Editorial

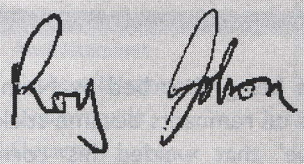
In this edition of SA Family Practice we take a brief detour around the cornea. I was inspired to do so by my colleague, Dr George Muntingh who described to me a patient similar to Numdi. I realised I had not heard of, nor even considered the possibility of a 'contact lens-drug interaction'. It is now part of my armamentarium of 'therapeutic red flags' – and one of the objectives of this edition's CPD is to alert you to this possibility, should you not already have been aware of it.

Dr Muntingh and his co-authors published a booklet locally from which I have quoted extensively in this article.[1]

The second patient presents a situation many of us may previously have recognised and/or managed, and he is included simply as a reminder.

Hopefully the pathogenesis leading to the third patient's problems is no longer occurring as frequently as it used to in South Africa.

By the time you read this, 2002 should be well underway. May it be a good year for all!



Roy Jobson

1. Hay L, Muntingh G. Drugs and Contact Lens Interactions. Karen Park. Biomed Publishers. 1994.

Corneal Calamities

Patient One

You are phoned on a Sunday morning by Numdi Kumalo who is in acute distress. He'd gone to bed with his contact lenses in place. (He'd been a bit drunk.) As he removed the first lens, he experienced an intense searing pain and had momentarily 'fainted'. He cannot open that eye properly, everything is completely blurred, and his eye is pouring tears.

You think back to the last time you saw Numdi. He had come to ask for a prescription for "Rocute – or something like that" to control his acne. His acne was really mild however, and in your opinion did not require isotretinoin. But Numdi had his own reasons for asking. He is carving a career for himself as a male model. You remember seeing him posing in some of the mail-drop advertisements of a certain large clothing store. He told you that his acne tended to flare up unexpectedly, and that he had recently lost a lucrative assignment because of this. Several of his colleagues are using the medication without any problem.

You did not make an immediate decision, but decided to send him for fasting blood lipids which is a recommendation for anyone using isotretinoin.[1] You thought you had reached a negotiated understanding about your concerns with him, and that he understood that the test was important as a baseline measure.

What you did not know was that Numdi didn't actually go for the blood tests, but instead went straight off to the dermatologist who had prescribed isotretinoin to his friends. The dermatologist had (predictably?) prescribed the isotretinoin.

Question 1:
What happened to Numdi that Sunday morning?

Answer 1:
Numdi had partially ripped off the superficial epithelial layer of his cornea as he had removed his contact lens.

Question 2:
What was the likely cause for this?

Answer 2:
Numdi's contact lens had become 'glued' to the cornea as a result of the lens becoming dehydrated, and absorbing all the fluid – including the major part of the tear film – between the lens and the cornea as he slept. Two main mechanisms for this were: (i) tear production is normally halted or markedly diminished during sleep; and (ii) isotretinoin itself has a drying effect on the eye through reduced tear production. Numdi was also systemically a little dehydrated from his excess alcohol intake. The effect was cumulative.

Question 3:
How would you manage this situation?

Answer 3:
I would immediately phone my friendly ophthalmologist for advice. Assuming that she/he is not available on a Sunday morning, I would treat Numdi's affected eye as for an 'arc' eye. I would apply one (compassionate) drop of local anaesthetic eye drops, insert antibiotic drops and cover the eye. I would try to rehydrate the other contact lens with copious sterile water (or normal saline), until the 'glue' holding the lens to the cornea became diluted and the bond released. Clean tap water could be used if nothing else is available. I would then arrange for Numdi to be seen by an ophthalmologist as an emergency if this is feasible, or admitted to hospital as soon as possible for follow-up by my colleague.

Question 4:
What are the constituents of tears and what formed the 'glue' in Numdi's case?

Answer 4:
Tears coat the eye in three definite layers. This is called the 'tear film'. The outermost lipid (oily) layer is secreted by the tarsal glands in the eyelids. Their openings line the eyelid margins. Each time a person blinks, the eyelids draw their secretion over the surface of the eye. The oil helps prevent the middle watery layer from evaporating too rapidly.
The middle watery-saline layer is secreted by the lachrimal gland, and is the component produced when a person cries. The innermost layer is mucus and contains mucopolysaccharides. This layer keeps the tear film adherent to the eyeball.
See Figure 1: Layers of the tear film.

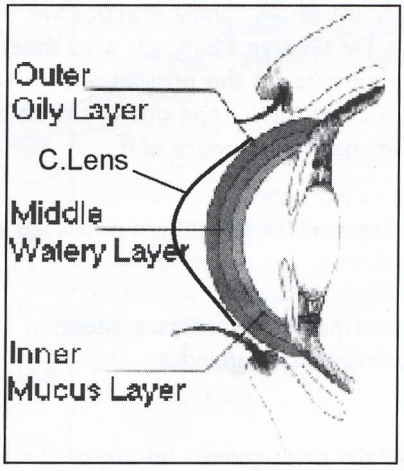


Figure 1: Layers of the tear film

While the watery layer was being absorbed by Numdi's contact lens, the mucous and oil remnants became stickier and drier forming the 'glue' that welded his corneal epithelium to the contact lens.

Question 5:
What other problems may be caused by 'drug-contact lens' interactions?

Answer 5:
Several drugs have direct actions on contact lenses. Drug actions on the eyes themselves may in turn have indirect actions on contact lenses.

Possible effects on the lenses themselves include:
- increased deposits on or even in the lenses
- discoloration of the lenses
- dehydration of the lenses

Effects on the eye include:
- corneal oedema
- decreased eye movements and diminished blink reflexes
- reduced tear production
- sore/irritated eyes

Lens Deposits
- Proteins, mucus, oils and salts that make up the tear film can be adsorbed or absorbed by contact lenses. A build up of these may damage the lenses and also dis-

tort the wearer's vision. The normal gas exchange between the eye and the environment may be affected leading to corneal oedema or loss of corneal clarity.

- Foreign substances such as dust, aerosol-sprays, make-up and body creams, bacteria, viruses, fungi, iron, etc. These irritants may create an uneven surface on the lens resulting in visual disturbances.

Variations in the manufacture of contact lenses result in certain lenses being more affected by lens deposits than others.

See Table 1 for a list of substances which may increase the likelihood of contact lens deposits.

Table 1: Lens deposits resulting from drugs and other substances

Drugs which may increase lens deposits	**Other causes of increased lens deposits**
Alcohol	Cosmetics
Anticholinergics	'Dagga'
Antihistamines	Eye ointments
Cyclic antidepressants	Protein diets
Disopyramide	Smoking
Dopamine	
Etretinate	
Isotretinoin	
Meclozine	
Methotrexate	
Methyldopa	
Morphine	
Oral contraceptives	
Phenothiazines	
Pimozide	
Thiazide diuretics	

Discoloration of lenses

This is mainly a problem in 'soft' contact lenses. Some drugs cause permanent discoloration, while with others it can be reversed – although often with difficulty. Rifampicin can enter lenses causing an orange discoloration and it can also react with compounds on the surface, damaging the lenses.
Table 2 lists drugs which may discolour contact lenses.

Dehydration of lenses

Although the damage to the lens caused by dehydration of the lens is usually reversible, the problem is the secondary damage that may be caused to the eye, as happened to Numdi. Dehydration of the lens may occur as a direct effect of a substance, such as with hypertonic eye drops,

Table 2: Contact lens discolorant drugs

Adrenaline (brown)	Fluorescein
Iodine preparations	Nitrofurantoin (brown)
Phenolphthalein (pink)	Phenylephrine
Pyridium	Rifampicin (orange)
Rose Bengal	Sulphasalazine (orange)
Tetracyclines	Tetrahydrozoline

or may be an indirect effect due to, for example, reduced tear formation – such as with isotretinoin. The lens absorbs the watery layer of the tear film leading to a breakdown in the tear film integrity. The latter becomes thickened and 'glue-like'.

Substances with a direct dehydrating effect on contact lenses, and an indirect dehydrating effect through reduced tear production are listed in Table 3

Table 3: Lens dehydration

Direct dehydration	**Indirect dehydration through reduced tear production**
Hypertonic eye drops	Antazoline
Sodium sulphacetamide	Anticholinergics
Pilocarpine	Antihistamines
	Beta-blockers
	Clonidine
	Cyclic antidepressants
	Dagga
	Disopyramide
	Ephedrine
	Etretinate
	Isotretinoin
	Meclozine
	Methotrexate
	Methyldopa
	Morphine
	Oral contraceptives
	Phenothiazines
	Pimozide
	Thiazide diuretics

Corneal oedema

Several agents contribute to corneal oedema, with oral contraceptives perhaps being the most noteworthy. Engorged corneal epithelium causes poor contact lens fit, eye discomfort, and lens shift – apart from visual disturbances. It is worth noting that pregnancy too can cause corneal oedema.

Table 4 lists some drugs which may cause corneal oedema.

Table 4: Drugs contributing to corneal oedema

Amantidine	Erythromycin
Amphotericin-B	Lithium carbonate
Chloramphenicol	Oral contraceptives
Chlorthalidone	Phenylephrine
Clomiphene	Pilocarpine
Cocaine	Primidone
Digoxin	

Reduced eye movements and diminished blink reflex

Eye movement and the blink reflex play a major role in the formation of the tear film. A proper contact lens fit depends on the presence of a normal tear film. Drugs that reduce eye movement and diminish the blink reflex may lead to eye discomfort and improper lens fit. Examples of these drugs are listed in Table 5.

Table 5: Drugs that reduce eye movement and diminish the blink reflex

Amiodarone	Muscle relaxants
Antihistamines	Pentazocine
Beta-blockers	Reserpine
Carbamazepine	Sedative hypnotics
Meprobamate	Tricyclic antidepressants
Methadone	

Irritated or sore eyes

Apart from tobacco smoke, which has a direct noxious effect on the eyes, other drugs may cause varying degrees of eye-irritation as a side effect. This would usually not be the primary side effect of the drugs but an idiosyncratic effect which may well occur in certain individuals. These are listed in Table 6.

Table 6: Possible eye irritants

Aspirin	Fluoro-uracil
Benzodiazepines	Hydralazine
Chloroquine	Ketoprofen
Clonidine	Methotrexate
Diltiazem	Verapamil

Question 6:
If Numdi had been a woman asking for isotretinoin, what other considerations would have to have been taken into account?

Answer 6:
Isotretinoin is extremely teratogenic. Women should have been on contraception for at least four weeks prior to starting the drug, it should be continued throughout the course of the treatment, and maintained for at least four weeks after stopping the drug. The risk of a serious birth defect in a child is about 25% if isotretinoin is taken during pregnancy.[1]

Patient Two

Mr AJ is a fit 70 year old who developed severe osteoarthritis in his left hip. He and you had been planning a total hip replacement for several years. He recently retired and decided it was time to go ahead with the operation. The orthopaedic surgeon was extremely pleased with the operation and how well it went. A few days after the operation, Mrs AJ phoned you to say that he had a funny blister on the right side of the tip of his nose and that he complained of a 'funny sensation' in his right eye. She said that the orthopaedic surgeon didn't seem concerned, and she wondered if this was something they should worry about.

Question 7:
What would this alert you to?

Answer 7:
He could be developing herpes zoster ophthalmicus (HZO). The typical sequence of a nasal lesion followed by an eye infection on the same side was first described by Hutchinson in the 19th century and is known as Hutchinson's sign.

Question 8:
What is the explanation for this association?

Answer 8:
The herpes zoster virus remains dormant in the trigeminal ganglion following primary infection (with varicella zoster virus i.e. chicken-pox). The nasociliary branch of the ophthalmic division of the trigeminal nerve supplies the surface of the nose and the eye – including the cornea.[2]

When you got to see Mr AJ he had clearly developed HZO of the right eye with profuse tears, conjunctivitis, and, although it was difficult to identify, there seemed to be a lesion on the cornea itself.

Herpes zoster ophthalmicus

HZO normally increases in incidence with age – peaking in the seventh decade of life, although it may occur in any person who is immunocompromised. Acute orbital and globe lesions may develop for up to 3 weeks after appear-

ance of the initial lesions – although as in our patient they may appear quite rapidly. The condition may resolve rapidly and completely – especially if treated with antiviral therapy within 72 hours of the first symptoms, or it may become chronic and linger for years making life a misery for the patient.

HZO needs to be differentiated from herpes simplex keratitis. Apart from the typical clinical picture of HZO, examination with a slit lamp supposedly shows that the dendritic lesions seen in HZO tend to be infiltrative, whereas the dendritic lesions seen with herpes simplex tend to be ulcerative. Differentiating between these conditions is important in that one would not use steroids in herpes simplex keratitis, whereas with HZO, steroids are often indicated.[3] [I'm not ashamed to say that I would prefer my friendly local ophthalmologist to differentiate between these conditions at the slit lamp level!]

Question 9:
What is the management of HZO?

Answer 9:
Antiviral agents, systemic corticosteroids, antidepressants, and adequate pain control.[3]

- Oral antiviral drugs (e.g., valaciclovir 1g tid for 7 days; acyclovir 600 to 800mg 5 times per day for 7–10 days – omitting the night time dose; or famciclovir 500mg tid for 7 days. NB: As far as I can ascertain famciclovir is not registered for this indication in South Africa – so using it would be what is called 'off-label' use. However it is used at this dosage and for this indication elsewhere.[4])
- Tricyclic antidepressants (e.g., amitriptyline, nortriptyline, or desipramine 25mg – 75mg every four hours for several weeks if needed, to inhibit acute and prolonged postherpetic neuralgia)
- Prednisone 40 to 60mg daily, tapered down slowly over 10 days
- Analgesics – beware of drug interactions
- Additional topical corticosteroids, antibiotics, cycloplegics, antivirals, and glaucoma medications as necessary for keratitis, iritis, or glaucoma

For postherpetic neuralgia that develops as a late complication, tricyclic antidepressants (as listed above, initially as a single night-time dose) may be helpful.

Patient Three

Nontombi is three years old. She is blind in both eyes. She was admitted to a remote rural hospital in an underserved area a couple of years ago with severe dehydration following an acute diarrhoeal disease. While in the ward she picked up measles and subsequently developed bilateral corneal perforations – with herniation (extrusion) of the iris from each eye. Nontombi's eyes subsequently became scarred, distorted, and sightless.

Question 10:
What was the most likely cause of her eye problems when she was admitted?

Answer 10:
Vitamin A deficiency associated with protein-energy malnutrition. Apart from its vital role in the physiology of vision, Vitamin A plays an important role in maintaining the integrity of epithelial tissues – including the epithelium of the cornea. The clinical eye-signs related to hypovitaminosis A are known as xerophthalmia. The typical sequence of events is night blindness, the appearance of Bitot's spots on the conjunctiva, conjunctival then corneal xerosis (dryness), keratomalacia, bulging and rupture of the cornea, scarring of the cornea with shrinking and distortion of the eyeball. A series of excellent descriptive photographs can be found as part of one of the South African Vitamin A Consultative Group's (SAVACG) technical reports.[5]

Conclusion:
Corneal calamities may have devastating effects for the victims – ranging from short-term discomfort to permanent blindness. As family physicians we need to be aware of these possible eye problems and if not able to manage them ourselves, at least be able to refer such a person to someone who can manage them appropriately.

References:

1. Laurence DR, Bennett PN, Brown MJ. Clinical Pharmacology. Edinburgh. Churchill Livingstone. 1997:280-281.
2. Melton CD. Herpes Zoster. eMedicine Journal, June 22 2001, Volume 2, Number 6. http://www.emedicine.com/EMERG/topic823.htm
3. Roque MR, Foster CS. Herpes Zoster. eMedicine Journal, June 21 2001, Volume 2, Number 6. http://www.emedicine.com/OPH/topic257.htm
4. Safrin S, Chambers HF. Antiviral Agents. In Katzung BG. (ed) Basic and Clinical Pharmacology 7th edition. Connecticut. Appleton & Lange. 1998:792.
5. The South African Vitamin A Consultative Group (SAVACG). Technical Report: Children aged 6-71 months in South Africa, 1994: Their anthropometric, Vitamin A, iron and immunisation coverage status. 1995. http://www.sahealthinfo.org/Modules/Nutrition/Appendix 2.5 Xerophthalmia.pdf