Effect of epidural administration of lidocaine, fentanyl and their combination on the minimum alveolar concentration of halothane in dogs

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ABSTRACT: The efficacy of lidocaine, fentanyl, combination of both (2 mg/kg of lidocaine, along with fentanyl in the dose of 0.005 mg/kg) and saline (as a control) administered epidurally to 40 healthy dogs was under investigation, regarding their influence on minimum alveolar concentration (MAC) of halothane. Basic vital parameters, such as heart rate, respiratory rate, saturation of hemoglobin with oxygen and end-tidal partial pressure of CO_2 were recorded. Minimum alveolar concentration of halothane after administration of lidocaine (0.75 ± 0.24%), or the lidocaine/fentanyl combination (0.43 ± 0.08%) was found to be significantly lower ($P < 0.05$) compare to control group (1.15 ± 0.20%). However, we have not found significant difference in the group given fentanyl alone (0.95 ± 0.35%) compare to control group. Mutual relationship between epidurally given lidocaine and fentanyl (same route of administration) can be called as simply additive. There were no significant deviations in basic parameters within groups. We conclude that epidural administration of combination of these drugs we are able to reduce the dose of general anesthetics, which is important in management of critically ill patients.

Keywords: MAC; lignocaine; peridural; intrathecal; analgesia; anaesthesia

Surgical procedures are often extensively painful for the patient. However, we are able to control pain by the means of specific drug regimens, both local and systemic. Pain control is deciding factor for management of general anaesthesia in most cases. Epidural anaesthesia is well-recognized as one of the most efficient analgesic procedures. It is useful particularly for caudal surgery, including rear limbs, as well as caudal abdominal and/or perineal region (Pascoe, 1992).

The most useful local anesthetics, feasible to epidural anaesthesia are bupivacain and lidocaine. Ever since opioid receptors have been found on the surface of spinal cord, opioids have been regarded at least as another option for epidural analgesia (Klide, 1992). The first report about opioids administered epidurally comes from Wang et al. (1979), and beside morphine, fentanyl derivates have been used most frequently, to date (Lascelles, 2000).

Binding of opioids to specific receptors on the spinal cord is considered to be one of the most stable, regarding dose-response (Yaksh, 1981). Combination of opioids with local anesthetics is widely used for optimalization of analgesia with the lowest possible dose regimens. Obviously, real advantage of the low-dose policy is in reduction of side effects of some specific drugs, while analgesic effect remains the same (Kaneko et al., 1994).

We can observe different pharmacodynamics in acting of opioids in combination with local anesthetics. Kaneko et al. (1994) describes some synergistic effect in both groups of drugs. According to

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Tejwani et al. (1992), local anesthetics likely improve binding capacity of opioid receptors, especially for morphine and buprenorphine. During the action, increase in anti-nociceptive effect plays a role. Afferent signal transmission is generally depressed, without involving efferent, sympathetic pathways (Wang et al., 1993). Data obtained from human patients suggest that epidural analgesia with local anesthetics only can be insufficient. The combination, on the other hand, allows a bit more effectiveness in selective blocking some functions, lowering the required initial dose of general anesthetics. The quality of anaesthesia depends mostly on the dose of epidural anesthetics (Fredman et al., 1997).

Although synergistic acting of opioids with local anesthetics remains not quite clear, there is enough evidence of some relationship in literature (Wang et al., 1979; Penning and Yaksh, 1992; Tejwani et al., 1992). Most of the studies have been dealing with combination of morphine and bupivacaine, while there is only a little data from human medicine published about lidocaine and fentanyl combination (Cook et al., 1990; Jones et al., 1990; Fredman et al., 1997; Cherng et al., 2001; Reinoso-Barbero et al., 2002; Yao et al., 2002). Data from veterinary medicine inform only about postoperative pain relief after lidocaine-fentanyl epidural administration (Pascoe, 1992). However, we have found lack of data concerning reduction of inhalation anaesthetics minimum alveolar concentration after lidocaine-fentanyl epidural administration.

The purpose of this study was to correlate three main groups of dogs, epidurally given fentanyl, lidocaine and combination of these drugs, respectively. We look at the dose-response to halothane by the means of minimum alveolar concentration (MAC).

MATERIAL AND METHODS

Study group of animals

Forty clinically healthy dogs (23 males and 17 females), with the average age of 6.5 ± 2.90 years, weighing 23.7 ± 12.57 kg, were included into a study. They were vaccinated and free of parasites. The inclusive criteria relied on physical examination and standard hematology and biochemistry of blood samples, taken previously. Dogs were fasted 24 hours prior anaesthesia (no water restrictions), while underwent one more standard physical examination. Then, they were randomized into 4 groups, 10 dogs each. Groups were named LID, FEN, LID-FEN and CONTROL, according to drugs used in them.

Protocol of the experiment

All animals were intravenously given medetomidine (Domitor, Pfizer) in the dose of 0.03 mg/kg for premedication. Then, 22G spinal catheter (Spinocan, B. Braun) was introduced through the gap between the last lumbar vertebra and sacral bone into epidural space (Skarda, 1996). Specific drug (or the combination) was administered via this catheter afterwards. The LID group was given lidocaine (Lidocain 2%, Egis Pharm.) in the dose of 2 mg/kg, FEN group was treated with fentanyl (Fentanyl-Janssen, Jansen Pharm.) in the dose of 0.005 mg/kg, while in LID-FEN group, the combination of both drugs in the same doses (2 mg/kg of lidocaine with 0.005 mg/kg of fentanyl), mixed in one syringe was used. In all groups, the drug concentration before administration was adjusted to the total volume of 0.2 ml/kg. In the last, control group, sterile saline solution in the dose of 0.2 ml/kg was used instead of drugs. All dogs were positioned into a sternal recumbency and left intact for as long as 10 minutes. After that, they were masked and induced by mixture of oxygen and halothane (Narcotan, Léčiva), then, they were intubated. They were maintained on spontaneous ventilation, connected to anesthetic machine and supplemented with oxygen in the continuous flow of 50 ml/kg/min. The depth of anaesthesia was controlled by adjustment of the dose of halothane via precise out-of-circuit vaporizer. Hypothermia was controlled by using isothermal water-filled underpad, heated in the range between 37–38°C. Heart rate (HR), respiratory rate (RR), end-tidal partial pressure of carbon dioxide (P_{ETCO_2}) and saturation of hemoglobin by oxygen (SpO_2) was monitored. While both HR and heart rhythm were measured by ECG (from II. lead) with the leads fixed to the both front and right rear leg. Saturation of hemoglobin with oxygen was obtained by pulse oxymetry from the sensor put on the tip of the tongue. A commercially available adaptor modified with a catheter was placed at the Y-piece of the breathing circuit. The catheter passed through the endotracheal tube, so that its tip rested in the thoracic portion of the trachea. Samples of airway gases were obtained from the catheter and

analyze by use of side stream capnograph and anesthetic agent monitor, which determined respiratory rate, end-tidal partial pressure of carbon dioxide and halothane concentration. All the information was collected and registered by monitoring system (Cardiocap, Datex-Ohmeda), which was calibrated before each procedure.

The tail-clamp method (Ko et al., 2000) was used to establish minimum alveolar concentration correctly. After beginning of anaesthesia, 15 minutes was allowed for patient stabilization and then the second caudal vertebra was bluntly squeezed by Backhaus towel clamp placed around, so sharp tips did not harm the skin. We held the pressure for 30 seconds or until response to the pain appeared. In case of reaction, we increased end-tidal concentration of halothane by 0.25%, waited another 5 to 10 minutes and repeated the squeeze the same way. If there was no response, end-tidal concentration of halothane was decreased by 0.25% and action repeated after 5 to 10 minutes.

Endpoints

As a true response to pain stimulus, we generally accept active movement of head or limbs, not regarding coughing, swallowing, chewing or increase in respiratory rate. Testing proceeded till the lowest end-tidal concentration of halothane for each drug regimen, with no response from the patient, was established. Cardiorespiratory data were recorded and collected during each procedure.

Statistical analyses

All the data were collected into tables and expressed as mean ± standard deviation (SD). Beside other parameters, the reduction in MAC for each group was calculated from the formula (Ko et al., 2000):

$$\text{percentage reduction} = \text{control MAC} - \text{treatment MAC} \times 100/\text{control MAC}$$

The differences between groups in various parameters were studied using parametric multiple comparisons (KyPlot, Version 2.0, Koichi Yoshioka). The factors of interest were lidocaine and fentanyl. The interaction of lidocaine and fentanyl was used to evaluate whether change in MAC departed from an additive model. If the interaction term was significant, then the effect was synergistic (the combination of lidocaine and fentanyl resulted in MAC lower than would have been expected if it was assumed that effects of the two drugs were additive). If the interaction term was not significant, then the main effects of lidocaine and fentanyl were examined. For all analyses, P value was set at 0.05.

RESULTS

As it can be seen from the graph and the table, there was significant ($P < 0.05$) decrease in MAC of halothane in LID group, as well as in LID-FEN group, compare to control. Moreover, significant

Table 1. Effects of epidural administration of lidocaine and fentanyl alone or lidocaine/fentanyl combination on the minimum alveolar concentration (MAC) of halothane in dogs

Variable	Epidurally used drugs			
	control	lidocaine	fentanyl	lidocaine/fentanyl
MAC (volume %)	1.15 ± 0.20	0.75 ± 0.24*	0.95 ± 0.35+	0.43 ± 0.08*
Percentage reduction of MAC	NA	34.8	17.4	62.6
HR (beats/min)	72.8 ± 23.7	74.0 ± 15.5	73.4 ± 6.9	71.3 ± 11.7
RR (breaths/min)	20.7 ± 14.6	14.0 ± 5.4	15.2 ± 10.9	9.4 ± 2.2
$Petco_2$ (kPa)	4.42 ± 0.98	5.22 ± 1.35	5.58 ± 0.74	6.22 ± 1.35
SpO_2 (%)	96.2 ± 2.6	97.6 ± 1.8	96.9 ± 2.2	96.2 ± 1.9

Values represent mean ± SD for 10 dogs of every group

NA = not applicable; SpO_2 = saturation of hemoglobin with oxygen; P_{ETCO_2} = end-tidal partial pressure of CO_2

*significantly ($P < 0.05$) different from control value

+significantly ($P < 0.05$) different from lidocaine/fentanyl value

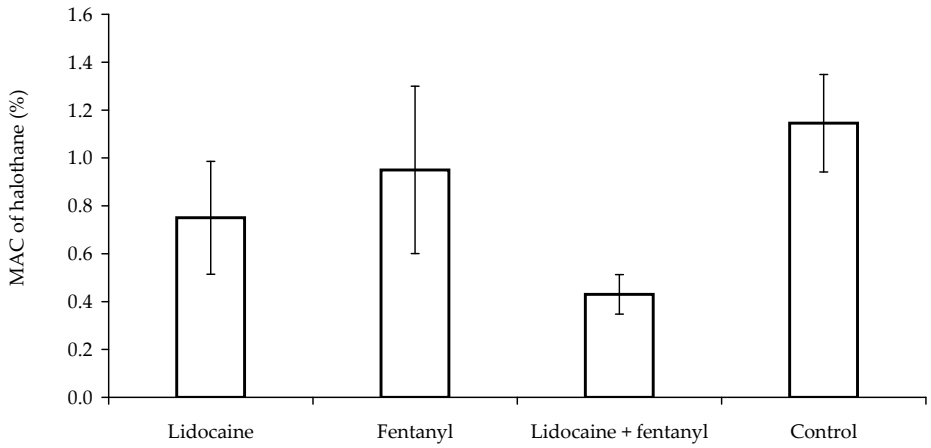

Figure 1. MAC of halothane after epidural administration of several drugs

($P < 0.05$) decrease was found for LID-FEN group, when compared with FEN group. Although MAC in FEN group was actually lower than control, the calculated difference was not significant ($P = 0.123$). There were not significant interactions found between lidocaine and fentanyl, so the effect of their combination can be declared as simply additive, not synergistic, nor antagonistic (Farghali, 2002). There were found no significant differences between groups in all the other parameters.

DISCUSSION

Real advantage of fentanyl given epidurally is clearly in its local effect, which should be similar as effect systemic (Loper et al., 1990). In our study, however, we would expect better analgesia, as reported by Inagaki et al. (1992). Administration of lidocaine along with fentanyl, on the other hand, reflects better analgesic properties, which is consilient with the literature (Harukuni et al., 1995).

During the study, we confirmed that epidural administration of lidocaine alone or fentanyl alone decreases MAC of halothane compare to control, while mixture of these agents, through an additive interaction, decreases this MAC even more.

We observed the lowest level of MAC for halothane after giving combination of lidocaine with fentanyl (0.43% vol.), which represents drop by 62.6%, almost twice as big as after giving lidocaine alone (34.8%). It is more likely the result of interaction between lidocaine and fentanyl, as published for other drugs from similar pharmacological groups, for instance bupivacaine and morphine (Jones, 2001). Statistically significant difference was discovered only between control group and groups LID and LID-FEN, respectively. Between groups LID and LID-FEN have not been found significant differences, a fact, corresponding with the human literature (Cook et al., 1990; Jones et al., 1990; Fredman et al., 1997). Generally, these studies report that local anesthetics and not opioids are effective for epidural analgesia.

Hodgson and Liu (2001) published results of a study evaluating depth of anaesthesia according to so called "Bispectral Index". They succeeded in reducing of inhalation anesthetics, after lidocaine was given epidurally, by 34%. This is a result confirming our data, as we observed reduction in MAC of halothane by 34.8%.

Addition of fentanyl to the local anesthetic does not improve analgesic properties of the mixture, but, due to liposolubility, it helps to accelerate the onset of action (Fischer et al., 1988; Cherng et al., 2001; Jones, 2001) and to hold the longer analgesic effect after surgery (Harukuni et al., 1995). We were not able to evaluate these criteria independently, as we tested the depth of anaesthesia and analgesia in the 15 minutes – in the peak of action of both drugs. We did not look at the quality of post-surgical analgesia, as well, since it was clearly beyond the scope. Some papers published recently show similar data, supporting our hypothesis by confirming improvement in analgesic effect using combination of lidocaine with fentanyl in humans (Yao et al., 2002), even in comparison with currently used morphine (Reinoso-Barbero et al., 2002).

Rather mild reduction of MAC of halothane observed in our study when FEN group is compared with control does not show the same results as previously published by Valverde et al. (1989) and Kashyap et al. (2003). These authors report signifi-

cant reduction in MAC of both halothane and isoflurane after epidural administration of morphine in humans. One would expect similar results using fentanyl, the drug known for its better analgesic properties than morphine. The explanation could be abovementioned liposolubility, reducing its meningeal permeability and cerebrospinal fluid potency (Jones, 2001).

We can see clinical usefulness especially in using the combination of fentanyl along with lidocaine for both higher efficacy and longer lasting, postoperatively (Pascoe, 1992). Lower MAC, which means lower dose of anesthetics, reduces significantly side effects, improving odds for the patient, undergoing surgery. The crucial part of the combination used for epidural anaesthesia is local anesthetic, while opioids, as it has been proven in humans, help in improving analgesic properties, especially for longer post-surgical analgesia.

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