NEW ANAESTHETIC FORMULATION FOR EPICUTANEOUS APPLICATION TESTED FOR CUTTING SPLIT SKIN GRAFTS

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SUMMARY

Ane-Pad (A 2358, Astra Läkemedel AB), a new local anaesthetic formulation for application to the skin has been tested in the removal of split skin grafts. Ane-Pad is a thin cotton pad, containing a solution of 10% ketocaine base in a solvent mixture of isopropanol, glycerol and water. The pad has been used on the donor sites of 173 patients with a minimum application time of 1 h before surgery. Eighteen patients complained of slight, transient irritation immediately after application. After removal of the pad erythema was present in 39 patients and oedema in eight. In 157 patients (90.8%) analgesia was adequate. Two patients (1.1%) needed additional anaesthesia. The concentration of ketocaine in the blood was measured in 101 patients and did not exceed 850 ng ml⁻¹. There were no systemic side-effects.

The cutting of split skin grafts in plastic surgery is often the most painful part of the operation, especially when the recipient site does not require excision or suturing.

It has been difficult to achieve anaesthesia of intact skin by epicutaneous application as the skin offers an almost complete barrier to diffusion. Aprotic solvents, such as dimethyl sulfoxide (DMSO) might be a suitable enhancer for a local anaesthetic drug but it is liable to produce undesirable effects (Kligman, 1965; Brechner, Cohen and Pretsky, 1967; Rubin, 1975). Monash (1957) described the use of alcoholic solvents for topical anaesthesia and in 1971, Adriani and Dalili showed that the available local anaesthetics tested did not penetrate sufficiently to produce anaesthesia after topical application on unbroken skin. Although some of the formulations tested by these authors were effective for a short time or under certain conditions (Dalili and Adriani, 1971), they were not effective enough to warrant clinical testing.

A mixture of isopropanol, glycerol and water in proportions which achieve a saturated solution has, in animal experiments, been found to be as effective as aprotic solvent mixtures (Åkerman, 1978). Epicutaneous application of certain compositions containing ketocaine produced very effective anaesthesia (Åkerman, 1978). Ketocaine (fig. 1) is a potent local anaesthetic agent, being particularly active with regard to surface anaesthesia and after infiltration (Piccolo, 1964; Appiani and Laveneziana, 1966).

Ketocaine (Recordati, S.P.A., Milan, Italy) is very lipid-soluble, the partition coefficient between cod liver oil and water being approximately 8000 for ketocaine as compared with about 36 for lignocaine (Åkerman, in preparation). A second property that may facilitate the uptake of ketocaine is the absence of labile protons.

Pettersson (1975) obtained promising results with a ketocaine solution in patients undergoing skin grafting. These results stimulated us to study a new formulation combining ketocaine with isopropanol, glycerol and water called A 2337, and a clinical trial in 86 patients was reported by Pontén and Öhlsén in 1977. The analgesia produced by the topical application of A 2337 was very satisfactory for cutting split skin grafts and the simple technique seemed to be of great value. The present study of a larger number of patients was performed using the formulation called A 2358 containing ketocaine (base) 0.100 g ml⁻¹, isopropanol 0.450, glycerol 0.120, water 0.250 and acetic acid 0.001 g ml⁻¹. This is the same composition as A 2337 with the small amount of acetic acid added.

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as an antioxidant. The proportions are such as to yield a saturated solution of ketocaine. All the solvent ingredients are necessary for efficacy as a surface anaesthetic, the relative proportions giving the best result of an interaction between the base and the solvent whereby the diffusion rate of the compound increases.

METHODS

A 2358 (Ane-Pad) has been tested on 173 patients, 115 men and 58 women. Their ages ranged from 14 to 86 yr (average 50.4 yr). Patients known to be pregnant were excluded.

The patients were classified with respect to the anaesthetic risk using the A.S.A. classification of physical status. Thirty-two patients (18.5%) were in group I and 79 (45.7%) in group II. Fifty-five (31.8%) were in group III and seven (4.0%) in group IV (fig. 2).

Twenty-six patients had a history of allergic reactions, but not to local anaesthetic drugs. Premedication was used in 119 patients (68.8%); 111 received diazepam 5–10 mg orally and five were given diazepam with pentazocine. One patient received diazepam and pethidine. Another received promethazine and pethidine, and one was given morphine and hyoscine.

Ane-Pad consists of 90% cotton wool and 10% viscous cellulose compressed to a felt-like consistency. The pad measures 10.5 x 12 cm, contains 5.3 ml of the sterile anaesthetic solution and is enclosed in heat-sealed aluminium foil (fig. 3). At room temperature the pad can be stored in the unbroken foil for 2 years without losing its pharmacological properties. After removal from the foil the pad was used immediately to avoid drying.

The selected donor site was shaved and cleaned on the day before operation. Early in the morning the pad or pads were applied directly to the donor site. The pads were covered with an occlusive sheet taped to the skin and slight compression was obtained by an elastic bandage.

In 81 patients (46.8%) one pad was used, in 66 (38.2%) two pads; three to four pads in 21 patients (12.1%) and five to eight pads in five patients (2.9%).

The skin grafts were taken with a Brown dermatome or a knife and no technical problems were encountered. There was no obvious difference in bleeding or in the healing time of the donor site compared with skin grafts taken under general or local anaesthesia. The thickness of the grafts was preset on the dermatome to thinner than 0.43 mm (24 patients), 0.43–0.51 mm (139 patients) and 0.53–0.58 (five patients), while a hand-knife was used in five patients.

The area of the grafts varied. In 104 patients the area was less than 50 cm² but in the rest grafts up to and greater than 500 cm² were taken.

The most frequently used donor site was the thigh (131 patients). The leg was used in four patients, the hip in two, the upper arm in 26 and the forearm in 11 patients.

Fig. 2. Age and risk groups. In each age group, patients are divided into two subgroups: risk groups I-II (open) and risk groups III-IV (hatched).

Fig. 3. The pad soaked in the anaesthetic compound is enclosed in foil.
Since the pads were not removed until the patient was prepared for surgery the duration of the application varied considerably, ranging from less than 1 h to 10 h. The mean duration was 3 h 5 min.

Arterial pressure and heart rate were measured before the pad was applied and when the pad was removed for operation. In the five patients to whom a large number of pads were applied, the e.cg. was examined hourly after the application until 3 h after the operation.

In 101 patients, venous blood samples were taken immediately after removal of the pads and 3 h later. The concentration of ketocaine was determined by means of gas chromatography and mass fragmentography (Berlin-Wahlen et al., 1977) at the Department of Analytical Chemistry, Astra Läkemedel AB, Södertälje, Sweden.

**RESULTS**

The pads rarely caused irritation. Only 18 patients (11.4%) stated that the pads caused a slight, transient, local irritation or a burning pain immediately after application. In a few cases this pain was quite intense but always of short duration—sometimes only a few seconds and never more than a minute. This seemed to occur when the skin was not completely intact, in the presence of a small wound after shaving. This minor discomfort, however, was never a problem and no patient requested the removal of the bandage.

When the bandage was removed erythema or oedema, or both, was often visible in the application area. In 39 patients (22.5%) erythema was moderate to pronounced (table I) and in eight patients (4.7%) there was moderate to pronounced oedema. Using the $\chi^2$ test there was a significant association ($P<0.001$) between the degree of erythema and the duration of application. Oedema, however, was not related to the application time. There appeared to be a relationship between the degree of erythema and the anaesthetic effect, although this could not be verified statistically.

When the skin graft was cut, 114 patients (65.9%) experienced no pain and only felt the pressure of the dermatome. Forty-three patients (24.9%) experienced some pain, but they did not object when the skin graft was cut, only mentioning the slight discomfort afterwards. In 13 patients (7.5%) the pain was described as moderate, but the operation could be completed without any further local or general anaesthesia. One patient (0.6%) described the pain as severe, but allowed the skin graft to be cut without additional anaesthesia. In two patients (1.1%) anaesthesia was supplemented by a local anaesthetic drug.

In one of these two patients the pad had been applied for only 35 min—insufficient to produce adequate anaesthesia. Thus it was possible to perform the planned operation in 98.9% of patients and in 90.8% the applied ketocaine formulation provided completely satisfactory surface anaesthesia. The local anaesthetic effect could be related to neither duration nor premedication.

The blood concentration of ketocaine (table II) increased with the number of pads applied and also with the duration of application. This increase was observed for 5 h and then a decrease occurred even in the presence of the pads, probably because of metabolism or alteration of the anaesthetic formulation. Three hours after removal of the pads the blood concentration of ketocaine had decreased.

None of the 173 patients found Ane-Pad disagreeable and no allergic reactions were noticed. No patient reported anything which could be interpreted as a toxic effect. No clinically significant change in arterial pressure or heart rate was detected.

<table>
<thead>
<tr>
<th>Pad</th>
<th>1-2 (n = 9)</th>
<th>2-3 (n = 39)</th>
<th>3-4 (n = 17)</th>
<th>4-5 (n = 8)</th>
<th>5-6 (n = 9)</th>
<th>6-7 (n = 1)</th>
<th>9-10 (n = 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 (n = 1)</td>
<td>506 (844)</td>
<td>106.0 (136.5)</td>
<td>539 (331)</td>
<td>232.5 (93.0)</td>
<td>250.0 (106.5)</td>
<td>207.0 (161.7)</td>
<td>239.2 (111.2)</td>
</tr>
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serial e.g. recorded in five patients did not show any adverse changes.

DISCUSSION

The results of the present study indicate that after cutaneous application of Ane-Pad the nerve endings are sufficiently blocked to permit the removal of split skin grafts. The average thickness of a split skin graft includes at least 50-75% of the thickness of the skin. In animal experiments (Åkerman, 1978) the distribution of \(^{3}\)H-labelled ketocaine in the skin was studied after application of A 2358. Radioactivity was detected at all levels of the skin with large concentrations in the stratum corneum and rapidly decreasing activity in the deeper underlying tissue.

It should be pointed out that Ane-Pad causes analgesia rather than the elimination of all sensory modalities. The cutaneous application of the ketocaine formulation gives rise to a loss of, or a decrease in, the perception of normally painful stimuli and a suppressed excitability of cutaneous C receptors (L. Juhlin, personal communication; Hallin, 1974). We have observed that the pressure of the dermatome was always felt, but that sensitivity to touch was distinctly reduced. However, touching and moving a hair in the area treated with Ane-Pad was felt very distinctly, presumably because the hair follicles penetrate to a dermal depth not reached by the anaesthetic. When testing for analgesia by pinprick, the pressure of the pin could be appreciated, but not pain. Sensitivity to cold was either unchanged or reduced, but sensitivity to warmth was increased. A luke-warm water wash of the test area was described as a very unpleasant experience.

The duration of application is of importance, at least 1 h being necessary to obtain adequate analgesia. The duration of analgesia was several hours and our patients complained much less of pain from the donor site immediately after operation and requested less analgesic than patients who had received general anaesthesia. We have noticed that occasionally the effect can last for 24 h or even more. After the application of A 2358 containing \(^{3}\)H-labelled ketocaine to animals (Åkerman, 1978), the half-life of the radioactivity in the skin was found to be 5-5.5 h while 10-15% of the activity remained in the tissue after 1 day.

The maximum blood concentration of ketocaine was 844 ng ml\(^{-1}\) after the application of six pads. This should be compared with the blood concentrations of 1.01-2.59 μg ml\(^{-1}\) noted 0.5 h after brachial plexus block with ketocaine hydrochloride 300 mg in 10 patients (Berlin-Wåhlin et al., 1977). As absorption is small after epicutaneous application, this technique appears to be free from toxicological effects. Our patients suffered no systemic side-effects after application of Ane-Pad.

In most patients there was some local erythema and slight oedema in about 50%. The degree of erythema increased with the duration of application and reached a maximum after 3 h. The erythema or oedema were, however, an advantage to the surgeon as they depicted the anaesthetic area. Both erythema and oedema disappeared more rapidly than the anaesthetic effect.

Usually, the skin on a donor site recovers very slowly. Full stability and thickness is not achieved for several months. We have observed that if Ane-Pad is applied during this time it will cause local irritation and even blister formation.

In a previous clinical study in our hospital (Pontén and Ohlsén, 1977) A 2337 was studied in 86 similar patients. The addition of acetic acid as antioxidant did not adversely influence the efficacy of Ane-Pad. Therefore, we have now studied a total of 259 patients. This new technique is a simple, time-saving and effective form of anaesthesia. The absence of systemic side-effects is of special advantage in old or seriously ill patients.

REFERENCES


**NEW ANAESTHETIC FORMULATION FOR CUTTING SPLIT SKIN GRAGTS**


NOUVELLE FORMULATION D'ANESTHESIQUE POUR APPLICATION EPICUTANEE ESSAYEE POUR LA COUPE DE GREFFES EPIDERMİQUES

**RESUME**

Une nouvelle formulation d'agent d'anesthésie locale: Ane-Pad (A 2358, Astra Lakemedel AB) pour application sur la peau a été essayée lors du prélèvement de greffes épidermiques. Ane-Pad est un mince tampon de coton, contenant une solution de ketocaine à 10% dans un mélange solvant d'isopropanol, de glycerol et d'eau. Le tampon a été utilisé sur le lieu du prélèvement de 173 patients, avec un temps d'application minimum d'une heure avant l'intervention. Dix-huit patients se sont plaints d'une irritation légère et transitoire immédiatement après l'application. Après retrait du tampon, on a constaté de l'irritabilité sur 39 patients et un œdème sur huit autres. Sur 157 patients (90,8%), l'analgesie a été adéquate. Deux patients (1,1%) ont dû recevoir un complément d'anesthésie. La concentration de ketocaine dans le sang a été mesurée sur 101 personnes et elle n'a pas dépassé 0,850 ng ml⁻¹. Il n'y a eu aucun effet secondaire systémique.

**FORMULACION ANESTETICA NUEVA PARA APLICACION EPICUTANEA COMPROBADA PARA EL CORTE DE INJERTOS PARTIDOS DE PIEL**

**SUMARIO**

Se hicieron ensayos con Ane-Pad (A 2358, Astra Lakemedel AB), una nueva fórmula de anestesia local para su aplicación en la piel respecto de la remoción de injertos partidos de piel. Ane-Pad consiste en un tampón de algodón delgado que contiene una solución de ketocaina base al 10% en una mezcla solvente de isopropanol, de glicerol y de agua. Se usó este tampaón en los lugares de los donantes en 173 pacientes con un tiempo mínimo de aplicación de 1 h antes de la operación. Diez y ocho pacientes se quejaron de una irritación ligera y pasajera inmediatamente después de la aplicación. Se comprobó, después de la remoción del tampón, que 39 pacientes tenían eritema e hipovaloración de 101 pacientes y este no superaba de 850 ng ml⁻¹. No hubo efectos colaterales sistémicos.