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Review Article

Dentistry Section

Health Hazards of Xylene: A Literature Review

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ABSTRACT

Xylene, an aromatic hydrocarbon is widely used in industry and medical laboratory as a solvent. It is a flammable liquid that requires utmost care during its usage. On exposure the vapours are rapidly absorbed through the lungs and the slowly through the skin. Prolonged exposure to xylene leads to significant amount of solvent accumulation in the adipose and muscle tissue. This article reviews the various acute and chronic health effects of xylene through various routes of exposure.

Keywords: Methyl hippuric acid, Biological exposure index, Occupational safety, Laboratory technicians and xylene toxicity

INTRODUCTION

Xylene is one of the top 30 chemicals produced in the United States in terms of volume. It is used extensively as a solvent in the rubber, printing and leather industries. It is also used as a thinner for paints, cleaning agent and in varnishes. A small amount of xylene is also found in airplane fuel and gasoline [1]. In the field of histopathology xylene is used as a clearing agent that gives translucency to the tissues. Technical grade xylene is a combination of the three isomers: Ortho, Para and Meta. This mixture is referred to as 'Xylol' [2].

Xylene is released primarily from industrial sources. One can also come in contact with xylene through automobile exhaust and a variety of consumer products such as cigarette smoke, paints, varnish, rust preventives and shellac. Skin contact with xylene-containing products is also a likelihood of exposure to xylene. Workers in certain occupation are likely to get exposed to xylene. They include distillers of xylene, metal workers, wood processing plant workers, furniture refinishers and biomedical laboratory workers [1].

Studies have shown that xylene is well-absorbed by the inhalational, oral and to some extent by the dermal route. According to a study by Riihimaki and Savolainen exercise increased the amount of xylene absorbed that was directly reflected by the amount of methylhippuric acid excreted in the urine. Once absorbed, xylene enters into the blood and gets distributed throughout the body. The biotransformation of xylene regardless of the isomer/route of administration proceeds through the oxidation of a side chain methyl group by mixed function oxidases in the liver to form methyl benzoic acids that conjugate with glycine to yield methyl hippuric acid which is excreted in urine. Most of the xylene that enters the body leaves within 18 hours after the end of the exposure [3]. Following prolonged exposure especially by occupational means it is likely to get accumulated chiefly in the muscle and adipose tissues. The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended Biological Exposure Index (BEI) for various chemicals including xylene [1]. The BEIs are not to be used for the diagnosis of an occupational illness but as an indicator of exposure to significant concentrations of the chemical substances if the workers show values of the analyte at/ above the value of its BEI [4]. The amount of biomarker of xylene exposure in urine can be analysed using techniques such as High Performance Liquid Chromatography (HPLC) and Gas Chromatography (GC) [1].

Jacobson and McLean has conducted a biological monitoring of xylene exposure in subjects of low level exposure using GC [2]. Mao and Chen have estimated the amounts of methyl hippuric acid in field workers who have been exposed to toluene, ethyl benzene and xylene using Gas Chromatography – Flame Ionization Detector (GC-FID) [5].

Matsui et al., has devised a technique to determine the urinary hippuric acid by HPLC [6]. Sabatini et al., have developed a method using HPLC-Tandem Mass Spectrometry which can be used for simultaneous measurement of biomarkers of various chemicals in urine samples. The health effects of xylene depend on the route of its exposure [7]. Inhalational exposure is the most common route of exposure [1,8].

INHALATIONAL EXPOSURE

Acute inhalational exposure to mixed xylene at 200 ppm for 3-5 minutes resulted in irritation of the nose and throat [9]. Morley et al., has reported an autopsy of a worker who died owing to several hours of exposure to xylene fumes while painting. Focal areas of intra-alveolar haemorrhage and pulmonary oedema with severe lung congestion were seen at the acute exposure of 100 ppm [10]. Uchida et al., has done an extensive study and reported the signs and symptoms of workers who have been chronically exposed to mixed xylene. A significant increase in throat and nasal irritation has been found in workers chronically exposed to xylene fumes [11]. Decreased pulmonary function and dyspnoea was reported by Hipolito RN among histology technicians chronically exposed to xylene in the laboratory.

In the same study cardiovascular effects such as flushing, palpitations and chest pains were seen among the histology technicians [12]. Several authors have reported various gastrointestinal symptoms such as gastric discomfort, nausea and vomiting in workers chronically exposed to xylene vapours. The authors have also specified that there was a cessation of such symptoms on terminating the exposure. Uchida et al., in his review of 175 workers chronically exposed to mixed xylene at 14 ppm has observed a reduction in the grasping power in the extremities. No adverse hepatic and renal effects were observed in the same study [11]. In the study by Hipolito RN and Uchida et al., several subjective neurological symptoms such as anxiety, dizziness, inability to concentrate and forgetfulness have been observed among subjects chronically exposed to vapours of xylene [11,12]. Taskinen et al., observed spontaneous abortions in female pathology technicians exposed to formalin and xylene although the study could not conclusively conclude that xylene was the direct cause of this effect [13].

ORAL EXPOSURE

In 1986 Abu Al Ragheb et al., reported the occurrence of pulmonary congestion and oedema in the post-mortem examination of a

person who had committed suicide by the consumption of xylene. He also observed no other adverse effects to the cardiovascular or gastrointestinal systems. He concluded that the death of the person was due to a centrally mediated depression of the respiratory system [14].

Condie et al., in his animal study of oral exposure to mixed xylene had observed an increase in hyaline droplet change in the male rats and early chronic nephropathic changes in the female rats exposed to mixed xylene for 90 days. It was therefore concluded that such continuous change could result in renal cell damage [15].

In the report of an accidental ingestion of xylene in a person by Recchia et al., it was found that it resulted in a persistent coma for more than 26 hours [16]. Condie et al., in his animal study reported signs of convulsions, hyperactivity, epistaxis and hypersalivation along with increased aggressiveness in rats given mixed xylene for 90 days [15].

DERMAL EXPOSURE

In acute dermal exposure of xylene by hand immersion technique in humans by Engstrom et al., and Riihimaki and Pfaffli, it was reported that it was associated with vasodilatation of the skin of the hand, dryness and scaling of the area and skin erythema of the hand. It was also found that in patients with a history of atopic dermatitis who were symptom-free, it resulted in the development of toxic eczema of the hands of such subjects on exposure to xylene. It was also found that in such patients a three time greater absorption rate of xylene was observed compared to the other subjects in the study [17,18].

Palmer and Rycroft in 1993 also reported the occurrence of urticaria in a female technician of cytology laboratory who was predominantly exposed to vapours of xylene in the occupational environment. It was effectively proved that it was as a result of direct exposure to xylene by the performance of a closed patch test which elicited severe erythema and whealing of the skin [19].

OCULAR EXPOSURE

Several studies such as Nelson et al., Uchida et al., and Hake et al., have observed irritation of the eye on exposure to xylene vapours [9,11,20]. Hine and Zuidema in their animal study of instillation of 0.1 ml of mixed xylene directly to the eyes of rabbits resulted in moderate irritation of the eyes [21].

The various literatures on the health effects of xylene are tabulated according to the different routes of exposure [Table/Fig-1-3].

DISCUSSION

Xylene, a synthetic hydrocarbon produced from coal tar is a widely used as a universal solvent. Various health effects due to xylene exposure have been documented in the literature. A number of theories exist for the mechanisms by which xylene exerts its toxic effects on the various systems of the body. The pulmonary, gastric and ocular effects of xylene are attributed to the irritant nature of the chemical [1]. Some authors have suggested that certain metabolic intermediates such as methylbenzaldehyde may be responsible for the toxic effects of xylene. Inhibition of pulmonary microsomal enzymes by the binding of such toxic metabolites thereby inactivating the enzymes also might contribute to the toxic nature of xylene [22].

The mechanism of nephrotoxicity of xylene may be related to the reactive metabolite formation which subsequently causes irritation of the renal tissues or direct membrane fluidization [1,22,23]. According to Franchini et al., the urinary β-glucuronidase levels in humans exposed to xylene are high thereby indicating a faster turnover of the renal cells due to toxicity of the toxic metabolites of the chemical [24].

Padilla and Lyerly in their study have demonstrated a decrease in the axonal transport of stimuli following xylene exposure [25]. A decreased hypothalamic catecholamine levels following exposure to xylene has been observed by Andersson et al., [26]. The toxic symptoms of the central nervous system such as dizziness could be attributed to the liposolubility of xylene in the neuronal membrane according to Savolainen and Pfaffli. He has also suggested that xylene disturbs the activity of the proteins that are essential for normal neuronal function [27].

System	Type	Dose	Time	Signs & symptoms	Reference
Respiratory system	Mixed	200 ppm	3-5 min	Nose & throat irritation	Nelson et al., 1943 [9]
Respiratory system	Mixed	10,000 ppm	Acute exposure (autopsy)	Death, severe lung congestion with focal interalveolar hemorrhage, pulmonary edema	Morley et al.,1970 [10]
Respiratory system	Mixed	Unspecified	Chronic occupational exposure	Labored breathing, impaired pulmonary function	Hipolito 1980 [12]
Respiratory system	p-xylene	100 ppm	1-7.5 hrs/ day for 5 days	Nose & throat irritation	Hake et al.,1981 [20]
Respiratory system	mixed	14 ppm	7 yrs	Nose & throat irritation	Uchida et al.,1993 [11]
GI	mixed	Unspecified		Nausea, vomiting, gastric discomfort	Hipolito 1980 [12]
GI	mixed		2 weeks	Anorexia, vomiting	Uchida et al.,1993 [11]
Hematology	mixed	14 ppm	7 yrs	No effects	Uchida et al.1993 [11]
Muscle	mixed	14 ppm	7 yrs	Decreased grasping power & muscle power in extremities	Uchida et al.,1993 [11]
Hepatic	mixed	14 ppm	7 yrs	No change in serum biochemical values	Uchida et al.,1993 [11]
Renal	mixed	10,000 ppm	Acute exposure	Increased blood urea, distal tube academia, decreased urinary clearance of endogenous creatinine, increased β-glucuronidase increased albumin, RBC and WBC excretion	Morley et al.,1970 [10]
Neuro	mixed	14 ppm	7 yrs	Increased anxiety, forgetfulness inability to concentrate, dizziness	Uchida et al., 1993 [11]
Reproductive	Along with formalin	14 ppm	7 yrs	Spontaneous abortions	Taskinen et al.,1989 [13]

[Table/Fig-1]: Inhalational route

System	Type	Dose	Time	Signs	Reference
RS	unspecified	suicide		Pulmonary congestion & edema	Abu Al Ragheb et al., 1986 [14]
Neuro	mixed	Accidental ingestion		Coma for 26 hrs	Recchia et al., 1985 [16]

[Table/Fig-2]: Oral route

System	Type	Dose	Time	Signs	Reference
Dermal	m-xylene	unspecified	unspecified	Skin erythema, vasodilatation, dryness, scaling of skin	Engstrom et al.,1977 [17]
Dermal	unspecified	unspecified	unspecified	Urticaria	Palmer and Rycroft 1993 [19]
Ocular	Mixed	200 ppm	3-5 min	Eye irritation	Nelson et al., 1943 [9]
Ocular	p-xylene	100 ppm	1-7.5 hrs for 5 days	Eye irritation	Hake et al., 1981 [20]
Ocular	Mixed	14 ppm	7 yrs	Eye irritation	Uchida et al. 1993 [11]

[Table/Fig-3]: Dermal and ocular route

Dermal absorption is also a major route of xylene exposure especially among the laboratory workers. Hino et al., has stated that workers with eczema of the hands had higher urinary methyl hippuric acids (xylene metabolite). He has attributed the removal of ceramide of the corneal layer of the skin epithelium thereby leading to the disruption of epithelial barrier to this exaggerated percutaneous absorption of xylene in such atopic individuals [28]. Gunasekar et al., has performed a histopathological study of the rodent skin epithelium exposed to xylene. Separation at the epithelial-connective tissue interface with infiltration of granulocytes was observed. At a molecular level, increased levels of interleukin and inducible nitric oxide synthase protein was observed serving as indicators of skin irritation [29].

Methods to reduce absorption of xylene following its acute exposure have been highlighted in literature. The first step is to immediately remove the person from the source of exposure. Dermal and ocular exposure can be dealt by decontaminating the area by thoroughly washing with tepid water or normal saline and mild soap. In case of oral exposure emesis with ipecac syrup could be done only when one is certain that there is no likelihood of aspiration thereby leading to aspiration pneumonitis [1,30]. Ellenhorn and Barceloux have suggested the usage of activated charcoal in order to limit the absorption of the chemical in the intestines [1,31]. Sevcik et al., has performed haemodialysis and haemperfusion in order to hasten the removal of xylene from the body [1,32].

Although exposure of personnel cannot be completely avoided it can be kept to a minimal by strict adherence to the occupational and safety health guidelines proposed by Agency for Toxins Substance and Disease Registry (ATSDR). The installation of an approved exhaust in the laboratory and a face mask or a full face organic respirator by the laboratory personnel can help limit the inhalational exposure. Impervious laboratory clothing made of Buna-N-Rubber and Viton gloves should be an integral part of the personnel protective equipment [33]. Staff using xylene should have a thorough knowledge of its handling characteristics. Emergency eye wash or quick drench facility should be made available to the personnel [1].

The biological exposure index of xylene according to ACGIH is 1.5 grams of methyl hippuric acid per gram creatinine in the urine of the exposed workers [4]. As the level of urinary methyl hippuric acid correlates to that of xylene exposure, steps should be taken to detect their levels in the urine of workers periodically. Increase in the levels of the urinary metabolite warrants the necessary steps to reduce their exposure [1,4].

In the field of medical technology histopathology technicians are occupationally exposed to xylene as it forms an integral part of pathological laboratory as a clearing agent of tissue samples. In recent years many researchers have identified xylene substitutes [8].

Ankle and Joshi have suggested the usage of diluted dish washing solution (DWS) to deparaffinise histopathological tissue sections [34]. Metgud et al., have done a study to compare the advantages of xylene free methods over conventional xylene during routine tissue processing. They concluded that such alternatives produced equally good histopathological results [35].

Kunhua et al., have suggested the usage of White oil No. 2 and 14% N-Heptane (SBO) as a novel non-toxic xylene substitute [36]. Premalatha et al., have reported that Mineral oil is a bio friendly substitute of xylene for deparaffinisation of histological sections [37]. Buesa and Peshkov have also highlighted the usage of vegetable oils and limonene based substitutes as clearing agents in the place of xylene [38,39]. The introduction of such substitutes can help in circumventing the toxic effects of xylene [38-40].

CONCLUSION

Workers in certain groups are at a greater risk of exposure to high concentrations of xylene. Literature suggests that xylene exposure causes toxic effects of various systems of the body. Personnel coming in contact with xylene should have an understanding of the various toxic effects of the chemical. Proper handling of the chemical, practice of personnel protective techniques and proper disposal of the used and unused chemical according to the state requirements can help limit the toxic health effects of xylene.

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