EFFECTS OF CONCENTRATION OF LOCAL ANAESTHETIC DRUGS IN EXTRADURAL BLOCK

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SUMMARY
An increase in the concentration of bupivacaine from 0.5% to 0.75% and etidocaine from 1.0% to 1.5% for extradural block resulted in a more rapid onset of sensory analgesia and motor blockade, a greater frequency of adequate analgesia, a greater depth of motor block and a longer duration of sensory analgesia and motor blockade. An increase in the concentration of prilocaine from 2% to 3% failed to reveal any significant advantage. The use of the more concentrated solutions of bupivacaine and etidocaine would appear to afford significant clinical advantages in extradural anaesthesia for surgery.

On account of the thickness of the spinal nerves, and their connective tissue covering in the extradural space, high concentrations of local anaesthetic drugs are required frequently if sensory and motor block are to be complete following extradural administration (Galindo et al., 1975). An increase in the concentration of a local anaesthetic drug will, in general, cause a more profound block, with a more rapid onset and increased duration of anaesthesia (Littlewood et al., 1977). However, two factors limit the maximum concentration which can be used in clinical practice. First, a plateau will be reached in effectiveness related to concentration such that further increases in the strength of the solution produce little or no further increase in the degree of conduction blockade (Covino and Vassallo, 1976). Second, increasing the concentration and the dosage will lead ultimately to systemic toxicity and, perhaps, to localized neural damage.

When surgical procedures are to be performed on conscious patients, the degree of nerve blockade should be complete. In the United States, where local anaesthesia tends to be more popular than in Europe, local anaesthetic drugs are used frequently in greater concentrations than are available elsewhere. However, there are few controlled studies to assess the clinical advantages of these more concentrated solutions (Bridenbaugh et al., 1976). In the present study, three local anaesthetic agents for extradural block were compared in a double-blind study: bupivacaine 0.5% and 0.75%, etidocaine 1% and 1.5%, and prilocaine 2% and 3%. Adrenaline 1:200 000 was used with etidocaine, as plain solutions of the 1.5% solution are not available commercially.

PATIENTS AND METHODS
The 60 patients studied were divided into three groups of 20, each group being allocated one of the three test drugs, bupivacaine, etidocaine or prilocaine. Within each group 10 patients received the more concentrated solution and 10 the less concentrated solution. The order of administration of the drugs was randomized and the investigators carrying out the assessment of nerve blockade were unaware of the concentration given.

The 40 patients in the bupivacaine and etidocaine studies were anaesthetized at the University of Massachusetts Medical Center and the 20 receiving prilocaine were anaesthetized at the Royal Infirmary, Edinburgh. Because of minor differences in routine there were small differences between the experimental programme in the two hospitals. In the American series the patients were premedicated with either pethidine 50–75 mg or morphine 5–10 mg and hydroxyzine 50 mg. For the extradural block a volume of solution between 15 and 20 ml was used, the exact amount being that which was thought appropriate by the anaesthetist with regard to the patient's age and condition. The patients were male or female (table I). In the...
**Table 1. Patient characteristics (mean and SEM)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Wt (kg)</th>
<th>Ht (cm)</th>
<th>Volume (ml)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine 0.5%</td>
<td>37.5±6.8</td>
<td>7M</td>
<td>71±35</td>
<td>173±0.25</td>
<td>16.7±0.65</td>
<td>83.5</td>
</tr>
<tr>
<td>Bupivacaine 0.75%</td>
<td>47.1±6.8</td>
<td>7M</td>
<td>73±6.8</td>
<td>173±0.25</td>
<td>16.8±0.9</td>
<td>126</td>
</tr>
<tr>
<td>Etidocaine 1.0%</td>
<td>33.7±6.8</td>
<td>5M</td>
<td>69±5.1</td>
<td>168±0.25</td>
<td>17.4±0.75</td>
<td>174</td>
</tr>
<tr>
<td>Etidocaine 1.5%</td>
<td>38.4±5.7</td>
<td>7M</td>
<td>71±7.1</td>
<td>170±0.25</td>
<td>15.5±0.8</td>
<td>232.5</td>
</tr>
<tr>
<td>Prilocaine 2%</td>
<td>46.2±3.2</td>
<td>10F</td>
<td>58±2.0</td>
<td>159±1.8</td>
<td>20</td>
<td>400</td>
</tr>
<tr>
<td>Prilocaine 3%</td>
<td>51.9±4.4</td>
<td>10F</td>
<td>67±4.0</td>
<td>161±1.5</td>
<td>20</td>
<td>600</td>
</tr>
</tbody>
</table>

Scottish series premedication comprised diamorphine 5 mg plus atropine 0.6 mg. A fixed dose of 20 ml was used for the extradural block and all these patients were female (table I).

An extradural catheter was inserted between the third and fourth lumbar vertebrae and advanced 2–3 cm into the extradural space, with the patient conscious, 1 h after premedication. After turning the patient supine and horizontal a test dose of 2% lignocaine 4 ml with adrenaline 1 : 200 000 was injected in the Massachusetts patients followed in 5 min by the main dose of the test drug. In the Edinburgh group no test dose was used.

Every 2 min the patient was assessed with regard to the spread and degree of nerve block. Analgesia was tested by pin-prick and the upper dermatomal limit noted. Motor block was assessed on a 0–3 scale where 0 = no motor block, 1 = inability to raise lower limb off the trolley, 2 = inability to flex the knee, 3 = total paralysis. Arterial pressure and heart rate were noted at each assessment. After 30 min the nerve block was assumed to be at or near its maximum and surgery was permitted.

After operation the patient was examined every 15 min to assess the regression of the block to the T12 level. The onset of analgesia was determined as the time to achieve spread to the dermatomes of T12, T10 and T6. The onset of motor block was the time to achieve a score of 1 or 2 in the degree of block as defined above, remembering that in not all patients was a score of 2 achieved.

The adequacy of analgesia was assessed by the need to provide additional analgesia or sedation during surgery. Duration of analgesia was taken as the time from injection to regression to T12—the time at which the patient undergoing abdominal surgery would require analgesia. Duration of motor block was taken as the time for the motor score to regress to 1 unit. This was not assessed in the case of prilocaine.

The results from the four groups of patients receiving either bupivacaine or etidocaine and the two groups receiving prilocaine were subjected to statistical analysis using either Student's $t$ test or $\chi^2$ test as appropriate. No comparison between prilocaine and the other two drugs was performed as different observers had been used and the experimental programmes varied slightly.

**RESULTS**

**Sensory analgesia**

The onset of analgesia is shown in table II. The onset to T12 and T10 was decreased by approximately 50% when the concentration of bupivacaine was increased from 0.5% to 0.75% ($P<0.01$). Etidocaine 1.5% was not significantly more rapid than etidocaine 1.0%, but both solutions showed a more rapid onset than bupivacaine 0.5 and 0.75% ($P<0.05$). There were no significant differences in the onset of analgesia between prilocaine 2% and 3%, both of which had onset times very similar to bupivacaine 0.5%.

The level of the highest dermatomes reached with the extradural blocks did not differ significantly between any of the drugs used. The spread in all the patients was adequate for the performance of lower abdominal surgery. There were no missed segments, but with bupivacaine the first sacral nerve required an average of 16–22 min for complete analgesia compared with 6–10 min with etidocaine.
Bupivacaine 0.5% and etidocaine 1.0% achieved analgesia requiring no additional medication in only six of the 10 patients in each group, while the more concentrated solutions achieved similar analgesia in nine of the 10 patients. In the prilocaine series the 2% solution achieved adequate analgesia in nine of the 10 patients, while analgesia was adequate in all cases in the 3% group.

Both bupivacaine 0.75% and etidocaine 1.5% produced a significantly longer duration of sensory analgesia than the less concentrated solutions (P<0.01). There were no significant differences between the two drugs when either the two less concentrated or the two more concentrated solutions were compared. The duration of analgesia with prilocaine was shorter than that with bupivacaine or etidocaine. The 3% solution produced analgesia with an average duration of 180 min compared with 165 min for prilocaine 2%. This difference was not statistically significant.

**Motor blockade** (table III)

The onset times for motor block with bupivacaine 0.75% was more rapid than with the 0.5% solution (P<0.01). The onset of motor block with bupivacaine 0.5% required 17.7±SEM 2.5 min and showed the greatest disparity between onset of sensory and motor blockade. All 20 patients receiving bupivacaine achieved at least a 1+ degree of motor block. However, three of the patients receiving bupivacaine 0.5% developed a 2+ degree of motor block compared with eight of the group receiving bupivacaine 0.75%. None of the bupivacaine-treated patients achieved a 3+ degree of motor blockade.

Etidocaine caused a more profound motor block than either prilocaine or bupivacaine. Nine of the 20 patients receiving either etidocaine 1% or 1.5% developed complete paralysis of the legs, and only one patient did not achieve a 2+ degree of motor block. Etidocaine 1.5% was faster in producing a 2+ degree of motor block than the 1% concentration (P<0.01).

Prilocaine 3% did not produce a more rapid onset of motor block than the 2% solution. The 3% concentration caused more motor block than the 2% prilocaine, but this difference was not statistically significant. Seventeen of the 20 patients in the prilocaine group had a 2+ degree of motor block.
The duration of motor blockade was significantly prolonged when the more concentrated solutions of bupivacaine and etidocaine were used \((P<0.01)\). The duration of motor block increased from \(149\pm16\) min for bupivacaine 0.5% to \(246\pm16\) min for the 0.75% solution. Etidocaine 1% produced a motor block for \(151\pm14\) min compared with \(239\pm19\) min for the 1.5% concentration. In no patient did motor block outlast sensory block.

**DISCUSSION**

The more concentrated solutions of bupivacaine (0.75%) and etidocaine (1.5%) produced a more rapid onset of sensory analgesia and motor blockade, a greater frequency of adequate analgesia and profound motor block, and a longer duration of sensory and motor block than the more dilute solutions. An increase in the concentration of prilocaine from 2% to 3% did not appear to be associated with a significant improvement in the effectiveness of the local anaesthetic agent.

In the United Kingdom, none of the concentrated solutions is available commercially. There are clearly considerable advantages to the use of the stronger solutions of bupivacaine and etidocaine in performing surgical procedures as opposed to their use for producing analgesia, for example in labour when motor block would be undesirable.

Although all solutions produced sufficient nerve blockade to allow the performance of the planned operations, additional sedation was required in 40% of patients receiving the weaker solutions of bupivacaine and etidocaine.

No side-effects were observed with any of the anaesthetic solutions. Blood concentrations of prilocaine, bupivacaine and etidocaine were not determined in this study. Previous investigations have shown an increase in the peak venous plasma concentration of all three agents as the concentration and total dosage administered to the extradural space was increased (Covino and Vassallo, 1976). However, the plasma concentrations following extradural administration of 0.75% bupivacaine 20 ml, 1.5% etidocaine 20 ml and 3% prilocaine 20 ml appear to be well below the concentration required for c.n.s. toxicity (Scott, Jebson and Boyes, 1973; Arthur et al., 1979). The only theoretical disadvantage of the more concentrated solutions is the greater risk of toxicity if the more concentrated solution was inadvertently injected to a vein or to the subarachnoid space.

The added clinical benefits which were obtained from the use of the more concentrated solutions of bupivacaine and etidocaine justify the risk against the benefit. Such is not the case with prilocaine 3%.

The increase in the strength of the solution of prilocaine does not yield the advantages seen with the other two drugs. Prilocaine 2% produces a satisfactory degree of sensory and motor block in most patients and it is the least toxic of all amide local anaesthetic drugs (Eriksson, 1966). Little additional value is obtained by using the 3% solution for extradural block. The smaller total dosage achieved with prilocaine 2% will reduce the frequency of its most irritating side-effect, methaemoglobinaemia, the severity of which has been shown to be dose-related (Lund and Cwik, 1965).

Since the 40 patients receiving either etidocaine or bupivacaine were randomized with regard to both concentration of solution and drug used, it was possible to compare the two drugs directly. Etidocaine was shown to produce a more rapid onset and a more profound degree of motor blockade. Several studies have indicated a longer duration after bupivacaine compared with etidocaine, but this was not seen in the present investigation. The addition of adrenaline to the etidocaine solutions may have been responsible for this lack of difference. No direct comparison between prilocaine and the other two drugs is strictly valid, but the similarity in duration of block of prilocaine 2% and 3% compared with bupivacaine 0.5% and etidocaine 1% is noteworthy. Since prilocaine is the least toxic of the amide-type local anaesthetic drugs while possessing highly satisfactory anaesthetic qualities, its extradural use, particularly in poor-risk patients, should be of value.

**REFERENCES**


EINIGE ASPEKTE DER ANWENDUNG GRÖSSERER KONZENTRATIONEN VON LOKALNARKOSEMITTELN BEI EXTRADURALER BLOCKIERUNG

ZUSAMMENFASSUNG
Eine Erhöhung der Konzentration von Bupivacaïne von 0,5% auf 0,75%, und bei Etiocain von 1,0% auf 1,5% bei extraduraler Blockierung führte zu einem schnelleren Einsatz sensorieller Analgesie und motorischer Blockade, einer größeren Frequenz ausreichender Analgesie, einer größeren Tiefe der motorischen Blockierung und einer längeren Dauer der sensoriellen Analgesie und motorischen Blockade. Eine Erhöhung der Konzentration von Prilocain von 2% auf 3% brachte keine zusätzliche Vorteile mit sich. Die Verwendung der stärkeren Konzentrationen von Bupivacaïne und Etiocain bringt anscheinend bedeutende klinische Vorteile bei der extraduralen Narkose bei chirurgischen Eingriffen mit sich.

EFFETS DE LA CONCENTRATION DES AGENTS ANESTHESIQUES LOCAUX UTILISES POUR LE BLOCAGE EXTRADURAL

RESUME
Lorsqu’on a augmenté la concentration de bupivacaïne de 0,5% à 0,75% et celle d’étiocain de 1% à 1,5% pour le blocage extradural, on a obtenu un début plus rapide de l’analgésie sensorielle et du blocage moteur, une plus grande fréquence d’analgésie adéquate, une plus grande profondeur du blocage moteur de même qu’une plus longue durée de l’analgésie sensorielle et du blocage moteur. L’augmentation de la concentration de prilocain de 2% à 3% n’a révélé aucun avantage significatif. L’usage de solutions de bupivacaïne et d’étiocain plus concentrées semble devoir présenter des avantages cliniques d’une certaine importance pour le blocage extradural avant une intervention chirurgicale.

EFECTOS DE LA CONCENTRACION DE ANESTESIA LOCAL EN EL BLOQUEO EXTRADURAL

SUMARIO
Un incremento desde 0,5% a 0,75% y del 1,0% a 1,5% en la concentración de bupivacaína y de etidocaina, respectivamente, para el bloqueo extradural, tuvo como resultado un inicio más rápido de la analgesia sensorial y del bloqueo motriz, una mayor frecuencia de analgesia adecuada, una mayor profundidad del bloqueo motriz y una mayor duración de la analgesia sensorial y del bloqueo motriz. Un incremento en la concentración de prilocain desde el 2% al 3% no reveló ninguna ventaja significativa. El uso de las soluciones de bupivacaína y de etidocaina más concentradas parece que presentan ventajas clínicas significativas en la anestesia extradural encaminada a la actividad quirúrgica.