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Case report

Vinblastine toxicity to the ocular surface

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Local ocular exposure to antineoplastic drugs occurs either during regular use of some of these drugs in ophthalmology or accidentally during the general use of these drugs. Many ocular side effects have been described after such intentional or accidental exposures. We describe a case of accidental ocular trauma by vinblastine. As in one of the only two previously published cases of ocular trauma by vinblastine, our patient showed acute keratopathy with a drop in visual acuity followed by the development of dry eyes and a subepithelial corneal scar. In addition, in an attempt to further evaluate the clinical course and the benefits of steroid treatment, nine rabbits were studied after ocular instillation of vinblastine. After the trauma, local steroid treatment was given in one eye of each rabbit; the second eye served as a control. The animal studies showed acute conjunctivitis and keratopathy with increasing severity in the first days and improvement thereafter. That course was similar to the one manifested in our patient. Local steroid treatment in the rabbit eye had no effect as compared with the control group. A possible mechanism for the induction of dry eyes is discussed.

Key words: Eye, ocular trauma, side effects, steroid treatment, vinblastine.

Introduction

The increased usage of antineoplastic drugs in ophthalmology raises interest in the local side effects of these drugs. Mitomycin C (MMC) and 5-fluorouracil (5-FU) applied topically are currently being used in ophthalmology for an increasing number of indications. Among the more frequent indications are reducing the risk for recurrence of pterygium after surgery and preventing fibrosis of filtration blebs after trabeculectomy surgery. These drugs can cause variable ocular side effects. MMC used for pterygium surgery can induce mild complications such as corneal epithelial erosions and delay in healing of surgical wounds, and severe complications such as secondary glaucoma, cataract, scleral melting and even corneal perforation.[1] Other studies reported an increasing incidence of keratopathy after the use of 5-FU during trabeculectomy surgery.[2]

Vinblastine is a vinca alkaloid antineoplastic drug used in the treatment of various solid and hematological tumors. Only two cases of toxic ocular damage by local exposure to vinblastine have been described in the literature.[3,4] Epithelial keratitis, dry eyes and subepithelial corneal scars were found in patients after exposure to vinblastine.

We report a case of accidental vinblastine-induced ocular damage, the results of a study on vinblastine damage to rabbit eyes and the effect of steroid treatment after such an insult in the rabbit.

Case report

A 42-year-old female nurse had accidentally splashed vinblastine sulfate solution 1 mg/ml (Teva Pharmaceutical Industries, Petah-Tikva, Israel) into both eyes while preparing the drug for infusion. After 12 h she had bilateral blurred vision and ocular discomfort. On examination, best corrected visual acuity was 5/6 in both eyes. Biomicroscopic examination with a slit lamp revealed an irregular cystic corneal epithelium that did not stain with fluorescein or rose bengal; the rest of the ocular examination was unremarkable except for short tear film break-up time in both eyes. Treatment with oral prednisone 40 mg/day and drops of dexamethasone phosphate 0.1% (Teva Pharmaceutical Industries) three times a day was started. Three days later the patient experienced pain in the left eye. On examination visual acuity had decreased to 6/9 in the right eye and 6/12 in the left eye. The right eye showed less corneal epithelial irregularities. The left eye was injected with diffuse punctate corneal

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epithelial defects (Figure 1) and flare (+1) in the anterior chamber. The symptoms and signs decreased gradually, and after 3 weeks the visual acuity was 6/6 in both eyes and the patient was comfortable. However, a subepithelial corneal scar was found in the left eye at the visual axis and Schirmer test results were 1 mm after 5 min in both eyes, indicating decreased tear production. After 1 year these findings remained unchanged.

Animal study

Methods

Nine albino rabbits were used in this study, the purpose of which was to evaluate the clinical course and pathological process following ocular exposure to vinblastine. Rabbits were used in compliance with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research. The animals were housed individually, and received food and tap water *ad libitum* on a 12 h light–dark schedule. In each eye benoxinate HCL 0.4% (Fischer Pharmaceutical, Tel Aviv, Israel) drops were placed into the conjunctival sac and, after 10 min, 0.5 cm^3 of vinblastine sulfate solution (1 mg/ml) was instilled into both rabbit eyes. Ten minutes later both eyes of each animal were irrigated with 100 cm^3 of 0.9% NaCl. In the left eye, subconjunctival injection of 10 mg methylprednisolone was given, followed by 0.1% dexamethasone phosphate eye drops three times a day. The right eye received drops of 0.9% NaCl (saline) three times a day and served as control. Biomicroscopical slit lamp examination was done on days 1, 3, 6 and 14. Animals were sacrificed after 4 h ($n = 1$), after 1, 3 and 6 days ($n = 2$ each time), and after 14 days ($n = 1$); one animal died during the study. All eyes including the eyelids were enucleated, fixed in buffered formalin, processed routinely and embedded in paraffin. Five-micron thick sections stained with hematoxylin & eosin were examined microscopically.

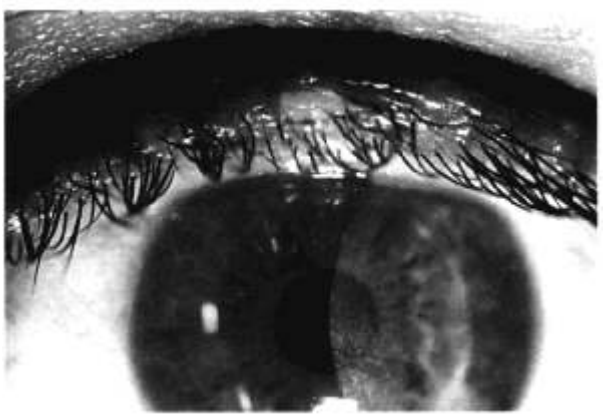

Figure 1. Slit lamp examination of the left eye 10 days after accidental exposure to vinblastine. Punctate keratitis affecting most of the cornea is seen.

Results

Clinical examination (Table 1) showed corneal epithelial irregularities that were found 4 h after the insult. Punctuate epithelial defects manifested at day 6. By day 14, the epithelium was intact. However, subepithelial small opacities were found. Histological examination (Table 2) of conjunctival tissue revealed acute inflammatory response in both eyes. In the cornea, epithelial irregularities and pits were observed starting at 4 h after the trauma and during the 14 days of evaluation. At no time was there any

Table 1. Clinical findings in rabbit eyes after vinblastine trauma

	Time after trauma	Right eye	Left eye
1	4 h	ND	ND
2	1 day	EI	EI, bullae
3	1 day	ND	ND
4	3 days	EI	EI
5	3 days	EI	EI
6	6 days	PEE, few bullae	PEE, few bullae
7	6 days	PEE, few bullae	PEE
8	14 days	some punctate opacities, no staining	some punctate opacities, no staining
9	died	—	—

ND, not done; EI, epithelial irregularities; PEE, punctate epithelial erosions.

Table 2. Histological findings in rabbit eyes after vinblastine trauma

	Time after trauma	Cornea		Conjunctiva	
		Right eye	Left eye	Right eye	Left eye
1	4 h	EI, pits	N	AIR	AIR
2	1 day	mild EE, pits	EI, pits, mild EE	AIR	AIR
3	1 day	mild EE, pits, vascularization of anterior stroma, AIR, EI	mild EE, EI, pits	AIR	AIR
4	3 days	N	N	AIR	AIR
4	3 days	N	N	AIR	AIR
6	6 days	many pits	many pits	AIR	AIR
7	6 days	N	pits	AIR	AIR
8	14 days	very mild EI	very mild EI, mild AIR	AIR	AIR
9	died	—	—	—	—

N, normal; ND, not done; EE, epithelial edema; AIR, acute inflammatory reaction; EI, epithelial irregularities.

significant clinical or histological difference between the steroid-treated eyes and the placebo group.

Discussion

Vinblastine binds to the protein tubulin and so interferes with microtubule action at mitosis and at other intracellular processes.[6] Vinblastine injury to the eyes as an occupational trauma was described previously in rare cases.[3–5] In our patient, vinblastine trauma caused severe conjunctival irritation and epithelial keratopathy. The epithelial damage was found 12 h after the trauma. At 3 days, punctate epithelial defects and irregularities appeared, and visual acuity dcreased to 6/12. Thereafter, normal epithelium replaced the affected one; by 3 weeks, the epithelial surface of the cornea was normal and visual acuity recovered to 6/6. However, dry eyes and a subepithelial scar remained. A similar pattern was found in the only two reports of vinblastine ocular trauma in the literature. In the first,[3] a few days after the trauma, epithelial keratitis with a decreased visual acuity (to hand movements) occurred; after 2 months the epithelium was normal and visual acuity was 5/6, but astigmatism of less than 1 diopter was found. In the second case,[4] a physician accidentally splashed vinblastine into both eyes. After 24 h, cystic and punctuate epithelial keratopathy were seen, followed by a decrease in visual acuity to 6/60 after 8 days. Ten weeks after exposure, visual acuity was 6/5. However, dry eyes and focal and confluent greyish mottling in Bowman's membrane manifested after the trauma.

Of particular interest is the marked dry eye that our patient was not aware of before the trauma. The dryness was found already 12 h after the trauma and remained thereafter. Dry eye which was not known before the trauma was found in one case before.[4] It is possible that the severe inflammatory reaction that occurred after the trauma caused damage to the conjunctiva and lacrimal ducts that resulted in dryness. Another possible cause for dryness may be vinblastine-induced neuropathy in the lacrimal apparatus. Interestingly, systemic high dosage of vinblastine was reported to cause a transitory dry mouth secondary to parotid malfunction.[6] Furthermore, vinca alkaloids are known to block axoplasmic transport in local application. This effect was used by iontophoretically applied vinblastine in the treatment of patients suffering from chronic localized pain.[7] Therefore, it is possible that vinblastine causes dry eyes by inducing toxic neurological damage in the lacrimal gland through a similar mechanism.

The animal studies, like in humans, showed severe toxic damage to the conjunctiva and the epithelium of the cornea. As in the previously published cases,[3,4] the clinical signs in the rabbit eyes peaked a few days after the exposure. Interestingly, these studies showed that recovery after vinblastine trauma is independent of steroids. The damage to the cornea by vinblastine is immediate, the affected epithelial cells are damaged and are replaced with time by normal epithelium.

In conclusion, vinblastine ocular trauma can cause

acute keratopathy, permanent subepithelial changes and probably dry eyes. At the present time intensive local steroid administration is not recommended in acute stage post-vinblastine trauma.

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