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

J G Lawrenson, D F Edgar, A C Gudgeon, J M Burns, M Geraint, N A S Barnard

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 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.

The topical application of ophthalmic drugs is most common in the form of aqueous drops. These have the disadvantage of a short corneal contact time, resulting in only a small amount of the drug passing into the eye. The majority is quickly removed via the nasolacrimal duct, with subsequent systemic absorption.

A novel ophthalmic drug delivery system (NODS, Smith and Nephew Pharmaceuticals Ltd) has been developed which delivers a precise amount of drug to the eye. The drug is incorporated into a soluble polyvinyl alcohol (PVA) flag. This is attached to a water soluble handle film via a thin soluble membrane (Fig 1). When this unit is placed in the lower fornix the segment containing the drug detaches from the carrier and gradually dissolves, releasing the drug. This delivery system produces a longer corneal contact time, resulting in greater bioavailability compared with conventional eye drops.

Other advantages include ease of sterilisation, no requirement for preservatives, and excellent long term drug stability.

This study examined the efficacy of different concentrations of proxymetacaine (proparacaine) NODS in producing and maintaining corneal anaesthesia, compared with the same drug as conventional eye drops. Corneal touch sensitivity was measured using a Cochet-Bonnet aesthesiometer, which has become the standard instrument for both clinical practice and research. Using this instrument touch thresholds have been shown to vary with age, corneal eccentricity, time of day, menstrual cycle, and contact lens wear. In an effort to minimise the variability associated with these factors the same paracentral corneal location was used for all subjects, who were all young males, none of whom were contact lens wearers.

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 of subjects viewing system of the slit-lamp, approached the cornea both smoothly and perpendicularly. Corneal contact was detected by the smallest visible bending of the nylon. The filament length was reduced from its maximum in 0.5 cm steps until the subject responded that the stimulus had been felt. The corneal touch threshold was taken as the maximum length of nylon which gave a 50% positive response from at least four applications. A number of 'dummy runs', in which the filament did not make contact were included to test subject reliability.

The four proxymetacaine preparations investigated were 35 μl of 0.5% eye drops (175 μg) (Ophthalmic, E R Squibb and Sons Ltd.), and three NODS doses (44, 74, and 124 μg) (Smith and Nephew Pharmaceuticals Ltd). Each subject attended on two occasions, separated by at least 7 days. On each visit each eye received one of the four preparations, randomised according to a 4×4 latin square design. To take account of the diurnal variation in corneal touch sensitivity both visits were at the same time of day.

On each visit the baseline sensitivity of the same paracentral corneal location was recorded. Following the instillation of a masked NODS dose or 35 μl of 0.5% proxymetacaine (delivered from a micropipette), sensitivity was measured with either the 0.08 or 0.12 mm diameter filament, as necessary, at 1, 2, 5, 10, 15, 20, 30, 45, and 60 minutes, and every 15 minutes thereafter until the touch sensitivity was restored to its baseline value. The procedure was then repeated for the second eye.

Corneal integrity was checked using the slit-lamp biomicroscope at the end of each session, and at a follow up appointment the next day.

Statistical analysis
In analysing the data the proportion of subjects achieving total anaesthesia for each NODS was compared with the proportion for the eyedrop (positive control) at each time point using McNemar’s test.

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 concentra-

Table 1 Results of McNemar’s test. The test compared the proportion of subjects achieving total anaesthesia for the eyedrop with the proportion for NODS at time intervals following drug instillation. The confidence limits refer to the difference between proportions.

<table>
<thead>
<tr>
<th>Minutes</th>
<th>Comparison</th>
<th>NODS (proportion)</th>
<th>Eyedrop (proportion)</th>
<th>Difference in proportions</th>
<th>Confidence limits</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>Eyedrop v 74 μg NODS</td>
<td>1-00 0.79</td>
<td>0.21 0.06 to 0.37</td>
<td>0.04</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Eyedrop v 124 μg NODS</td>
<td>0.96 0.32</td>
<td>0.64 0.47 to 0.82</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Eyedrop v 44 μg NODS</td>
<td>0.88 0.32</td>
<td>0.36 0.13 to 0.58</td>
<td>0.02</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Eyedrop v 74 μg NODS</td>
<td>0.93 0.32</td>
<td>0.61 0.43 to 0.79</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Eyedrop v 124 μg NODS</td>
<td>0.89 0.44</td>
<td>0.86 0.75 to 0.99</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Eyedrop v 44 μg NODS</td>
<td>0.92 0.32</td>
<td>0.28 0.12 to 0.45</td>
<td>0.01</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Eyedrop v 74 μg NODS</td>
<td>0.95 0.54</td>
<td>0.71 0.55 to 0.88</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td>30</td>
<td>Eyedrop v 124 μg NODS</td>
<td>0.96 0.90</td>
<td>0.25 0.09 to 0.41</td>
<td>0.02</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Eyedrop v 74 μg NODS</td>
<td>0.21 0.02</td>
<td>0.21 0.06 to 0.37</td>
<td>0.04</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>
A comparison of the efficacy and duration of action of proxymetacaine applied using NODS or eye drops

Efficacy and duration of anaesthesia

A comparison of the efficacy and 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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