Upsala J Med Sci 111 (2): 189–200, 2006

Ropivacaine May Have Advantages Compared to Bupivacaine in Porcine Endotoxemic Shock

[1]Diana K. Mutschler, [2]Urban Gustafsson, [3]Samar Basu, [4]Anders O. Larsson and [1]Mats B. Eriksson

[1]Department of Surgical Sciences, Anaesthesia and Intensive Care, Uppsala University Hospital, SE-751 85 Uppsala, Sweden. [2]AstraZeneca R & D, SE-151 85 Södertälje, Sweden. [3]Department of Geriatrics and Clinical Nutrition Research, Uppsala University Hospital, SE-751 85 Uppsala, Sweden. [4]Department of Medical Sciences, Clinical Chemistry, Uppsala University Hospital, SE-751 85 Uppsala, Sweden.

ABSTRACT

Patients that undergo major abdominal surgery often receive epidural postoperative analgesia. Septic complications are frequently seen in this cohort. In a porcine model of endotoxemic shock, resembling human gram-negative septic shock, we evaluated the effects of two widely used local anaesthetics, bupivacaine and ropivacaine given intravenously. In the endotoxin-ropivacaine group mixed venous saturation and platelet count were higher as compared to endotoxemic controls. Mean arterial blood pressure and platelet count were higher in ropivacaine-endotoxin pigs than in bupivacaine-endotoxin ones. Bupivacaine augmented endotoxin-mediated decrease in left ventricular stroke work index. Ropivacaine displays pathophysiological advantages compared to bupivacaine in septic shock, which may be explained by improved tissue perfusion by ropivacaine.

INTRODUCTION

Septic complications may be seen in the postoperative phase; especially after major bowel surgery (1, 2). Intra-abdominal bacteria may enter the bloodstream and hereby cause a septic condition. This may progress to full-blown septic shock, a feared disorder with high mortality, which is frequently seen in intensive care units. Septic shock is associated with impairment of several vital functions *e.g*. decreased cardiac performance, pulmonary disturbances, production of lipid peroxidation metabolites, and activation of both the complement and the coagulation cascades (3, 4). Gram-negative septic shock can be replicated by intravenous application of endotoxin in the anesthetized pig (5, 6).

Received 7 November 2005
Accepted 23 November 2005

Local anaesthetics inhibit prostaglandin-mediated receptor signalling, which may explain some of the effects of local anesthetics on physiologic responses such as platelet aggregation, fever, inflammation, and hyperalgesia in the perioperative period (7). Furthermore, the local anaesthetic agent lidocaine decreased the inflammatory reaction in experimental small-bowel obstruction (8) and in experimental lung injury (9). Intravenous lidocaine improved hemodynamics, reduced activation of the cytokine network and increased survival in experimental endotoxemia (10-12), a condition characterized by an extensive inflammatory reaction.

Anaesthetic management of major bowel surgery often comprises the use of epidural anaesthesia for postoperative pain relief. The local anaesthetic agents bupivacaine and ropivacaine are frequently used drugs for continuous epidural analgesia because of their long duration time. Since knowledge concerning these two long acting local anaesthetics is most limited in septic conditions, we wanted to explore the possible pharmacological effects of bupivacaine and ropivacaine in an experimental sepsis model. Furthermore, both ropivacaine and bupivacaine may have anti-inflammatory potencies as the structurally closely related local anaesthetic lidocaine, since they all modulate the inflammatory response by limiting toxic oxygen metabolite production in an inflammatory rat model (13). As ropivacaine is reported to be less toxic than bupivacaine even in equipotent doses (14), we also wanted to investigate possible differences between these two anaesthetics in an animal model replicating human gram-negative septic shock.

MATERIALS AND METHODS

Porcine Model

Twenty-nine healthy piglets of Swedish Country Breed, 10-12 weeks of age, weighing between 21.4 and 28.9 kg were included in this experiment, which was approved (C212/98) by the Animal Ethics Committee of Uppsala University, Sweden. Each animal was anesthetized by an intramuscular injection of 6 mg x kg^{-1} of Zoletil forte vet® (Zoletil 100®; Tilétamine-Zolazépam; Boehringer Ingelheim Vetmedica, Ingelheim, Germany) mixed with 2.2 mg x kg^{-1} of Rompun Vet® (Xylazin; Bayer, Leverkusen, Germany) and 0.04 mg x kg^{-1} of atropine. A continuous intravenous (IV) infusion of sodium pentobarbital (Apoteksbolaget, Umeå, Sweden; 8 mg x kg^{-1} xh^{-1}) was given in order to maintain anaesthesia. Twenty mg of morphine (Pharmacia, Uppsala, Sweden) was injected iv for analgesia prior to tracheotomy, which was rapidly performed in all pigs.

A Servo 900C ventilator (Siemens-Elema, Stockholm, Sweden) provided volume-controlled ventilation. An O_2/N_2O mixture (FiO_2: 0.3) was administered during the surgical preparation followed by O_2 in medical air (FiO_2: 0.3). The ventilatory minute volume was set to obtain an initial $PaCO_2$ between 5.0 and 5.5 kPa and thereafter kept constant during the experiment. The respiratory rate was 25 x min^{-1} and the inspiratory / expiratory time was 1:3. A positive end expiratory pressure of 5 cm H_2O was used throughout the experiment. During the experimental period, an

isotonic glucose (139 mmol/L) and sodium chloride (70 mmol/L) solution was infused at a rate of 8 mL x kg^{-1} x h^{-1}, as well as 0.9% sodium chloride at 22 mL x kg^{-1} x h^{-1}.

Surgical procedures comprised the application of an arterial cannula (into the right common carotid artery) used for blood sampling and monitoring of mean arterial blood pressure (MAP; mm Hg); a 7F Swan-Ganz-catheter equipped with a thermistor (into a branch of the pulmonary artery), and a urinary catheter. Cardiac output (CO; L x min^{-1}) was measured by the thermodilution technique. Central venous pressure (CVP; mm Hg), pulmonary capillary wedge pressure (PCWP; mm Hg), mean pulmonary arterial pressure (MPAP; mm Hg), and heart rate (HR; L x min^{-1}) were determined by a Solar 8000 monitor (Marquette Medical Systems Inc., Milwaukee, WI, USA). The left ventricular stroke work index (LVSWI; mJ x kg^{-1} x m^{-2}) was calculated as MAP x stroke index [stroke index = CO x HR^{-1} x BSA^{-1} (BSA = Body surface area (=0.112 x Body Weight $(kg)^{2/3}$; m^{-2}))] (15). Blood samples, serving as baseline values, were collected from all animals immediately before the start of the bupivacaine-, ropivacaine- or endotoxin-infusion, and thereafter every hour throughout the experiment. The total amount of blood sampled for analysis was less than 5% of each animal's blood volume (16). After centrifugation (1800 x g for 10 min) the plasma samples were stored at –70∞C until analysis. Blood gases were analyzed by an ABL 300 (Radiometer, Copenhagen, Denmark). Arterial and mixed oxygen saturation (SaO_2, and SvO_2, respectively; %) were measured by a hemoxymeter™ (Radiometer, Brønshøj, Denmark).

Protocol

The 29 piglets were allocated by randomization in blocks, to one of the following protocols: 24 animals received intravenous endotoxin (*E. Coli* 0111: B4; Sigma Chemicals, St Louis, MO, USA) at 4 µg x kg^{-1} x h^{-1} until duplication of the MPAP, considered as the onset of a severe experimental endotoxin-induced sepsis (17, 18), and thereafter at 1 µg x kg^{-1} x h^{-1} throughout the 6 h experimental period. The time between the start of the endotoxin-infusion and the doubling of MPAP was 30 – 35 min. Twelve of the animals received either ropivacaine (Narop® (Naropin)), 5mg x mL^{-1}, n = 6, AstraZeneca, Södertälje, Sweden) or the equivalent dosage of bupivacaine (Marcain® Marcaine)), 5mg x mL^{-1}, n = 6, AstraZeneca, Södertälje, Sweden) as an iv bolus of 30 mg each during 5 min immediately after baseline sampling, and thereafter at 15 mg x kg^{-1} x h^{-1} iv during the experiment. The other twelve piglets in the endotoxin group, serving as controls, were given the corresponding volume of saline instead of the local anaesthetic agent. The animals were, still under anaesthesia, killed by an overdose of iv potassium after the termination of the 6 h experiment.

The doses were chosen to mimic the amounts of ropivacaine and bupivacaine respectively, administered in clinical practice for epidural analgesia. Furthermore, these quantities are in the same equipotent range as the dosage of lidocaine chosen in several other animal assays (9, 12). Both ropivacaine and bupivacaine are absorbed rapidly from the epidural space into the circulation, although their kinetics vary (19,

20). It should also be remembered that epidural administration of local anaesthetics, but not saline, cause profound effects on hemodynamics (21). In these circumstances, we decided to administer our drugs iv in order not to interfere pharmacological effects with circulatory changes caused by epidurally administered local anaesthetics.

Five piglets were solely treated with local anaesthetics (three pigs received ropivacaine, two pigs bupivacaine) in combination with saline instead of endotoxin as internal controls to show the stability of the animals' condition during the experimental period. Since ropivacaine and bupivacaine, respectively were evaluated against saline, we decided to use two separate control groups. There were no significant differences in weight, vitals signs or other parameters, between these two control groups.

Laboratory investigations

Radioimmunoassay of 8-iso-$PGF_{2\alpha}$ (an oxidative injury indicator).

Unextracted heparinized plasma samples were analysed for 8-iso-$PGF_{2\alpha}$ as an index of oxidative injury by a newly developed radioimmunoassay in our laboratory (22). The cross-reactivity of the 8-iso-$PGF_{2\alpha}$ antibody with 15-keto-13,14-dihydro-8-iso-$PGF_{2\alpha}$, 8-iso-$PGF_{2\beta}$, $PGF_{2\alpha}$, 15-keto-$PGF_{2\alpha}$, 15-keto-13,14-dihydro-$PGF_{2\alpha}$, TXB_2, 11b-$PGF_{2\alpha}$, 9b-$PGF_{2\alpha}$ and 8-iso-$PGF_{3\alpha}$, respectively was 1.7, 9.8, 1.1, 0.01, 0.01, 0.1, 0.03, 1.8 and 0.6 %. The detection limit of the assay was about 23 pmol/l. This analysis is relevant to apply in the oxidative injury studies as an index of in vivo lipid peroxidation through free radical catalysis mechanism.

Radioimmunoassay of 15-keto-dihydro-$PGF_{2\alpha}$ (an inflammatory response indicator).

Unextracted heparinized plasma samples were analysed for 15-keto-dihydro $PGF_{2\alpha}$as an index of inflammatory response by a newly developed radioimmunoassay in our laboratory (23). The cross-reactivity of the antibody with $PGF_{2\alpha}$, 15-keto-$PGF_{2\alpha}$, PGE_2, 15-keto-13,14-dihydro-PGE_2, 8-iso-15-keto-13,14-dihydro-$PGF_{2\alpha}$, 11b-$PGF_{2\alpha}$, 9b-$PGF_{2\alpha}$, TXB^2 and 8-iso-$PGF_{2\alpha}$ was 0.02, 0.43, <0.001, 0.5, 1.7, <0.001, <0.001, <0.001, 0.01%, respectively. The detection limit was about 45 pmol/l. This analysis is relevant to apply in inflammatory injury, and other physiological and pathophysiological studies, as an index of *in vivo* enzymatic lipid peroxidation.

Platelet count.

Platelet count was analyzed in sodium citrate plasma samples by a Coulter STKS cell counter (Coulter Diagnostics, Hileah, FL)

Statistics

The statistical analysis was performed by Clinical Data Care, Lund, Sweden, using SAS software (SAS Institute 1997). The different variables have been analyzed using a repeated measurement analysis (ANOVA multivariate approach). Wilcoxon

rank sum test was used to evaluate differences between groups at specific time points during the experimental procedure. A p value < 0.05 was considered significant. The results were expressed as mean ± 1 SD.

RESULTS

The different study groups were comparable in all physiological baseline variables (e.g. age, weight, body surface area, or respiratory and hemodynamic parameters). All piglets receiving iv endotoxin responded with duplication of MPAP during the first 30 minutes, followed by subsequent derangements of respiratory and circulatory parameters. The 5 pigs that received local anaesthetics, but not endotoxin remained physiologically stable in all variables throughout the 6 h experimental procedure.

Effects on platelet count

After two hours of endotoxemia the platelet count was higher in the endotoxemic ropivacaine treated pigs than in the endotoxemic controls. These responses of the groups were significantly different when averaged over all time points (p=0.02; Fig. 1). The platelet count was significantly higher in the ropivacaine treated endotoxemic animals as compared to endotoxemic controls at 4 h and 5 h (both: p=0.04). Also, the platelet count was higher in endotoxemic ropivacaine treated pigs at all time points as compared to bupivacaine treated endotoxemic pigs. This difference was most expressed at three hours, but lasted throughout the 6 h endotoxemic period (p=0.04).

There was no significant difference in platelet count between bupivacaine + endotoxin pigs as compared to the saline + endotoxin group (Table 1).

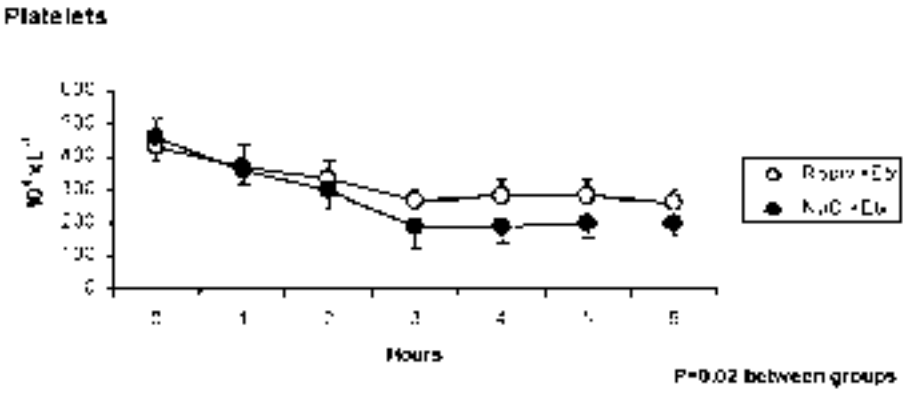

Fig. 1. Effect of a continuous infusion of ropivacaine on platelet count (Platelets; 10^6 x L^{-1}) during endotoxemia. Ropiv.+Etx, ropivacaine and endotoxin group (n=6). NaCl+Etx, controls received saline and endotoxin, (n=6). Mean ± 1SD.

Platelets	Time (hours)	Bupivacaine + Endotoxin	Saline + Endotoxin
	0	394 ± 96	365 ± 146
	1	321 ± 59	319 ± 141
	2	304 ± 79	236 ± 116
	3	156 ± 62	149 ± 89
	4	193 ± 89	191 ± 118
	5	202 ± 84	206 ± 121
	6	202 ± 77	188 ± 111

Table 1. Effect of a continuous infusion of ropivacaine or bupivacaine, respectively, on platelet count (Platelets; 10^6 x L^{-1}) during endotoxemia. Controls received saline and endotoxin. Mean ± 1SD.

Effects on mixed venous saturation (SvO_2)

During the first three hours of the experimental period there was no difference in SvO_2 between ropivacaine injected endotoxemic pigs compared to saline injected endotoxemic controls. However, during the last three hours of the experiment SvO_2 was higher among the ropivacaine treated pigs than in controls. Statistical analysis of the different response profiles revealed that SvO_2 was significantly higher (p=0.02) in ropivacaine treated endotoxemic animals compared to endotoxemic controls. Table 2.

SvO_2	Time (hours)	Ropivacaine + Endotoxin	Saline + Endotoxin	Bupivacaine + Endotoxin	Saline + Endotoxin
	0	72 ± 4	68 ± 10	71 ± 3	68 ± 5
	1	60 ± 20	66 ± 5	67 ± 6	71 ± 4
	2	50 ± 15	48 ± 11	54 ± 4	63 ± 5
	3	49 ± 18	43 ± 15	35 ± 8	45 ± 9
	4	54 ± 15	35 ± 14	40 ± 12	48 ± 6
	5	58 ± 14	40 ± 11	51 ± 14	57 ± 5
	6	61 ± 17	45 ± 12	57 ± 12	60 ± 5

Table 2. Effect of a continuous infusion of ropivacaine or bupivacaine, respectively, on mixed venous saturation (SvO_2; %) during endotoxemia. Controls received saline and endotoxin. Mean ± 1SD.
P = 0.02 between Ropivacaine + Endotoxin *vs* Saline + Endotoxin at 1-6 h.

No difference was found in SvO_2 between the endotoxemic piglets treated with bupivacaine compared to ropivacaine treated or compared to controls.

MAP

In the ropivacaine treated endotoxemic group MAP was significantly higher from the 3rd to the 5th h of the experimental period as compared to bupivacaine treated controls (p=0.04, 0.04, 0.03, respectively; Table 3).

MAP	Time (hours)	Ropivacaine + Endotoxin	Saline + Endotoxin	Bupivacaine + Endotoxin	Saline + Endotoxin
	0	99 ± 13	102 ± 5	104 ± 13	104 ± 19
	1	110 ± 36	110 ± 17	108 ± 6	118 ± 12
	2	88 ± 28	75 ± 16	94 ± 8	112 ± 9
	3	97 ± 34[a]	80 ± 20	68 ± 15	92 ± 20
	4	104 ± 34[a]	76 ± 26	74 ± 20	98 ± 22
	5	102 ± 32 [b]	82 ± 28	79 ± 20	103 ± 25
	6	99 ± 32	82 ± 31	78 ± 21	106 ± 20

Table 3. Effect of a continuous infusion of ropivacaine or bupivacaine, respectively, on mean arterial pressure (MAP; mmHg) during endotoxemia. Controls received saline and endotoxin. Mean ± 1SD.
a : P = 0.04 *vs* Bupivacaine + endotoxin;
b : P = 0.03 *vs* Bupivacaine + endotoxin.

Effects on left ventricular stroke work index (LVSWI)

There was a marked reduction in LVSWI in both ropivacaine and bupivacaine injected endotoxemic pigs. However, during endotoxemia the bupivacaine treated group showed more pronounced deterioration of LVSWI than did the endotoxemic controls (Table 4). This difference between the groups was significant over time (p=0.04).

LVSWI	Time (hours)	Ropivacaine + Endotoxin	Saline + Endotoxin	Bupivacaine + Endotoxin	Saline + Endotoxin
	0	3.5 ± 0.6	3.6 ± 0.3	4.0 ± 0.5	3.7 ± 0.8
	1	3.7 ± 1.9	4.0 ± 0.6	3.8 ± 0.5	4.6 ± 0.9
	2	2.4 ± 1.3	1.8 ± 0.9	2.6 ± 0.5	3.3 ± 0.5
	3	2.3 ± 1.3	1.6 ± 1.3	1.2 ± 0.5	1.8 ± 0.6
	4	2.7 ± 1.3	1.3 ± 1.1	1.4 ± 0.7	2.0 ± 0.6
	5	2.9 ± 1.2	1.4 ± 1.0	1.9 ± 0.6	2.4 ± 0.5
	6	3.0 ± 1.2	1.6 ± 1.1	2.2 ± 0.7	2.7 ± 0.3

Table 4. Effect of a continuous infusion of ropivacaine or bupivacaine, respectively, on left ventricular stroke work index (LVSWI; mJ x kg^{-1} x m^{-2}) during endotoxemia. Controls received saline and endotoxin. Mean ± 1SD.
P = 0.04 between Bupivacaine + Endotoxin vs Saline + Endotoxin at 1-6 h.

Effects of ropivacaine versus bupivacaine on enzymatic and non-enzymatic lipid peroxidation

In the group of ropivacaine-treated endotoxemic pigs, there was at 1 h a significant increase in the production of this free radical mediated prostaglandin metabolite (p=0.02) as compared to the bupivacaine + endotoxin group. During the remaining part of the experiment, the difference in production of 8-iso-$PGF_{2\alpha}$ was less expressed and did not reach statistical significance. There was no difference

between the two local anaesthetics regarding their effect on the production of 15-keto-dihydro-$PGF_{2\alpha}$, a cyclooxygenase-mediated prostaglandin metabolite indicating inflammatory injury (Table 5).

8-iso-$PGF_{2\alpha}$	Time (Hours)	Ropivacaine + Endotoxin	Saline + Endotoxin	Bupivacaine + Endotoxin	Saline + Endotoxin
	0	199 ± 95	148 ± 34	54 ± 27	46 ± 24
	1	492 ± 267	352 ± 153	114 ± 18	161 ± 96
	2	361 ± 94	370 ± 57	106 ± 40	115 ± 62
	3	273 ± 92	312 ± 119	136 ± 35	145 ± 40
	4	227 ± 75	306 ± 156	105 ± 44	105 ± 39
	5	187 ± 33	243 ± 57	83 ± 44	62 ± 27
	6	155 ± 46	196 ± 80	62 ± 42	44 ± 22
15-keto-$PGF_{2\alpha}$	**Time (Hours)**	**Ropivacaine + Endotoxin**	**Saline + Endotoxin**	**Bupivacaine + Endotoxin**	**Saline + Endotoxin**
	0	896 ± 500	941 ± 503	531 ± 336	503 ± 182
	1	3883 ± 4157	7074 ± 5953	3260 ± 1265	3409 ± 1683
	2	2151 ± 1140	3539 ± 3499	2105 ± 1488	2249 ± 1622
	3	2275 ± 1125	2002 ± 435	2535 ± 1456	2515 ± 1403
	4	1836 ± 471	1866 ± 660	1509 ± 1070	1098 ± 381
	5	1530 ± 578	1188 ± 276	818 ± 415	765 ± 313
	6	1061 ± 568	1134 ± 408	566 ± 234	496 ± 151

Table 5. Effect of a continuous infusion of ropivacaine or bupivacaine, respectively, on endotoxin-induced enzymatic and non-enzymatic lipid peroxidation (as evaluated by plasma 8-iso-PGF_{2a} and 15-keto-dihydro-$PGF_{2\alpha}$, respectively; pmol x L^{-1}). Mean ± 1SD.

DISCUSSION

This study was performed to investigate the effects of two commonly used local anaesthetic agents *e.g.* ropivacaine and bupivacaine in a pig model mimicking human gram-negative septic shock, a condition with high mortality rate which may originate after major colo-rectal surgery. In such procedures the epidural technique is frequently used peri- and post-operatively. Lidocaine has been investigated regarding its ability to modulate experimental septic shock (9, 11, 24), but ropivacaine and bupivacaine have not been investigated previously concerning their effects during endotoxemia, a condition characterized by an expressed inflammatory reaction. Although this model of porcine endotoxemic shock is widely used, it should be clearly stated that any animal model may only indicate human reactions and responses. However, animal experiments may help to exclude, or to point out the possible necessity of future studies where humans are involved.

In the present study ropivacaine treatment was associated with higher mixed venous saturation and platelet count during endotoxemia as compared to saline injected controls. In comparison to bupivacaine treated animals the ropivacaine group showed increased

MAP and platelet count. These effects appeared during the second half of the experimental period. At present, it can not be determined whether these effects are due to an initial reaction, which is not blunted by the presence of local anaesthetics or whether a certain "critical level" of these compounds has to be reached in order to moderate the physiological consequences of endotoxemic shock. Systemic endotoxemia is very early associated with trapping of blood cells (platelets, leukocytes) in the different organ tissues, which in turn will lead to reduced tissue perfusion and to organ dysfunction.

Endotoxin parenterally administered to dogs has been found to induce trapping of platelets in the lungs and thereby reducing the platelet concentration in the blood (25, 26). Ropivacaine has anti-inflammatory properties by inhibiting leukocyte rolling and adhesion in the hamster cheek pouch microvasculature (27), and thereby improving the tissue perfusion. Thus, the present finding of higher blood platelet counts in our pig model seen with iv ropivacaine may partly be explained by a reduced trapping of platelets in the lung tissue, and thereby increasing the number of platelets in the blood. As a consequence, the anti-inflammatory effect of ropivacaine may favour improved tissue microcirculation (28), which could be of benefit for organ survival during septic conditions. One mechanism of this response may be that ropivacaine interacts with different ion channels on the platelet cell membrane (27). Furthermore, the increase in mixed venous saturation (SvO2) found with ropivacaine could also speak in favour of a more effective exchange between blood and tissue in the peripheral vascular system.

The reason for the differences between ropivacaine and bupivacaine regarding their interactions with the endotoxin-mediated pathophysiological responses can, at hand, not be fully explained. However, it should be noted that ropivacaine is superior to bupivacaine in maintaining the number of circulating platelets, indicating that platelet aggregation or activation was less prone to occur in the ropivacaine treated pigs. From this point of view, it is interesting that treatment with the combination of two platelet anti-aggregating agents, cilostazol and aspirin, completely inhibited the enhanced pulmonary hemodynamic response to fMLP, a neutrophil chemotactic agent in endotoxin primed rat lungs (29). Platelets, more than coagulation, seem to contribute to some endotoxin-mediated pathophysiological events, since the hemodynamic consequences of experimental septic shock were far less accentuated in dogs pre-treated with an antiplatelet serum compared to controls or defibrinogenated dogs (26). Furthermore, counteracting platelet accumulation by gadolinium counteracts endotoxin-induced hepatic damage (30).

The fact that ropivacaine, but not bupivacaine, elicited an expressed, but non-significant, increase in 8-iso-$PGF_{2\alpha}$ at 1 h, might indicate that ropivacaine possibly may cause a temporary free radical mediated lipid peroxidation. If so, this does not appear to be associated with any negative pathophysiological consequences during porcine endotoxemia. In contrast, we have previously shown that propofol, which markedly reduced both endotoxin-mediated free radical lipid peroxidation and cyclooxygenase catalysed lipid peroxidation at 1 – 4 h, also counteracted endotoxin-induced deterioration of arterial oxygen tension at 2 – 4 h (31).

Since local anaesthetic agents are rapidly absorbed from the epidural space into the circulation (19, 20) it may be of importance that ropivacaine does not aggravate the dreaded

consequences of endotoxemia. Bupivacaine, which has a well-known cardiotoxic potential, caused a further reduction in endotoxin-mediated decrease in LVSWI. This finding may be an inference to the fact that bupivacaine reduced MAP during the later phase of the experiment, whereas ropivacaine did not exert such an effect. Although human studies are necessary before any definite recommendation can be given in the clinical situation, it should be noted that our pig model is suitable for standardizing endotoxemic trauma and evaluating some effects of experimental pharmacological intervention.

ACKNOWLEDGEMENTS

The authors wish to thank Pernilla Rönnlund at Clinical Data Care, Lund, Sweden for statistical analysis of our material. We also wish to express our gratitude to Mikael Åström, Clinical Data Care, Lund, Sweden for constructive discussions concerning these analyses. Anders Nordgren provided excellent assistance and experience in the animal laboratory at Uppsala University Hospital, Sweden. Eva Seiby is acknowledged for excellent technical assistance. We also wish to thank AstraZeneca R & D, Södertälje, Sweden for financial support and valuable discussion in the preparation of this paper. This work was also financed by grants from the Laerdal Foundation for Acute Medicine, Stavanger, Norway

REFERENCES

1. Montravers P, Lepers S, Popesco D (1999). Prise en charge post-operatoire. Reanimation des sepsis intra-abdominaux apres intervention chirurgicale. Presse Med 28: 196-202.
2. Bjerkeset T, Digranes A (1980). Systemic prophylaxis with metronidazole (Flagyl) in elective surgery of the colon and rectum. Surgery 87: 560-566.
3. Basu S, Eriksson M (1998). Oxidative injury and survival during endotoxemia. FEBS Lett 438: 159-160.
4. Shoemaker WC, Appel PL, Kram HB, Bishop MH, Abraham E (1993). Sequence of physiologic patterns in surgical septic shock. Crit Care Med 21: 1876-1889.
5. Modig J. Adult respiratory distress syndrome (1989). Comp Path Bull 21: 2-4.
6. Mutschler DK, Eriksson MB, Wikstrom BG, Lind L, Larsson A, Berggren-Kiiski R, Lagrange A, Nordgren A, Basu S (2003). Microdialysis-evaluated myocardial cyclooxygenase-mediated inflammation and early circulatory depression in porcine endotoxemia. Crit Care Med 31: 1780-1785.
7. Honemann CW, Heyse TJ, Mollhoff T, Hahnenkamp K, Berning S, Hinder F, Linck B, Schmitz W, van Aken H (2001). The inhibitory effect of bupivacaine on prostaglandin E(2) (EP(1)) receptor functioning: mechanism of action. Anesth Analg 93. 628-634.
8. Nellgard P, Jonsson A, Bojo L, Tarnow P, Cassuto J (1996). Small-bowel obstruction and the effects of lidocaine, atropine and hexamethonium on inflammation and fluid losses. Acta Anaesthesiol Scand 40: 287-292.
9. Mikawa K, Maekawa N, Nishina K, Takao Y, Yaku H, Obara H (1994). Effect of lidocaine pretreatment on endotoxin-induced lung injury in rabbits. Anesthesiology 81: 689-699.
10. Taniguchi T. Lidocaine attenuates the hypotensive and inflammatory responses to endotoxemia in rabbits (1996). Crit Care Med 24: 642-646.
11. Taniguchi T. Effects of lidocaine administration on hemodynamics and cytokine responses to endotoxemia in rabbits (2000). Crit Care Med 28: 755-759.
12. Fletcher JR, Ramwell PW. Lidocaine treatment following baboon endotoxin shock improves survival (1979). Adv Shock Res 2: 219-232.
13. Leduc C, Gentili ME, Estebe JP, Le Corre P, Moulinoux JP, Ecoffey C (2002). The effect of local anesthetics and amitriptyline on peroxidation in vivo in an inflammatory rat model: preliminary

reports. Anesth Analg 95: 992-6.
14. Dony P, Dewinde V, Vanderick B, Cuignet O, Gautier P, Legrand E, Lavand'homme P, De Kock M (2000). The comparative toxicity of ropivacaine and bupivacaine at equipotent doses in rats. Anesth Analg 91: 1489-1492.
15. Morrison PR, Meyer MP (1964). Constants for use in body surface area formula: Mammals. In: Altman P.L. and Dittmer D.S, eds. Biology Data Book. Washington D. C, USA: Fed Am Soc Exp Biol: 121-122.
16. Hannon JP, Bossone CA, Wade CE (1990). Normal physiological values for conscious pigs used in biomedical research. Lab Anim Sci 40: 293-298.
17. Eriksson M, Lundkvist K, Drott P, Saldeen T, Eriksson Ö (1996). Beneficial effects of pre-treatment with vitamin A on cardiac and respiratory functions in endotoxaemic pigs. Acta Anaesthesiol Scand 40: 538-548.
18. Santak B, Radermacher P, Adler J, Iber T, Rieger KM, Wachter U, Vogt J, Georgieff M, Trager K (1998). Effect of increased cardiac output on liver blood flow, oxygen exchange and metabolic rate during longterm endotoxin-induced shock in pigs. Br J Pharmacol 124: 1689-1697.
19. Karmakar MK, Aun CS, Wong EL, Wong AS, Chan SK, Yeung CK (2002). Ropivacaine undergoes slower systemic absorption from the caudal epidural space in children than bupivacaine. Anesth Analg 94: 259-65.
20. Ala-Kokko TI, Partanen A, Karinen J, Kiviluoma K, Alahuhta S (2000). Pharmacokinetics of 0.2% ropivacaine and 0.2% bupivacaine following caudal blocks in children. Acta Anaesthesiol Scand 44: 1099-1102.
21. Elowsson P, Norlen K, Jakobson S (2001). Continuous positive pressure ventilation during epidural blockade-effects on cardiac output distribution. Acta Anaesthesiol Scand 45: 95-103.
22. Basu S (1998). Radioimmunuassay of 8-iso-prostaglandinF2alfa: an index for oxidative injury via free radical catalysed lipid peroxidation. Prostaglandins Leukot Essent Fatty Acids 58: 319-325.
23. Basu S (1998). Radioimmunoassay of 15-keto-13,14-dihydro-prostaglandin F2alpha: an index for inflammation via cyclooxygenase catalysed lipid peroxidation. Prostaglandins Leukot Essent Fatty Acids 58: 347-352.
24. Kodama S, MikawaK., Nishina K, Maekawa N, Kagawa T, Obara H (2000). Lidocaine attenuates sepsis-induced diaphragmatic dysfunction in hamsters. Crit Care Med 28: 2475-2479.
25. Myrvold HE, Brandberg A. Lewis DH (1973). Platelets and fibrinogen in the acute response to endotoxin in dogs. Bibl Anat 12: 216-222.
26. Myrvold HE, Brandberg O, Lindquist O, Busch C, Lewis DH (1977). The role of platelets and fibrinogen in experimental septic shock. Acta Chir Scand 143: 131-137.
27. Martinsson T, Oda T, Fernvik E, Roempke K, Dalsgaard CJ, Svensjo E (1997). Ropivacaine inhibits leukocyte rolling, adhesion and CD11b/CD18 expression. J Pharmacol Exp Ther 283: 59-65.
28. Hahnenkamp K, Theilmeier G, Van Aken HK, Hoenemann CW (2002). The effects of local anesthetics on perioperative coagulation, inflammation, and microcirculation. Anesth Analg 94: 1441-1447.
29. Song C, Suzuki S, Kubo H, Chida M, Hoshikawa Y, Tabata T, Kondo T (2004). Effects of antiplatelet agents on pulmonary haemodynamic response to fMLP in endotoxin primed rats. Thorax 59: 39-44.
30. Pearson JM, Brown AP, Schultze AE, Ganey PE, Roth RA (1996). Gadolinium chloride treatment attenuates hepatic platelet accumulation after lipopolysaccharide administration. Shock 5: 408-415.
31. Basu S, Mutschler DK, Larsson AO, Kiiski R, Nordgren A, Eriksson MB (2001). Propofol (Diprivan-EDTA) counteracts oxidative injury and deterioration of the arterial oxygen tension during experimental septic shock. Resuscitation 50: 341-348

Corresponding author: Mats Eriksson MD, PhD, Assoc. Prof
Inst. Surgical sciences;
Department of Anaesthesia and Intensive Care
University Hospital of Uppsala
SE-751 85 Uppsala, Sweden
Telephone: +46-18-32 02 25, Fax: +46-18-55 93 57
E-mail: Mats.Eriksson@Surgsci.uu.se