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ORIGINAL ARTICLE

Influence of bupivacaine injection dose rate on cardiovascular depression, subsequent hemodynamic course, and related bupivacaine plasma levels in piglets

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Abstract
Purpose Systemic local anesthetic (LA) toxicity resulting from inadvertent intravascular injection of LA is a rare but potentially fatal event. Early recognition of intravascular injection and approaches to improve therapeutic safety are required. This study investigated the influence of intravascular injection dose rate of bupivacaine on bupivacaine plasma levels and timing of LA-induced cardiovascular compromise.
Methods Forty-five piglets, anesthetized with sevoflurane, were randomized into three groups. Bupivacaine was intravenously infused at a rate of 1, 4, or 16 mg/kg/min (groups A, B, and C, respectively) until mean arterial pressure (MAP) dropped to 50% of initial value. Thereafter, bupivacaine infusion was stopped and spontaneous hemodynamic course was observed. Time to MAP 50%, amount of bupivacaine infused, bupivacaine plasma level at infusion stop, spontaneous survivors, or time from bupivacaine stop to circulatory arrest were recorded.
Results Median time to MAP 50% was 297, 119, and 65 s, respectively, in groups A, B, and C ($P < 0.001$). Median corresponding total amounts of bupivacaine infused were 5.0, 7.8, and 17.0 mg/kg ($P < 0.01$), and median bupivacaine plasma levels were 53.8, 180.0, and 439.8 μmol/l ($P < 0.001$). Five of 15 piglets in group A recovered spontaneously; in groups B and C, all animals died within 120 and 21 s, respectively.
Conclusion Higher dose rates of bupivacaine showed much higher plasma bupivacaine levels related to absolute infused dose at MAP 50% and were associated with an increased mortality. Slow administration of LA is recommended to allow timely detection and stopping of inadvertent intravascular administration.

Keywords Local anesthetics · Cardiac toxicity · Regional anesthesia · Pediatric anesthesia

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Introduction

Systemic local anesthetic (LA) toxicity caused by inadvertent intravascular injection of LA is a rare but potentially catastrophic complication of regional anesthesia [1, 2]. Strategies for early recognition of intravascular injection and approaches to increase therapeutic safety are therefore required [3–5]. Slow injection of LA is generally recommended on the assumption that toxicity is thereby reduced. So far, however, data documenting a clinical benefit from the slow injection of LA are lacking.

In clinical practice, pediatric patients, especially those with low body weight, are at highest risk for fast, high-speed LA injection (mg/kg body weight over time). A volume of 2 ml can be injected within 5 s, whereas in an adult patient 40 ml LA solution cannot be injected within such a short period. Additionally, the smaller-sized syringes used for children have plungers with a smaller surface area compared to those for adults, which means that with similar pressure LA can be injected very rapidly in

pediatric patients. In a single-shot caudal block, high LA doses related to children's body weight are administered. These amounts represent potentially toxic doses of LA, especially when inadvertently injected into the vascular system. Regional anesthesia in children is often performed as the last step during preparation before surgery, so injections are often performed quickly to compensate for other delays in preparing the patient.

The present study investigates the influence of dose rate of intravenously administered bupivacaine on elapsed time to occurrence of hemodynamic collapse and coinciding cardiovascular morbidity and mortality as well as bupivacaine plasma concentrations in piglets. We hypothesize that in accidental intravascular administration of bupivacaine, a slow injection technique assists in recognition of cardiovascular depression at lower bupivacaine plasma concentrations, with a higher probability for spontaneous recovery and a prolonged time interval for starting resuscitation before asystolic cardiac arrest occurs.

Methods

After approval from the local Ethics Committee for Animal Experiments, 45 healthy male and female piglets (up to 6 weeks of age) were used. Because there were no similar studies to perform sample size calculation, a relatively large number of animals were chosen in this pilot study to take into account the known large interindividual variability in systemic toxic reactions caused by LA [6].

General anesthesia was induced and maintained using sevoflurane (sevorane; Abbott, Baar, Switzerland). For anesthesia induction the sevoflurane vaporizer was set to 8 vol% using 4 l fresh gas flow. Later, inspiratory sevoflurane was reduced according to anesthesia depth. For maintenance, end-tidal sevoflurane of 4.5–6.0 vol% was required. After establishing a peripheral venous access in an auricular vein, the trachea was intubated with a cuffed tracheal tube and the lungs were artificially ventilated (Cato; Draeger Medical, Liebefeld, Switzerland). Inspiratory O_2 of 50–60 vol% was provided. End-tidal CO_2 was held between 4.5 and 5.0 kPa.

Monitoring (Datex-Ohmeda AS3; Anandic Medical Systems, Diessenhofen, Switzerland) consisted of pulse oximetry, three-lead electrocardiogram (ECG), invasive arterial blood pressure measurement after cutdown cannulation of carotid artery, end-tidal gas analysis (sevoflurane, O_2, CO_2), and rectal temperature control to guide normothermia. A central venous line was inserted into the external jugular vein by cutdown for administration of maintenance fluids (Ringer lactate with 2% glucose; Dr. G. Bichsel, Interlaken, Switzerland) and bupivacaine (Duracain 0.125%; Sintetica, Mendrisio, Switzerland and Carbostesin 0.5%; AstraZeneca AG, Zug, Switzerland). Arterial blood was sampled for determination of baseline plasma protein level concentration and blood gas analysis before starting bupivacaine infusion. Total protein plasma level was assessed as a global parameter for appropriate protein production. Blood gas analysis assured normoventilation. The pigs were randomly allocated to three groups. Plain bupivacaine was continuously infused through the central venous line using a syringe infusion pump (Alaris TIVA; IVAC Corporation, Hampshire, UK) at three different rates: in group A, bupivacaine was infused at a rate of 1 mg/kg/min (bupivacaine 0.125%, 0.8 ml/kg/min), in group B at 4 mg/kg/min (bupivacaine 0.125%, 3.2 ml/kg/min), and in group C at 16 mg/kg/min (bupivacaine 0.5%, 3.2 ml/kg/min). Because of the speed rate limitation of the syringe infusion pump, we had to increase the bupivacaine concentration in group C.

Dead space in the bupivacaine infusion line was 0.36 ml. Considering the high injection speed rates (0.8–3.2 ml/kg/min), the dead space was ignored. Bupivacaine was stopped when mean arterial pressure (MAP) was reduced by 50% from the starting value. Blood samples to assess bupivacaine plasma level were then immediately taken. Bupivacaine plasma levels were determined using high pressure liquid chromatography with mass spectrometry detection (Institute for Clinical Chemistry, University of Zurich). This assay has a coefficient of variance of 1.9% for clinically used plasma levels and 5.9% for excessive toxic plasma levels, respectively. Spontaneous hemodynamic course was observed. Time to MAP 50%, total amount of bupivacaine infused, bupivacaine plasma level at infusion stop, spontaneous survivors, or time from bupivacaine stop to circulatory arrest were recorded.

Primary outcomes were total amount of bupivacaine infused until MAP 50% and bupivacaine plasma level at infusion stop. Secondary outcome was spontaneous hemodynamic course either to recovery (survivors) or to death (time from bupivacaine stop to cardiac arrest).

Randomization was performed manually by drawing lots. Epidemiological data, time to MAP 50%, bupivacaine infused, and bupivacaine plasma levels were compared using Kruskal–Wallis and Mann–Whitney U tests. Computer package SPSS version 16.0 (SPSS, Chicago, IL, USA) was used from the hospital resources for this purpose. Data are presented as median and range. $P < 0.05$ was considered to be significant.

Results

Demographic variables, baseline conditions, and study results are expressed in Table 1. Time to MAP 50% was

Table 1 Demographic variables and measured values at start of anesthesia (T_1), at start of bupivacaine infusion (T_2), and at mean arterial pressure (MAP) 50% (T_3)

Variable	Group A ($n = 15$)	Group B ($n = 15$)	Group C ($n = 15$)
T_1			
Weight (kg)	4.9 (4.5–6)	5 (4.1–5.7)	5.2 (4.5–5.5)
Sex (M/F)	11/4	10/5	9/6
Plasma protein level (g/l)	36 (25–47)	34 (27–49)	36 (30–46)
T_2			
pH	7.449 (7.367–7.516)	7.479 (7.356–7.555)	7.475 (7.392–7.547)
MAP (mmHg)	47 (44–52)	46 (44–54)	49 (45–60)
Heart rate (bpm)	133 (92–167)	139 (115–160)	122 (109–153)
T_3			
Time to MAP 50% (s)	297 (186–1495)$^{\ddagger,\#\#}$	119 (85–207)$^{**,\#\#}$	65 (48–79)‡,**
Heart rate (bpm)	97 (54–132)	86 (61–120)	76 (37–107)
Bupivacaine infused (mg/kg)	5.0 (3.1–24.4)$^{\dagger,\#}$	7.8 (5.5–12.9)$^{*,\#}$	17.0 (12.0–20.0)†,*
CV bupivacaine infused (%)	84.8	25.6	11.8
Plasma-bupivacaine (μmol/l)	53.8 (40.6–101.9)$^{\ddagger,\#\#}$	180 (103.3–686.1)$^{**,\#\#}$	439.8 (245.0–693.0)‡,**
CV plasma-bupivacaine (%)	28.6	69.5	24.7
Ratio plasma-bupivacaine to bupivacaine infused	11.2 (2.9–22.2)	21.0 (14.2–60.9)	26.3 (16.2–41.2)
Spontaneous survivors	5	0	0
Time MAP 50% to death (s)	(78–∞)	120 (30–296)	21 (10–123)

Results are given in median (range)

CV coefficient of variance

* $P < 0.01$, ** $P < 0.001$ significant, compared with group A

† $P < 0.01$, ‡ $P < 0.001$ significant, compared with group B

$^{\#}$ $P < 0.01$, $^{\#\#}$ $P < 0.001$ significant, compared with group C

shortest in group C (65 s; range, 48–79 s), longer in group B (119 s; 85–207 s); and longest in group A (297 s; 186–1,495 s) ($P < 0.001$ for group A compared to group B, group A to C, and group B to C). Time course of heart rate and MAP during bupivacaine infusion are shown in Fig. 1.

Total amount of bupivacaine infused until MAP decreased to 50% of initial value was 5.0 (range, 3.1–24.4) mg/kg in group A, 7.8 (5.5–12.9) mg/kg in group B, and 17.0 (12.0–20.0) mg/kg in group C ($P < 0.01$ for group A compared to group B; $P < 0.001$ for group A compared to C and group B compared to C) (Fig. 2). Corresponding bupivacaine plasma levels at MAP 50% were 53.8 (4.6–101.9) μmol/l in group A, 180.0 (103.3–686.1) μmol/l in group B, and 439.8 (245.0–693.0) μmol/l in group C ($P < 0.001$ for group A compared to group B, group A to C, and group B to C) (Fig. 3). There was marked variability within the groups concerning total amount of bupivacaine infused as well as in bupivacaine plasma levels. The relationship between bupivacaine plasma levels and total bupivacaine infused was 2.5 fold higher with a rapid infusion rate compared to a slow infusion rate. Neurological signs such as seizures or related movements were not observed in any of the 45 piglets. Five of 15 piglets in group A spontaneously recovered, whereas in group B and C all animals died within 120 and 21 s, respectively, from pulseless electrical activity or from asystolic cardiac arrests (Fig. 4).

Discussion

This study investigated the impact of different intravenously applied bupivacaine dose rates on duration to cardiovascular depression, related bupivacaine plasma levels, and subsequent hemodynamic course. The main findings were that with higher dose rates of bupivacaine there was a shorter time to 50% reduced blood pressure of initial value. However, when blood pressure was reduced to 50% a significant higher total dose of bupivacaine was already administered, causing higher mortality, reduced time to death, and higher absolute bupivacaine plasma level. Surprisingly, there were overproportionally high bupivacaine plasma levels with higher dose rates at MAP 50%. These data should convert suggestions to inject LA slowly into a fact-based recommendation.

Earlier investigations have shown that an intravenous bolus injection of LA causes a sharp peak in the arterial LA plasma level [7–9]. Subsequent decrease in plasma level

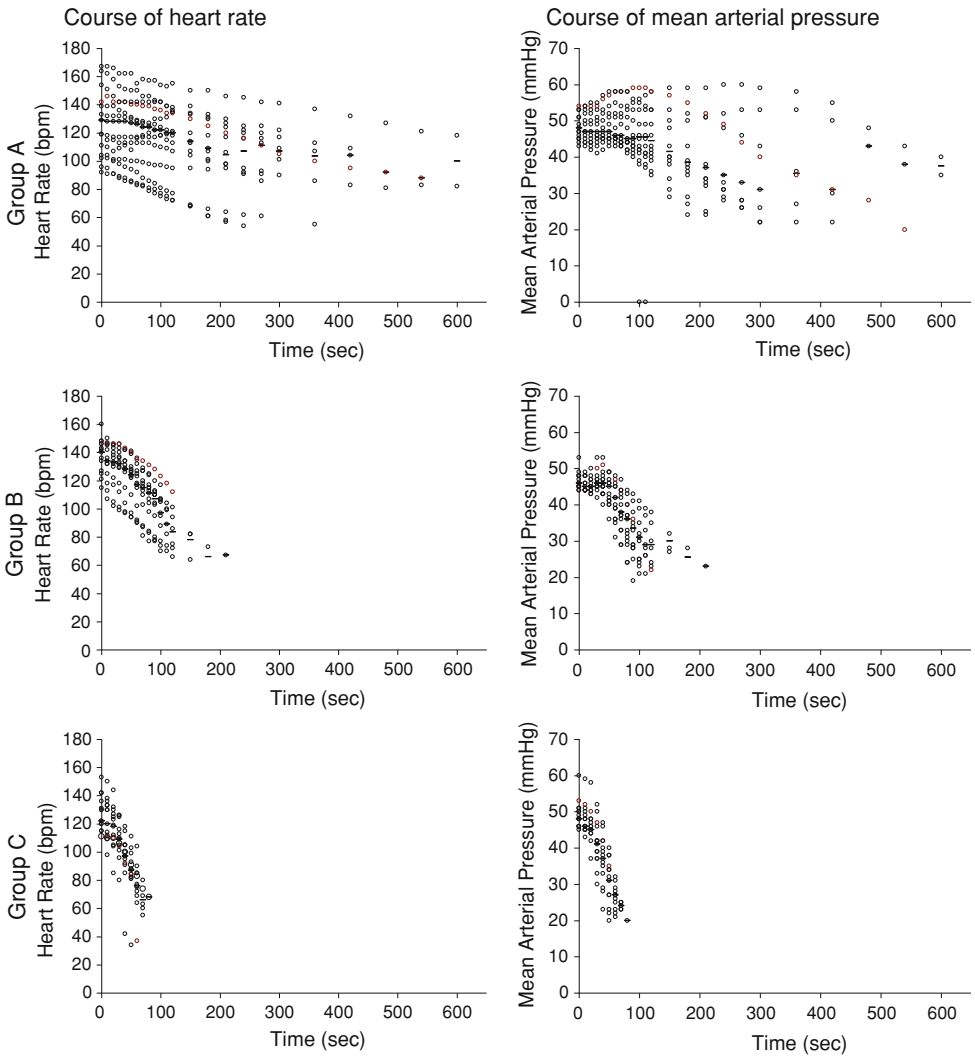

Fig. 1 Time course of heart rate (*left*) and mean arterial pressure (*right*) during bupivacaine infusion ($n = 15$ pigs per group). Median is shown by a *dash*

depends upon blood flow, uptake into organs and various tissues (distribution), and metabolism and excretion (elimination) [7]. For bupivacaine there is a rapid decrease in plasma level over only a few minutes, caused by very rapid distribution into well-perfused organs and a very high first-pass uptake (80–90%) within the lungs [10, 11]. With a slow injection technique there is more time available for initial distribution of the drug. Mather et al. [7] found in a conscious sheep model that prolonging intravenous infusion time of 37.5 mg levobupivacaine from 1 to 3 min reduces arterial C_{max} by $\sim$40%. Corresponding to the results of Mather in the current pig study, a disproportionately higher bupivacaine plasma level related to total injected amount of bupivacaine was found in higher dose rates compared to lower dose rates. This finding is explained by a more pronounced distribution of bupivacaine by cardiac output and uptake within different tissues. Although reduction in blood drug concentrations is undoubtedly beneficial, the most important feature of reduced injection speed or dose fractioning is that it gives the anesthesiologist an early sign to cease further administration of bupivacaine and more time to react before cardiac arrest occurs, as clearly demonstrated by the results of this study where MAP 50% occurred at lower doses of bupivacaine if slowly injected. If the drug administration was stopped at this point, the spontaneous hemodynamic course and survival were significantly better. Five of 15 pigs in group A spontaneously recovered, whereas all pigs in group B and C died. The animals showed a continuous decrease in heart rate and MAP progressing to pulseless electric activity and asystole, most likely the result of cardiac depression caused by bupivacaine toxicity.

In addition, previous investigations with a slow and a fast bupivacaine infusion rate [5] showed that with the slower infusion rate T-wave elevation in the ECG appeared at lower administered doses. We hypothesize that, although the LA solution was given into a central vein, the circulation time needed to distribute the drug from the injection

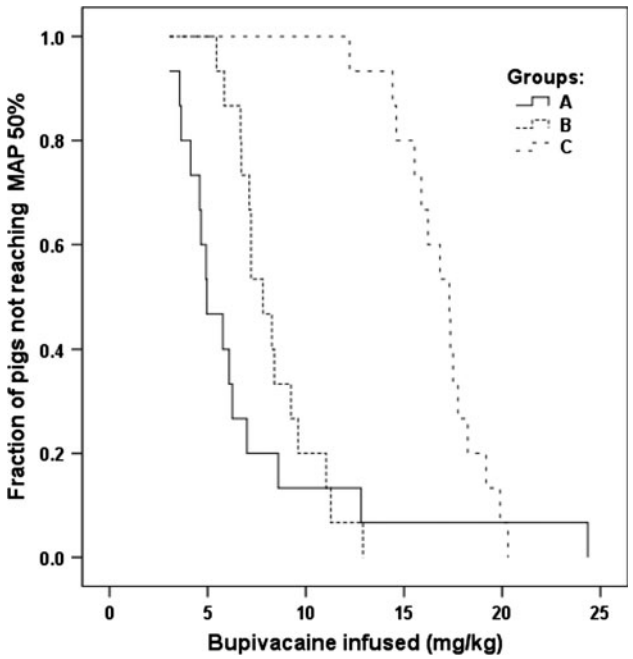

Fig. 2 Kaplan–Meier plot of total amount of bupivacaine infused (mg/kg) until mean arterial pressure (MAP) decreased to 50% of pre-infusion value

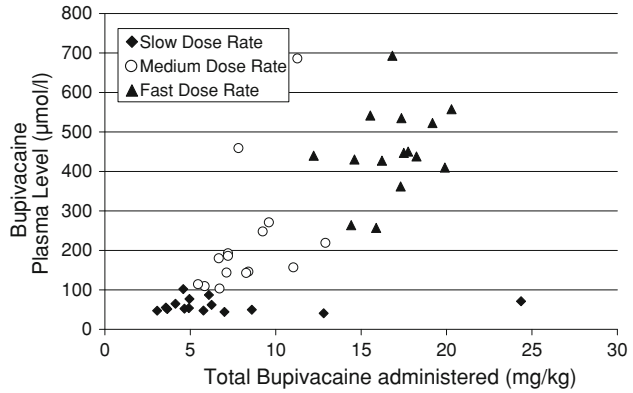

Fig. 3 Distribution of total amounts of bupivacaine infused and related plasma levels at achievement of 50% of initial mean arterial pressure

site into cardiac tissue is responsible for the delay in ECG alteration in the fast infusion group. This finding clearly underlines the necessity for slow LA administration: not only to avoid high plasma peak levels but also to not miss LA-related ECG alterations requiring early cessation of LA injection.

The large variability of bupivacaine plasma levels found in this study is explained, not by inaccuracy of the laboratory testing method (CV for clinically used plasma levels, 1.9%; for excessive toxic plasma levels, 5.9%) or sampling technique, but by individual differences in pharmacokinetics [6].

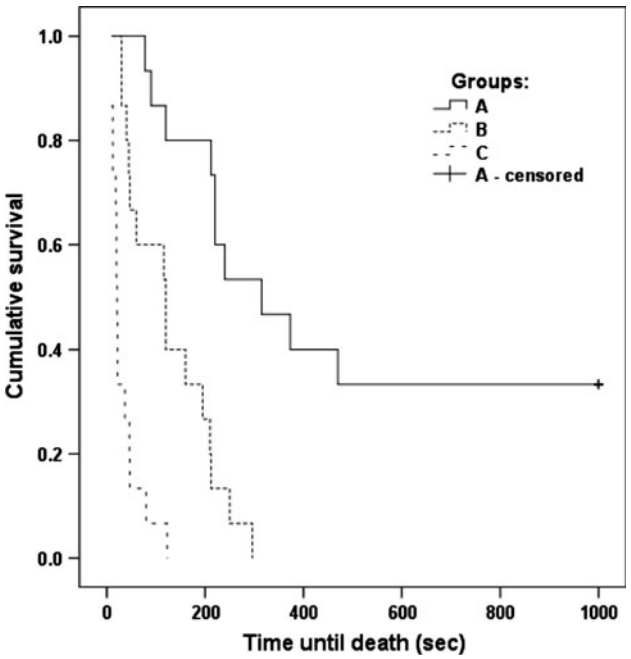

Fig. 4 Kaplan–Meier plot of time from stop of bupivacaine infusion until cardiac arrest

The toxic threshold of LA is subject to a huge variability between individuals [6, 12, 13]. Therefore, this intoxication study was not designed with a fixed bupivacaine dose to study the spontaneous hemodynamic course with different injection rates. By administering a fixed drug dose in all subjects, the individual responsiveness, pharmacokinetics, and dynamics to the drug will bias the results. Intoxication will not be equal among the subjects studied, and therefore the clinical course will also be different. In contrast, administering individually adapted drug dosages targeted to a clinically defined intoxication level (for example, depressed blood pressure to 50% of initial MAP, as used in this study) has the advantage that intoxication degree is as uniform as possible in all subjects, which provides a pathophysiologically uniform basis to compare the courses. In addition, in daily practice it is also the clinical marker that alerts the anesthesiologist to a problem. For humans there is no defined toxic dose and, moreover, there is no maximum safe dose. There are case reports in which intoxication occurred before the predetermined (within recommended range) LA dose injection was completed [14–16] and with very low doses of bupivacaine injected [13]. In these cases, the anesthesiologist stopped the LA injection in response to the clinical deterioration of the patient.

There are limitations in this study. Compared with humans we applied huge doses of bupivacaine in this pig study because in pigs very high bupivacaine doses are needed to provoke severe hemodynamic disturbances.

Udelsmann and colleagues [17] injected 4 mg/kg bupivacaine intravenously in 40 healthy pigs. The subjects tolerated the drug and recovered spontaneously to nearly baseline cardiovascular values. Nyström and coworkers [18] infused bupivacaine at a rate of 1 mg/kg/min in pigs, and there was no cardiac arrest up to >6 mg/kg. To reliably induce cardiovascular arrest in pigs other investigators applied 10 mg/kg bupivacaine intravenously as a bolus injection [19]. Therefore, the results of this pig study have to be interpreted qualitatively and not quantitatively.

In conclusion, this animal model clearly demonstrates that with a slow LA injection technique cardiac toxicity (hemodynamic depression) can be recognized at an earlier stage with lower doses of administered bupivacaine, lower plasma bupivacaine levels, and higher chance of successful outcome. Although often ignored, slow injection of LA must become the standard of care and regularly taught in pediatric anesthesia.

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Conflict of interest None.

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