hyperventilation and adrenergic discharge, which may contribute to the induction of ventricular tachyarrhythmia (41). A prolonged corrected QT interval due to antipsychotics and hypothermia in psychiatric patients should also be regarded as the mechanism between toluene-induced psychosis and sudden unexplained death (42,43). Toluene may also effect the autonomic nervous system (central or peripheral) that is essential for maintaining appropriate cardiac rhythm.

Toluene in similar doses may cause cardiomyopathy in one individual but nothing in others, as frequently seen in our experience. Therefore, there might be some genetic and environmental factors that increase toluene's toxicity or have an additive effect to its toxicity. If a person has an increased risk of sudden death (e.g., mutations in genes of cardiac ion channels), it should be expected that toluene exposure could have an additive effect. It has already been discussed that co-administered antiasthmatics, antipsychotics, and narcotic agents may increase the risk for sudden death. Because abused inhalants are common in household products and are relatively inexpensive, they are accessible to children who are too poor or too young to access other drugs. However, inhalant abuse appears to be a gateway phenomenon among younger adolescents. Children who abuse inhalants early in life are more likely to use other illicit drugs later in life (44,45). They may sometimes inhale toluene concurrent with abuse of cannabis, heroin, amphetamines, or cocaine, which may increase the risk of sudden death.

In conclusion, toluene-induced sudden death is not purely associated with its isolated cardiac toxicity. Toluene exposure may result in various organ

toxicities and many types of cardiac involvement, the combinations of which may induce sudden death. Some genetic and environmental factors may also contribute to the pathogenesis of sudden sniffing death syndrome due to toluene exposure. Further research is needed to make more definitive conclusions.

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