Corneal toxicity from vinblastine solution

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SUMMARY The case is reported of a male physician who accidentally sprayed some vinblastine solution into his eyes. The resulting lesions are described.

Epithelial keratopathy is a recognised complication of chemical injury to the eyes with vinblastine solutions (Grant, 1974; Mosci, 1967). The present report describes a diffuse superficial corneal change following accidental splashing of a vinblastine solution into the eyes of a young physician. Symptoms appeared only after a delay of 24 hours. In addition to the corneal changes, most of which resolved, the patient had persistent dry eyes. The corneal changes are described and their relationship to vinblastine exposure discussed.

Case report

On 28 October 1976 a 24-year-old male physician accidentally sprayed approximately 1 ml of a

vinblastine solution (1 mg/ml pH 3.5 to 5.0) into his face while preparing the solution for injection (vinblastine sulphate, Velbe). The physician irrigated the right eye immediately with water but not the left, which he thought uninvolved. No initial discomfort occurred, but within 24 hours he observed bilateral haloes round lights and conjunctival redness.

Examination in the eye department on 29 October showed the visual acuity to be right 6/5, left 6/4. The family history and past medical history added nothing of relevance. Slit-lamp examination showed bilateral conjunctival injection, diffuse right cystic epithelial keratopathy (Tripathi and Bron, 1973), combined discrete and confluent punctate epithelial keratopathy (PEK), punctate epithelial erosions (PEE), and epithelial microcysts (Fig. 1a, b), and left upper nasal punctate keratopathy (Fig. 2). No ocular discharge was noted.

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Fig. 1 Right eye 7 days after exposure to vinblastine. A. Diffuse cystic epithelial keratopathy seen by retroillumination against the red reflex. B. Macrophotograph of microcysts seen by retroillumination

Fig. 2 Diagram to show the distribution of epithelial changes in the 2 eyes, 1 day after exposure

Over the next 8 days the patient experienced increasing blepharospasm, photophobia, epiphora, and lid swelling mainly on the right, and a fall in right visual acuity to 6/60. The left visual acuity remained unaltered at 6/4. Slight swelling of the right side of the face was apparent, and bilateral, non-tender, small preauricular lymph nodes were palpable. During this period epithelial bullous patches developed in the upper portion of the right corneal epithelium. A mild chamber reaction with fine scattered keratic precipitates appeared on the right. Rose bengal staining of the entire right and left nasal interpalpebral area occurred.

Initial therapy with topical chloramphenicol was changed to topical hypromellose, dexamethasone 0.1%, and cyclopentolate 1%, with little improvement at first. On 5 November the patient was admitted to hospital for closer observation and treatment.

During the entire episode the corneal sensation remained normal. Ocular pressures were also normal (16 mmHg right and left). Schirmer values (basal) were right 15 mm and left 5 mm on 2 November 1976, right 12 mm and left 6 mm on 7 November 1976. However, subsequent values were repeatedly in the subnormal range, e.g., right 2 mm and left 1 mm on 18 November 1976, and right 0 mm and left 1 mm on 13 January 1977. Reflex tears (nasal stimulation) were, however, normal on the latter date, right 18 and left 12 mm.

The right corneal changes were confined to the epithelium. The stroma and endothelium were normal. In the upper nasal quadrant the left cornea showed mild punctate epithelial keratitis and in Bowman's membrane focal and confluent greyish mottling with ill-defined borders. Also in the upper cornea small perineural stromal opacities appeared and resolved over a period of 1 week. During the patient's 5 days in hospital topical steroid therapy was increased to dexamethasone 0.1% hourly and betamethasone ointment nocte to the right eye.

On this regimen the corneal changes, especially on the right, improved, so that 6 weeks after the

initial injury only rare non-staining punctate epithelial changes remained in the right cornea.

After 10 weeks vision had returned to 6/5 in the right eye. However, in the left cornea, the changes in Bowman's membrane remained unaltered. During this entire episode the fundi and the ocular media, including the lens (Betrix, 1974a, b), remained normal. No conjunctival scarring of the lids, fornices, or globes was noted throughout the period of observation.

INVESTIGATIONS

Repeated conjunctival scrapings, stained with Gram and Giemsa stains, yielded no epithelial inclusion bodies and few polymorphs. A few eosinophils were seen. Repeated viral, fungal, and bacterial cultures were also negative. Acute and convalescent titres for herpes simplex, zoster virus, adenovirus, and psittacosis—LGV showed weak dilutions (1:16) at 1 week without subsequent rises. Repeated laboratory investigations for haematology, sedimentation rate, SMA 12, urine analysis, antinuclear antibody, rheumatoid factor, and lupus erythematosus cells were negative, except for a slightly elevated initial calcium 2.7 (normal 2.12 to 2.52) and total protein 84 (normal 60 to 80) standard international units, which were normal on later studies. Serology tests for syphilis and chest x-rays were negative. The Mantoux test was positive (dilution 1:1000), but the patient had received BCG previously.

Experimental studies. Four Dutch rabbits were given 5 drops vinblastine (Belbe) solution into the right eye. After a 30-second wait the vinblastine was irrigated with water from 3 of the rabbits, but not the fourth. There was immediate staining with rose bengal, and by 12 hours PEE and PEK were noted in all 4 rabbits. All rabbits had similar changes but more marked in the non-irrigated eye. A slight mucous discharge and a mild conjunctival injection occurred within 24 hours. The PEK slowly resolved over a period of 2 weeks without any treatment.

Discussion

Vinblastine is a vinca alkaloid which is used as an antimetabolite. It blocks mitosis in metaphase (Johnson *et al.*, 1963). Vinca alkaloids bind specifically with the protein tubulin. Disruption of the microtubules of the mitotic spindle disturbs segregation of the chromosomes in mitosis and leads to cell death (Goodman and Gilman, 1970). Mosci (1967) described a case of vinblastine splashed into an eye which resulted in an acute keratitis, with temporary reduction of vision to hand movements. A diffuse epithelial keratitis stained with fluorescein and showed minute grey opacities, some of which later

became confluent. Although there were no permanent corneal changes, an astigmatism of less than 1 dioptre was said to persist.

The ocular changes described in our patient were unusual. The onset of symptoms and signs shortly after accidental exposure to vinblastine solution suggested that the eye disorder was a result of vinblastine toxicity. The epithelial corneal changes were in keeping with the previous report (Mosci, 1967). However, the associated preauricular adenopathy and lid and facial swelling suggested an alternative infective aetiology. This was not borne out by conjunctival cytology and cultures or assessment of antibody titres against chlamydia and common ocular viruses. The corneal and conjunctival appearances did not suggest an infective cause. Sarcoidosis was considered because of the transient uveitis and reduced tear production. However, the Mantoux test was positive, and the raised calcium and total protein values recorded initially were not confirmed at subsequent tests.

If vinblastine was the cause of this patient's eye signs then it is difficult to understand how it might be responsible for producing a persistent dry eye. One possibility is that the patient already suffered from dry eyes at the time of chemical injury and that this was masked by reflex tearing when the keratopathy was most active. Although there have been few reports of accidental ocular damage in man caused by vinblastine, such accidents are not

rare, and the manufacturers are familiar with such episodes, which they consider are responsible for transient changes only. However, no attempts have been made to document the changes photographically, and no report has appeared in the English-language literature. It is with this in mind that the above case has been reported. It is of note that the subepithelial corneal changes persisted in the left cornea.

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