Many attempts have been made to provide analgesia of the skin, since venepuncture often causes pain and increases anxiety, in adults as well as in children. Preparations containing lignocaine (Monash, 1957; Lubens et al., 1974), benzocaine (Dalili and Adriani, 1971), combinations of local anaesthetics with dimethylsulphoxide (DMSO) (Kligman, 1965; Brechner, Cohen and Pretsky, 1967) and ketocaine in alcoholic solutions (Pettersson, 1978) have been tried. Physical methods such as iontophoresis have been applied to improve penetration through the intact skin (Rapperport, 1971; Russo et al., 1980). However, no formulation has gained wide acceptance, mainly as a result of inadequate relief of pain, local irritation or toxic reactions.

The objectives of this study were to evaluate the efficacy of EMLA (Eutectic Mixture of Local Anaesthetics) cream in obtunding the pain produced by venepuncture, and to evaluate possible adverse reactions to the preparation. EMLA cream is a preparation containing a mixture of the bases of lignocaine and prilocaine (Juhlin, Evers and Broberg, 1979).

SUBJECTS AND METHODS
Forty volunteers, participating in an occupational health investigation of hospital staff at the Karolinska Hospital, were invited to participate in the present study. Eight venous blood samples were required from each individual, and the effects of EMLA and a placebo were evaluated in connection with the sampling. The volunteers were informed about the aims and the nature of the study via a printed form, in accordance with the Helsinki declaration, and written consent obtained. The investigation was approved by the peer review committee of the hospital and the Swedish National Board of Health and Welfare.

EMLA 5% cream consists of a eutectic mixture of lignocaine base 25 mg ml⁻¹ (107 mmol litre⁻¹) and prilocaine base 25 mg ml⁻¹ (113 mmol litre⁻¹). An emulsifier, a viscosity increasing agent and water form the other constituents. In the placebo cream the anaesthetics were substituted by an inert oil. Both formulations were visually and cosmetically identical.

The study was double-blind, randomized and of cross-over design and, to obtain as much information as possible about EMLA, each volunteer was scheduled to receive five applications of the active formulation and three of placebo.

One hour before the venous blood sampling, a thick layer of cream (about 2 ml) was applied to the skin over a vein in the cubital fossa or, as a second
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choice, on the dorsum of the hand. The cream was covered with Blenderm tape 1523 (3M) or a thin plastic wrap, to form an occlusive dressing. The bandage was removed immediately before venepuncture and the skin inspected for any local reaction. After disinfection with 0.5% chlorhexidine in 70% ethanol, the cannula was inserted.

The degree of pain was marked by each volunteer on a 100-mm visual analogue scale (VAS) with a range from "no pain" to "painful". A new scale was used for each evaluation. Local reactions in the form of oedema, erythema and blanching were recorded on a four-point scale: none, slight, moderate or severe.

The intrasubject differences (mean VAS scores) between EMLA and placebo were tested by the Wilcoxon signed ranks test. For the analysis of differences of application time, the paired t test was used.

RESULTS

Results from 31 volunteers (24 female) (median age 31 yr, range 18–48 yr) were analysed. The median number of EMLA applications per subject was 5 (range 2–5) and for placebo 3 (range 1–3). Nine subjects did not complete the study because of administrative problems such as holidays, sick-leave etc. No subject was excluded from the study because of adverse reactions to the treatment.

Of the 220 applications, 81% were in the cubital fossa, 15% on the dorsum of the hand and 4% on the lower arm. There was no difference between EMLA and placebo in regard to the duration of application. In total, there were 140 applications of EMLA and 80 with placebo. EMLA was superior to placebo in all but three volunteers, in whom both preparations produced similar effects (fig. 1). The individual pain scores after application of placebo cream were scattered over the whole scale, while the majority of scores after EMLA were near the "no pain" end of the scale, indicating a decrease in the pain experienced with the active formulation.

The between subject differences in mean pain score between EMLA and placebo are presented in figure 2. Treatment with EMLA resulted in significantly lower mean pain scores ($t = 4.74, P < 0.001$).

Transient local skin reactions after both EMLA and placebo consisted of blanching, erythema and, in a few patients, oedema at the site of application. The reactions were almost equally distributed between active and placebo treatments (table I) and did not increase in severity with repeated application.

<table>
<thead>
<tr>
<th></th>
<th>EMLA</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Blanching</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>Erythema</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Oedema</td>
<td>4</td>
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DISCUSSION

The present investigation in adult, unpremedicated volunteers confirms the analgesic effect of EMLA cream noted in other studies (Ehrenström-Reiz and Reiz, 1982; Hallén and Uppfeldt, 1982).

In our previous study in children (Hallen and Uppfeldt, 1982), the evaluation of the degree of pain was made, by nurses, on a three-point verbal scale.
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Fig. 2. The relationship between individual mean pain scores with EMLA or placebo. Each dot represents one person. Dots above the broken line show individuals with higher mean pain score with placebo than with EMLA. The thin horizontal and vertical lines represent the median pain score after EMLA and placebo, respectively.

However, even that rather crude method showed a significant difference in favour of EMLA over placebo. In the present study a visual analogue scale was used to provide a more sensitive evaluation of differences in the pain experienced (Ohnhaus and Adler, 1975; Revill et al., 1976; Scott and Huskisson, 1976).

In adults, EMLA cream has been shown to penetrate the intact skin, and it has been used successfully as a topical analgesic for superficial skin procedures. The eutectic mixture of lignocaine and prilocaine was more effective than emulsions of either base alone. In the EMLA emulsion 80% of each droplet consisted of lignocaine and prilocaine, in contrast to only 20% active substance in the single component formulation. This was probably the main reason for the eutectic mixture being the more effective (Juhlin, Evers and Broberg, 1980).

We conclude that EMLA cream decreases substantially the pain produced by routine venous cannulation. Thus, the first experience of an anxious patient in the operating room need not be a painful venepuncture.

ACKNOWLEDGEMENT

The authors thank Mr Olov Stockman for the statistical analyses.