SPREAD OF EXTRADURAL ANALGESIA FOLLOWING CAUDAL INJECTION IN CHILDREN
A statistical study

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SUMMARY
Data on the segmental spread of analgesia from three independent studies of caudal extradural blocks in children with three different local anaesthetic agents were examined with multiple regression techniques to find the effects of age on dose requirements. All three studies confirmed the existence of a linear relationship between the spread of analgesia and age. As there were no significant differences between the three regression lines a common regression line was calculated. This may be used as a guideline for predicting dose requirements in the daily routine of anaesthesia. By injecting a mixture of a radio-opaque substance and 4% lignocaine it was shown by comparison of the radiological spread of the solution and the distribution of clinical analgesia that the latter always exceeded the former by four to six segments. This may indicate the occurrence of diffusion.

In 1969, Bromage published evidence of an age-dependent predictable increase of extradural dose requirement, following the lumbar approach, in children up to the age of 18 yr 6 months. However, his data for children less than 10 yr were few and did not include children younger than 4 yr. We published data on the extradural spread of 1% lignocaine on caudal injection (Schulte-Steinberg and Rahlfs, 1970), corroborating Bromage's findings of an upward slope of the regression line and the predictability of the extradural dose requirement in this age group. Further investigations with 1% mepivacaine and 0.25% bupivacaine in two additional groups (Schulte-Steinberg and Rahlfs, 1972), with techniques of analysis similar to those of the previous studies, showed a similar extradural spread for these solutions also.

Earlier investigations have shown that the dose-response is highly correlated with age and with weight and height also (Schulte-Steinberg and Rahlfs, 1970, 1972). However, age was the best predictor. In the present study, based on our earlier data, the dose-response-age relationship has been studied in detail.

Regression techniques were used to:
(1) Analyse the dose-response-age relationship of the three treatment groups.
(2) Analyse the differences between the three treatment groups.
(3) Develop methods of predicting the dose-response based upon age.

Finally, the results of x-ray studies with combined injection of radio-opaque material and local anaesthetic solutions are presented. The significance of physical spread and the extent of analgesia will be discussed including the factors affecting the flow of solutions in the extradural canal in the child.

METHODS
The extradural spread of analgesia on caudal injection was examined in one group of 52 and two groups of 50 children. The patients were between 0 and 12 yr of age and had no diseases other than that requiring surgery. Each group received one of three local anaesthetic solutions: 1% lignocaine, 1% mepivacaine or 0.25% bupivacaine, all with adrenaline.

As no patient co-operation could be expected in this age group, general anaesthesia was induced by inhalation with halothane, and nitrous oxide in oxygen in a partial rebreathing system. Once the eyelid reflex had disappeared, the patient was turned on his side. The skin over the sacrum was cleansed and the sacral cornua were identified. A 20-gauge needle was inserted through the skin overlying the sacral hiatus. The needle was positioned at an angle of 65–70° to the horizontal, in an upward direction, with the bevel towards the feet. On piercing the sacrococcygeal ligament, there was a characteristic yield until the needle point was arrested by the anterior table of the sacrum (fig. 1). This was taken as a sign that the extradural space had been entered. As distinct from
the technique in adults, the needle was not advanced to the sacral canal; thus puncturing of the dural sac was avoided. A test solution was now injected. The entire procedure lasted not more than 2-3 min. The volume of local anaesthetic solution was estimated at 0.1 ml per dermatome to be blocked per year of age. The doses thus obtained remained below the maximum doses calculated for the child's weight. Once the injection was completed, the child was placed supine and cleansing of the operative area was started without delay.

If there was no alteration in heart rate, breathing or size of pupils following surgical stimulation, or if, having changed, these indices returned to the baseline values, this was taken as indicating a satisfactory level of analgesia. Subsequently, either the initial concentration of halothane was reduced or halothane was discontinued. The level of general anaesthesia was just sufficient to prevent the child from moving.

At the end of the surgical procedure the child's reaction to painful stimuli (pricking with a 20-gauge needle) in unblocked areas allowed the determination of the exact level of analgesia. This pinprick test was performed several times on each side in the presence of two or three observers. If there was not unanimous consent about the level of analgesic dermatomes, the patient was excluded from the series.

For comparison with data of previous authors the dose requirements were expressed as :

\[
\frac{\text{Dose of analgesic solution (ml) injected}}{\text{Number of analgesic dermatomes}}
\]

**Statistical methods**

(a) **Model.** Previous publications have demonstrated that there is a linear relationship between the response and age, and it was assumed that a simple linear first-order model would accommodate the data:

\[
Y = \beta_0 + \beta_1 X + \varepsilon
\]

The least squares method was applied to give estimates \(b_0\) and \(b_1\) of the parameters \(\beta_0\) and \(\beta_1\), so that:

\[
\hat{y} = b_0 + b_1 X
\]

where \(\hat{y}\) denotes the predicted value of \(Y\) (response) for a given value of \(X\) (age). The parameters \(b_0\) and \(b_1\) may be interpreted as the intercept and slope of a regression line fitted to the data (Draper and Smith, 1966).

(b) **Test.** Methods for testing the hypotheses \(\beta_0 = 0\) and \(\beta_1 = 0\) are given in standard textbooks on statistical methods. Testing the equality of the three treatment groups may be performed, if all groups are combined within a larger linear model. One possible model for testing group differences concerning the three regression lines might be:

\[
E(y) = b + b_1 X_1 + b_2 X_2 + b_3 X_3 + b_4 X_4 + b_5 X_5
\]

where the meaning of the \(X\) is:

\[
X_1 = 1 \text{ if group } 1 \\
= -1 \text{ if group } 3 \\
= 0 \text{ otherwise}
\]

\[
X_2 = 1 \text{ if group } 2 \\
= -1 \text{ if group } 3 \\
= 0 \text{ otherwise}
\]
\[ X_3 = \text{age} \]
\[ X_4 = X_1 \cdot X_3 \]
\[ X_5 = X_2 \cdot X_3 \]

Then a test for parallelism of the three slopes is given by:

\[ H_{01} : b_4 = b_5 = 0 \]

A test for the equality of intercepts is given by:

\[ H_{02} : b_1 = b_2 = 0 \]

If neither hypothesis can be rejected, a simple regression model can be fitted, based on the pooled data from all three treatment groups.

(c) Prediction. A prediction of a particular value for a given age is given by inserting age into the model equation \( \hat{y} = b_0 - b_1X \). Then the \((1 - \alpha)\) confidence interval for these particular values is given as:

\[ \hat{y} \pm t_{n-2} s\sqrt{1 + \alpha' (X'X)^{-1} \alpha} \]

where \( s \) is the square root of \( s^2 \), the estimator of \( \sigma^2 \) (error), \( X \) is the design matrix and \( \alpha \) the given age value.

RESULTS

A simple linear model was fitted to each of the three treatment groups, giving the equations:

- Treatment 1: lignocaine: \( Y = 0.05869 + 0.0070X \)
- Treatment 2: mepivacaine: \( Y = 0.10226 + 0.00699X \)
- Treatment 3: bupivacaine: \( Y = 0.08356 + 0.00758X \)

The regression equations are shown graphically in figures 2, 3 and 4. The empirical data have been plotted too, so that the spread of the data about the line may be inspected and possible divergencies from linearity detected.

Figure 5 shows all three regression lines. It can be seen that the lines are virtually identical. Indeed, the test for parallelism results in \( F_{2, 146} = 1.5323 \) corresponding to \( P = 0.2178 \); the test for equality results in \( F_{2, 146} = 0.9515 \) and is not significant (table I).

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Sum of squares</th>
<th>d.f.</th>
<th>Mean squares</th>
<th>( F )</th>
</tr>
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<tr>
<td>Intercept differences</td>
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<td>2</td>
<td>0.0088</td>
<td>0.9515</td>
</tr>
<tr>
<td>Age</td>
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<td>1</td>
<td>9.0582</td>
<td>984.3740*</td>
</tr>
<tr>
<td>Parallelism</td>
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<td>2</td>
<td>0.0141</td>
<td>1.5323</td>
</tr>
<tr>
<td>Residual</td>
<td>1.3435</td>
<td>146</td>
<td>0.0092</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>11.3959</td>
<td>151</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* \( P \leq 0.001 \).

Adequacy of the model

The adequacy of the model was tested by a probability plot of the residuals \((y - \hat{y})\). Only at the higher age classes was there some disturbance of the regular pattern, a fact which may be detected also in the straight lines plots with the individual data. However, this irregularity is not crucial for the model and the tests performed.

In addition, the variance in the different age classes was calculated. The variance increased gradually until
Fig. 3. Segmental dose requirements related to age for 1% mepivacaine.

Fig. 4. Segmental dose requirements related to age for 0.25% bupivacaine.

the age of 4 yr. Thereafter the number of patients was too small to allow valid conclusions. However, the difference between the variances was not too great to prevent model building and testing.

As there are no differences between the treatment groups, a general model may be calculated which is given as:

\[ y = 0.0764 + 0.00762X_1 \]

where \( X_1 \) is the age expressed in months. The multiple \( R^2 \), which gives the proportion of variance of \( y \), which is explained by the predictor variable, is 0.879; this is an unusually high value for biomedical research (1.00 is the maximum). The regression equation is plotted in figure 6. The interrupted lines give the 95% confidence limits for a particular observation. It may be seen that these limits are large, in spite of good predictability (\( R^2 = 0.879 \)). It should be noted that the limits for an expected value of \( y \), which are usually given in experimental research, are much narrower. However, the purpose of this plot is to give a prediction for a future single patient.

**DISCUSSION**

Three independent studies with three different local
anaesthetic agents all confirmed the existence of a linear relationship between spread of analgesia and age. This relationship could be established with high precision with a coefficient of determination $R^2 = 0.88$. As there were no statistically significant differences between the regression lines of the three studies, a common regression line was calculated. This may be used as a guide-line for predicting dose requirements. It is interesting to note that there is good agreement with the results presented by Bromage (1969) for the age groups greater than 4 yr. The present study shows that the same linear relationship applies to very young (0–4 yr) children also. The agreement with Bromage's findings is surprising since he used the lumbar approach as opposed to the caudal approach employed by us. Incidentally, an
equal spread of analgesia on both sides of the body was observed in all our patients.

For practical purposes it should be pointed out that the regression line reflects only the expected or mean response. To allow a margin of safety the anaesthetist should add 0.1 ml per spinal dermatome to the volume taken from the regression line.

The tendency towards increasing variation of the few data points for the age 6–7 yr may indicate the start of transformation of the juvenile extradural fat (Tretjakoff, 1926) into the firmly packed adult type of fat which offers more resistance to a regular spread. At the same time, widely patent intervertebral foramina allow more of the injected solution to escape from the neural canal as can be seen from the post-mortem study of a 24-h-old baby (figure 7).

In an attempt to find out whether physical spread of injected solutions and the distribution of analgesia would correspond, 4% lignocaine and the watersoluble radio-opaque substance iothalamic acid 60 (Conray 60, Byk-Gulden Pharmazeutika, Konstanz, West Germany) were mixed. Before using this mixture, it was established that it would stay in solution. After 16 h of observation in a test-tube the mixture had not changed. An x-ray of the test-tube showed an even distribution of the contrast medium.

The solution was injected caudally in 10 boys who were undergoing surgery. At the end of the operative procedure the level of analgesia was determined in the usual manner. The gonads were shielded and the level of spread of the solution was determined by x-ray (fig. 8). The difference between physical spread and the level of analgesia obtained can be seen in figure 9. Each pair of data points represents one patient. The level of analgesia exceeded the physical spread of the solution in the neural canal by four to six spinal segments on each occasion.
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It may be argued that the upper limit of the spread cannot be determined accurately by x-ray when a lapse of time until the end of the operation has occurred, since water-soluble substances are eliminated rapidly from the vertebral canal during life. However, in the postmortem study (fig. 7) 2 ml of contrast medium also failed to extend beyond the lumbar region. From our clinical studies we know that this volume of local anaesthetic would have been sufficient to block several thoracic dermatomes in addition. Therefore we believe that the higher level of analgesia could be a result of diffusion, presumably at the dural sleeves, as shown by Bromage (1962), and in the paravertebral region by escape through the intervertebral foramina.

REFERENCES

múltiple para descubrir los efectos que la edad produce sobre las dosis requeridas. Los tres estudios confirmaron la existencia de una relación lineal entre la difusión de analgesia y la edad. Debido a que no existían diferencias significativas entre las tres líneas de regresión, se calculó una línea de regresión común. Esto puede emplearse como guía para predecir las dosis requeridas en la rutina diaria de anestesia.

Mediante la inyección de una mezcla de una sustancia radio-opaca y 4% de lignocaina, se demostró mediante la comparación entre la difusión radiológica de la solución y la distribución de analgesia clínica que éste último siempre excedió al primero por 4–6 segmentos. Esto puede indicar la ocurrencia de difusión.