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ORIGINAL ARTICLE

Age and bupivacaine plasma concentrations following radical cystectomy

Maria Gerou · Antonia Steves · Michael Musch · Franz-Josef Wittstamm · Darko Kröpfl · Harald Groeben

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Abstract
Purpose Continuous epidural analgesia with bupivacaine for postoperative analgesia can increase its plasma concentrations. Whether this effect can be aggravated with increasing age is unknown. Therefore, bupivacaine concentrations were prospectively monitored in patients undergoing radical cystectomies.
Methods We analyzed plasma concentrations of bupivacaine in 38 consecutive patients scheduled for radical cystectomy. All patients received general and epidural anesthesia (10 ml bupivacaine 0.5 % followed by bupivacaine 0.375 % every 90 min) and postoperative continuous epidural analgesia (bupivacaine 0.25 % with sufentanil 0.5 μg/ml). For 4 subsequent days, bupivacaine plasma concentrations were measured and the correlation of bupivacaine plasma concentrations with the patient's age were analyzed. Data (mean ± SD) were analyzed by 2-way ANOVA with post hoc analysis or regression analysis.
Results The median age of the patients was 70 years (range 41–86). Postoperatively, bupivacaine plasma concentrations increased significantly. No correlation of plasma concentrations and age could be found. Maximal bupivacaine concentrations of the younger patients were not different from the older patients. No neurological or cardiovascular symptoms of bupivacaine intoxication were found.
Conclusion In conclusion, continuous epidural administration of bupivacaine leads to increasing plasma concentrations. No age dependent differences in bupivacaine plasma concentrations could be found. Therefore, in our patients with intact liver function, we did not find a reason for an age-related restriction in the use of continuous epidural analgesia.

Keywords Bupivacaine · Local anesthetic intoxication · Cystectomy · Age

M. Gerou · H. Groeben (✉)
Department of Anesthesiology, Critical Care Medicine and Pain Therapy, Kliniken Essen-Mitte, Henricistr. 92, 45136 Essen, Germany
e-mail: h.groeben@kliniken-essen-mitte.de

A. Steves · M. Musch · D. Kröpfl
Department of Urology, Pediatric Urology, and Urologic Oncology, Kliniken Essen-Mitte, Essen, Germany

F.-J. Wittstamm
Department of Internal Medicine, Kliniken Essen-Mitte, Essen, Germany

Introduction

Over the last 20 years, the mortality rate for radical cystectomies has markedly improved in particular in patients older than 65 years [1–3]. Overall, age is not a contraindication for these extensive surgical procedures. The improvement can be ascribed to developments in the surgical technique and the effort put into interdisciplinary perioperative management of these patients, known as the fast track concept. One of the cornerstones of the fast track concept is the continuous intra- and postoperative use of epidural anesthesia and analgesia [4–6].

However, there are studies suggesting that the clearance of amide local anesthetics seems to be decreased in elderly patients, indicating a risk of accumulation and intoxication with continuous administration of amide local anesthetics over several days [7–12].

Therefore, to evaluate the risk of bupivacaine accumulation and intoxication in elderly patients, we measured

bupivacaine plasma concentrations postoperatively for 4 days in consecutive patients with a wide range of age, scheduled for radical cystectomies and urinary diversion.

Materials and methods

After approval by the local ethics committee, 40 consecutive patients scheduled for radical cystectomy gave their informed written consent to participate in this study. The inclusion criterion was a duration of postoperative epidural analgesia for 4 days or more. Exclusion criteria were contraindications for epidural anesthesia or refusal of epidural analgesia and compromised liver function.

All patients were diagnosed with intramural bladder cancer and scheduled for radical cystectomy with pelvic lymphadenectomy and urinary diversion. The day before surgery, blood was drawn for the measurement of baseline liver function tests. On the day of surgery a thoracic epidural catheter was placed at the T7/8 or T8/9 thoracic vertebral interspace in a sitting position and a test dose of 3 ml of 0.5 % bupivacaine was administered. Subsequently, general anesthesia was induced with propofol (2.7 ± 1.4 mg/kg) rocuronium (0.6 ± 0.3 mg/kg), and remifentanil (0.12 ± 0.04 μg/kg/min), maintained with isoflurane (0.3–0.5 %), and remifentanil (0.04 ± 0.02 μg/kg/min) in combination with epidural anesthesia.

Patients were orally intubated and mechanically ventilated with an air/oxygen gas mixture. Two intravenous lines, a gastric tube, a temperature probe, a triple-lumen central venous and an arterial catheter were placed. Body temperature was maintained above 36.0 °C. Intraoperative fluid management was left to the discretion of the attending anesthesiologist.

Thirty minutes prior to skin incision, epidural anesthesia was initiated with 10 ml of 0.5 % bupivacaine and maintained with additional doses of 10 ml of 0.375 % bupivacaine every 90 min (high-dose bupivacaine administration). At the end of surgery all patients were awakened and extubated and transferred to the intensive care unit. Duration of surgery was documented.

Postoperatively, according to a standardized protocol, patients received 0.25 % bupivacaine with 0.5 μg sufentanil per ml epidurally with 6 ml (range 5–10) per hour depending on the demands of the patients [numerical rating score (NRS) ≤3 with 0 for no pain and 10 for worst imaginable pain]. Patients were visited 2 times a day and on request. If pain increased above a NRS of 3, boluses of bupivacaine (5 ml 0.5 %) were injected and added to the cumulating dose. No bolus was given within the last 60 min prior to blood sampling. According to the patient's pain, the bupivacaine infusion rate was reduced by 1 ml per visit, i.e. not more than 2 ml of reduction per day. Epidural analgesia was maintained at least until the afternoon of the 4th day. Prior to surgery, immediately postoperatively, and on the 1st and 4th postoperative day, electrocardiograms were taken to detect ischemia or changes possibly due to bupivacaine intoxication (changes in QT time).

Preoperatively, on the evening of the day of surgery, and every morning between 7.30 and 8.30 a.m. on the 4 subsequent days, 8 ml of venous blood were drawn for measurements of bupivacaine plasma concentrations. Cumulative doses of bupivacaine were calculated for 24 h from 8.00 a.m. to 8.00 a.m. the following day. Bupivacaine was measured by high pressure liquid chromatography (Waters GmbH, Eschborn, Germany) with a photodiode array detector, and spectrophotometric detection at 200 nm. The lower level of detection was 0.01 μg/ml with a coefficient of variation less than 0.5 %.

Data analysis

Data are presented as mean ± SD. Sample size was calculated based on an alpha-error of 0.05, a beta-error of 0.2, a standard deviation of 0.5 μg/ml, with a minimal difference to be detected of 0.5 μg/ml to a minimum of 17 patients for each group. Forty consecutive patients were recruited for the study. After the recruitment was completed two groups of patients were formed. The study population was divided by the median of age to form two groups of the same sample size.

The following a priori null hypothesis was tested: maximal bupivacaine plasma concentrations following continuous postoperative administration are not different between the younger half and the older half of the patients.

The hypothesis was tested using a 2-way ANOVA followed by a post hoc test with Bonferroni correction for multiple testing. Patients' characteristics were tested using Student's *t*-test. Null hypotheses were rejected and significant differences assumed with $p < 0.05$.

Results

Demographic data and duration of surgery are presented in Table 1. Two patients were excluded from the analysis because of an early termination of epidural analgesia prior to the 4th day due to an accidental dislocation of the catheter ($n = 1$) and on request of the patient ($n = 1$). Median age of the patients was 70. Patients at the age of 70 and younger were compared to patients older than 70. Except for the age, there were no significant differences between groups (Table 1).

Radical cystectomy was indicated due to recurrent high grade bladder cancer and performed via a median

Table 1 Anthropometric data, duration of surgery, ASA status, intraoperative i.v. fluids and postoperative creatinine (mean ± SD)

	≥70 ($n = 19$)	>70 ($n = 19$)	p value
Height (cm)	172 ± 10	172 ± 9	0.94
Weight (kg)	80 ± 18	77 ± 14	0.61
Age (years)	58 ± 9	77 ± 4	<0.0001
Gender (f/m)	7/12	6/13	0.73
ASA (I/II/III)	2/9/8	1/4/14	0.14
Surgery (min)	360 ± 67	330 ± 53	0.14
Fluid crist. (ml)	5,026 ± 1,496	4,878 ± 1,263	0.75
Fluid coll. (ml)	605 ± 315	694 ± 251	0.35
Creatinine (mg/dl)	0.7 ± 0.2	1.1 ± 0.5	0.0046

Table 2 Cumulated bupivacaine dose per body weight (mean ± SD; $p = 0.1749$) and postoperative day (POD)

	<70 ($n = 19$)	>70 ($n = 19$)
Day of surgery (mg/kg)	6.1 ± 2.1	5.8 ± 1.9
POD 1 (mg/kg)	11.5 ± 3.9	10.8 ± 2.8
POD 2 (mg/kg)	17.2 ± 6.6	15.9 ± 3.7
POD 3 (mg/kg)	22.8 ± 9.5	20.8 ± 4.7
POD 4 (mg/kg)	26.9 ± 12.7	25.3 ± 5.8

laparotomy. Furthermore, all patients underwent simultaneous pelvic lymphadenectomy and urinary diversion (ileal conduit $n = 29$, ileal neobladder $n = 7$, continent pouch $n = 2$, uretero-sigmoidostomy $n = 1$, ureterocutaneostomy $n = 1$). At the end of surgery all patients were awakened, extubated and transferred to the intensive care unit.

The total dose of bupivacaine administered from the time of surgery until the 4th postoperative day was not different between the two groups of patients (Table 2; $p = 0.28$). Bupivacaine plasma concentrations increased significantly during the observation period in both groups (Fig. 1; $p < 0.0001$).

Bupivacaine plasma concentration at the end of the high-dose administration during surgery did not show a significant difference between the young and old age groups (0.7 ± 0.3 vs 0.7 ± 0.3 µg/ml; $p = 0.78$). Subsequently, during low dose epidural bupivacaine administration for postoperative analgesia, no significant difference between groups could be found at any time point, either (Fig. 1; $p = 0.96$). Fourteen patients required bolus of bupivacaine (8 in the group of younger and 6 in the group of older patients). Only 2 patients asked for a total of three bolus (within 2 days). Accordingly, the maximal individual bupivacaine plasma concentration was not different between groups (Fig. 1; $p = 0.64$).

Correlation of the maximal postoperative bupivacaine plasma concentrations with the age of the patients (range

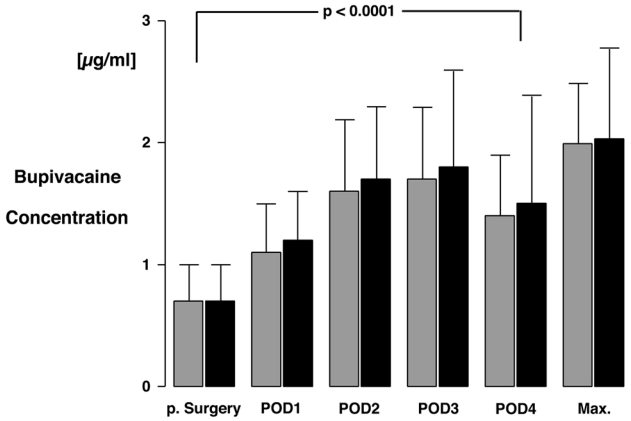

Fig. 1 Postoperative bupivacaine plasma concentrations in 38 patients due to thoracic epidural analgesia following radical cystectomy (mean ± SD). Nineteen patients were 70 years old or younger (*gray bars*) and 19 patients were older than 70 years (*black bars*). Bupivacaine plasma concentrations increased significantly for both groups without a significant difference between the two age groups. Maximal bupivacaine plasma concentrations are presented on the right (Max.; p = non significant)

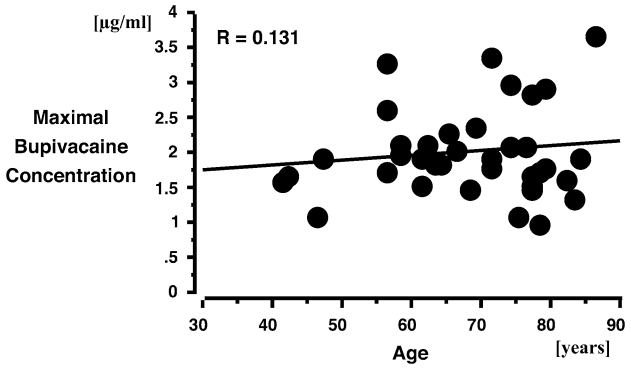

Fig. 2 Maximal individual bupivacaine plasma concentrations during 4 postoperative days in 38 patients following radical cystectomy. Bupivacaine plasma concentrations are presented in relation to the age of the patients. No evident correlation of age and maximal bupivacaine plasma concentrations could be found ($R = 0.131$; equation $y = 1.542 + 0.007x$; intercept = 1.542; $p = 0.4343$)

45 years, median 70 years) did not reveal any age-related dependency (Fig. 2; $R = 0.131$; equation $y = 1.542 + 0.007x$; intercept = 1.542; $p = 0.4343$). The cumulative dose of bupivacaine correlated with the corresponding bupivacaine plasma concentrations without any age-related differences (Fig. 3; $R = 0.522$; equation $y = 0.7564 + 0.035x$; intercept = 0.756; $p < 0.0001$).

Patients were visited at least twice daily. No signs of neurologic intoxication or changes of the electrocardiogram could have been associated with increased bupivacaine plasma concentrations. There were no differences between the two groups concerning transfusion requirements (young 0.53 ± 1.07 vs old 0.84 ± 1.30 U of red

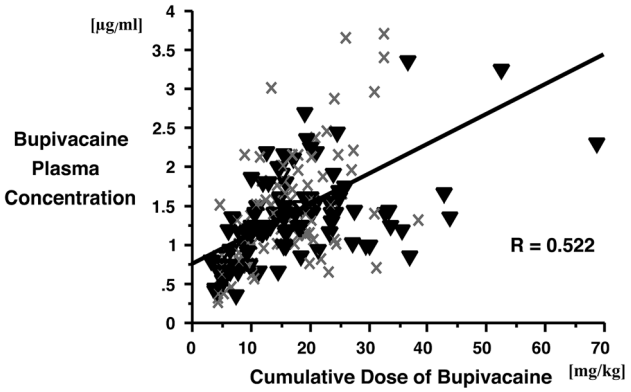

Fig. 3 Individual postoperative bupivacaine plasma concentrations of 38 patients in relation to their cumulative dose per kg body weight (x = group of older patients; *triangle* group of younger patients). There was a significant correlation from the day of surgery to the 4th postoperative day ($R = 0.522$; equation $y = 0.7564 + 0.035x$; intercept = 0.756; $p < 0.0001$)

packed cells; $p = 0.42$). Intravenous fluid requirements are presented in Table 1.

Discussion

Continuous epidural administration of bupivacaine leads to increasing plasma concentrations of bupivacaine up to the 3rd postoperative day. No age-related differences in bupivacaine plasma concentrations could be found.

One cornerstone of the fast track concept for patients undergoing major abdominal surgery is the continuous epidural administration of local anesthetics for analgesia and sympathicolysis [4–6]. In particular, elderly patients with significant co-morbidities seem to benefit from this concept [1]. However, there is concern that with increasing age the continuous administration of local anesthetics over days might lead to accumulation and intoxication [13]. Therefore, the aim of the study was to evaluate the relationship between age and bupivacaine plasma concentrations following several days of continuous epidural administration.

We found increasing bupivacaine plasma concentrations in both age groups up to the 3rd postoperative day. On the 4th postoperative day, bupivacaine plasma concentrations started to decline with decreasing need for epidural analgesia. This can be explained in terms of a saturation kinetic determined by the continuous administration and the metabolic capacity of the patient's liver, and a decreasing need for analgesia.

In 1987 Burm et al. [10] measured and calculated the pharmacokinetics of lidocaine and bupivacaine following a single epidural administration using stable isotopes. They proposed that, with continuous administration, a steady state of bupivacaine plasma concentration should be reached after four half lives of bupivacaine, i.e. in less than 24 h [10]. The plasma concentration after 24 h should not exceed 1.0 µg/ml. Their calculation for the plasma concentration after 24 h matched our results [10]. However, subsequently the bupivacaine plasma concentrations still increased in our patients to more than 2.0 µg/ml. Similarly, plasma concentrations have been measured by Ross et al. [14]. Ross et al. measured bupivacaine plasma concentrations for 44 h in 9 patients with continuous epidural analgesia following major abdominal surgery (0.125 % bupivacaine with 20 ml/h). They found increasing plasma concentrations up to their final measurement. Although bupivacaine plasma concentration exceeded 2.0 µg/ml in 7 of 9 patients, none of the patients developed symptoms of bupivacaine intoxication [14]. These results were confirmed most recently by our own results with levobupivacaine [15]. Following continuous epidural administration of levobupivacaine, plasma concentrations increased over days to concentrations that have been reported to cause neurological symptoms or ECG alterations, but none of these symptoms could be detected in these patients [15].

With meticulous measurements, cardiac effects, such as QRS widening and decrease of stroke volume index, can be detected at plasma concentrations below 2 µg/ml, while neurological symptoms occur with plasma concentrations of 2.7 µg/ml and higher [16–20]. Life-threatening cardiovascular symptoms were described in animal studies at plasma concentrations of 9.4 µg/ml [21, 22]. However, all these results were described in settings of acute intoxications, with unintentional intravascular injections in man or deliberate high-dose intoxications in animals.

In 1975, Scott demonstrated that the threshold of critical intoxication with amide local anesthetics depends on the duration of administration [23]. Administration over a longer period of time leads to tolerance of higher plasma concentrations [23]. This might explain why we did not find any neurological symptoms of intoxication in our patients, despite plasma concentrations up to 3.7 µg/ml.

We measured bupivacaine plasma concentrations resulting from high-dose intraoperative epidural administration to the subsequent continuous relatively lower dose for postoperative analgesia. Subsequently, postoperative administration of bupivacaine was adapted according to the patient's pain and included the option of bupivacaine bolus administration on request.

Our results could have been altered by bolus administration of bupivacaine, but based on an established standard for postoperative analgesia, we had a low rate of bolus requirements. Only 14 patients required a bolus, which was always administered during the day, hours after the last and about 12 h or more prior to the next blood sampling for bupivacaine plasma concentrations. Hence, we think that bupivacaine bolus administration did not alter our results.

Furthermore, studies on age-related changes in the clearance of local anesthetics are complicated by the fact that, so far, no boundary has been defined where age-related metabolic changes start to alter the metabolism of local anesthetics. This makes it difficult to define study groups of old and young patients. Therefore, we decided to divide our study population by the median of age. This way, we could analyze two groups of the same sample size and use a range of 45 years of age.

In conclusion, we found that continuous administration of bupivacaine for epidural analgesia leads to increasing bupivacaine plasma concentrations up to the 3rd postoperative day. With an equal total dose of bupivacaine in a group of young versus elderly patients, no age-dependent differences in bupivacaine plasma concentrations could be found. None of the patients developed neurological or cardiovascular symptoms of local anesthetic intoxication. Therefore, in our group of patients with normal liver function, we could not find a reason to restrict the use of continuous epidural analgesia with bupivacaine as part of the fast track concept. However, we have to stress the point that our statistical approach was set to test the hypothesis that there is a difference (which could be rejected), not to prove equality, which would require a different study design.

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