A comparison of the efficacy and duration of action of topically applied proxymetacaine using a novel ophthalmic delivery system versus eye drops in healthy young volunteers

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Abstract

A novel ophthalmic drug delivery system (NODS) has been developed to give precise and controlled delivery of a drug to the eye. The drug is incorporated into a polyvinyl alcohol film flag attached to a carrier. When applied to the eye the flag detaches and gradually dissolves, releasing the drug. We investigated corneal anaesthesia produced by different concentrations of proxymetacaine NODS, and conventional eye drops. Subjects consisted of 28 normal males (mean age 25.3 (SD 3.9) years). Corneal touch sensitivity was measured with a biomicroscope mounted Cochet-Bonnet aesthesiometer. Each subject attended for two visits separated by 7 days. On each visit each eye randomly received one of four proxymetacaine preparations: 44 μg, 74 μg, 124 μg NODS, or 35 μl of 0.5% proxymetacaine drops (175 μg). Corneal touch sensitivity was measured before, and at 1, 2, 5, 10, 15, 20, 30, 45, and 60 minutes following instillation. Complete anaesthesia was achieved in the majority of subjects within 1 minute of instillation. The lowest NODS dose (44 μg) produced longer lasting anaesthesia than the 35 μl drop (175 μg) (p<0.05). Higher NODS doses produced a correspondingly greater increase in the duration of anaesthesia. The greater bioavailability achieved by this vehicle allows much lower drug concentrations to be used, reducing the likelihood of systemic adverse reactions.

Subjects and methods

Subjects consisted of 28 men with a mean age of 25.3 (SD 3.9) years. These were recruited from a university undergraduate population and included: 16 (57.1%) whites, 10 (35.7%) Asians, one (3.6%) black African, and one (3.6%) oriental. They had no history of ocular pathology, and none of the subjects were contact lens wearers. A screening examination excluded any corneal pathology.

Two versions of the Cochet-Bonnet aesthesiometer were used to measure the touch sensitivity of a paracentral corneal location. One aesthesiometer incorporated a 0.08 mm diameter nylon monofilament, covering a range of 2–90 mg/0.005 mm², and the other a 0.12 mm filament diameter with a range of 11–145 mg/0.0113 mm². The aesthesiometer was attached to a slit-lamp biomicroscope using a mount which allows precise control of filament orientation. The filament tip, held in constant focus through the

Figure 1 A diagrammatic representation of NODS – a novel ophthalmic delivery system. The drug is contained within the medicated flag which becomes detached from the carrier after the membrane film dissolves in the conjunctival sac.
Results
For the purpose of this study total anaesthesia was assumed when there was no subjective touch sensitivity to a 1 cm length of the 0-12 mm diameter filament. For each preparation the onset of anaesthesia was extremely rapid. This was followed by a variable interval of maximal anaesthesia, with a gradual restoration of full sensitivity (Fig 2).

In three out of a total of 84 separate NODS instillations complete anaesthesia was not achieved, and there was a rapid return to baseline sensitivity. These anomalies were included in the statistical analysis, and account for the fact that full anaesthesia was not achieved by 100% of subjects for both the 44 μg and 124 μg NODS (Fig 2).

The results of the statistical analysis are summarised in Table 1. At 10 minutes following drug instillation only the 74 μg NODS was significantly different from the eyedrop (p<0.05). All NODS doses were significantly different from the drop at 15 and 20 minutes (p<0.05), and after 30 minutes a significant difference was found for the 74 and 124 μg preparations. All comparisons made before 10 minutes and at time intervals in excess of 30 minutes were not significant (p>0.05).

No adverse corneal or systemic reaction was observed with any of the preparations used.

Discussion
Ideally a topical local anaesthetic should produce a rapid onset of anaesthesia, and a sufficient duration of action to perform the particular procedure— for example, tonometry or foreign body removal, followed by a rapid return to full sensitivity. In drug development, the lowest concentration of an anaesthetic agent is selected which is consistent with these requirements. The present study compared the time course of corneal anaesthesia induced by different concentrations of proxymetacaine, either in the form of NODS or as conventional eye drops.

All proxymetacaine preparations produced little or no stinging on instillation and were well tolerated by all subjects. In the vast majority of subjects complete anaesthesia was achieved for all four preparations within 1 minute of instillation. All NODS produced longer lasting anaesthesia than the eyedrop which incorporated a higher drug concentration (for example, the 44 μg unit contained a quarter of the 175 μg dose in the 35 μl eyedrop). The greater bioavailability achieved by this vehicle, by virtue of the sustained release of proxymetacaine from the PVA flag, allows much lower drug concentr-
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...tions to be used. To achieve an equivalent duration of anaesthesia to the standard eyedrop a still lower NODS dose than the minimum used in the present study would be required. However, should more prolonged anaesthesia be necessary then the NODS vehicle could be used to produce extended periods of anaesthesia from a single instillation.

With three NODS units complete anaesthesia was not achieved. The most likely explanation is that the PVA membrane was blinked out of the conjunctival sac soon after instillation. This is strengthened by the observation, in one individual, of the incompletely dissolved membrane on the lower eyelid margin. It is therefore important to be aware of this possibility when using NODS.

Although NODS would reduce the likelihood of a systemic adverse reaction, it is possible that by maintaining a higher tear film concentration of the drug the vehicle could increase the risk of an ocular adverse response. Although few ocular or systemic reactions to proxymetacaine have been reported, subclinical reactions have been shown to occur. A significant increase in corneal epithelial cell sloughing occurs for 6 hours after a single instillation of 0.5% proxymetacaine drops, and morphological changes in corneal epithelial cells were observed after using the drug in ointment form.

In conclusion, NODS is an effective vehicle for proxymetacaine. The vehicle has several advantages over the available eye drop formulations. It is a preservative free, single dose system which has been demonstrated to give improved bioavailability. However, NODS may possibly increase the risk of an ocular adverse reaction.

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5 Barnard NAS. The aesthesiometer as a slit lamp biomicroscope attachment. Optometry Today 1991; May: 12-3.