SPINAL ANAESTHESIA WITH HYPERBARIC BUPIVACAINE

Effects of Age on Neural Blockade and Pharmacokinetics

B. T. VEERING, A. G. L. BURM AND J. SPIERDIJK

With advancing age the central and peripheral nervous systems degenerate [1, 2]. These changes may have an impact on both the dose requirement of local anaesthetics and the quality and duration of the neural blockade. With extradural administration of bupivacaine, ageing results in a more extensive spread of analgesia and a more rapid onset of analgesia at the caudad segments [3, 4]. With subarachnoid administration of glucose-free bupivacaine, ageing results in a more rapid onset of analgesia and a decrease of the time to attain the maximum degree of motor blockade [5, 6], in addition to a slight increase of the spread of analgesia [5, 7] and a longer duration of analgesia [6].

Data on the impact of ageing on the clinical effects following subarachnoid injection of hyperbaric solutions are scarce. With hyperbaric amethocaine no effects of ageing have been observed [8, 9]. Reports on the effects of ageing after subarachnoid injection of hyperbaric bupivacaine solutions are lacking and they cannot be inferred from data derived from studies with glucose-free bupivacaine, because the addition of glucose alters the local anaesthetic profile of bupivacaine: with hyperbaric solutions the quality and duration of motor blockade of the lower limbs decrease and the duration of analgesia is shortened [10-13].

Ageing also affects the pharmacokinetics of local anaesthetics. In two recent studies [4, 6] we demonstrated an increase of the terminal half-life after extradural administration of bupivacaine and an increase of the peak plasma concentration after subarachnoid administration of glucose-free bupivacaine. In both studies ageing resulted in a marked reduction of the total plasma clearance of bupivacaine. Effects of ageing on the pharmacokinetics after subarachnoid administration of hyperbaric bupivacaine solutions have not been reported. Again, these effects cannot be inferred from data obtained with glucose-free bupivacaine solutions, because the pharmacokinetic profiles after administration of hyperbaric and glucose-free solutions differ: in younger patients a difference in the time to peak plasma concentrations of bupivacaine has been established [14, 15].

In this study we have investigated the influence of ageing on both the quality and duration of the neural blockade, and on the plasma concentration profiles after subarachnoid administration of a hyperbaric solution of bupivacaine.
TABLE I. Patient characteristics (mean±SD). In group 1 patients were aged between 20 and 55 yr, in group 2 patients were older than 55 yr.

<table>
<thead>
<tr>
<th>n</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>15</td>
<td>33±10</td>
<td>78±10</td>
</tr>
<tr>
<td>Group 2</td>
<td>15</td>
<td>73±9</td>
<td>80±7</td>
</tr>
</tbody>
</table>

PATIENTS AND METHODS

Thirty male patients (20–86 yr, ASA status I–II) undergoing minor orthopaedic, urological or lower abdominal surgery were enrolled in the study. After approval by the Committee on Medical Ethics of the University Hospital, informed consent was obtained from each patient. Patients were allocated to two groups according to their age (table I). Patients with a history of neurological disease, hepatic disease or bleeding diathesis were excluded from the study.

Premedication consisted of lorazepam 1–2 mg sublingually, 1.5 h and atropine 0.25–0.5 mg i.m., 45 min before the spinal procedure. A rapid i.v. infusion of dextrose in saline 500 ml was administered before the subarachnoid injection. Thereafter the infusion rate was maintained at 2 ml kg⁻¹ h⁻¹. A central venous catheter was placed in the superior vena cava via the basilic or the cephalic vein after local infiltration with 0.5 % lignocaine, the catheter being advanced until the tip was located at least 6 cm proximal to the junction of the azygos vein and the superior vena cava. The correct location of the catheter tip was verified by radiography.

After local infiltration of the skin with 0.5 % lignocaine the dural puncture was performed with a 25-gauge spinal needle through an 18-gauge introducer, using a midline approach at the L3/4 space. During the procedure the patient was sitting. When a free flow of clear cerebrospinal fluid was obtained and after aspiration, the local anaesthetic was injected without barbotage at a rate of approximately 0.15 ml s⁻¹. After injection of 0.5 % bupivacaine 3 ml in 8 % glucose the patient remained sitting for 2 min and was then placed in the supine horizontal position. During the operation no sedatives were administered. Systemic arterial pressure, measured with an automatic cycling device (Accutorr 1, Datascoppe) and heart rate (from the ECG) were monitored during induction and surgery, and in the recovery room. If the systolic arterial pressure decreased more than 30 % below the preanaesthetic value or to less than 100 mm Hg, ephedrine 5 mg was given i.v.

Analgesia was assessed and defined as absence of pain to pinprick. Motor blockade was evaluated bilaterally using a modified Bromage classification by asking the patient to raise the extended leg, flex the knee and flex the ankle, and was rated per joint (0 = no, 1 = partial, 2 = complete blockade). The results obtained for both extremities were added, giving a maximum score of 12 (complete motor blockade). Assessments were made every 5 min during the first 30 min after the injection, then at 15-min intervals until complete recovery. The following variables were calculated:

- time to initial onset of analgesia at the L1/2 dermatomes;
- time to initial onset of motor blockade;
- time until maximum cephalad spread of analgesia;
- time until maximum caudad spread of analgesia;
- highest level of analgesia;
- maximum number of segments blocked;
- maximum score of motor block;
- time until the level of analgesia had receded two segments;
- time until recovery of analgesia at the T12 dermatome;
- time until total disappearance of analgesia;
- time until total recovery from motor blockade.

Central venous blood samples (5 ml) were collected before the spinal injection and 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 90, 120, 150, 240, 360, 480, 600, 720, 960, 1200 and 1440 min after injection. Plasma was separated by centrifugation at 2,500 g, stored at −20 °C and assayed for bupivacaine using a capillary gas chromatographic method with a coefficient of variation less than 6 % [16]. The individual peak plasma concentrations (C_{max}) of bupivacaine, and the time at which these were reached (T_{max}) were determined. Terminal half-lives (T_{1/2}^x) were calculated from the rate constants (k_x) obtained by linear regression analysis of the log-linear part of the plasma concentration v. time curve:

\[ T_{1/2}^x = 0.69/k_x \]

The area under the plasma concentration–time curve (AUC) was determined using the linear trapezoidal rule, including extrapolation to
SPINAL ANAESTHESIA: EFFECTS OF AGEING

infinity [17]. The mean plasma clearance (Cl) was calculated according to the following equation:

\[
Cl = \frac{D}{AUC}
\]

where \( D \) is the administered dose.

Values were expressed as mean ± SD. Statistical comparisons were undertaken with the Mann–Whitney \( U \) test. Spearman rank correlation coefficients were calculated to show the interrelationships between the upper level of analgesia and age, and between \( T_{\text{max}} \) and age. The relationship between the clearance and age was determined by linear regression and correlation analysis. \( P < 0.05 \) was considered statistically significant.

RESULTS

In all patients analgesia attained a level high enough to provide analgesia for surgery; no supplementary analgesic or sedative medication was necessary. No serious cardiovascular changes occurred. One elderly patient (81 yr) required ephedrine 5 mg i.v. for treatment of hypotension below 100 mm Hg. The mean decrease from control mean arterial pressure during the first 1 h did not exceed 10% in the young and 15% in the old patient group. There was no statistical correlation between the height of the block and the decrease in mean arterial pressure in either group. Postspinal headache developed in one younger patient (24 yr), and was treated successfully with a single extradural blood patch.

All blocks were symmetrical; no patient developed a level of analgesia that varied by more than one segment between the two sides of the body. The spread of analgesia during the first 30 min after the administration is presented in figure 1. After 10, 15, 20 and 30 min the older patients developed a significantly higher spread

![Diagram showing analgesia spread](image)

**Fig. 1.** Mean cephalad and mean caudad spread of analgesia at times up to 30 min in the older (●—●) and younger (○—○) patient groups. (SD bars in only one direction.) Differences between the older and younger patient groups:

*\( P < 0.05 \); **\( P < 0.01 \).

**Table II.** Characteristics of neural blockade after subarachnoid administration of 0.5% hyperbaric bupivacaine (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial onset time (min)</td>
<td>3.7 ± 0.8</td>
<td>3.9 ± 1.0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Time to maximum cephalad spread (min)</td>
<td>10.9 ± 4.0</td>
<td>14.1 ± 3.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Time to maximum caudad spread (min)</td>
<td>4.6 ± 2.3</td>
<td>3.7 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Maximum number of segments blocked</td>
<td>11.9 ± 1.5</td>
<td>13.6 ± 2.0</td>
<td></td>
</tr>
<tr>
<td>Highest level (T dermatome)</td>
<td>11.1 ± 1.6</td>
<td>8.7 ± 1.8</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Duration highest level (min)</td>
<td>58 ± 26</td>
<td>70 ± 25</td>
<td></td>
</tr>
<tr>
<td>Two-segment regression (min)</td>
<td>88 ± 31</td>
<td>104 ± 28</td>
<td></td>
</tr>
<tr>
<td>Time to recovery at T12 (min)</td>
<td>95 ± 28</td>
<td>139 ± 39</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Time to total recovery (min)</td>
<td>357 ± 53</td>
<td>355 ± 67</td>
<td></td>
</tr>
<tr>
<td>Motor blockade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial onset time (min)</td>
<td>6.2 ± 2.9</td>
<td>3.9 ± 1.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Time to maximum degree (min)</td>
<td>12.3 ± 5.2</td>
<td>10.3 ± 4.6</td>
<td></td>
</tr>
<tr>
<td>Patients with complete block (%)</td>
<td>67</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Time to total recovery (min)</td>
<td>167 ± 49</td>
<td>192 ± 36</td>
<td></td>
</tr>
</tbody>
</table>
compared with the younger patients. The time to maximal cephalad spread was significantly longer and the upper levels of analgesia were significantly higher in older patients (table II). In addition there was a moderate correlation between the maximal height of analgesia and age ($r_s = 0.74$, $P < 0.005$) (fig. 2). No differences were found in caudad spread between the two groups. The time to initial onset of motor blockade was significantly shorter in the group of older patients ($P < 0.01$), but the time at which the maximum degree of motor blockade was attained was similar in both groups. Complete motor blockade of the lower limbs occurred in 10 of the 15 younger patients and in 13 of the 15 older patients.

Age had no effect on the disappearance of analgesia from the two upper dermatomes. The time to recovery from analgesia at the level of T12 was longer in the older patient group ($P < 0.01$). Age did not influence the total durations of analgesia and motor blockade.

Figure 3 shows representative examples of plasma concentration $v.$ time curves of an older and a younger patient. The results of the pharmacokinetic analysis are shown in table III.

**Table III. Pharmacokinetic data obtained after subarachnoid administration of 0.5\% hyperbaric bupivacaine (mean ± SD)**

<table>
<thead>
<tr>
<th>Group</th>
<th>$T_{\text{max}}$ (min)</th>
<th>$C_{\text{max}}$ (ng ml$^{-1}$)</th>
<th>$T_{1%}$ (min)</th>
<th>Cl (ml min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>65 ± 38</td>
<td>71 ± 28</td>
<td>334 ± 64</td>
<td>525 ± 172</td>
</tr>
<tr>
<td>Group 2</td>
<td>107 ± 28</td>
<td>75 ± 23</td>
<td>427 ± 138</td>
<td>366 ± 134</td>
</tr>
<tr>
<td>$P$</td>
<td>&lt; 0.01</td>
<td>&lt; 0.05</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>
Peak plasma concentrations of bupivacaine were similar in both groups, but the corresponding peak times were significantly longer in older patients. In addition, there was a moderate correlation between the time to peak concentration and age ($r_s = 0.55, P < 0.001$) (fig. 4). The terminal half-life was significantly prolonged ($P < 0.05$) and the total plasma clearance was significantly lower in the older patients ($P < 0.01$). There was a moderate inverse correlation between total plasma clearance and age ($r = -0.57, P < 0.001$) (fig. 5).

**DISCUSSION**

The most important clinical features of spinal anaesthesia are the height (level) and duration of sensory analgesia. Factors which influence the extent and duration of the neural blockade after subarachnoid administration of hyperbaric bupivacaine include the baricity of the solution [10, 13, 18-20], the position of the patient [21-23], the injected volume [24-27], and the concentration of the local anaesthetic in the solution [24, 26, 28]. This study shows that age is another factor.

Our results clearly demonstrate that, with hyperbaric bupivacaine solutions, ageing results in both a slightly higher level of analgesia, at the cost of an increase in the latency time to maximal spread, and a slightly faster onset of motor blockade. These changes are of minor clinical significance. It is not surprising that ageing alters the clinical profile of local anaesthetics: it results in a gradual degeneration of the central and peripheral nervous systems [1, 2], changes in the anatomical configuration of the lumbar and thoracic spine [29] and, possibly, a reduction of the volume of the CSF [30]. These alterations may all contribute to the increased spread of analgesia and the more rapid onset of motor blockade with a hyperbaric solution. In addition, the specific gravity of the CSF increases with age [31, 32], making the local anaesthetic solution less hyperbaric. This may decrease the spread of the solution. However, clinically, this effect is dominated by the factors just mentioned, which promote the spread of analgesia.

The results obtained in this study with hyperbaric bupivacaine solutions contrast with those, obtained by Park, Balingit and Macnamara [8] and Tuominen and colleagues [9] with hyperbaric amethocaine. However, both those studies [8, 9] used different volumes and techniques and therefore comparison with the present results is difficult. In well controlled studies in
TABLE IV. Pharmacokinetic data obtained after subarachnoid administration of glucose-free 0.5% bupivacaine (from Veering and colleagues [6]) and hyperbaric 0.5% bupivacaine in 8% glucose (mean ± SD).

*Statistical difference between group 1 and group 2 in that patient study.

<table>
<thead>
<tr>
<th></th>
<th>Glucose-free 0.5% bupivacaine</th>
<th>Hyperbaric 0.5% bupivacaine</th>
<th>Effect of age</th>
<th>Effect of glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 1</td>
<td>Group 2</td>
</tr>
<tr>
<td></td>
<td>20-55 yr &gt; 55 yr</td>
<td>20-55 yr &gt; 55 yr</td>
<td>(P)</td>
<td>(P)</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (min)</td>
<td>75 ± 25</td>
<td>96 ± 23*</td>
<td>71 ± 28</td>
<td>75 ± 23</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (min)</td>
<td>84 ± 53</td>
<td>105 ± 54</td>
<td>65 ± 38</td>
<td>107 ± 28*</td>
</tr>
<tr>
<td>( T_{\text{f}} ) (min)</td>
<td>288 ± 64</td>
<td>270 ± 93</td>
<td>334 ± 64</td>
<td>427 ± 138*</td>
</tr>
<tr>
<td>( Cl ) (ml min(^{-1}))</td>
<td>461 ± 94</td>
<td>284 ± 74*</td>
<td>525 ± 172</td>
<td>366 ± 134*</td>
</tr>
</tbody>
</table>

younger patients, comparisons between hyperbaric solutions of amethocaine and bupivacaine revealed a quite similar action of both local anaesthetics [21, 28, 33, 34].

The marked prolongation of the duration of analgesia at the T12 dermatome in the older patients would allow more time for the performance of lower abdominal surgery in this group.

The results obtained in this study differ from those obtained by us in a previous study, concerning the influence of age after subarachnoid administration of glucose-free bupivacaine solutions [6]. Using glucose-free bupivacaine solutions we observed a significantly more rapid onset of analgesia at the caudal segments, no significant effect on the highest level of analgesia, and a marked prolongation of the total duration of analgesia with advancing age. Furthermore, the time to attain the maximum degree of motor blockade was significantly shorter in older patients. In fact, a glucose-free solution of 0.5% bupivacaine is slightly hypobaric (baricity at 37 °C, 0.9990), resulting in a one-segment further spread in patients who remain sitting for 2.5 min or longer after injection of the glucose-free solution compared with patients who remain sitting for 2 min after the injection [35]. Under clinical conditions the distribution of a glucose-free solution of 0.5% bupivacaine resembles that of isobaric solutions more than that of truly hypobaric solutions. As a result of the more restricted spread and, consequently, a higher drug concentration in the CSF, the effects of isobaric solutions always last much longer [36-38]. Furthermore, addition of glucose to the solution may alter the pharmacodynamic profile of the local anaesthetic, for example by altering the osmolality [35] or by interference with the absorption of the local anaesthetic from the subarachnoid space into the general circulation [14, 15, 39, 40].

The pharmacokinetic data obtained in this study also differ from those in the study with glucose-free bupivacaine solutions [6]. With hyperbaric solutions, ageing did not affect the peak plasma concentrations of bupivacaine, but did prolong the corresponding peak times and the terminal half-life. With glucose-free bupivacaine solutions, ageing increased the peak plasma concentration, but did not alter the peak time or terminal half-life. The difference in the results obtained with different bupivacaine solutions suggest that glucose interferes with the pharmacokinetics.

In order to distinguish between the effects of ageing and those of addition of glucose the data obtained in this study and the data obtained in the study with glucose-free bupivacaine solutions were re-analysed, using a two-way analysis of variance (table IV). This analysis confirmed the observations from the present study concerning the effects of age: ageing does not influence \( C_{\text{max}} \) of bupivacaine, but prolongs the corresponding \( T_{\text{max}} \) and \( T_{\text{f}} \) and decreases \( Cl \). In addition, the analysis demonstrated that addition of glucose decreases \( C_{\text{max}} \), prolongs \( T_{\text{f}} \) and increases \( Cl \), but does not alter \( T_{\text{max}} \). The effects of glucose on \( C_{\text{max}} \) and \( T_{\text{max}} \) differ from those reported by Axelsson and colleagues [14] and Burm and colleagues [15], who both found that glucose decreased \( T_{\text{max}} \) but did not alter \( C_{\text{max}} \). This reason for this discrepancy remains unclear.

In conclusion, the present study demonstrates that advancing age alters both the neural blockade characteristics and the pharmacokinetics after subarachnoid administration of hyperbaric
solutions of bupivacaine. The results clearly show an effect of ageing on the disposition, that is, the total plasma clearance of bupivacaine. The effect of ageing on the time at which the peak plasma concentration is obtained, suggests an effect on the initial absorption, but may also be the result of the decreased total plasma clearance. The effect on the terminal half-life, which in fact reflects a slow absorption half-life in younger patients [40], indicates that the late absorption proceeds more slowly in older patients. This slowing of the absorption is not accompanied by a prolongation of the duration of analgesia in the upper and lower dermatomes.

ACKNOWLEDGEMENTS

The authors thank Mr D. C. D. de Lange for his assistance with the clinical experiments, Mrs M. P. R. R. Gladines, Mrs A. Muller-de Ruiter and Mr A. A. Vletter for their assistance with the laboratory investigations and Mrs W. C. E. van Leeuwen and Mrs M. P. M. Toelen for typing the manuscript.

REFERENCES

35. Kalso E, Tuominen M, Rosenberg PH. Effect of posture and some CSF characteristics on spinal anaesthesia with isobaric 0.5% bupivacaine. *British Journal of Anaesthesia* 1982; 54: 1179–1184.