Research article

INFLUENCE OF EPINEPHRINE AND MEDETOMIDINE ON SYSTEMIC ABSORPTION OF LIDOCAINE APPLIED EPIDURALLY IN ANESTHETIZED SWINE

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Epinephrine and alpha 2 agonist drugs are often used with epidural anesthesia to minimize local anesthetic systemic absorption, as well as to prolong the duration of the block. The aim of the current study was to determine by which extent epinephrine and medetomidine influenced lidocaine systemic absorption rate following epidural application. This was achieved by monitoring the serum lidocaine concentration in a porcine model. During general anesthesia, the first group received epidurally plane lidocaine, the second received lidocaine containing epinephrine (1 : 80.000), and the third lidocaine with medetomidine (15 µg/kg). Venous blood samples were taken before and 5, 10, 20, 30, 45, 60 and 90 minutes following epidural administration of the anesthetic. The effects of epinephrine and medetomidine were comparable. They both failed to cause a significant decrease in serum lidocaine concentration (p>0.05). In these settings we were unable to demonstrate a greater capacity of these two adrenergic agonists for reducing lidocaine systemic uptake and, accordingly, its systemic toxicity potential.

Key words: epidural, lidocaine, serum concentration, epinephrine, medetomidine, swine

INTRODUCTION

Neuraxial block is an increasingly used form of regional anesthesia designed to abolish nociception on the spinal level without the associated central nervous system (CNS) depression. In veterinary medicine epidural anesthesia is most frequently used for facilitating various diagnostic and obstetrical procedures, as well as to allow numerous surgical procedures involving the pelvic cavity, perineum and rear limbs

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[1,2]. Epidural and spinal anesthesia have been shown to decrease surgical stress response, intraoperative blood loss, and to lower the incidence of postoperative thromboembolic events along with morbidity and mortality in high risk patients [3,4]. When compared with general anesthesia, epidural administration of local anesthetics also results in less postoperative pulmonary complications, regardless of the risk of bronchial constriction due to sympathetic blockade [5]. In addition, the neuraxial block has been used as an adjunct to general anesthesia, for extending analgesia into the postoperative period, as well as for providing analgesia for non surgical patients without harmful side effects associated with systemic administration of opioids [3,4,6]. However, besides sympathetic blockade and other possible complications, the major concern with this approach remains local anesthetic systemic toxicity and its rate of absorption into the blood stream after epidural administration. Following epidural administration, in order to reach the site of action the local anesthetic needs to cross the spinal meninges [7]. It can either be taken up by the epidural fat, resorbed into the systemic circulation via venous blood vessels, or cross the dura mater and enter the cerebrospinal fluid [8]. Adrenergic agonists have been frequently combined with local anesthetics to prolong the motor – sensory block through the supposed mechanism of decreasing epidural blood flow and by causing antinociceptive effects via interaction with alpha-2-adrenoceptors located in the brain and spinal cord [9-13]. Previous studies clearly indicate that epinephrine due to its vasoconstrictive action tends to decrease local anesthetic serum peak concentration during central and peripheral block [11,14-16]. Nevertheless, studies with alpha-2-agonist drugs such as clonidine or dexmedetomidine showed less conclusive results regarding that matter [15,17]. Although it seems reasonable to expect that medetomidine through its agonist action on postsynaptic alpha-2-adrenoceptors could influence lidocaine systemic uptake by the same mechanism as epinephrine, at this point there are still insufficient data to support this assumption. The aim of this study was to compare by monitoring serum lidocaine concentration at 5, 10, 20, 30, 45, 60 and 90 minutes following epidural administration in the porcine model, to which extent epinephrine and medetomidine can influence lidocaine systemic absorption rate.

MATERIALS AND METHODS

The research was approved by the Institutional Ethics Committee and Ministry of Agriculture, Republic of Croatia. Sixteen healthy piglets of mixed Landras breed aged two to four months of both genders were housed at the Clinic for Surgery, Orthopedics and Ophthalmology at the Faculty of Veterinary Medicine University of Zagreb in standard microclimatic conditions. All animals were considered healthy on the basis of clinical examination which comprised body temperature (rectal thermometer) and heart and respiration rate measurements (chest auscultation). The animals were fasted for 12 hours, and water was withheld 4 hours prior to the experiment.

The animals were randomly divided into three groups according to the epidurally applied anesthetic mixture; group one (L; n = 5) received epidurally plain 2% lidocaine (Lidokain®, Belupo, Croatia) in a dose of 1ml/5kg. Group two (LE; n = 5) received 2% lidocaine with 12.5 µg/ml (1: 80.000) of epinephrine (Lidokain-adrenalin®, Belupo, Croatia) in a dose of 1ml/5kg, and group three (LM; n = 6) received 2% lidocaine with 15 µg/kg of medetomidine (Domitor®, Pfizer, Finland) 1 ml/5kg.

The animals were premedicated with 0.1 mg/kg of intramuscularly administered (IM) acepromazine (PromAce® Injectable, Fort Dodge, USA) and 5 mg/kg IM of ketamine (Narketan® 10, Vetoquinol, Switzerland). Thirty minutes following premedication an intravenous catheter was placed in the *v. auricularis*. During the whole procedure the animals received 0.9% sodium chloride solution i.v. in a dose of 10 ml/kg/h. General anesthesia was used to minimize suffering during arterial blood sampling and to facilitate the epidural administration of drugs by avoiding potentially dangerous rapid movements of the animals. Anesthesia was induced with intravenously applied sodium thiopental (Nesdonal®, Abbott Laboratories, USA) in a dose of 5 mg/kg. Following endotracheal intubation, anesthesia was maintained with isoflurane (Forane®, Abbott Laboratories, USA) in 100% oxygen. The vaporizer was set at 3% during the first five minutes, after which anesthesia was maintained with 1.5% isoflurane. During anesthesia the vital functions of the animals were monitored including SpO_2, ECG, invasive arterial blood pressure and $EtCO_2$ (Datex Ohmeda, USA).

Epidural anesthesia was applied 20 minutes following induction. Animals were placed in sternal recumbency, and the skin was aseptically prepared prior to the epidural application of the anesthetic. The epidural needle was introduced between L7-S1 by using the "loss of resistance" technique to identify the epidural space. Instead of performing the epinephrine test dose, epidural drug administration was preceded by syringe aspiration in order to eliminate the possibility of intravascular injection or puncture of the dura. In the case that blood or cerebrospinal fluid was aspirated, epidural anesthesia would be discontinued and the animal excluded from the experiment.

Venous blood samples were obtained from the cephalic vein and stored into sterile test tubes (BD vacutainer SST, 4 ml, Plymouth, UK). In all three groups, blood samples were taken prior to epidural anesthesia and 5, 10, 20, 30, 45, 60 and 90 minutes following epidural administration of the anesthetic. Blood samples were centrifuged at 15,800 revolutions per minute (RPM) for 90 seconds, and 1 ml of blood serum was stored into a sterile plastic cuvette at -70 °C pending analysis. Serum lidocaine concentration was measured using gas chromatography mass spectrophotometry (Varian 3400 CX-Saturn 4D, USA) [18].

Statistical analysis was performed by using STATISTICA, version 6.1. (StatSoft, USA). Serum lidocaine concentration was evaluated using multiple regression analysis with peak serum lidocaine concentration as the dependent variable, while the combination of medetomidine and epinephrine with lidocaine and serum lidocaine concentration

measured in the described time intervals were the independent variables. Variance analysis and Duncan test were used for the evaluation of the results pertaining to hemodynamic parameters. The level of significance was set at P = 0.05 and the results were expressed as mean values ± SD.

RESULTS

Average body weight of animals in the L group was 38.2 ± 13.2 kg, LE group 28.6 ± 2.2 kg and LM group 34.8 ± 10.3 kg.

Serum lidocaine concentrations are displayed in Table 1.

Table 1. Serum lidocaine concentration (µg/ml) measured in all three groups of animals (L –lidocaine group, LM – lidocaine + medetomidine group, LE – lidocaine + epinephrine group). Data are presented as mean ± SD

Time (min) Group		0	5	10	20	30	45	60	90
Lidocaine	LE	0±0	1.64± 1.76	0.93± 0.31	0.86± 0.10	0.90± 0.21	0.78± 0.19	0.71± 0.26	0.68± 0.21
concentration	LM	0±0	1.38± 0.70	1.26± 0.43	0.98± 0.27	0.87± 0.23	0.78± 0.23	0.71± 0.14	0.56± 0.13
(µg/ml)	L	0±0	1.10± 0.58	1.10± 0.46	1.21± 0.42	1.04± 0.31	1.03± 0.37	0.95± 0.38	0.74± 0.27

The maximum peak serum lidocaine concentration (C_{max}) in LE (1.64±1.6 µg/ml) and LM (1.38±0.70 µg/ml) group was recorded five minutes following administration. C_{max} value in the L group was recorded in the twentieth minute (1.21±0.42 µg/ml). Ten minutes following administration serum lidocaine concentration in LE group decreased to 0.93±0.31 µg/ml, but the difference was not statistically significant when compared to the serum lidocaine concentration measured in L group (1.10± 0.46 µg/ml; p>0.05). In LM group a slight decline in serum lidocaine concentration was recorded in the twentieth minute (0.98±0.27 µg/ml), while 30 minutes following administration serum lidocaine concentration measured in LM group (0.87± 0.23 µg/ml) was very close to the value measured in LE group (0.90±0.21 µg/ml). Both recorded values were statistically insignificant in comparison to the value measured in L group (1.04 ± 0.31 µg/ml). The lowest serum lidocaine concentration was recorded 90 minutes following administration in LM group (0.56 ± 0.13 µg/ml).

Hemodynamic parameters are shown in Table 2. Mean arterial pressure values recorded in LE group were significantly lower than those measured in L and LM group (p ≤ 0.05). The highest mean arterial pressure was recorded in the LM group during the first 20 minutes following epidural application. Correspondingly, systolic and diastolic pressure was significantly lower in LE group when compared to the remaining two groups (p ≤ 0.05). In the LE group the recorded heart rate values were significantly

higher than those recorded in L and LM group between the tenth and fortieth minute of the experiment (Table 2).

Table 2. Hemodynamic parameters measured in all three groups of animals (L –lidocaine group, LM –lidocaine + medetomidine group, LE –lidocaine + epinephrine group)

Time (min)	Group	Systolic pressure (mmHg)	Diastolic pressure (mmHg)	Mean arterial pressure (mmHg)	Heart rate (bpm)
0	LE	97.80±17.57	59.00±15.23	72.40±13.43	163.22±59.43
	LM	115.60±14.93	61.40±20.91	82.20±20.63	153.40±42.97
	L	135.50±32.98	76.00±20.48	101.67±25.29	116.67±24.28
2	LE	98.67±10.50[a]	47.00±2.00[a]	65.00±4.00[a]	158.82±54.72
	LM	134.80±12.64[b]	91.20±14.89[b]	108.40±12.92[b]	149.20±34.63
	L	122.33±20.60[a.b]	70.33±12.58[b]	90.67±15.04[b]	115.35±21.08
5	LE	86.25±11.32[a]	46.00±3.56[a]	61.50±3.00[a]	178.60±64.16
	LM	137.20±11.61[b]	94.42±11.69[b]	111.20±10.71[b]	137.20±21.99
	L	119.67±29.28[b]	65.00±12.12[c]	86.00±16.52[c]	115.80±20.54
10	LE	85.60±11.15[a]	51.40±8.96[a]	62.33±4.73[a]	182.20±61.18[a]
	LM	134.00±12.63[b]	89.80±16.35[b]	106.80±15.55[b]	144.60±31.45[a.b]
	L	123.00±27.22[b]	64.33±12.74[a]	83.33±18.01[a.b]	107.55±14.25[b]
15	LE	85.25±14.93[a]	49.75±6.70[a]	62.75±4.99[a]	177.60±64.74[a]
	LM	133.00±12.81[b]	86.20±15.67[b]	104.20±14.65[b]	141.00±17.71[a.b]
	L	123.67±24.42[b]	64.67±13.28[a]	85.33±17.04[b]	108.37±17.76[b]
20	LE	83.40±13.94[a]	43.00±11.47[a]	58.20±8.11[a]	178.20±49.67[a]
	LM	122.60±12.72[b]	71.40±13.76[b]	95.60±10.90[b]	132.02±15.42[b]
	L	121.37±25.29[b]	65.00±17.35[b]	84.00±21.66[b]	105.20±17.91[b]
30	LE	83.40±3.21[a]	46.40±10.26[a]	58.40±8.20[a]	171.02±61.99[a]
	LM	112.00±18.64[b]	69.60±11.28[b]	80.60±14.10[b]	128.82±14.64[a.b]
	L	125.00±22.61[b]	65.00±12.17[b]	84.33±17.62[b]	103.70±17.40[b]
40	LE	88.20±6.22	42.00±8.92[a]	59.60±6.43[a]	167.40±53.17[a]
	LM	109.00±14.32	68.80±9.98[b]	83.60±8.79[b]	130.60±13.69[a.b]
	L	94.00±39.15	80.67±23.67[b]	100.00±24.04[b]	100.68±18.59[b]
50	LE	82.60±10.01[a]	43.00±9.67[a]	60.00±4.47[a]	144.24±47.28
	LM	112.80±20.39[a.b]	65.00±20.36[b]	81.20±19.54[b]	112.84±11.80
	L	124.00±39.60[b]	65.00±22.63[b]	87.00±28.28[b]	99.68±20.28
60	LE	79.00±13.47[a]	44.40±10.06[a]	58.20±3.11[a]	155.84±60.88
	LM	112.50±15.29[a.b]	69.75±8.02[b]	83.25±10.05[b]	115.75±23.31
	L	126.55±35.99[b]	67.50±21.92[b]	89.50±27.58[b]	101.83±21.15
75	LE	85.00±9.85[a]	41.80±8.04[a]	59.00±2.55[a]	161.62±64.86
	LM	106.62±14.79[a.b]	57.80±12.81[a.b]	73.80±11.14[a.b]	122.80±29.35
	L	124.05±32.46[b]	82.50±40.31[b]	96.50±36.06[b]	101.35±21.03
90	LE	89.22±9.50[a]	46.80±5.26[a]	59.80±6.50[a]	162.64±68.98
	LM	121.60±12.64[b]	69.60±14.24[b]	87.82±14.33[b]	125.02±40.27
	L	108.50±3.54[b]	54.00±0.00[a.b]	74.50±3.54[a.b]	97.87±15.55

Data are presented as mean ± SD.
[a]– significantly different from group L; [b]– significantly different from group LM (p ≤ 0.05)

DISCUSSION

Results of the current study showed that epinephrine and medetomidine within different time frames both influenced lidocaine systemic absorption rate almost to the same extent, but the decrease in serum lidocaine peak concentration was not statistically significant. In previous studies epinephrine has been shown, not only to decrease local anesthetic systemic absorption rate, but also to prolong duration and improve quality of the epidural block when applied in combination with the moderately potent lidocaine, as well as with more dilute solutions of potent local anesthetics like bupivacaine or ropivacaine [11,16,19,20]. On the contrary, the most likely reason why the same results were not recorded when epinephrine was added to concentrated solutions of bupivacaine and ropivacaine is that duration of action of these agents exceeds the duration of epinephrine's effects [16]. Furthermore, prolonged duration and improved quality of the epidural block can be at least in one part explained by epinephrine's ability to induce analgesia through the interaction with alpha-2-adrenergic receptors located in the brain and spinal cord [9-11,13]. Mazoit et al. [15] managed to significantly decrease serum lidocaine peak concentration in orthopedic patients using epinephrine in a concentration of 1 : 200.000 and clonidine (300 µg/2ml) with epidurally administered lidocaine (20 ml of 2% solution). Both agents caused a significant decrease in serum lidocaine concentration, and possible explanation for this result lies within the relatively high dose of clonidine used in this case, which suppressed its central antihypertensive effect mediated by its action of decreasing central sympathetic outflow [3,6,15]. When used in smaller doses (5 to 10 µg/ml), clonidine seems to promote lidocaine systemic absorption rather than decreasing it [17]. In contrast to partially selective clonidine (alpha-2 to alpha-1 selectivity ratio 220), medetomidine is 7 times more selective for alpha-2-receptors, with alpha-2 to alpha-1 selectivity ratio of 1620 [21,22]. Medetomidine has less agonist action on presynaptic alpha-2-adrenoceptors when compared to clonidine, and can produce pronounced transient vasoconstriction due to its interaction with postsynaptic alpha-2-adrenoceptors, while in the later course of action usually induces sympatholysis and hypotension [23-25]. According to expectations, in our study medetomidine began to act in 20 minutes following administration, and showed its vasoconstrictive potency within the epidural space to be virtually the same as that of epinephrine. In the thirtieth minute, the measured value of serum lidocaine concentration in LE group was 0.90 ± 0.21 µg/ml, which was very close to the value measured in LM group (0.87 ± 0.23 µg/ml). The same trend continued through the whole experiment, suggesting that medetomidine in a dose of 15 µg/kg, though acting with a certain delay, has effects comparable to those of epinephrine. Brose and Cohen [9] used several concentrations of epinephrine (1 : 400.000, 1 : 300.000 and 1 : 200.000, respectively) with 2% lidocaine in pregnant women scheduled for cesarean section, and were unable to demonstrate significant differences in either maternal or fetal serum lidocaine levels between patients given plain and epinephrine containing lidocaine solution. The authors suggested that enhanced epidural blood flow caused by inferior vena cava

compression along with decreased vascular reactivity to catecholamines commonly observed during pregnancy might have been the key factor which led to epinephrine's loss of vasoconstrictive potency within the epidural space.

It has been suggested that a reduction in local anesthetic peak serum concentration may be a result of epinephrine's effect on systemic circulation [4]. Sharrock et al. [26] demonstrated that intravenous administration of a low epinephrine dose significantly influences local anesthetic serum concentration following epidural application. Arterial blood concentrations of bupivacaine were found to be significantly lower in patients receiving epinephrine infusions in comparison to those receiving phenylephrine. As this outcome was evidently not a result of local anesthetic reduced clearance from the injection site, the assumption was made that epinephrine mediated an increase in cardiac output which probably caused its greater volume of distribution, which in turn led to decreased blood concentration of bupivacaine. The fact that the same result was not recorded in patients given phenylephrine further indorses the theory because, unlike low epinephrine doses, phenylephrine induces increased systemic blood pressure which results in reflex bradycardia and a transient decrease in cardiac output [27]. The same effect was observed in our study, where epinephrine following absorption from the epidural space also induced a significant arterial pressure drop followed by compensatory tachycardia (Table 2). Vnuk et al. [1] also recorded similar hemodynamic values, as well as increased cardiac output in dogs epidurally receiving lidocaine -epinephrine mixture in comparison to those receiving lidocaine alone.

Considering that relatively high concentrations of epinephrine and medetomidine used in this study, we can only speculate why a significant decrease in serum lidocaine concentration failed to occur. Inadequate dosing of epinephrine and medetomidine can hardly be accounted for this result, because epinephrine concentration was 2.4 times higher than those usually employed for epidural anesthesia, and medetomidine in the used dose had an effect very similar to that of epinephrine. Epinephrine concentrations of 1 : 200.000 or even lower have been proven effective in decreasing local anesthetic serum peak concentration [14], and yet in our case, the same result was not observed. Although relatively high, the epinephrine dose was still in the so called "therapeutic range", which was measurable by its agonist action on beta-2-adrenoceptors in the muscle vasculature, leading to a reduction in systemic vascular resistance and cardiac output increase. Even though otherwise shown to decrease local anesthetic peak serum concentration through increasing its volume of distribution [26,28], in our case the increase in cardiac output did not result in the expected outcome.

Nevertheless, it needs to be pointed out that our study differs substantially from the ones listed above, because all of the animals were anesthetized and none of them were exposed to surgical stimulation which through sympathetic activity normally provides a counterbalance to the depressant action of general anesthetics on the vasomotor function [26]. On the other hand, to assume that general anesthesia played a part in opposing epinephrine's action at the injection site does not seem very reasonable, hence the recorded hemodynamic parameters clearly indicate that epinephrine was

more than abundant in the systemic circulation (Table 2). This eliminates the only remaining plausible explanation for these results, hence there were no other known elements such as increased intraabdominal pressure that would oppose adrenergic agonists' action at the injection site.

Interestingly, medetomidine caused an increased systemic vascular resistance during the first twenty minutes following administration, while it seems to have preserved its action on postsynaptic alpha-2-adrenoceptors in the vasculature within the epidural space during the entire experiment. Nonetheless, alpha-2-adrenoceptor agonists are usually given with a different purpose, so further increasing the medetomidine dose to accomplish the epinephrine – like effect within the epidural space may not be advisable because of its undesirable effects on systemic circulation.

CONCLUSION

Results of the current study indicate that both epidurally applied adrenergic agonists in the stated dosages do not significantly influence the lidocaine systemic absorption rate. Therefore, a potential benefit from their action in reducing lidocaine systemic toxicity seems limited.

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UTICAJ EPINEFRINA I MEDETOMIDINA NA SISTEMSKU RESORPCIJU EPIDURALNO PRIMENJENOG LIDOKAINA KOD ANESTEZIRANIH SVINJA

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Epinefrin i alfa 2 agonisti se uvek koriste u epiduralnoj anesteziji da umanje sistemsku apsorpciju lokalnog anestetika i da produže trajanje epiduralnog bloka. U serumu svinja se određivala koncentracija lidokaina, stoga je cilj ove studije da se odredi do koje mere epinefrin i medetomidin utiču na sistemsku apsorpciju lidokaina nakon epiduralne primene. Tokom opšte anestezije prvoj grupi je epiduralno aplikovan lidokain, drugoj lidokain s epinefrinom (1: 80000), a trećoj lidokain sa medetomidinom (15 μg/kg). Krv iz vene je uzorkovana pre, 5, 10, 20, 30, 45, 60 i 90 minuta nakon epiduralne primene anestetika. Poređeni su efekti epinefrina i medetomidina, ali ni jedan nije signifikantno smanjio serumsku koncentraciju lidokaina (p>0,05). Ove kombinacije adrenergičnih agonista nisu smanjile sistemsku resorpciju lidokaina. U skladu s tim, potencijalno je moguća sistemska toksičnost lidokaina.