EFFECTS OF PREOPERATIVE EPIDURAL MORPHINE AND INTRAMUSCULAR BUPRENORPHINE IN PIGS SUBJECTED TO ABDOMINAL SURGERY: A PILOT STUDY

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ABSTRACT: Nine pigs (25 ± 1 kg) were anaesthetised with medetomidine (0.05 mg/kg, IM) and tiletamine-zolazepam (5 mg/kg, IM), and maintained with isoflurane. Group M was treated with epidural morphine (0.12 mg/kg; n=5) preoperatively. Group B received intramuscular buprenorphine (0.1 mg/kg; n=4) before surgery and 12 h later. Cardiorespiratory parameters were recorded every 10 min. Pre- and postoperative behaviours were videotape recorded for a total of 60 h/pig. Physiological parameters and opioid concentrations were assayed with repeated measurement ANOVA; p<0.05. Arterial blood pressure and PaCO₂ were higher and respiratory rate was lower during anaesthesia in group B compared to group M. The other parameters did not differ between groups. Twelve hours postoperatively, pigs in group M exhibited signs of decreased activity level. 50% of the pigs in group B increased their activity level while the others decreased their activity levels compared to preoperative levels. Twenty-four hours postoperatively, 25% of the pigs in group M and 100% of the pigs in group B had decreased body weight compared to preoperative values. In conclusion, buprenorphine resulted in respiratory depression during anaesthesia and unpredictable behavioural effect. Pigs treated with epidural morphine had lower postoperative activity but higher weight gain and feed consumption measured at 24h postoperatively.

KEYWORDS: anaesthesia, analgesia, cardiorespiratory parameters, pain assessment, behaviour.

RESUMO: Nove suínos (25 ± 1 kg) foram anestesiados com medetomidina (0,05 mg/kg, IM) e tiletamina-zolazepam (5 mg/kg, IM), e a anestesia foi mantida com isofluorano. Grupo M recebeu morfina epidural (0,12 mg/kg; n=5) pré-operativamente. Grupo B recebeu buprenorfina intramuscular (0,1 mg/kg; n=4) antes e 12 h após a cirurgia. Parâmetros cardiorespiratórios foram mensurados a cada 10 min. O comportamento pré- e pós-operatório foram gravados num total de 60 h/suino. Os parâmetros fisiológicos e as concentrações séricas dos opióides foram avaliados pela análise de variância (ANOVA); p<0.05. A pressão arterial e a PaCO₂ aumentaram enquanto a frequência respiratória diminuiu durante a anestesia no grupo B em comparação com o grupo M. Não houve diferença entre os grupos nos demais parâmetros. Doze horas após a cirurgia, os suínos do grupo M obtiveram decréscimo no seu nível de atividade. 50% dos animais do grupo B exibiram aumento de atividade enquanto os demais tiveram uma diminuição no nível de atividade, comparados com os valores pré-cirúrgicos. Vinte quatro horas após a cirurgia, 25% dos suínos do grupo M e 100% do grupo B diminuíram seu peso corporal comparado com os valores pré-operatórios. Conclui-se que buprenorfina resulta em depressão respiratória durante anestesia com efeito comportamental imprevisível. Suínos tratados com morfina epidural tiveram menor nível de atividade pós-operatório, porém apresentaram maior ganho de peso e consumo alimentar durante 24h após a cirurgia.
PALAVRAS-CHAVE: anestesia, analgésia, parâmetros cardiorrespiratórios, avaliação da dor, comportamento.

INTRODUCTION

Preoperative analgesia is recommended to prevent the painful sensation caused by surgery and to diminish the noxious stimuli during the postoperative period (VAIDA et al., 2000). Also, by using preoperative analgesia the postoperative recovery time is decreased and the subsequent analgesic requirements in the animal are minimised (http://sinclairresearch.com; 3-Sep-2002).

An animal that experiences pain often exhibits behavioural changes. The modification of behavioural patterns differs between animal species (SANFORD et al., 1986). In pigs, pain can be expressed in various ways such as squealing and attempt to escape. Also, pigs can become unwilling to move and may hide in the bedding materials (SANFORD et al., 1986; HARVEY-CLARK, GILESPIE & RIGGS, 2000). Such a high degree of inactivity can produce a range of undesirable physiological changes such as pressure sores, urine scalding and faeces soiling which may contribute to the aggravation of the pain that the animal is suffering (DENNIS & MELZACK, 1983; FLECKNELL, 1999; SHORT, 1999). Moreover, pain can result in reduced feed consumption and hence weight loss. Therefore, both weight gain and feed consumption can be regarded as pain indicators in animals (HARVEY-CLARK, GILESPIE & RIGGS, 2000; ROUGHAN & FLECKNELL, 2004).

Opioids are frequently used for treatment of moderate to severe pain in most species (BOWDLE, 1998). However, opioids have short serum half-lives in pigs, leading to a need for repeated restraint and drug administration to achieve adequate analgesia (MOON & SMITH, 1996; HARVEY-CLARK, GILESPIE & RIGGS, 2000). Therefore, it is important to evaluate analgesic protocols in an attempt to minimise pain both during and after surgery. One possible approach is to use epidural analgesia in pigs. The advantages of epidural morphine in pigs are that it produces a long-lasting analgesia (UMMENHOFER et al., 2000) with satisfactory muscle relaxation in the hind legs and abdomen (SKARDA, 1996) and produces analgesia without major physiological changes (MALAVASI et al., 2006). In pigs, the onset time and analgesic duration of a single injection of epidural morphine are reported to be approximately 30 min (MALAVASI et al., 2006) and 12 - 33 h, respectively (UMMENHOFER et al., 2000).

Buprenorphine is a morphine-like opioid drug that has a relatively long analgesic action and minimal adverse effects in pigs. Administered intramuscularly (IM) it has a slow onset of action of approximately 30 - 60 min (HERMANSEN, PEDERSEN & OLESEN, 1986) and the full analgesic effect in pigs has been reported to last 7 - 24 h when given in a relatively high dose (HARVEY-CLARK, GILESPIE & RIGGS, 2000). Buprenorphine is reported to be approximately 30 - 50 times more potent than morphine (COWAN, LEWIS & MACFARLANE, 1977). In rats, buprenorphine has been reported to have a bell-shaped dose response curve (DAHAN et al., 2005). This dose response curve corresponds to agonistic characteristics at low doses and less effective or even antagonistic characteristics at higher doses in selected conditions such as different pain stimuli (SADÉE, ROSENBAUM & HERZ, 1982).

Both epidural morphine and IM buprenorphine have properties to become the analgesia of choice for use in pigs (UMMENHOFER et al., 2000; RODRIGUEZ et al., 2001; MALAVASI et al., 2006). Therefore, the hypothesis to be tested in the present study is that epidural morphine produces fewer physiological and behavioural changes compared to IM buprenorphine when used for preoperative analgesia in pigs. Thus, the aim of this study was to evaluate the effects of epidural morphine and intramuscular buprenorphine on physiology and behaviour in pigs subjected to abdominal surgery.
MATERIAL AND METHODS

Ten crossbreed pigs (Swedish Landrace x Yorkshire) were purchased from a conventional gilt-producing herd. On arrival, the pigs were seven weeks old and clinically healthy, and there were an equal number of males and females. They were housed in individual pens with straw as bedding. They were kept within sight and sound of one another at a light regime of 8 h light/16 h dark. Throughout the study, the pigs were fed 1 kg commercial finisher diet (Singel Flex®, Odal, Sweden) twice daily at 8:00 h and 15:00 h and had free access to water. The pigs were allowed two weeks to acclimatize. When the experiment started the animals weighed 25 ± 1 kg. Due to severe hypotension and thus missing blood values during surgery, one pig in group B had to be excluded from the study (n=9). The experimental protocol was approved by the Ethical Committee for Animal Experiments, Uppsala, Sweden.

The pigs were fasted for 12 h before the general anaesthesia but water was supplied ad libitum. Anaesthesia was induced by intramuscular administration 0.05 mg/kg of medetomidine (Domitor®vet 1 mg/mL; Orion, Espoo, Finland) and 5 mg/kg of tiletamine-zolazepam (Zoletil forte vet; Virbac, Carros, France) (2.5 mg/kg of zolazepam and 2.5 mg/kg of tiletamine). Fifteen minutes after injection, the animal was intubated with an appropriate endotracheal tube size for maintenance of inhalation anaesthesia with isoflurane (Isoflo®vet; Schering-Plough, Kent, UK), supplied with oxygen and air (inspired oxygen concentration 50%; Vaporizer Isotec 5; Datex-Ohmeda, Helsinki, Finland). All animals were allowed to breathe spontaneously throughout the anaesthesia. An experienced animal nurse, blinded to the treatment, continuously adjusted the isoflurane concentration to achieve an adequate depth of anaesthesia. Intravenous fluid with electrolyte solution (Rehydrin with glucose 25 mg/mL; Fresenius Kabi AB, Uppsala, Sweden) was administered at a dosage of 5 mL/kg/h. In addition to the anaesthesia, the pigs were randomly chosen to receive epidural morphine (group M; n=5) or intramuscular buprenorphine (group B; n=4). Epidural morphine was given at a dosage of 0.12 mg/kg (Morfine epidural 2 mg/mL; Pharmacia & Upjohn, Stockholm, Sweden) diluted in saline. The administration of the epidural injection was according to STRANDE's technique (1968). Intramuscular buprenorphine was given at a dosage of 0.1 mg/kg (Temgesic® 0.3 mg/mL; Schering-Plough, Brussels, Belgium). Pigs in group B received a second injection of buprenorphine 12 h after the first administration.

Throughout the anaesthesia and surgical procedure, the following physiological parameters were monitored continuously and recorded every 10 min: respiratory rate (RR); tidal volume (TV); expired minute ventilation (VE); inspired oxygen fraction (FIO₂); end-tidal carbon dioxide concentration (ETCO₂); end-tidal isoflurane concentration (ETiso; Capnomac Ultima; Datex-Ohmeda, Helsinki, Finland); oxygen saturation of haemoglobin (O₂-sat Hb); heart rate (HR; Cardiocap II; Datex, Helsinki, Finland); and invasive arterial blood pressure was measured through a catheter placed in the auricular artery (mean pressure, ABPμ; Sirecust 730; Siemens, Germany). Arterial blood samples were collected twice, after induction of anaesthesia and immediately after the surgical procedure, and analysed for arterial carbon dioxide and oxygen tension (PaCO₂, PaO₂) and pH (ABL™ 5; Radiometer Medical A/S, Copenhagen, Denmark). Rectal temperature was measured with a digital thermometer at the same time as the blood sampling. After administration of additional opioid analgesia, the preparation for the surgery took approximately 20-30 min. The pigs were positioned in left lateral recumbency for the caecum cannula insertion. The surgical procedure was according to the method described by van LEEUWEN et al. (1991). Blood samples (4 mL) were collected from the external jugular vein
into vacutainer tubes without additives at five different times: 30 min, 1 h, 1 h 30 min, 12 h and 24 h after the first drug application, for opioid serum concentration analysis.

Each pig was videoaped for a total of 60 h. The recordings included one 24-h session recorded approximately one week before surgery, and 36 h after the surgical procedure starting immediately after animals were returned to their pens. Two black and white video cameras with a wide-angle lens (Computar CE IP66) were positioned approximately 1 m in front of each pen. Behaviour was recorded with a time-lapse videocassette recorder (Panasonic, AG-TL350) and a video multiplexer (Panasonic, WJ-FS409). A researcher, blinded to the treatments, watched all videotapes and manually recorded the behaviour of the pigs, using instantaneous sampling with an interval of 10 min for the whole 60-hour period. An ethogram based on earlier observations of four pigs of the same age, breed and weight was used (MALAVASI et al., 2006). The following behaviours were regarded as active: standing up, walking, running, jumping, interacting with blanket or straw, rooting, eating and drinking. The inactive behaviours comprised: lying down quietly, lying down agitatedly and sitting position. If an active behaviour occurred simultaneously with an inactive behaviour, such as sitting and rooting activities, the pigs were regarded as active. The first 12 h immediately after surgery were also continuously recorded for analysis of frequency and latency of each activity, including an additional inactive behaviour of staying under a heat lamp.

The pigs were weighed on an electronic scale immediately before surgery and once daily during the two consecutive postoperative days. Daily feed consumption was measured at each feeding time, including the day before surgery and the two consecutive days.

The physiological data during anaesthesia and the opioid serum concentrations were tested with repeated measurements ANOVA. The level of statistical significance was set at p < 0.05. For behavioural analysis, the activities were categorized into active and inactive behaviours. To further understand the drug's effect on pig behaviour, the latency of the first observation of a few activities (i.e. tentative of standing up, standing up with balance, drinking and eating) was also analysed. Weight and feed consumption measured once during the two consecutive days after surgery were calculated as changes in kilograms and percentage, respectively. Then the changes in weight and feed consumption between treatments were compared qualitatively.

RESULTS

The surgery lasted for 60 to 90 min and during the general anaesthesia three pigs, one pig from group M and two pigs from group B, exhibited short episodes of leg movement in response to the surgery. The recovery time defined as the time span from the end of inhalation anaesthesia until the animal was conscious was 2 - 44 min in group M and 5 - 133 min in group B.

Physiological parameters such as respiratory rate, mean arterial blood pressure and PaCO₂ different significantly between groups (Table 1). PaCO₂ and mean arterial blood pressure was higher at the end of surgery in pigs treated with buprenorphine compared to pigs in the morphine group. Also, pigs treated with buprenorphine had decreased RR compared to group M. Two out of four pigs treated with 10M buprenorphine exhibited a severe decrease in respiratory rate 10 min after the drug administration. The pig that had the longest postoperative recovery time in group B also had a period of apnoea and needed artificial ventilation for 2 min during inhalation anaesthesia. No other physiological parameter measured differed between groups (Table 1). Throughout the study, isoflurane requirement measured after the expected onset of action of the opioids did not differ between morphine treated pigs and buprenorphine treated pigs.
Table 1 - Physiological parameters (mean ± SD) measured throughout isoflurane anaesthesia and a standardized surgical abdominal procedure in pigs treated either with epidural morphine (M) or intramuscular buprenorphine (B). (*) indicates significant differences between treatment groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Before surgery</th>
<th>Time point during surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>M</td>
<td>101 ± 25</td>
<td>0 - 20 min 83 ± 15</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>93 ± 28</td>
<td>71 ± 13 71 ± 7 63 ± 6 75 ± 9</td>
</tr>
<tr>
<td>mABP (mmHg)</td>
<td>M</td>
<td>106 ± 19</td>
<td>104 ± 14 101 ± 15 101 ± 7</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>114 ± 21</td>
<td>111 ± 14 120 ± 15 122 ± 14 111 ± 13</td>
</tr>
<tr>
<td>RR (mpm)</td>
<td>M</td>
<td>50 ± 8</td>
<td>50 ± 7 45 ± 9 47 ± 9 47 ± 8</td>
</tr>
<tr>
<td>TV (mL)</td>
<td>B</td>
<td>83 ± 18</td>
<td>96 ± 19 109 ± 24 102 ± 22 96 ± 18</td>
</tr>
<tr>
<td>Etiso (%)</td>
<td>M</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.2 0.5 ± 0.2 0.5 ± 0.1 0.5 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>0.5 ± 0.1</td>
<td>0.5 ± 0.1 0.5 ± 0.2 0.6 ± 0.2 0.6 ± 0.1</td>
</tr>
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</table>

The highest plasma morphine concentration was observed 1 h after the epidural administration and ranged from 23.6 - 141.1 ng/mL. Twenty-four hours after the epidural injection, morphine was still measurable with serum concentrations ranging from 0.05 - 64 ng/mL. The plasma concentration of buprenorphine changed significantly over time and the highest value measured was observed 1 h after the intramuscular injection. During the surgical procedure the mean buprenorphine concentration was 9.9 ± 6.3 ng/mL. Twelve hours after the first buprenorphine administration the plasma concentration were still detectable and ranged from 1.0 - 12.7 ng/mL.

None of the pigs had any signs of specific pain-related behaviour during the postoperative period, as evaluated subjectively by the veterinarian during the clinical examinations. During the first 12 h after surgery, all pigs treated with epidural morphine had a lower activity level compared to preoperative day. Two out of four pigs treated with buprenorphine showed higher activity of 15 and 16%, respectively. The other two pigs treated with buprenorphine showed lower activity level of 21% and 29%, respectively, at this time. During the next 12 - 36 h postoperatively (i.e. day 1), the activity level was higher in all pigs from both treatment groups compared to preoperative levels (Figure 1).
The latency to the first observation of standing up, eating and drinking was defined during the first 12 h postoperatively. All pigs attempted to stand up ("tentative of standing up") within 5 min after they were returned to their pens. After the pigs were able to stand up, they began eating earlier than drinking (Fig. 2). One out of four pigs treated with buprenorphine did not eat at all during the first 12 h after surgery. Also, three of five pigs treated with morphine and three of four pigs treated with buprenorphine did not drink throughout this period.

![Figure 1 - Changes in activity level (%) compared to data measured before surgery (pre-op) in pigs treated with epidural morphine (---) and intramuscular buprenorphine (—) throughout pre-operative day (pre-op), after surgery (op) and 24 h postoperatively (day 1 post-op).](image1)

During the first 12 h postoperatively, four out of five pigs treated with epidural morphine were sitting while eating or rooting.

One pig from group M was excluded due to episodes of emesis during the postoperative period. Thus, four pigs were included in each treatment group for weight and feed consumption measurements. Twenty-four hours postoperatively, one out of four pigs treated with morphine weighed less than before the surgery. At this time, all pigs that received buprenorphine showed decreased body weight compared to preoperative data. Even after 48 h three out of four pigs in group B had not regained their preoperative weight. Two out of four pigs treated with
buprenorphine had a reduction of 80% in feed consumption after the first 12 h postoperatively. On the next postoperative day, two out of four of the pigs in group M and three out of four pigs in group B increased their feed consumption.

**DISCUSSION**

In the present study, treatment with systemic buprenorphine prior to surgery in anaesthetised and spontaneously breathing pigs resulted a decrease in respiratory rate and a slight but significant hypoventilation compared to treatment with epidural morphine. In addition, buprenorphine caused transient respiratory depression in two pigs and an apnoea episode in one pig 10 min after intramuscular injection. Buprenorphine has been suggested to produce fewer respiratory side-effects compared to other opioids for example in rats (LILES & FLECKNELL, 1992; ROUGHAN & FLECKNELL, 2004) and sheep (NOLAN, LIVINGSTON & WATERMAN, 1987). DAHAN and co-workers (2005) have reported that the dose of buprenorphine that produces no respiratory effect in rats is 0.1 mg/kg. The recommended doses of buprenorphine in pigs range from 0.005 to 0.1 mg/kg (RODRIGUEZ et al., 2001). However, HERMANSSEN, PEDERSEN & OLESEN (1986) showed that 0.1 mg/kg is the appropriate dose to provide sufficient and long lasting analgesia in pigs subjected to noxious stimuli (i.e. hot plate, needle prick and cannulation of ear vein). Therefore, the dosage chosen in the present study (0.1 mg/kg) might be in the dosage range of buprenorphine that is associated with some respiratory depression in pigs. Further studies to determine the limits of this dosage range are required.

In an earlier study our group have found that preoperative epidural morphine does not result in major behavioural changes in pigs during the early postoperative period (MALAVASI et al., 2006). In that study, pigs were treated with preoperative epidural morphine and transdermal fentanyl patch applied immediately after caecal cannula insertion. During the first 12 h postoperatively, the pigs showed activity levels similar to the preoperative recordings. The absence of behavioural effects seen in those pigs could be related to a synergic analgesic effect of epidural morphine and transdermal fentanyl patch (MALAVASI et al., 2006). Thereafter, the next 24 h postoperatively, the pigs in that study showed lower activity levels, which were also seen throughout the present study. The low activity observed in the present study can be explained by factors such as sedation and alteration of motor function. ROBISON et al. (1999) have reported that epidural morphine in dogs produces moderate sedation after orthopaedic surgery. In humans, there are some reports of numbness and weakness of one or both legs after receiving epidural injection (LITTLELL, 1991). Additionally, the high volume solution used in the present study might have affected the motor function. STRANDE’s study on the epidural technique in 1968 did not include a behaviour study and the effects on locomotion have until now not been reported. Another factor that can result in lower activity level is when pain causes an animal to become immobile (DENNIS & MELZACK, 1983; FLECKNELL, 1999). In the present study, the pigs treated with epidural morphine showed better feed consumption and weight gain compared to pigs in group B despite their lower activity during postoperative period. Pigs from group B received a second injection of buprenorphine, which can be responsible for higher activity level seen in the latest postoperative period compared to group M. Therefore, future studies using epidural catheter to apply supplemental morphine postoperatively to awaken pigs is recommended.

In contrast to the behavioural effect of epidural morphine, IM buprenorphine resulted in both increased and decreased activity level in this study. It has been reported that buprenorphine increases spontaneous locomotory activity in rats (COWAN, DOXEY & HARRY, 1977; LILES
& FLECKNELL, 1991; ROUGHAN & FLECKNELL, 2004), mice (COWAN, DOXEY & HARRY, 1977), sheep (NOLAN, LIVINGSTON & WATERMAN, 1987) and pigs (HERMansen, PEDERSEN & OLESEN, 1986; HARVEY-CLARK, GILEspIE & RIGGS, 2000). The decrease in activity level seen in two of our pigs treated with buprenorphine could indicate that these pigs needed additional analgesia. These pigs also showed the lowest weight gain, feed consumption and buprenorphine serum concentrations, which further indicates that they might have needed additional analgesia. HARVEY-CLARK, GILEspIE & RIGGS (2000) have stated that all pigs treated with IM buprenorphine (0.1 mg/kg) after thoracotomy required supplemental dose of buprenorphine (0.1 mg/kg to effect) postoperatively 5 – 8 h after the initial dose. Even rats treated with buprenorphine after abdominal surgery needed additional analgesia (ROUGHAN & FLECKNELL, 2004).

To assess the effects of an analgesic drug in pigs the researcher needs to consider the results from behavioural analysis as well as weight and feed consumption measurements. Buprenorphine has been reported to cause depressed feed consumption in pigs (HARVEY-CLARK, GILEspIE & RIGGS, 2000) and rats (LILES & FLECKNELL, 1991). In the present study all pigs treated with intramuscular buprenorphine showed loss of weight and less feed consumption. Therefore, although 50% of the pigs in group B had increased activity this was not related to increase in weight gain or feed consumption.

Epidural morphine has previously been suggested to provide satisfactory analgesia for surgical procedures such as caecal cannula insertion that evokes both somatic and visceral pain in pigs (MALAVASI et al., 2006). This type of surgery is frequently performed in nutritional (KIEN et al., 1997) and infection studies in pigs (JACOBson et al., 2001). Therefore, further studies are required to determine the analgesic effect of buprenorphine and its duration in pigs subjected to procedures that include both somatic and visceral pain in the postoperative recovery period. The recommended dose is supported by studies such as that of HERMansen, PEDERSEN & OLESEN (1986) that evaluates analgesia for somatic pain. Therefore, dosage and dose intervals of opioids for analgesic treatment of visceral procedures are needed to be established in the future.

In conclusion, intramuscular buprenorphine caused respiratory depression with unpredictable behavioural effect that interfered with weight and feed consumption. Pigs treated with epidural morphine had lower postoperative activity but higher weight gain and feed consumption measured at 24h postoperatively.

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