Ocular Toxicity of Paraquat

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Paraquat (1,1'-dimethyl-4,4'-bipyridinium ion) is a widely used nonselective herbicide (THOMSON 1967). It is available for the control of garden weeds (Weed and Grass, Ortho) and is also used extensively in agriculture for the control of emerged weeds in orchards and as a defoliant and crop dessicant. Accidental and fatal ingestions of concentrated paraquat solutions have occurred in man (BULLIVANT 1966). Fatalities resulted mainly from progressive pulmonary fibrosis with associated liver and kidney damage. While the toxic nature of this herbicide has been experimentally studied after systemic and dermal administration to animals (CONNING et al. 1969; CLARK et al. 1966), little quantitative information is available concerning ocular toxicity from paraquat. Cant and Lewis (1968) and Swan (1968) have reported that severe eye injury in man resulted after accidental splashing of a concentrated paraquat-diquat solution into the eye. Joyce (1969) reported serious ocular injury as a result of splashing paraquat solution into the eye. A study was therefore undertaken to ascertain the dose-response relationships and the nature and severity of ocular damage from paraquat.

METHODS

Fifteen male New Zealand white rabbits, weighing 2.5 to 2.8 kg, were used in this investigation. The rabbits were housed individually with food and water available ad libitum. The animals were free of any ocular irritation or inflammation for at least one month prior to experimentation. For testing purposes each eye was considered as an independent statistical unit and the thirty eyes were then assigned to treatments with the aid of random number tables. Observations of ocular lesions were conducted by individuals unaware of pretreatment procedures received by the animal.

Five dose levels of paraquat hydrochloride were studied with the control eyes receiving normal saline. Each dose level was therefore administered to 5 eyes. Nine rabbits received different doses in each eye while 6 rabbits were given the same dose in both eyes. The dose levels were prepared by diluting an appropriate volume of paraquat with distilled water to produce the following concentrations: 6.25%, 12.5%, 25%, 50% and 100% of a 242 mg/ml paraquat ion solution, kindly supplied by Chevron

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Chemical Co., Richmond, California. The biotoxicity of this technical grade solution was comparable to crystalline paraquat hydrochloride when assayed for lethality in male Swiss-Webster mice, weighing 30-35 g. The LD_{50} after intraperitoneal injection of the technical or crystalline compound was approximately 39 mg/kg of paraquat hydrochloride (32.5-46.8 mg/kg, Slope = 1.5), as calculated by the method of Litchfield and Wilcoxon (1949).

The lower eyelid was retracted and 0.2 ml of the test solution pipetted into the lower conjunctival sac. The eye was then held shut for one minute so that the tissues would be adequately bathed in the administered solution. Ocular reactions were observed beginning at 12 hours after instillation and continued daily for 20 days. Observations were made without magnification and also with the use of the binocular loupe.

Ocular lesions were quantified according to the Draize scale (1959) which rates the severity of damage in the cornea, iris and bulbar and palpebral conjunctivae. The cornea was scored on the density of the opacity and the total area involved. The iris was scored on the degree of inflammation and the conjunctivae was scored on the extent of redness, chemosis and discharge. Numerical values assigned to the observed lesions were such that the maximal toxicity score was equal to 120. The Draize numerical score increases with the severity of the ocular lesions and changes in the cornea and iris may represent up to 80% of the maximal score. The cornea and iris are weighted more heavily in scoring because of the vital roles played by these organs in vision.

RESULTS

The time-course of ocular changes after the administration of paraquat is shown in Fig. 1. Saline treated eyes were clearly distinguishable from paraquat treated eyes. At the lower paraquat concentrations of 6.25% and 12.5% severe conjunctival reactions were observed with occasional instances of slight corneal damage at the 12.5% concentration. A typical case would show crimson red conjunctival vessels, swelling with partially closed lids, considerable mucopurulent discharge, and some diffuse areas of corneal opacification. With the higher concentrations of 25% and 50%, the iris became congested and swollen, the degree and area of corneal opacification increased, and a pannus reaction occurred. At the 50% dose level, which had a maximum average Draize rating of 76, nearly all the eyes showed complete corneal opacification (Fig. 2) with severe iritis and conjunctivitis.

Surprisingly all the rabbits that had received 0.2 ml of the 100% solution in at least one eye and the rabbit that received

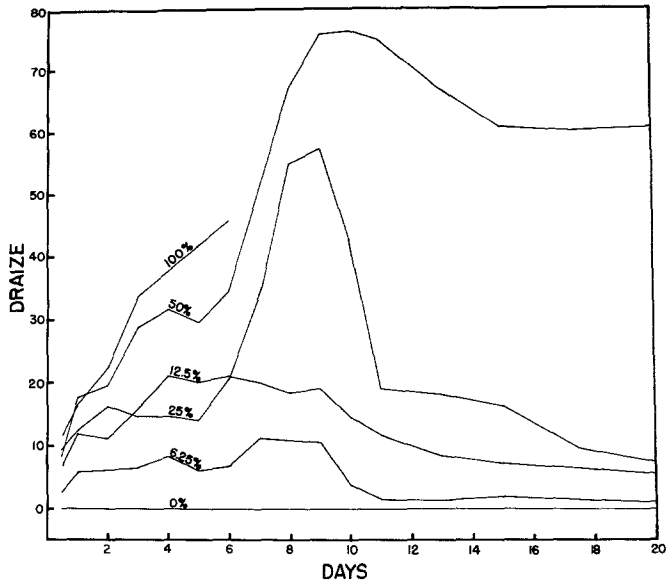

Fig. 1. The time-course of ocular changes after application of paraquat to the rabbit eye.

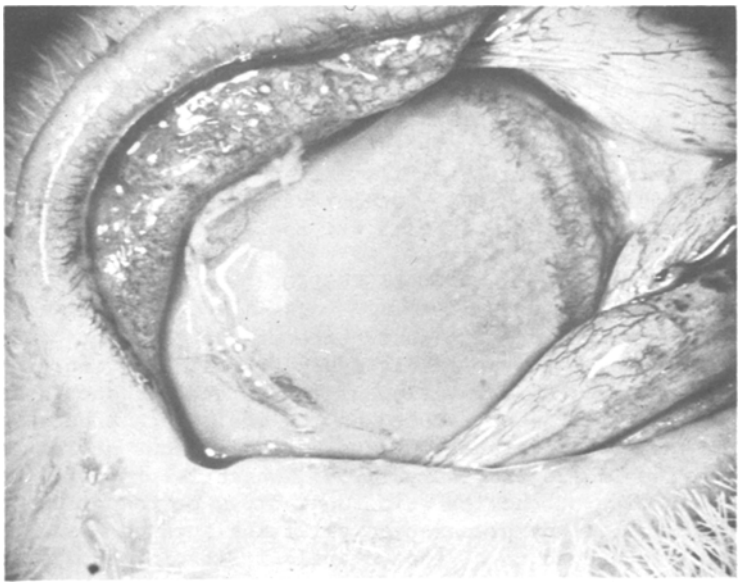

Fig. 2. Total corneal opacification on day 9 after applying 28.2 mg of paraquat ion in 0.2 ml of water to the rabbit eye.

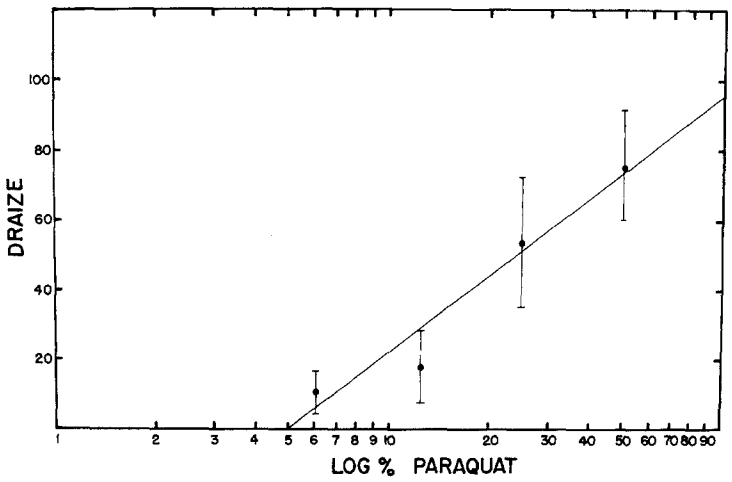

Fig. 3. Dose-related ocular changes after paraquat. Values represent the mean ± S.E. N = 4 for each point below 100%.

the 50% solution in both eyes, died within 6 days after application of paraquat. The data observed in the 100% group are also included in Fig. 1.

The quantitative relationship between the dose of paraquat and ocular toxicity is illustrated in Fig. 3. The Draize scores were obtained at 9 days after application, that is, at the time of the maximal effect (Fig. 1). Although the results were somewhat variable at each dose, ocular damage is significantly correlated to the dose of paraquat applied to the eye.

DISCUSSION

The results indicate that concentrated paraquat solutions are highly toxic to the rabbit eye. Pannus, the condition arising from vascular invasion of the cornea, is such a severe reaction that it is not scored on the Draize scale because the Draize scale was designed to assess less serious ocular reactions. The Draize procedure (1959), which is primarily used for the evaluation of chemicals in food, drugs or cosmetics, in fact state that "... Any preparation eliciting such damaging reactions (pannus) is deemed to be too severely irritating for use about the eyes." However, no specifications were made regarding the

concentrations of the substance to be tested.

When applied in the field, the dilution of the paraquat concentrate (242 mg/ml of the ion) ranges between 1:800 (0.125%) and 1:10 (10%) depending on method and purpose of application. Severe ocular toxicity has been reported in persons handling a concentrated paraquat-diquat mixture (CANT and LEWIS 1968; SWAN 1968). Joyce (1969) reported irreversible ocular lesions in a gardner's eye when accidentally splashed with a concentrated paraquat solution. Swan (1969) reported 7 instances of dilute paraquat spray (0.25%) entering the eyes of field operators. It is possible that dust from sprayed fields could also be a source of ocular exposure. In the cases reported by Swan (1969) recovery from the eye irritation was complete within 24 to 48 hours after therapeutic treatment. Thus, the ocular effects of paraquat appear to be dose-related; at lower doses, the effects are reversible whereas ocular lesions at concentrations approaching the undiluted solution are most likely irreversible.

It was surprising to find that rabbits receiving paraquat concentrate via the ocular route died within 1 week after application. Apparently death was not due to fibrotic lung changes since the rabbit is different from man and other species in that the characteristic delayed fibrotic pulmonary lesions from paraquat are not observed in this animal (BUTLER and KLEINERMAN 1971). The lethal doses administered via the ocular route to rabbits are comparable to the lethal doses found by Butler and Kleinerman (1971) when using the intraperitoneal route in rabbits. The mechanisms underlying systemic toxicity after ocular administration of paraquat merit further investigation.

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