SURFACE ANAESTHETIC PROPERTIES OF THE NEW LOCAL ANAESTHETIC AMIDE ETIDOCaine (DURAnEST): 

A laboratory evaluation

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SUMMARY

The surface local anaesthetic properties of the new local anaesthetic amide etidocaine (Duranest) were studied in experimental animals. Etidocaine produced topical local anaesthesia of high intensity, rapid onset and with a comparatively long duration of action following corneal, intranasal and intratracheal application. The surface anaesthetic activity of etidocaine was substantially greater than that of lignocaine, similar to that of bupivacaine but less than that of amethocaine. When applied to the mucous surfaces of the nose and the respiratory tract, etidocaine was less toxic than amethocaine and bupivacaine but more toxic than lignocaine. The data justify a clinical evaluation of etidocaine as a surface anaesthetic.

Etidocaine (Duranest) is a new local anaesthetic amide, which seems to combine favourable properties such as rapidity of onset, a high incidence of satisfactory anaesthesia and a long duration of action in peripheral nerve blocks and extradural anaesthesia (Adams, Kronberg and Takman, 1972; Lund, Cwik and Pagdanganan, 1973; Bridenbaugh et al., 1973). Studies in animals (Adams, Kronberg and Takman, 1972) and man (Scott, Jebson and Boyes, 1973) suggest that the toxicity of etidocaine is intermediate to that of lignocaine and the long-acting local anaesthetic agents bupivacaine and amethocaine. As far as we know, there are no reports of studies of etidocaine as a topical local anaesthetic agent. The present study in experimental animals was undertaken to elucidate the surface local anaesthetic properties of etidocaine and to compare these with those of amethocaine, bupivacaine and lignocaine. Methods were used which made it possible to evaluate both the relative anaesthetic potency of the new compound and its safety following administration to different mucous surfaces. A new technique was developed for a more detailed study on the effects of the application of etidocaine to the respiratory tract, there being a need for an agent that has a better therapeutic ratio than a drug such as amethocaine, since toxic effects are common (Adriani and Campbell, 1956; Axelsson, 1960) because of the rapid absorption of local anaesthetic agents from this site of application.

MATERIAL AND METHODS

Corneal anaesthesia was studied in rabbits (New Zealand White, 1.8–3.0 kg) by the application of 0.25 ml of the solutions to the conjunctival sac for 0.5 min. Frequency, latency period and duration of block of the corneal reflex to pin-pricking were recorded.

The topical anaesthetic effect of the different compounds on the nasal mucosa was studied in the rabbit according to the method of Nieschultz, Hoffman and Popendiker (1958). One-half ml of the test solution was applied to one nostril by a polyethylene catheter with an occluded tip and multiple side perforations. A small brush was introduced into the nostril at regular intervals after the application, and the block of the sneeze reflex was recorded.

A new technique (Åkerman and Håegerstam, unpublished) using guineapigs (Dunkin-Hartley, 260–350 g), was developed for the assessment of surface anaesthesia of the respiratory tract. The animals were anaesthetized with 0.6 ml of 1.0% pentobarbitone sodium (Mebumalum NFN) given into the peritoneum. An incision was made between two tracheal rings through which a specially designed polyethylene catheter was inserted about 2 cm into the trachea and fixed. After recovery from the operation the cough reflex was provoked by inserting a plastic tube, sealed and perforated at the end, through the fixed catheter and moving the tube up and down in the...
trachea. A 0.05-ml volume of the test solution was applied through a syringe attached to the tube. Absence of the cough reflex upon repeated mechanical stimulation was taken as a criterion for block.

For determination of blood concentrations, 0.05 ml of lignocaine 2.0%, etidocaine and bupivacaine respectively was administered as described above to guineapigs under pentobarbitone anaesthesia. Samples of arterial blood were withdrawn from the carotid artery at regular intervals after the administration. The blood concentrations of lignocaine were determined by gas chromatography according to the technique of Svinhufvud, Örtengren and Jakobsson (1965). Gas chromatographic analysis of bupivacaine and etidocaine was performed by the method of Örtengren (unpublished)*.

The compounds used were etidocaine (Duranest), bupivacaine (Marcaine), lignocaine (Xylocaine) and amethocaine. All agents were used as the hydrochlorides supplied by Astra Läkemedel AB, Sweden. The compounds were dissolved in saline 0.85%. The pH of the solutions was 6.0–7.0 in all tests except for the very high concentrations used in the toxicity trial, in which the pH was less (4.0–6.0).

The Wilcoxon rank test (Snedecor and Cochran, 1967) was used to determine values of statistical significance. Values of P less than or equal to 0.05 were considered as statistically significant differences.

RESULTS

**Corneal application.** As indicated by the minimum concentrations required for complete block of the corneal reflex to pin-pricking, the local anaesthetic activity increased in the following order: lignocaine, etidocaine, bupivacaine and amethocaine (fig. 1). The blocks produced by etidocaine were of longer duration (P<0.01) than those obtained with lignocaine in equal dosage, and not different from those with bupivacaine except at 0.5% (0.05>P>0.01). The blocks produced by amethocaine had durations which were longer than those of both etidocaine (P<0.01) and bupivacaine (P<0.05). The time of onset of the block was rapid, and differences between the compounds were not observed at concentrations giving complete anaesthesia. There were no indications of tissue damage or acute toxicity with any of the compounds in the concentrations used.

**Intranasal application.** Minimum concentrations for complete block of the sneeze reflex upon application to the nasal mucosa of the rabbit were less for amethocaine and etidocaine (0.125%) than for bupivacaine (0.25%) and lignocaine (0.5%). Figure 2 shows that etidocaine, amethocaine and bupivacaine had a virtually identical duration of action at the various concentrations tested. Toxic effects (ataxia or convulsions) were observed in some of the animals which were given 1.0% amethocaine and bupivacaine, but not in those which had been given 1.0% and 2.0% etidocaine and lignocaine. Etidocaine had a longer action (P<0.01) than lignocaine at 1.0% and 2.0%.

**Intratracheal application.** Etidocaine and bupivacaine were equally effective and more potent than lignocaine but less potent than amethocaine following application of 0.05 ml of the test solutions to the tracheobronchial mucosa of the guineapig (fig. 3). Ataxia or loss of the righting reflex, or both, were observed in animals given 1.0% amethocaine, 2.0% bupivacaine and 10.0% lignocaine. One animal had a convulsion after 1.0% amethocaine and 2.0% bupivacaine. Etidocaine 2% did not cause any toxic signs and produced blocks that were longer (P<0.01) in application to the nasal mucosa of the rabbit were less for amethocaine and etidocaine (0.125%) than for bupivacaine (0.25%) and lignocaine (0.5%). Figure 2 shows that etidocaine, amethocaine and bupivacaine had a virtually identical duration of action at the various concentrations tested. Toxic effects (ataxia or convulsions) were observed in some of the animals which were given 1.0% amethocaine and bupivacaine, but not in those which had been given 1.0% and 2.0% etidocaine and lignocaine. Etidocaine had a longer action (P<0.01) than lignocaine at 1.0% and 2.0%.

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* Information on application to author.
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duration than those produced by the other com-
ponents at concentrations with which there were no
over systemic effects. The acute toxicity by the
intratracheal route was studied further by the appli-
cation of high concentrations of the compounds. The
threshold doses for convulsions or fatalities (table I),
were greater for etidocaine than for amethocaine and
bupivacaine but less than for lignocaine.

Arterial blood concentrations of etidocaine, bupi-
vacaine and lignocaine in anaesthetized animals after
application to the mucosa of the tracheobronchial
tree of a total dose of 1.0 mg are shown in figure 4.

TABLE I. Intratracheal toxicity in the guineapig.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Threshold convulsive dose* (mg/kg)</th>
<th>Threshold lethal dose (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amethocaine</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>3.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Etidocaine</td>
<td>5.2</td>
<td>14.0</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>16.7</td>
<td>36.4</td>
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</tbody>
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*Total doses of 0.25–20 mg were administered to groups of
5–8 animals.

Fig. 2. Block of the sneeze reflex in the rabbit. Mean dura-
tions of block after administration of amethocaine (□),
bupivacaine (●), etidocaine (+) and lignocaine (○) in
0.5 ml (pH 6.0–6.8), n=6. Frequency was 5/6 with 0.125%
bupivacaine and 0.25 % lignocaine. Figures in brackets refer
to frequency of toxic signs (ataxia or convulsions).

Fig. 3. Tracheobronchial anaesthesia in the guineapig.
Mean durations of block of the cough reflex produced after
application of 0.05 ml of the test solutions (pH 6.0–6.8) to
groups of 5–8 animals. Symbols: amethocaine (□), bupiva-
caine (●), etidocaine (+) and lignocaine (○). Frequency of
toxic signs is shown in brackets.

Fig. 4. Mean arterial blood concentrations (bases) of bupi-
vacaine (●), etidocaine (+) and lignocaine (○) after intra-
tracheal administration of 1.0 mg (0.05 ml of 2.0 % solutions,
pH 6.0–6.5) to guineapigs. The number of animals used is
shown in brackets.
Blood concentrations of bupivacaine at all time intervals after administration were higher (P < 0.01) than those of etidocaine and lignocaine. The blood concentrations of etidocaine and lignocaine were practically identical. Peak blood concentrations were obtained as early as a few minutes after the application. The disappearance curves were biphasic. The average half-life values during the initial rapid disappearance were 12 min for bupivacaine, 9 min for etidocaine and 8 min for lignocaine. The corresponding half-life values during the slower phase were 28, 22 and 37 min respectively. It should be noted that, in conscious animals, overt systemic effects were produced by the 1.0-mg dose of bupivacaine but not by the same dose of etidocaine and lignocaine. This implies that a blood concentration of bupivacaine in the region of 4 μg/ml is associated with toxic signs. Peak blood concentrations of etidocaine and lignocaine of about 2 μg/ml produced no overt signs of toxicity.

DISCUSSION

The results of this study have shown that the new local anaesthetic amide etidocaine (Duranest) is capable of producing topical local anaesthesia of high intensity, rapid onset and comparatively long duration of action in experimental animals. The surface anaesthetic activity of etidocaine on some differing sites of application was substantially greater than that of lignocaine, but less than that of amethocaine. Etidocaine and bupivacaine showed approximately the same activity. According to Henn and Brattsand (1966) and Åberg (1970), bupivacaine is a slightly weaker surface anaesthetic than amethocaine.

Because of its high efficiency, amethocaine is frequently employed for surface anaesthesia of mucous membranes. Topical local anaesthesia with amethocaine may, however, be complicated by toxic reactions particularly following application to the respiratory tract for bronchoscopy or bronchography (Adriani and Campbell, 1956; Axelson, 1960). The findings of our study confirm previous observations (Åström and Persson, 1961) that the margin between effective and toxic doses of amethocaine is small when administered to the mucous surfaces of the nose and respiratory tract. Applied intranasally to the rabbit, amethocaine and bupivacaine at 1.0% caused untoward systemic reactions in contrast to the equally effective 1.0% etidocaine solution and the still more effective 2.0% solution of etidocaine. Thus according to this animal data etidocaine may be safer, for use on the nasal mucosa, than amethocaine and bupivacaine, but equally efficacious. This applies also to the intratracheal route of administration, even if there do not seem to be any profound differences among these three drugs. For example, tracheobronchial anaesthesia of the same intensity and duration was obtained with a dose of etidocaine twice that of amethocaine. Threshold convulsive and lethal doses were, however, approximately three and seven times greater, respectively, for etidocaine compared with amethocaine administered by the same route.

The general character of the blood concentration curves of bupivacaine, etidocaine and lignocaine after intratracheal application is indicative of rapid absorption. A similar response, resembling that after intravenous administration, has been observed previously with amethocaine (Adriani and Campbell, 1956; Hansen, 1969). Scott, Jebson and Boyes (1973) found that etidocaine gave significantly lower plasma concentrations than bupivacaine upon i.v. administration in man. The same difference was observed in our study. Thus, peak blood bupivacaine concentrations were significantly greater than those of etidocaine (and lignocaine), and bupivacaine disappeared more slowly from the blood after these drugs were administered to the respiratory tract in equal doses. Scott, Jebson and Boyes (1973) suggested differing distribution into peripheral tissues as one possible reason for this difference between the local anaesthetic agents. It is also possible that differing redistribution may be of significance for the toxicity of the compounds. According to Boyes (1973), etidocaine produced the lowest concentration in the brain after equal subcutaneous doses of lignocaine, etidocaine and bupivacaine to guineapigs.

Great caution should always be used in predicting effects in human subjects from experimental results in animals. Nevertheless, the present findings in laboratory animals indicate that etidocaine can be classified as a local anaesthetic agent resembling amethocaine rather than lignocaine with regard to surface anaesthetic properties on mucous membranes. In animals, etidocaine was found to have a more favourable "therapeutic ratio" than amethocaine following surface application. This advantage may not be so apparent in the clinical situation in view of the fact that the systemic hydrolysis of amethocaine appears to be relatively fast in man (Moore et al., 1972). Furthermore, the incidence of fatalities and toxicity with amethocaine reported by Adriani and Campbell (1956) was directly related to gross overdosage by inexperienced personnel. The consequences of using doses in excess of the recommended range might,
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however, prove to be less severe with etidocaine than with amethocaine. Whether etidocaine combines good surface anaesthetic properties with satisfactory tolerance in man can be proved only by further experimentation which the present data justify clearly.

REFERENCES


PROPRIETES ANESTHESIQUES TENSOACTIVES DU NOUVEL AGENT ANESTHESIQUE LOCAL AMIDE ETIDOCAINE (DURANEST):

Estimation de laboratoire

RESUME

On a étudié sur des animaux de laboratoire les propriétés anesthésiques tensionactives du nouvel agent anesthésique local: l'amide etidocaine (Duranest). L'étidocaine a produit une anesthésie locale de haute intensité, un commencement rapide et un effet de durée comparativement longue, lors de son application sur la cornée, de l'application intranasale ou de l'application intratrachéale. L'activité anesthésique en surface de l'étidocaine a été plus forte que celle de la lignocaine, sensiblement la même que celle de la bupiva¬caine, mais appréciablement moindre que celle de l'amétho¬caine. Appliquée sur les surfaces muqueuses du nez et dans les voies respiratoires, l'étidocaine a été moins toxique que l'améthocaine et la bupivacaine, mais plus toxique que la lignocaine. Ces données justifient une évaluation clinique de l'étidocaine en tant qu'agent anesthésique tensioactif.

OBERFLÄCHEN-ANÄSTHESIEEIGENSCHAFTEN DES NEUEN LOKALANÄSTHESIEMITTLS AMID ETIDOCAINE (DURANEST):

Eine laboratoriumsstudie

ZUSAMMENFASSUNG


PROPIEDADES ANESTESICAS SUPERFICIALES DEL NUEVO ANESTESICO LOCAL DE AMIDA ETIDOCAINA (DURANEST):

Una evaluacion en laboratorio

SUMARIO

Se estudiaron en animales experimentales las propiedades anestésicas locales de superficie del nuevo anestésico local amida etidocaina (Duranest). La Etidocaina produjo una anestesia local de gran intensidad un efecto rápido y una duración relativamente larga de la acción después de su aplicación en la cornea, por vía intranasal e intratracheal. La actividad anestésica superficial de la etidocaina fue bastante mayor que la de la lignocaina, semejante a la de la bupivacaina pero algo más baja que la de la ametocaina. Aplicada a las superficies mucosas de la nariz y el conducto respiratorio, la etidocaina era menos tóxica que la ametoca¬ina y la bupivacaina, pero más tóxica que la lignocaina. Los datos justifican una evaluación clínica de la etidocaina como anestésico superficial.