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Toxic Materials to Cornea

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Abstract
Every day; many chemical agents, materials or medicines whether in the pharmaceutical industry or daily life are offered for consuming for human beings. At this point, it has great importance that if the substances threaten heath or not. Because the toxicity of materials can lead to many target organ damage. The eye, together with many anatomical layers that make it up is among the target organs exposed to toxicity. In this review, we handled the classification, effects and treatment methods of toxic materials on the corneal layer of the eye.

Keywords: Cornea, toxic materials, chemicals, eye

INTRODUCTION

Toxic material is a chemical substance that breaks down normal physiological and biochemical mechanisms when it enters the living organism (human and warm-blooded animals) through mouth, respiration, skin, and infection, or causes the death of the creature in an excess amount. For corneal toxicity; there are many methods of classification based on the disease, route of exposure and duration or agent (Grant, 1986). This review will focus on the classification system according to the route of exposure and time course which is divided into two main titles as nonspecific and systemic effects. Local effects are also divided into two parts as immediate effects and delayed effects (Dart, 2003).

Topical ophthalmic drugs, often after long-term use may cause iatrogenic toxicity in patients with acute or chronic ocular surface impairment. Topical anaesthetic abuse although initially nonspecific; at a later time may manifest itself with findings such as corneal infiltrates, iritis, Wessely ring, and hypopyon (Rocha et al. 1995). Systemic drug use can cause deposits which have low functional importance in the cornea (often in the epithelial layer) (Grant, 1986). Most of the time, preservatives (e. g. benzalkonium) or the excipients (e. g. EDTA) cause more toxic effects than drugs. Drug information sheets do not provide concerning notice on this topic because from these sources it is difficult to achieve an accessible rate of adverse reaction development chance or an index of toxicity (Anon. 2000).

Regarding the assessment of toxicity; some toxic reactions are self-specific and can not be get measured outside of clinical methods. Nevertheless, for drugs with short-term and presumable toxic effects, the presence of a toxicity index that can be used to compare all topical treatments will help in managing topical treatment. At the present time, available tests are Draize test in rabbits and in vitro tests on human cell cultures that include ATP assays for cell viability, scanning EM, and vital staining (Geerling et al. 2002).

The possibility of drug toxicity, especially in cases with exacerbations of, or poorly controlled, the ocular surface disease must always be kept in mind. In treatment; alternative less toxic drugs can be prescribed, or the treatment can be completely terminated. Avoiding preserved medications and materials known to be toxic in high-risk situations (ie aminoglycosides, some glaucoma medications, antivirals, chronic disease, dry eyes and patients on multiple topical therapies) is effective to protect from toxicity (Dart, 2003).

Table 1: Classification by route of exposure and time course.

Local action, immediate effects	**Examples**
Caustic chemicals	Acids and alkalis
Solvent splashes	Solvent splashes
Detergent or surfactant splashes	
Cationic	Benzalkonium
Anionic	Triton X, sodium lauryl sulfate
Nonionic	Tween
Lacrimators	Tear gases
Local action, delayed effects	**Examples**
Corneal epithelial edema	Diethylamine
Corneal epithelial injury	Mustard gas, dimethyl sulfate (methylating agent)
Corneal epithelial vacuoles	n-Butanol (industrial solvent)
Discoloration from vapours or dust	Aniline
Late scarring and distortion	Mustard gas, dimethyl sulfate
Corneal endothelial injury	Intracameral injections
Systemic Effects	**Examples**
Corneal epithelial deposits	Amiodarone, chloroquine, mepacrine
Corneal stromal deposits	Metals (copper, gold, mercury, silver)
	Drugs (indomethacin, chlorpromazine)
Lacrimation	Arsenic, chloral hydrate, heroin
Inflammation	Pactolol, Isotretinoin
Photosensitized keratitis	Methoxsalen (psoralen used for PUVA)
Corneal epithelial vacuoles	Thiacetazone (antimycobacterial)
Corneal endothelial injury	Animals only (dichloroethane in dogs)

1. Local Effects

1.1. Immediate Effects

1.1.1. Acids

A molecule or ion able to give a proton or hydrogen ion H+ or, alternatively, able to set up a covalent bond with an electron pair is an acid. They damage by denaturing and precipitating proteins in the cornea they contact. The

coagulated protein's role as a barrier. Hereby it gets ahead of further penetration. Hydrofluoric acid is excluded from a general statement where the fluoride ion rapidly penetrates the cornea and damages anterior segment layers. Early eye irrigation, medical treatment, and surgical intervention are among the cure options (Barouch and Colby, 2008).

1.1.2. Alkalis

A basic, ionic salt of an alkali metal or alkaline earth metal chemical element is called an alkali that also can be described as a base that dissolves in water. Alkali liquor has a pH greater than 7.0 (Barouch and Colby, 2008). Alkali ingredients penetrate the layers of cornea more quickly than acids because of their lipophilic structure. They cause saponification of fatty acids in the cell membrane. Alkalis also demolish the corneal stromal components (Fish and Davidson, 2010). The destructed layers then secrete proteolytic enzymes, which lead to further damage (Singh et al. 2013). The treatment is similar to acids (Barouch and Colby, 2008).

1.1.3. Alcohol

Alcohol is an organic compound in which the hydroxyl functional group (–OH) is bound to a saturated carbon atom. Alcohol has several uses worldwide like in alcoholic beverages, as a fuel or in scientific, medical, and other industries. Alcohol contact to the cornea, especially during the long exposure time, cause several damages in cornea like the destruction of microvilli, intercellular junction damage and cellular edema (Kim et al. 2002). The same treatment procedure is alike with the treatment of other chemical burns of the cornea.

1.1.4. Aldehydes

An aldehyde is an organic compound consists of a functional group with the structure −CHO, contains a carbonyl centre (a carbon double-bonded to oxygen) with the carbon atom also bonded to hydrogen and to an R group. Of all aldehydes, most common forms in use by priority order are formaldehyde, butyraldehyde, and acetaldehyde. A splash of aldehyde solution (generally formaldehyde) can cause great and increasing pain, epiphora, persistent opacification, vascularization and edema of the cornea (Kohlpaintner et al 2008). The same treatment procedure is used with other chemical corneal burns.

1.1.5. Ether

Ether are organic compounds that contain an ether group—an oxygen atom connected to two alkyl or aryl groups. Animal studies indicated that exposure with the vapor of ether which is strongly irritant to the eyes can cause deep corneal erosion and milky corneal opacities (Thiess, 1973). Irrigation, medical treatment, and surgical intervention are choices for therapy.

1.1.6. Benzalkonium

Benzalkonium chloride is an organic salt that is used as a biocide, a cationic surfactant and as a phase transfer agent. Benzalkonium chloride exposure with the higher concentration and the longer duration cause corneal epithelial dysfunction, which can damage the corneal epithelial barrier (Cha et al. 2004).

1.1.7. Triton X

Triton X-100 is a widely used detergent that consists of hydrophilic polyethylene oxide chain and an aromatic hydrocarbon lipophilic or hydrophobic group. Triton's usage includes industrial purpose, Ingredient in influenza vaccine, permeabilizing unfixed (or lightly fixed) eukaryotic cell membranes, solubilizing membrane proteins etc. It can cause diffuse loss of corneal endothelial cells, with nuclear remnants scattered on the descemet membrane (Koley and Bard, 2010).

1.1.8. Tween

Tween-20 and Tween-80 are polysorbate surfactants with a fatty acid ester moiety and a long polyoxyethylene chain. Tween can make corneal epithelial cell toxicity happen (Grant et al. 1992).

1.1.9. Tear Gases

Tear gas also called lachrymatory agent is a type of chemical weapon which includes pepper spray (OC gas), CS gas, CR gas, CN gas (phenacyl chloride), nonivamide, bromoacetone, xylyl bromide, syn-propanethial-S-oxide (from onions), and Mace (a branded mixture). It affects the lacrimal gland nerves. It can cause loss of vision. While there is no specific antidote treatment for tear gas, it is useful to get away from the gas immediately, enter into the fresh air and remove contaminant clothes (Yeung and Tang, 2015).

1.2. Delayed Effects

1.2.1. Diethylamine

Diethylamine formularized $(CH_3CH_2)_2NH$ is an organic secondary amine. It's generally used in commercial products. Toxicity induces multiple corneal erosion and edema (Brieger and Hodes, 1951).

1.2.2. Mustard Gas

Mustard gas also called sulphur mustard is the organic compound synthesized by treating sulphur dichloride with ethylene. Sulphur mustard used widespreadly as chemical warfare agent during World War I. Mustard gas cause porcelain white lesions and varicose vessels in the areas neighbouring the cornea and keratitis (Solberg, 1997).

1.2.3. Dimethyl sulfate (methylating agent)

Dimethyl sulphate is a colourless, odourless, oily chemical with formula $(CH_3O)_2SO_2$. Dimethyl sulphate used as a reagent for the methylation in chemistry. Corneal exposure causes immediate discomfort, gray-white opacification, and necrosis (Lewin and Guiller, 1993).

1.2.4. n-Butanol (industrial solvent)

n-Butanol or n-butyl alcohol or normal butanol is a 4-carbon structured primary alcohol. Industrial uses of n-Butanol include pharmaceutics, perfumery, textiles, cleaning formulations, food etc. Contamination of n-Butanol cause loosing the corneal epithelium from stroma and vacuolar keratopathy (Welt, 1950).

1.2.5. Aniline

Aniline is the prototypical aromatic amine that fundamentally used is in the manufacture of precursors to polyurethane, synthetic dye industry, medicine, rocket fuel, and other industrial chemicals. Erosions of the epithelium, opacity, vascularization, infiltrates and ulceration can be occured depending on the corneal exposure of aniline (Thomas et al. 2007).

2. Systemic Effects

2.1. Amiodarone

Amiodarone is an antiarrhythmic drug used in the treatment and prevention of various irregular heartbeats. Amiodarone causes micro-deposits called cornea verticillata (also called vortex or whorl keratopathy) in the cornea are related to dosage and duration of therapy, especially at doses greater than 400 mg/day, for longer than 6 months use. Depending on the corneal microdeposits, vision problems (e.g. halo, blurry), photophobia and dry eyes may occur. If the deposits are not symptomatic and not progressive, there is no need for dosage reduction or termination of the drug treatment (Passman et al. 2012).

2.2 Chloroquine

Chloroquine is used primarily in the treatment of malaria, but also used in the treatment of diseases such as extra intestinal amebiasis, porphyria cutanea tarda, sarcoidosis, rheumatoid arthritis, and lupus erythematosus. Chloroquine may cause cornea verticillata just like amiodarone. Corneal lesions may appear insidious. However, there is no definite relationship between dose or duration of treatment and corneal deposit accumulation (Hobbs et al. 1961). With long-term doses, the routine ophthalmologic examination is recommended.

2.3. Hydroxychloroquine

Hydroxychloroquine uses include malaria, rheumatoid arthritis, lupus, porphyria cutanea tarda, post-lyme arthritis. Hydroxychloroquine may cause cornea verticillata just like amiodarone and chloroquine. Hydroxychloroquine is less toxic than chloroquine and is safer to use. It has been shown that corneal deposits caused by hydroxychloroquine are dose-related. Corneal deposits, which may appear several weeks after the onset of antimalarial treatment are completely reversible after cessation of drug therapy (Anon., 2012).

2.4. Mepacrine

Mepacrine also called quinacrine uses include malaria, giardiasis and lupus erythematosus. In patients receiving long-term antimalarial mepacrine treatment; corneal deposits, visual halos, and blurred vision may occur which are reversible (McEvoy, 1990).

2.5. Copper

Copper is a reddish-gold metal which is an essential element. An adult human needs copper at a certain amount per day, to help enzymes transfer energy in cells. Excess copper is toxic. Copper-containing intraocular foreign materials or high blood serum levels may lead to deposition of copper in the cornea. Deposition of copper can result in reduced visual acuity and distortion of colour vision. Penicillamine is an important option in treatment (Sullivan et al. 2001).

2.6. Gold

Local or systemic long-term use of gold-containing medicines may cause gold accumulation in the cornea. This is called chrysiasis. The density of gold deposits is closely related to the duration of treatment and the dose administered (Sullivan et al. 2001).

2.7. Mercury

Mercury toxicity is often seen in workers working in a variety of industrial areas, such as thermometers and batteries. Mercury taken from external sources in the body passes through the systemic circulation to the aqueous humour (Sullivan et al. 2001). Deposits may cause discoloration and epithelial erosion in the cornea (Grant et al. 1993).

2.8. Silver

The colour change in the ocular tissues caused by local or systemic silver uptake is called ocular argyrosis. Most common pathological effect of argyrosis on the visual system is reduced dark adaptation (Gallardo et al. 2006).

2.9. Indomethacin

Indomethacin is a nonsteroidal anti-inflammatory medicament generally used to reduce pain, fever, swelling, and stiffness from inflammation. Mechanism of action is the form of inhibition the production of prostaglandins. Indomethacin medication can cause whorl-like stromal opacities in the cornea. Complaint of light sensitivity may also occur in some patients (Brayfield, 2014).

2.10. Chlorpromazine

Chlorpromazine which classified as a low-potency typical antipsychotic is a very effective antagonist of dopamine receptors. It is used to treat psychotic disorders (such as schizophrenia), mood disorders (such as bipolar disorder), attention deficit hyperactivity disorder, queasiness and spew, anxiety before surgery, and unhealed hiccough following other precautions in a human being. The veterinary use of chlorpromazine as an antiemetic in dogs and cats, or, less often, as a sedative prior to anaesthesia. Chlorpromazine may cause corneal and lenticular deposits in high dosages for long periods of time (Lopez-Munoz et al. 2005).

2.11. Amantadine

Amantadine is a frequently preferred drug because of its antiviral and antiparkinsonian properties. The mechanism of antiviral activity involves interference with the viral protein, M2, a proton channel. Antiparkinsonian activity is about antagonism of the NMDA-type glutamate receptor which causes an increase of dopamine release, and blockage of dopamine reuptake. In veterinary medicine, amantadine has used to protect birds against avian influenza in poultry farms. Amantadine may cause corneal endothelial dysfunction, corneal edema and punctate corneal staining in long-term treatment (Chang et al. 2008).

2.12. Arsenic

Arsenic is a metalloid chemical element with symbol As, and atomic number 33. Arsenic and its compounds commonly used in car batteries, electronic devices, production of pesticides, treated wood products, herbicides, insecticides, military, and medicine. Arsenic trioxide is used in agriculture. Topical contamination of arsenic may cause edema and opacity in the cornea (Chiou, 1999).

2.13. Chloral hydrate

Chloral hydrate is a colourless solid that has used as a sedative and hypnotic pharmaceutical drug, also a useful laboratory chemical reagent and precursor. The systemic use of chloral hydrate may cause punctate keratitis in the cornea (Krachmer et al. 2011).

2.14. Heroin

Heroin is also known as the generic name diamorphine is a kind of opioid. Medically it is used to relieve pain or in opioid replacement therapy. Heroin may cause epithelial impairment, stromal ulcer in the cornea (Rook et al. 2006).

2.16. Practolol

Practolol is an antiarrhythmic drug that is a selective antagonist of beta receptors (beta-1 blockage). Prolonged practolol administration may induce epitheliolysis and stromal ulceration of the cornea (Rahi et al. 1976).

2.17. Isotretinoin

Isotretinoin is a kind of retinoid, meaning vitamin A derivative, widely used in the treatment of severe acne, skin cancer, lamellar ichthyosis, neuroblastoma etc. During the treatment, corneal opacity or inflammation of the cornea may occur in some patients (Sehgal et al. 2006).

2.18. Methoxsalen (psoralen used for PUVA)

Methoxsalen is a drug obtained from plant extracts and used in the treatment of psoriasis, eczema, vitiligo and some cutaneous lymphomas. It is thought that the drug effect is created by changing the way the skin cells absorb UVA radiation. Methoxsalen may induce destruction of corneal endothelial cells (Menon et al. 1988).

2.19. Thiacetazone (antimycobacterial)

Thiacetazone is an oral antibiotic used in the treatment of tuberculosis. It is thought to interfere with mycolic acid synthesis. It may cause corneal vacuoles, endothelium or

epithelium injury (Grayson et al. 2010).

2.20. Dichloroethane in dogs (Animals only)

Systemic administration of 1, 2-dichloroethane causes corneal clouding specifically in the dog, but its lethality is approximately equivalent in dogs, cats, rabbits, and rats. Acute exposure may cause necrosis of the corneal endothelium (Kuwabara et al. 1968).

CONCLUSION

In the light of a detailed and extensive literature search, many drugs and chemicals used in systemic or ocular pharmacotherapy have been reviewed. The diagnosis of toxicity, classification method, epidemiology, pathogenesis, treatment, and prevention of disease was defined and debated.

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