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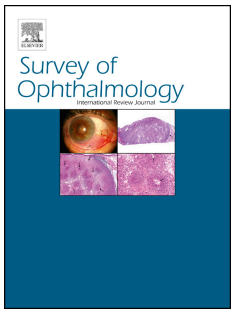

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Effects of Tear Gases on the Eye

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Abbreviations:

Chloroacetophenone (CN)

o-chloro-benzylidne malononitrile (CS)

Oleoresin capsicum (OC).

Intensive care unit (ICU)

Abstract

Chemical agents that target the eyes have been a popular choice for law enforcement during riots and for military training for nearly a century. The most commonly used agents are chloroacetophenone (CN, formerly sold as Mace®), *o*-chloro-benzylidene malononitrile (CS), and oleoresin capsicum (OC or pepper spray, current ingredient for Mace®). Initially, the majority of severe ocular injuries were caused by the explosive force rather than the chemical itself. The development of sprays reduced the severity of ocular injuries, but resulted in a variety of chemical injuries. The effects on eyes include conjunctival injection, complete corneal epithelial defects, pseudo-pterygium, corneal neovascularization, persistent conjunctivalization, corneal opacities, and reduced visual acuity. Current management, based on limited human studies, emphasizes decontamination and symptomatic treatment. We review the literature related to clinical and histopathological effects of tear gas agents on the eye and their management.

Key words: tear gas, lacrimators, mace, eye injuries, pepper spray, oleoresin capsicum, chloroacetophenone,

1. Introduction

Riot control agents are defined by World Health Organization as “chemical agents that are capable, when used in field concentrations, of rapidly causing a temporary disablement that lasts for little longer than the period of exposure.”[A] Out of the multiple forms of riot control agents, lacrimating chemicals that target the eyes are a popular choice. Lacrimators, or tear gases, quickly incapacitate the victims by causing eye pain, lacrimation, and blepharospasm. Tear gases are considered effective as a ‘non-lethal’ form of crowd control, and while permanent damage is rare, there are reports of adverse ocular effects. An effective form of riot control agent should not cause long lasting or permanent damage, so we review the ocular complications that have been reported from their use

Use of irritating gas such as sulfur and burning wax is recorded as early as 428 BC, during the war between the Athenians and Spartans.[38] Modern day chemical agents that cause excessive lacrimation with blepharospasm were first developed and used by Germany during World War I.[31] These riot control agents have also been referred to as lacrimators, tear gases, harassing agents, and irritating agents.[39] Since their development, tear gases have been used in wars, civil disturbances, as well as military training and exercises. While the Chemical Weapons Convention prohibited the use of these agents as a method of warfare, the United States currently does not classify riot control agents as chemical warfare agents.[B] Today, the most commonly used lacrimating agents are chloroacetophenone (CN), o-chloro-benzylidene malononitrile (CS), and oleoresin capsicum (OC).

Chloroacetophenone was developed towards the end of World War I specifically as a lacrimating agent.[34] Although it was reportedly never used during this war, CN quickly became the primary riot control and military training compound used by the military and law enforcement agencies.[31] Tear gas dispensers containing CN that could fit into a purse were commercially available to the public in 1920s.[19,31] Initially all tear gas devices utilized an explosive to dispel the CN. A typical tear gas weapon would fire a cartridge packed with CN powder along with an explosive charge.[31] In 1965 CN became available as a pressurized aerosol spray under the brand name Mace®.[42] Although CN was largely replaced with CS owing to a better toxicity profile, it is still commonly used in the police force as Mace®.[34]

British chemists Corson and Stoughton, hence the nickname CS, first discovered 2-chloro-benzylidene malononitrile in 1928 while exploring condensation reactions of dinitriles.[7] It was not until in 1950s when Chemical Defense Experimental Establishment (Porton, England) developed CS as a riot control agent.[25] In 1959 CS completely replaced CN in the military, and it was extensively used by the US Army during the Vietnam War for tunnel denial.[25] Today CS is used worldwide by the police force for crowd control and by the military as a confidence builder for protective mask training.[1] All US.Army recruits are exposed to CS gas during the mask confidence training, and all solders issued a protective mask must complete the mask training annually.[22]

Modern day pepper spray contains oleoresin capsicum, a natural mixture of over 100 compounds that is extracted from the *Capsicum* genus chili peppers.[34] The exact composition of oleoresin capsicum is determined by various factors such as ripeness of

the chili, the environment which the plants are grown, and the method of extraction.[34] The use of OC sprays by police became widespread in the 1980s, and it was legalized for civilian use in the majority of states by 1990s.[42] The current Mace® spray that is available to the public actually contains OC instead of CN. Recruits at some law enforcement academies are exposed to OC sprays as part of their training. [C,D,E,F,G,H,I,J]

2. Chemical properties and mechanisms of action of lacrimating agents

The mechanism of action of CN is not fully understood. Studies suggest that it acts as an S_N2 alkylating agent that induces tissue damage by inactivating thiol and sulfhydryl groups of enzymes such as lactic dehydrogenase, glutamic dehydrogenase, and pyruvic decarboxylase.[38] The molecular formula is C_8H_7OCl with molecular weight of 154.5. It has a melting point of 54℃ and boiling point of 247℃.[34]

CS is an S_N2 alkylating agent like CN, but the former is considered ten times more potent while being less toxic.[1] The molecular formula is $C_{10}H_5N_2Cl$ with a molecular weight of 188. It has a melting point of 93℃ and boiling point of 310℃.[34]

The principle constituent of OC is capsaicin (8- methyl-6-trans-nonenoyl-vanillylamide), a compound that is mainly responsible for the pungent property of chili peppers.[34] Closely related capsaicinoid analogues include homocapsaicin, nordihydrocapsaicin, nonivarnide (N-vanillyl-n-nonamide), dihydrocapsaicin, and homodihydrocapsaicin.[34] The molecular formula is $C_{18}H_{27}NO_3$ with a molecular weight

of 305. It has a melting point of 64℃ and boiling point of 210℃.[34] Given the variation of the chemical composition among both natural and synthetic OC preparations, there may be considerable inconsistency in effectiveness.[17] Application of capsaicin to skin or eye causes intense pain by acting on the sensory nerve fibers and stimulating the release of substance P. [47] Repeated use of capsaicin actually depletes available substance P within nerve fibers, which reduces the ability to experience pain, and analgesics containing capsaicin use this principle.[42]

3. Ocular effects of lacrimating agents (see Table 1)

3.1 Effects of chloroacetophenone (CN)

The majority of the early reported ocular injuries from CN were caused by the close range explosion of tear gas weapons.[30,32,46] Injury from explosive type weapon consists of various components including the force of the blast, thermal energy, debris from cartridge, and the chemical agent.[31] Since CN is in powder form, the powder itself can also act as debris that penetrates the eye. Given the multiple components of these weapons, the injuries from the explosive weapons are not caused by tear gas alone. [31]

The manifestations seen in patients who were shot with tear gas at close range include dense initial conjunctival edema with powder infiltration leading to corneal clouding, corneal opacity, and deep and extensive neovascularization.[19,32] Hoffman observed that corneal defects heal slowly, and the degree of visual acuity recovery can vary from complete recovery to only light perception depending on the distance and concentration of tear gas.[19] Additional complications included secondary glaucoma,

cataracts, vitreous hemorrhage, loss of corneal sensitivity, and damage to the optic nerve.[19,32]

Levine and Stahl a studied 14 eyes from 13 men enucleated after close range explosive injuries.[30] The five eyes that were enucleated within 2 months after the insult all displayed “intense, suppurative, necrotizing keratitis” and coagulative necrosis with iridocyclitis.[30] Nine eyes were enucleated eight months to 15 years after the injury, most of which were elective procedures because of blindness, vascularizing keratitis, or for cosmetic purposes.[30] Interestingly, many of the eyes that underwent delayed enucleation showed chronic perforating corneal ulceration histologically.[30] They suggested that CN may have caused neuroparalytic keratopathy by denaturing the enzymes associated with sensory nerve fibers, which put the cornea at increased risk for ulcerations.[30]

The development of Mace® essentially eliminated the explosive injuries and significantly reduced the severity of ocular injuries from tear gases;[2,27,37,49] however, Mace® can still cause lasting ocular injury, especially when used at close range. Studies in rabbits and monkeys show that close range spraying or direct instillation of liquid Mace® led to corneal opacities, melanosis, and permanent dense corneal scars.[31,37] MacLeod also found that the degree of injury is higher if the eyes were anesthetized prior to the exposure.[31] Case series describing close range exposure to Mace® in humans describe second degree burns, pseudopterygium, reduced corneal sensitivity, punctate epithelial corneal defects, stromal opacities, denudation of corneal epithelium, Descemet membrane folds, corneal scars, and anterior chamber reaction.[33,37] In the 12 cases of Mace® exposure presented by Rose, the victims had

no opportunity for quick irrigation.[37] In nine cases, the corneal epithelial defect resolved within 72 hours, while three cases displayed confluent punctate corneal staining that persisted up to 3 weeks, one of which displayed peripheral corneal stromal opacity for 5 months.[37] Oksala examined five cases of close range CN exposure, and four of the patients had corneal opacifications for up to 4 months; all patients recovered useful vision with time.[33]

Proper and well controlled uses of Mace® have been shown to be safe and effective in some instances. Mace® used in a psychiatry ward for behavioral control, followed by ocular irrigation and evaluation by a physician, reduced the injury rate of the caretakers without any adverse effects to the patients.[49] It is unclear whether ocular exams were performed on these patients. Importantly, there have been a number of deaths after CN exposure. The deaths are all from respiratory causes such as acute pulmonary edema or necrotizing laryngotracheobronchitis resulting from prolonged exposure to CN in an enclosed space.[5,44]

3.2 Effects of o-chloro-benzylidne malononitrile (CS)

CS is considered to be less toxic than CN and it is less likely to cause ocular injuries. One animal study comparing CN and CS exposure showed that only CN had the potential for causing long term ocular damage.[13] At the same concentrations, CN caused iritis and corneal opacities, while CS only caused transient conjunctivitis.[13] Another study demonstrated that direct instillation of CS into monkey and rabbits did not cause corneal damage.[36] Dimitroglou systematically reviewed 35 studies related to CS exposure.[9] Of the 90 cases reported, 57% showed ocular effects such as lacrimation,

blepharospasm, eye pain, conjunctivitis, and reduced vision.[9] In the two cases reporting reduced vision, visual acuity returned to normal in approximately two days, a recovery also seen in another study in which instillation of 1% CS into the conjunctival sac did not produce any corneal damage, and the visual acuity returned to normal within several minutes. [9,36] Others have also reported that ocular symptoms are transient and rapidly reversible with no permanent damage;[2,50,52] however, there are still risks of serious injury at close range exposure.[15]

Although there are no known adverse ocular complications, CS has been associated with more serious pulmonary complications and hypersensitivity reaction. Hill presented a case of multisystem hypersensitivity reaction to CS that lasted 6 months and required an intensive care unit (ICU) stay.[18] As mentioned earlier, the military routinely use CS in mask training for recruits. During a strenuous military training, CS exposure resulted in four cases of ICU admissions for hypoxia that resolved within 72 hours.[45] Hout showed that recruits have a significantly higher risk of acute respiratory illnesses after exposure to CS. [23] Hout also raised a concern that daily average exposure to CS exceeded the threshold limit value for both the trainees and chamber operators.[24] It also remains unclear what the long term sequelae are from repeated exposures.

3.3 Effects of Oleoresin capsicum (OC)

The concentration of OC in sprays vary from 1%-15% depending on the manufacturer.[42] While there are extensive studies done regarding the toxicology and

pharmacology of capsaicin, there are only few studies of OC.[34] This may be because OC is frequently used in foods and is widely considered to have minimal toxicity.[6] Pepper sprays are not completely safe, as there have been a number of reports of ocular complications from OC.[43] There has also been one death attributed to OC in an asthmatic where the autopsy revealed severe epithelial lung damage.[43]

Animal studies show degeneration of corneal trigeminal nerve fibers following subcutaneous injections of capsaicin in mice and delay in corneal healing and wound closure following retrobulbar injection with topical capsaicin in rabbits. [12,41] In humans, exposure to OC led to transient reduction in corneal sensitivity, focal epithelial cell damage and necrosis, limbal ischemia, pseudopterygion, corneal neovascularization and temporary corneal epithelial swelling.[47,49,54] In the 47 subjects exposed to OC and examined by Zollman, reduced corneal sensitivity at 1 hour returned to baseline after one week.[54] Vesaluoma found that, although OC caused a transient decrease in corneal sensitivity, a single exposure appeared to be harmless to corneal tissue.[47] There was, however, an abnormal “spiral like sub basal plexus” in the cornea of an officer with a history of multiple OC exposure.[47]

While OC exposure seems to cause little to no damage in a well-controlled experimental setting, real world exposure has been associated with more severe effects. Brown found that OC caused corneal erosions in 7% of patients in a jail ward emergency room, and there have been other reports of prolonged corneal defects and corneal ulcers, severe cases of complete epithelial defects, and conjunctival chemosis followed by neurotrophic superficial keratitis.[3,8,20,28,40] Holopainen described four patients who developed deep corneal and conjunctival lesions that took weeks to

months to resolve.[20] One of those patients was only exposed to the solvent without the OC, suggesting that the toxic solvent may be partly responsible for the adverse effects. In one case of delayed irrigation, pepper spray led to a permanent reduction in visual acuity due to irregular astigmatism associated with corneal opacity.[10] In a unique case of a child exposed to OC, a 2-year-old boy initially presented only with mild edema and injection, but presented 3 weeks later with significant conjunctival proliferation that eventually had to be surgically excised.[14] Unprotected exposure to OC during a riot has also been associated with dry eyes.[35] A recent study by Kearney showed that 7% of 4544 cases of OC exposure warranted medical evaluation, with ocular symptoms the most common cause.[26] They also showed that law enforcement training was associated with increased likelihood of severe ocular symptoms.[26]

4 Management

Currently there is no antidote available for lacrimating agent exposure, and management, which mainly consists of decontamination and symptomatic treatment, is only based on limited human studies.[4]

Lacrimating agents being air-borne, both the victim and care provider need to be protected from further exposure. In the immediate aftermath of an exposure, victims should first be reassured, withdrawn from the contaminated area, and moved to a well ventilated space.[29] As lacrimating agents are several times heavier than air, medical staff should attempt to stay on higher ground, and patients should be lifted off the ground whenever possible.[4] Medical staff should wear appropriate personal protection

against secondary contamination.[21] 45 minutes of aeration may be sufficient to reduce OC on contaminated materials to a safe level.[29, K] While decontamination of CS and CN on fabric from a spray only consists of simple aeration, heavy level of exposure may require treatment with an alkaline solution and steam. [29,L] Contact lenses and contaminated clothing should be removed and discarded,as they may retain particles.[29,42]

There are conflicting views regarding irrigation of the eyes after CS exposure. Some suggest that the eyes should be thoroughly flushed with water or saline for 10 to 20 minutes[39], while others advocate evaporation of particles with air from an electrical fan or hair dryer.[19,27,53] Breakell suggested that evaporation technique has not been helpful and that irrigation with saline resulted in significant improvement in symptoms.[2] There is also a concern that blow-drying may cause further contamination by dispersing residual CS.[16] Boric acid eye wash is contraindicated.[11] Based on limited evidence, most authors recommend irrigation with water or saline after exposure[1,2,4,11,29,38,39,42], especially irrigating the upper and lower palpebral cul-de-sac,where there may be accumulation of the offending compound.[29]

Additional symptomatic treatment consists of oral analgesics, topical antibiotics, and mydriatics.[1,11] Topical anesthetics are not recommended for the treatment of conjunctivitis.[38] Extensive ophthalmologic examination is required for persisting symptoms to search for retained particles and corneal erosion.[1,11] One limited randomized study showed that baby shampoo was not superior in reducing eye discomfort to water alone.[52] A small study suggests that diphoterine may have a role as

an eye and skin prophylactic and decontamination solution for CS exposure, but further studies are needed.[48]

5 Conclusion

While CS and OC sprays are considered safe by many, exposure (particularly when repeated) may result in long-term ocular complications, and asthmatics are especially vulnerable to pulmonary complications. Post-exposure management is largely based on decontamination and symptomatic treatment, and there are no specific antidotes or evidence-based effective methods. Hence, their use cannot be deemed completely safe. Civilian authorities and the military use these chemicals in dangerous situations such as riots because it is felt they do not have long term sequelae; however, there is not enough evidence-based research to conclude decisively that these sprays do not have permanent sequelae to the exposed individuals. Future research should fill three major gaps in our current knowledge. First, the long term effects of exposure should be explored. Second, although the literature is limited, there is documentation of serious side-effects (both ocular and systemic), and newer agents or methods could be developed that do not cause lasting damage. When such disabling agents are used, there should be management guidelines in place for decontamination to help minimize any long term effects. Finally, the effectiveness, risks, and benefits of exposing our military or law enforcement personnel to such chemicals during training should be explored.

6 Method of literature search

For this review, we searched Medline, PubMed, Web of Science, Embase and Toxnet databases for all articles published before 31 August 2015. Key words were searched independently and in various combinations: tear gas, lacrimators, mace, eye injuries, (cornea OR corneal) damage, pepper spray, chloroacetophenone, oleoresin capsicum, o-chloro-benzylidne malononitrile. The search was broad and not restricted by any filters. We included articles from the non-English language literature if translated abstract providing adequate information or translated full-text was available from the publisher. We also searched reference lists of articles obtained from the above search. We included articles related to clinical and histopathological effects of tear gas agents on the eye and subsequent management. Articles were excluded if they did not specify the compound being studied or did not report ocular effects.

7 Disclosure

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Table 1: Studies on ocular effects of chemical agents: chloroacetophenone (CN), o-chloro-benzylidene malononitrile (CS), and oleoresin capsicum (OC).

Author	Year	Agent	Subjects	Setting	Ocular Complications	Other complications	Treatment
Stein[44]	1964	CN	29 year old man	30 minute exposure to tear gas grenade in closed room	Conjunctival injection, miosis	Death due to pulmonary edema	N/A
Uhde[46]	1948	CN	20 year old soldier	Sprayed from 3 gal decontaminating apparatus	Corneal epithelial defect that recovered within 24 hours	None reported	Homatropine and 10% Albucid
			Second lieutenant	Accidental detonation of grenade at close range	Permanent blindness in both eyes	None reported	N/A
Oksala[33]	1975	CN	26 year old man	Sprayed from less than 1 meter	Large epithelial abrasion initially with stromal edema and cells in the anterior chamber. Punctate epithelial defects and vague opacities in the stroma at three weeks	None reported	Topical atropine and chloramphenicol
			36 year old man	Sprayed from less than 1 meter	Total epithelial defect that took 30 days to heal, pseudo-pterygium and conjunctival scar	None reported	Atropine, chloramphenicol , and corticosteroid
			40 year old man	Sprayed at near distance	Total epithelial defect, opacity in corneal stroma at 3 weeks	None reported	Atropine, chloramphenicol , and corticosteroid
			27 year old metal worker	Sprayed at 50 cm	Total epithelial defect that healed after 23 days, small corneal opacification present at 4 months	None reported	Atropine, chloramphenicol , and corticosteroid
			42 year old	Near range shot from spray	Large epithelial abrasion, cloudiness in the stroma for 4 weeks	None reported	Atropine, chloramphenicol , and corticosteroid
			40 year old man	Near range shot from tear gas pistol	Powder particle embedded in the cornea, total epithelial defect that healed in two weeks	None reported	Atropine, chloramphenicol , and corticosteroid

Rose[37]	1968	CN	12 Cases	Mace exposure	3 cases of confluent punctate corneal staining for 124 to 21 days, 1 case of peripheral superficial corneal stromal opacity at 5 months	Confusion, loss of recent memory, and dysequilibrium compatible with methyl chloroform toxicity	Irrigation
			Rabbit	3 rabbits sprayed at 6 inches	One of the rabbits developed a dense scar in the line of vision		
Midtbo[32]	1964	CN	18 year old boy	Pistol fired at close range and the entire charge hit the face	Dense opacities of both cornea leading to blindness in both eyes		Atropine, chloramphenicol, and penicillin
Chapman[5]	1977	CN and CS	33 year old male	Indiscriminate use of CS and CN in prison (6 CN grenade, 14 CN projectiles, and 0.4 L of 8% CS gas)	"red eyes"	Death due to acute necrotizing laryngotracheo-bronchitis	
Macleod[31]	1969	CN	Rabbit	0.1 ml of liquid Mace applied to eye. Four with anesthesia and four without	Lasting corneal opacities in anesthetized group		
			Monkey	Direct instillation, close range (4 cm), and long distance (6 feet)	Dense corneal opacities in close range, streaks of melanin pigments on the cornea in direct instillation		
Kiel[27]	1997	CS	6 (2 hit by spray directly)	Illegally obtained CS sprayed in to a public house	Slight conjunctival injection, periorbital skin undamaged	No respiratory or dermal sequelae	Ventilation with electric fans, no irrigation
Breakell[2]	1998	CS	8 males 15 females	Exposed at a crowded night club	Irritation improved with irrigation	One asthmatic required nebulizer	Irrigation with saline, air evaporation did not help

Weinberg[50]	1970	CS	44 patients	Mace used for behavioral control at psychiatry ward	None reported	None reported	Cold water flushing of the eyes and skin followed by examination by a physician
Thomas[45]	2002	CS	9 marines	CS exposure during strenuous military training	None reported	All had cough and shortness of breath, five had hemoptysis, four required ICU admission for hypoxia, all recovered after 72 hours	
Hill[18]	2000	CS	30 year old man	Sprayed heavily with Mace in prison		Multisystem hypersensitivity reaction to CS that lasted 6 months and required an ICU admission	
Voegeli[49]	2014	OC	49 year old man	Intoxicated, sprayed at short distance	Severe chemical burn, corneal erosion for three weeks, pseudo-pterygium with corneal neovascularization at four weeks, persistent conjuctivalization at six months	None reported	Dexamethasone, neomycin, and polymyxin for two weeks and systemic treatment with tetracycline and vitamin C for ten days
Holopainen[20]	2002	OC	Four cases	Two OC, one mock spray, one unidentified Russian pepper spray	All showed long lasting, deep corneal and conjunctival erosion that resolved in weeks/months. One found to have corneal nerve damage via confocal microscopy. No permanent change in VA. Two complained of dry eyes		

Epstein[10]	2001	OC	One case	Immediately handcuffed after being sprayed, receiving no ocular irrigation for more than 9 hours	Permanent decline in VA due to irregular astigmatism associated with corneal opacity		Polymyxin-bacitracin ointment, tobramycin-dexamethasone drops
Shimada[40]	2012	OC	21 year old military police officer	Pepper spray to the face during a drill	1 mm x 4 mm corneal ulcer that resolved with treatment		Topical erythromycin, scopolamine, and artificial tears
Vesaluoma[47]	2000	OC	10 volunteers	Volunteers sprayed with OC spray at 1.5 - 2.5 cm	Focal epithelial cell damage that healed within 1 day, Transient decrease in corneal sensitivity, Abnormal spiral like sub basal plexus was seen in a cornea of a police officer who was previously exposed to OC 15 times.		Washed with cold water and soap for 5 to 15 minutes
Zollman[54]	2000	OC	47 cadets	Sprayed at 1 meter during training exercise	VA unaffected, corneal sensitivity decreased at 10 min and 1 hr, At 1 week corneal sensation and slit lamp exam normal		Water irrigation along with artificial tear drop, topical anesthetic, or topical NSAID
Brown[3]	2000	OC	100 cases	Chart review of pepper spray exposure between 1994 and 1996	Corneal abrasion in 7%		
Gallar[12]	1968	OC	Rabbit		Retrobulbar combined with topical capsaicin for 3 weeks delated epithelial migration rate and wound closure times		
Das[8]	2005	OC	75 year old man	Exposure to OC spray	Conjunctival necrosis and epithelial defect that healed in 1 week. Subtotal corneal epithelial defect that healed in 2 weeks		Topical fluorometholone acetate, ascorbate, citrate, atropine sulphate, and chloramphenicol

Rasier[35]	2014	OC	96 people, 82 had protective goggle	Exposure to OC spray during Gezi Park protests	Unprotected group had lower Schirmer results		
Gerber[14]	2011	OC	2 year old boy	Accidental ocular OC exposure	Significant conjunctival proliferation that was refractory to treatment with corticosteroids		Surgical excision