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Epidural anaesthesia with levobupivacaine and ropivacaine : effects of age on the pharmacokinetics, neural blockade and haemodynamics

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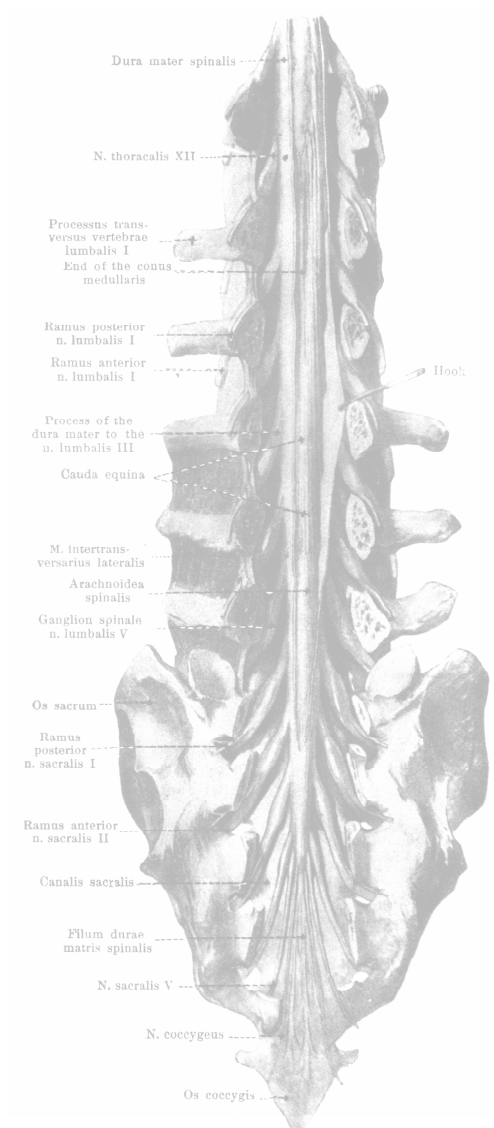
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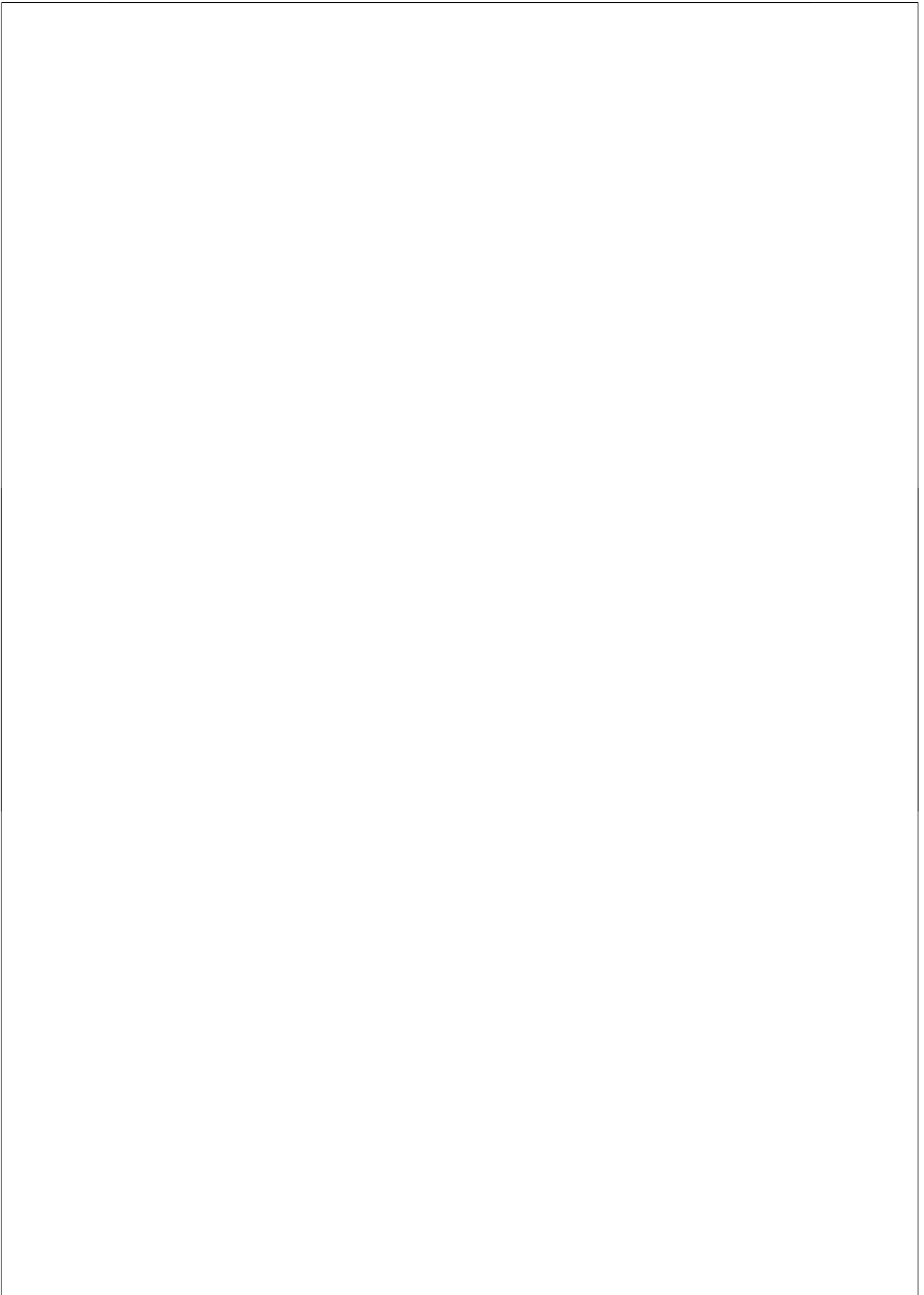
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Section III



Haemodynamic Effects



**THE EFFECTS OF AGE ON NEURAL BLOCKADE AND
HAEMODYNAMIC CHANGES FOLLOWING EPIDURAL
ANAESTHESIA WITH ROPIVACAINE 1.0%**

CHAPTER 11

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As the elderly population continues to increase, the number of elderly surgical patients will continue to grow. Lumbar epidural anaesthesia is often employed in elderly patients as part of an anaesthetic regimen for orthopaedic, urological, gynaecological or lower abdominal surgery. Studies in our institute have shown that elderly patients are more sensitive to epidural anaesthesia with bupivacaine.^{1,2} In these studies the upper level of analgesia increased, and the time until maximal caudad spread decreased with increasing age. Furthermore, elderly patients had a faster onset and an enhanced intensity of motor blockade.

Ropivacaine, a recently introduced long-acting local anaesthetic, which only contains the S(-)-enantiomer has proven in clinical studies to provide effective epidural anaesthesia in concentrations ranging from 0.5% - 1.0%.³ Studies in animals and in humans have shown that, compared with bupivacaine, the systemic toxicity of ropivacaine is reduced.⁴⁻⁶

Although ropivacaine is frequently used in elderly patients, there are few data about the effect of age on the sensory and motor blockade and haemodynamic changes after epidural anaesthesia with ropivacaine. The primary objective of this study was to confirm or refute the hypothesis that age affects the upper analgesia levels after epidural administration of a fixed dose of ropivacaine. In addition, other aspects of neural blockade and haemodynamic changes were studied.

Methods

Patients

The protocol of this study was reviewed and approved by the Committee on Medical Ethics of the Leiden University Medical Center. Fifty-five patients ASA physical status I or II, who had given their informed consent, were enrolled in one of three groups, according to their age (group 1: 18-40 years; group 2: 41-60 years; group 3: 61 years and older). They underwent minor lower limb, urological, gynaecological (excluding obstetrics) or lower abdominal surgery. Patients who had diabetes, had a history of neuromuscular disease or bleeding diathesis, were suffering from clinically significant peripheral arteriosclerosis, or were hypersensitive to amide local anaesthetics, were excluded. Patients, who had a history of previous lumbar surgery, radiculopathy or chronic back pain and who weighed more than 110 kg, or were shorter than 150 cm were also excluded. In addition, pregnant women were excluded.

Procedures

Patients were fasting from midnight before surgery. Antihypertensive medication was continued on the day of surgery. Patients were premedicated with temazepam 20 mg (< 60 years) or 10 mg (≥ 60 years) orally, 45 min before the induction of epidural anaesthesia. A rapid intravenous (i.v.) infusion of 500 ml saline 0.9% was administered before the induction of epidural anaesthesia, and subsequently, an infusion rate of $2 \text{ ml.kg}^{-1}.\text{h}^{-1}$ was maintained. The epidural puncture was performed with the patient in the sitting position, at the L3-L4 interspace using a midline or paramedian approach. The appropriate lumbar interspace was determined by counting the spines of the vertebrae, from both the cranial and caudal directions, and the iliac crest was palpated to confirm the position of the fourth lumbar vertebra. After local infiltration of the skin with prilocaine 1.0%, the epidural space was identified with the loss of resistance to saline technique. Subsequently, with the bevel of a 16-gauge Tuohy epidural needle pointing cephalad, a test dose of 3 ml prilocaine 1.0% with epinephrine $5 \mu\text{g.ml}^{-1}$ was administered. Three minutes later, when there were no signs of inadvertent intravascular or subarachnoid injection and after negative aspiration of cerebrospinal fluid or blood, 15 ml ropivacaine 1.0% (AstraZeneca, Södertälje, Sweden) was administered slowly at a rate of 1 ml.s^{-1} . The patient was then placed in the horizontal supine position.

Assessments

Systemic arterial pressure, measured with an automatic cycling device (Cardiicap, Datex), and heart rate, from the electrocardiogram, were recorded at the ward, before the epidural administration of ropivacaine, during the induction of epidural anaesthesia, and during surgery. They were recorded at 5-min intervals during the first 0.5 h after induction of anaesthesia and thereafter at 15-min intervals until at least 30 min after arrival at the recovery room. Reference values for heart rate and mean arterial pressure (MAP) were calculated by averaging the values obtained at the ward, before epidural administration and at its completion. When the coefficient of variation exceeded 20%, or when the ratio of the maximum of the 3 values and the mean value exceeded 1.20, the average of the 2 lowest values were taken as the baseline value. Hypotension was defined as a decrease in systolic blood pressure more than 30% of the preanaesthetic value or a systolic blood pressure < 90 mm Hg. Hypotension was treated by administering ephedrine 5 mg i.v. and crystalloid fluids. Bradycardia ($< 55 \text{ beats.min}^{-1}$) was treated by administering 0.5 mg atropine i.v.

Analgesia was assessed bilaterally in the anterior axillary line by pinprick using a short bevelled 25-gauge needle. Analgesia was defined as the inability to detect a sharp pinprick. Results from both sides were averaged. Assessments were made every 5 min

during the first 30 min and subsequently every 15 min until complete regression of the sensory blockade. Motor blockade of the lower limb was evaluated by asking the patient to raise the extended leg (flexion of the hip) and to flex the knee and ankle, and it was rated per joint (0 = no, 1 = partial, 2 = complete blockade). The results obtained in both extremities were added, giving a maximum score of 12 (complete motor blockade). Assessments of motor blockade were made immediately after the assessment of the analgesia levels.

Statistical analysis

Sample sizes were calculated as described by Zar.⁷ On the basis of a previous study with bupivacaine,² we assumed a within-groups variance of 3.38 in the upper level of analgesia, the primary outcome variable. A difference of 2 segments in the upper level of analgesia was considered significant. With a two-sided type 1 error of 0.05 and a power of at least 0.80, 18 patients per group (total 54 patients) were required to reveal a difference in the upper level of analgesia of 2 segments between any two groups. Frequencies or population percentages were compared using the χ^2 test where appropriate. The distribution of analgesia and motor blockade data, and the values of the haemodynamic variables were tested for normality using the Kolmogorov-Smirnov test.⁸ Although some parameters (times to regression over 2 and 4 segments and times until total recovery from analgesia and motor blockade) met the criteria of a normal distribution, we decided to analyse the data non-parametrically. The Kruskal-Wallis test was used to test whether at least one of the groups had a different distribution. When a significant difference was observed, groups were compared two by two using the Mann-Whitney *U*-test. Subsequently, the estimate for the mean difference between the two groups and the 95% confidence interval (95% CI) for the median difference were calculated.⁹ The sequentially rejective Bonferroni-Holm method¹⁰ (*i.e.*, the largest difference between the age groups was required to attain significance at the 0.0167 level, the second largest difference at the 0.025 level, and the smallest difference at the 0.05 level in order to attain an overall significance level of 0.05) was used to adjust for multiple comparisons in all statistical analyses. All statistics were calculated using the software package SPSS 10.0 (SPSS Inc, Chicago, IL).

Results

Patients

Group characteristics and demographic data are presented in Table 1. Fifty-four of 55 patients who received the epidural dose were analysed. One patient was excluded from analysis because a spinal tap occurred. Of these included patients, one experienced pain at the site of surgery, which was treated with a single dose of alfentanil 0.5 mg i.v. and one received propofol sedation during surgery because of anxiety. Three patients suffered from surgical complications: one patient had a bladder perforation, one acquired the transurethral resection-syndrome and one had a mild allergic reaction to chlorhexidine. The number of patients in the three study groups differed slightly. Because of the difficulties encountered in the recruitment of younger patients it was decided to include patients irrespective of their age after 50 patients had been recruited. The ratios of men to women were comparable between the groups. In the youngest age groups more patients were ASA I, whereas in the oldest age group, more patient were ASA II. The patients' height differed between the age groups ($P = 0.04$). The median difference between the youngest and oldest age group was 8 cm (95% CI: 2-14). Four patients (one in the middle age group and three in the oldest age group) had well-documented hypertension and were treated with β -antagonist medication.

Table 1. Group characteristics and demographic data of all patients.

	Group 1 (18-40 years) (n = 15)	Group 2 (41-60 years) (n = 20)	Group 3 (≥ 61 years) (n = 19)	Total (n = 54)
Age (years)	30 (18-40)	51 (41-59)	71 (61-82)	52 (18-82)
Gender (M/F)	14/1	17/3	15/4	46/8
ASA (I/II)	13/2	19/1	5/14	37/17
Height (cm)	183 (163-193)*	179 (157-190)	172 (154-185)*	179 (154-193)
Weight (kg)	82 (50-100)	78 (57-100)	75 (61-102)	75 (50-102)

Median (range), as appropriate; * the difference between group 1 and 3 is significant ($P = 0.012$).

Analgesia and motor blockade

Values of the parameters of analgesia and motor blockade are shown in Table 2. The upper level of analgesia was different among all groups ($P = 0.001$), being lowest in the youngest group and highest in the oldest group of patients (Figure 1).

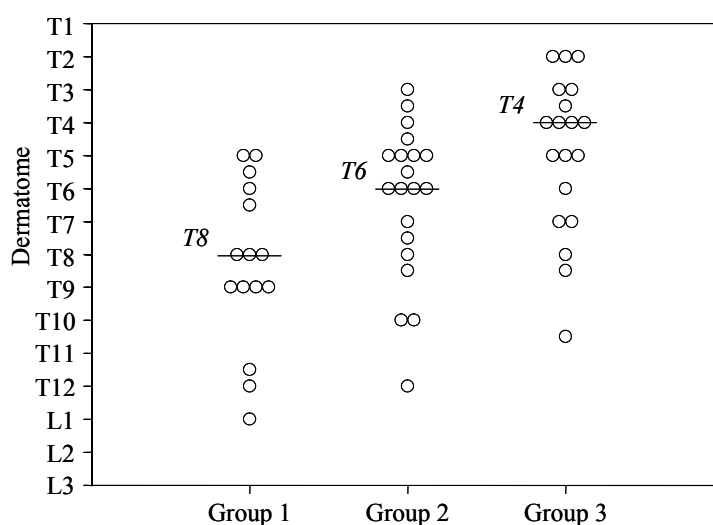


Figure 1. Median (horizontal lines) and individual (dots) upper levels of analgesia for the three age groups (Group 1: 18-40 years; Group 2: 41-60 years; Group 3: ≥ 61 years).

The median difference between the youngest and middle age group was 2 segments (95% CI: 0.5–4), between the middle and oldest group 1.5 segments (95% CI: 0–3) and between the youngest and oldest group of patients 3.5 segments (95% CI: 3–5). The time from maximal cephalad spread of analgesia until the upper level of analgesia had regressed by two segments was different between age groups. Median differences were 52 min (95% CI: 8–98) and 70 min (95% CI: 60–118) when the youngest group was compared with the middle and oldest age groups, respectively. No difference among groups were observed for time to initial onset of analgesia at dermatome level L1–L2, time until maximum caudad and cephalad spread, time from maximal cephalad spread until the upper level of analgesia had regressed by four segments, and time until total recovery from analgesia. Maximum degree of motor blockade was different between age groups ($P = 0.003$). The median difference between the youngest and the oldest age group was 3 (95% CI: 1–4), being less intense in the youngest age group. Time to initial onset of motor blockade and time until complete recovery from motor blockade were not different among the age groups.

Table 2. Variables of analgesia and motor blockade.

	Group 1 (18-40 years) (n = 15)	Group 2 (41-60 years) (n = 20)	Group 3 (≥ 61 years) (n = 19)
Variables of analgesia			
Time to initial onset of analgesia at dermatome level L1-L2 (min)	5 (5-15)	5 (5-20)	5 (5-10)
Time until maximum caudad spread (min)	23 (10-35)	18 (8-53)	15 (10-53)
Time until maximum cephalad spread (min)	30 (10-75)	21 (10-45)	20 (10-45)
Upper level of analgesia (dermatome)	T8 (L1-T5)*	T6 (T12-T3)*	T4 (T11-T2)*
Time to regression over 2 segments (min)	143 (45-298) [†]	190 (100-340) [†]	203 (90-355) [†]
Time to regression over 4 segments (min)	228 (150-360)	244 (130-400)	258 (105-378)
Time until total recovery from analgesia (min)	400 (303-485)	408 (325-585)	430 (333-535)
Variables of motor blockade			
Time to initial onset of motor blockade (min)	20 (5-30)	13 (5-23)	15 (10-20)
Maximum degree of motor blockade (0-12)	9 (2-12) [‡]	12 (6-12)	12 (2-12)*
Time until complete recovery from motor blockade (min)	240 (73-433)	245 (165-523)	300 (100-380)

Median (range); maximum degree of motor blockade: 0 = no block, 12 = complete motor block, see text for details; * the differences between Group 1 and 2 ($P = 0.02$), 2 and 3 ($P = 0.046$), 1 and 3 ($P = 0.0005$) are significant; [†] the differences between Group 1 and 2 ($P = 0.02$), 1 and 3 ($P = 0.003$) are significant; [‡] the difference between Group 1 and 3 is significant ($P = 0.001$).

Haemodynamics

Haemodynamic data are shown in Table 3. Median reference values for heart rate were not different for the three age groups, nor were the times to reach the minimal value for heart rate or the maximal decrease in heart rate during the first hour after induction of epidural anaesthesia. However, the incidence of bradycardia was more frequent in the oldest age group than in the younger age groups ($\chi^2 = 8.5$; $P = 0.01$). One patient in the youngest age group suffered from severe bradycardia that was treated by precordial thump and atropine i.v. Recovery was uneventful. Median reference values for the MAP were different between the age groups ($P < 0.007$), being highest in the oldest age group. The median difference between the youngest and oldest group was 10 mm Hg (95% CI: 4–16 mm Hg). The maximal decrease in MAP during the first hour after induction of epidural analgesia differed between age groups ($P < 0.0001$), being largest in the oldest group (Figure 2). The median difference in maximal decrease of MAP between the middle and oldest group was 15 mm Hg (95% CI: 7–23) and 19 mm Hg (95% CI: 11–28) between the youngest and oldest group. The time until the minimum value of MAP was reached did not differ between the groups. The number of patients suffering from hypotension differed among the groups ($\chi^2 = 10.2$; $P = 0.006$), being smallest in the youngest and largest in the oldest group of patients.

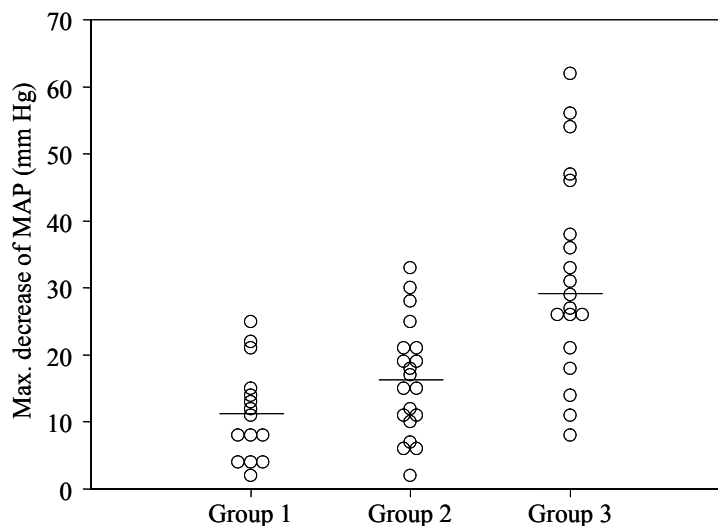


Figure 2. Median (horizontal lines) and individual values (dots) of the maximum decrease of the mean arterial blood pressure (MAP; mm Hg) during the first hour after the induction of epidural anaesthesia for the three age groups (Group 1: 18–40 years; Group 2: 41–60 years; Group 3: ≥ 61 years).

Table 3. Haemodynamic data.

	Group 1 (18-40 years) (n = 15)	Group 2 (41-60 years) (n = 20)	Group 3 (≥ 61 years) (n = 19)
Heart rate			
Reference value (beats.min ⁻¹)	67 (56-85)	71 (58-101)	68 (53-90)
Time to minimum value (min)	32 (6-63)	45 (8-63)	28 (6-61)
Maximum decrease (beats.min ⁻¹)	11 (0-32)	8 (0-15)	12 (0-43)
Number of patient with bradycardia	4	3*	11*
MAP			
Reference value (mm Hg)	93 (83-103) [†]	98 (74-113)	101 (91-121) [†]
Time to minimum value (min)	28 (5-60)	23 (6-63)	18 (8-60)
Maximum decrease (mm Hg)	11 (2-25) [‡]	16 (2-33) [‡]	29 (8-62) [‡]
Number of patients with hypotension	3 [§]	8	14 [§]

Median (range), as appropriate; MAP = mean arterial pressure; * difference is significant between Group 2 and 3 ($\chi^2 = 7.8$; $P = 0.005$); [†] difference is significant between Group 1 and 3 ($P = 0.002$); [‡] difference is significant between Group 2 and 3 ($P = 0.0009$) and Group 1 and 3 ($P = 0.0001$); [§] difference is significant between Group 1 and 3 ($\chi^2 = 9.7$; $P = 0.002$).

Discussion

This study showed that with increasing age the highest level of analgesia increased. In addition, motor blockade was more intense in the oldest compared with the youngest patients. We found no effect of age on the time to maximal caudad spread of analgesia and onset of motor blockade, as observed in previous studies with bupivacaine.^{1,2} The maximum decrease of MAP during the first hour after the epidural administration was more profound, and the number of patients that had one or more episodes of hypotension or bradycardia was increased in the oldest group.

Elderly patients exhibit anatomical and physiologic changes that influence the clinical course during epidural anaesthesia. An increased sensitivity to local anaesthetics, as in older patients, can be attributed to the declining number of myelinated fibers in the dorsal and ventral roots and to the increased permeability, which is caused by the deterioration of

myelin sheaths.¹¹ In older patients, longitudinal spread of the local anaesthetic in the epidural space is promoted by sclerosis and calcification of the intervertebral foramina¹¹⁻¹³ and a reduced fatty tissue content of the epidural space.¹⁴ This reduction may contribute to a more compliant and less resistant extradural space.^{14,15} Furthermore, the number of axons in peripheral nerves decreases with advancing age, and the conduction velocity diminishes, particularly in motor nerves.¹⁶ The clinical course of epidural anaesthesia may be further influenced by a shift of the site of action from a predominantly paravertebral site in the young to a subdural or transdural site in the elderly. This may be partly caused by an increased permeability for local anaesthetics of the dura, because of an increased size of the arachnoid villi.¹¹ With increasing age, changes in the connective tissue ground substances may result in changes in local distribution, *i.e.*, in the distribution rate of the local anaesthetic from the site of injection (the epidural space) to the sites of action.¹⁷

Some investigators, while evaluating the influence of age on the analgesic spread, demonstrated an increased upper level of analgesia with advancing age after a fixed epidural dose of a local anaesthetic.^{1,2,18,19} On the other hand, others found that the influence of age on the upper level of analgesia varies with different volumes, and they emphasized the interindividual variability.²⁰⁻²²

Veering *et al.*^{1,2} studied the influence of age on the clinical profile of bupivacaine 0.5% after epidural administration. They demonstrated that the highest analgesia level and intensity of motor blockade increased with age. Wolff *et al.*²³ studied 3 groups of mainly elderly patients (mean age: 60-65 years) and found a high cephalad spread (median: T4 in all groups) after a fixed epidural dose of different concentrations of ropivacaine (20 ml of either 0.5%, 0.75% or 1.0%) and an intense motor blockade with the 1.0% solution.

In contrast to previous studies with bupivacaine,^{1,2} the time to maximal caudad spread and time to initial onset of motor blockade were not different among age groups in the present study. These findings can be explained by the high concentration of the solution used in our study. A high concentration of the local anaesthetic solution at the sites of action may have promoted a rapid onset of analgesia at the caudal segments and a rapid onset of motor blockade in all age groups. This could have masked the influence of age on these parameters. The reason for choosing a concentration of 1.0% of ropivacaine was that it had proved to provide excellent epidural anaesthesia for orthopaedic surgery.

The difference in height between the youngest and oldest age group corresponds with the increase in average height of the Dutch population (1.3 cm per 10 years during the past 50 years). Because differences in the length of the back are relatively small compared with differences in height, and height is weakly correlated with the number of spinal segments blocked, these differences will not affect the results of this study.²⁴

Our study demonstrated that epidural administration of 15 ml ropivacaine 1.0% was associated with a significant decrease in MAP, particularly in the oldest age group. Nine of the 19 eldest patients experienced a decrease in MAP > 30% during the first hour after epidural induction of anaesthesia. The most likely explanation for the hypotension is the high cephalad spread of analgesia because all patients experiencing hypotension had the highest level of analgesia above the T5-dermatome. Nevertheless, a detrimental effect of age on haemodynamic homeostasis could have contributed to the observed haemodynamic changes.

Hypotension is common with high levels of epidural anaesthesia because of blockade of the preganglionic sympathetic nerve fibres leading to relative hypovolemia and decreased venous return.²⁵ Splanchnic nerve blockade (T6-L1) will result in pooling of the blood in capacitance vessels of the splanchnic bed, contributing to the observed hypotension in patients with high levels of analgesia. In addition, decreased cardiac reserves, structural changes in the arterioles and changes in the autonomic nervous system with increasing age may contribute to substantial hypotension in elderly patients. Epidural anaesthesia extending to high thoracic levels (T1-T4) leads to blockade of the preganglionic cardio accelerator nerve fibres. This may result in reduction of the heart rate. The development of bradycardia after lumbar epidural analgesia extending to low thoracic levels may be the result of decreased cardiac sympathetic tone, decreased venous tone, reflex decrease in heart rate resulting from a decreased degree of pacemaker stretch, or reflex decrease in heart rate mediated via ventricular mechanoreceptors.²⁵

The haemodynamic effects after lumbar epidural administration of a local anaesthetic in elderly patients has been poorly studied. Wolff *et al.*²³ found a high incidence of hypotension and bradycardia with either 20 ml ropivacaine 0.75% or 1.0% in elderly patients. A further reduction of the volume of the local anaesthetic solution seems to be feasible because in our study the administration of 15 ml was also associated with a high incidence of hypotension and bradycardia in older patients.

In conclusion, age influences the clinical profile of ropivacaine 1.0% after epidural administration. With advancing age, the upper level of analgesia and the intensity of the motor blockade increase. Although this solution provides effective epidural anaesthesia, it is associated with a high incidence of bradycardia and hypotension, particularly in elderly patients. Whether this is merely a consequence of the high level of anaesthesia or an additional effect of age on the haemodynamic effects of epidural anaesthesia requires clarification. Further studies are required to determine the optimum dose to provide epidural anaesthesia in the elderly patient.

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