Analgesic, Behavioural and Cardiopulmonary Effects of Epidurally Injected Medetomidine (Domitor®) in Goats

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With 3 tables

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Summary

This study was carried out in order to evaluate the analgesic, sedative, immobilizing and cardiopulmonary effects of medetomidine in goats after lumbosacral epidural injection of three (10, 20 and 30 μg/kg body weight) doses. The volume of the injection for all three medetomidine doses was 5 ml in sterile water. Seventeen clinically healthy, Small East African goats of either sex and weighing between 12 and 22 kg (mean ± SD; 14.8 ± 2.5 kg body weight) were used. The animals were randomly assigned to two groups. Seven goats were used for evaluating analgesic, behavioural and cardiopulmonary effects while 10 were used for experimental surgery. The cardiopulmonary values and rectal temperature were determined and recorded at time 0 (preinjection) and at 5, 10, 15, 20 and 30 min, and thereafter at 15-min intervals up to 180 min after injection. Analgesia of the flank and perineum was determined at time 0 (preinjection) and at 5, 10, 15, 20, 30 and 60, 120 and 180 min using a scoring system. The spread of analgesia to the thorax, neck, forelimbs and head was also determined and recorded. The onset and duration of lateral recumbency was noted and recorded. Medetomidine at the given doses induced variable cardiopulmonary depression, which was not detrimental to the animals. All three doses (10, 20 and 30 μg/kg) of medetomidine induced adequate analgesia of the flank and perineum. Analgesia extended to the thorax, neck, forelimbs and head was also determined and recorded. The duration of lateral recumbency was 136 and 166 min for the 20 and 30 μg/kg medetomidine doses, respectively. The duration of lateral recumbency was not determined for the animal given 10 μg/kg medetomidine. Signs of sedation (lowering of the head, drooping of the lower lip, partial to complete closure of the eyes and salivation) were noted after administration of all three doses. It can be concluded from this study that all three doses induced adequate analgesia of the flank and perineum. Surgical analgesia of the flank of goats was achieved after lumbosacral epidural administration of 20 μg medetomidine/kg, diluted in 5 ml of sterile water. Surgery was not performed with the other doses (10 and 30 μg/kg) of medetomidine.

Introduction

Medetomidine is a more selective and full agonist for central α₂-adrenergic receptor than xylazine and detomidine. It is used intramuscularly or intravenously as an analgesic and as a sedative in dogs and cats (Short, 1992). Its use for lumbosacral epidural analgesia in dogs (Vesal et al., 1996) and cats (Duke et al., 1994a,b) and after caudal epidural injection in cattle (Lin et al., 1998) has recently been reported. Such studies have not been reported in sheep and goats. The objective of this study was to evaluate the analgesic, sedative, immobilizing and cardiopulmonary effects of lumbosacral epidural injection of medetomidine in goats.
Materials and Methods

Experimental animals

Seventeen clinically healthy, Small East African goats of either sex and body weights ranging from 12 to 22 kg (mean ± SD; 14.6 ± 2.5 kg) were used. Of these goats, 11 were males and eight were females. These animals were randomly assigned to two groups of seven and 10 goats. Of the seven animals, one was used for evaluating the sedative and immobilization effects while the other six were used for evaluating analgesia and cardiopulmonary effects of each dose tested. The seven animals were randomly assigned to the three dose treatments of 10, 20 and 30 μg/kg of body weight of medetomidine with a 1-week interval between injections. The 10 animals were used for experimental surgery at the end of the evaluation study.

Epidural placement of needle and drug administration

The lumbosacral region was aseptically scrubbed to prevent introduction of pathogens into the lumbosacral epidural space. The area was cleaned, shaved and disinfected using Savlon® (cetrimide and chlorohexidine), 70% alcohol and iodine, in that order.

A sterile, 18-gauge, 10-cm spinal needle was inserted into the epidural space at the lumbosacral interspace as described by Gray and McDonell (1986). A precalculated dose of medetomidine, adjusted to a total volume of 5 ml by addition of sterile water for injection, was administered over 20 s through the needle previously placed epidurally. After epidural injection of the test dose, animals were positioned in a right lateral recumbent position and analgesia and cardiopulmonary data were determined and recorded. The animal scheduled for the sedation and locomotion study was released in a quiet room and observed from a distance.

Sedative, locomotive and analgesic effects

Sedation was defined as decreased mental awareness, lowered head, drooping of the lower lip and ears, partial to complete closure of eyelids, ataxia and recumbency. The onset of these signs was noted and recorded. Analgesia was determined at time 0 (preinjection) and at 5, 10, 15, 30, 60, 120 and 180 min after drug administration. The degree of sensory perception to needle pricks in the perineal and flank regions was graded by using a scoring system of 0–3 as described by Skarda and Muir (1996a,b). The spread of analgesia to the thorax, neck, forelimbs and head was also determined and recorded. A score of 0 (no analgesia) was given if there was an avoidance response to pricking the surface of the skin. A score 1 (mild analgesia) was given if there was no avoidance response to superficial skin pricks by the needle. A score of 2 (moderate analgesia) was given if there was no avoidance to the insertion of half the needle length, and a score of 3 (adequate analgesia) was given if there was no avoidance response to inserting the needle through the skin and the underlying tissues (deep muscle pricks). During each test period, superficial skin prick and deep muscular pricks were given using a 1.5-inch (3.6-cm), 21-gauge needle.

Heart and respiration rates, blood pressure and rectal temperature

These parameters were measured at time 0 (preinjection) and at 5, 10, 15, 20 and 30 min, and thereafter at 15 min intervals up to 180 min, after epidural injection. The heart and respiration rates were measured by thoracic auscultation, using a stethoscope. The systolic and diastolic arterial pressures were measured oscillometrically, using the HEM 705 CP digital human prototype (Omron, Omron Corp., Tokyo, Japan) as described by Mpanduji (1998), with the cuff placed around the neck region. The mean arterial blood pressure was calculated as described by Remillard et al. (1991). Rectal temperature was recorded continuously using a digital thermometer (Exacon® Scientific, Rosklede, Denmark) with the thermocouple probe placed deep into the rectum.

Experimental surgeries

Ten clinically health goats were used for surgical procedures performed in the flank region. The procedures included laparotomy, rumenotomy and one Caesarean section.

Data analysis

Data were analysed in accordance with SAS/STAT™ (1988). The mean scores of analgesia and cardiopulmonary data were subjected to analysis of variance. The least square mean (LSM) was used for multiple comparisons of means. Data were considered significantly different when \( P \) was less than 0.05.
Results

General observations and behavioural effects

Epidural administration of all three doses of medetomidine produced deep sedation. The animal that was given 10 μg/kg of medetomidine became first sternally then laterally recumbent, and demonstrated salivation and drooping ears and lower lip 3–9 min after injection. The animal which was given 20 μg/kg of medetomidine showed unco-ordinated movements, salivation and drooping lower lip within 3–6 min, which was followed by lateral recumbency 10 min later. Signs of sedation (low head carriage, intermittent sternal and lateral recumbency, vocalization and copious salivation) developed slowly for the animal which was given 30 μg/kg of medetomidine. With all three doses, sedation continued until the end of the 180-min observation period. All animals urinated at least twice towards the end of the observation period. Bloat of variable onset and extent was also observed. Lateral recumbency lasted 136 and 166 min for the 20 and 30 μg/kg medetomidine treatments, respectively. The animal, which was given 10 μg/kg of medetomidine, failed to use its hind limbs for 3 days. It was therefore killed and replaced with another animal.

Analgesic and cardiopulmonary effects

Lumbosacral epidural injection of medetomidine induced adequate analgesia of the flank and perineum within 5 min after drug administration. Analgesia extended to the thorax, forelimbs, neck and head. All three doses of medetomidine induced adequate analgesia throughout the 180-min observational period (Table 1). No significant differences were noted between the various levels of analgesia on the flank and perineal region, except at t = 180 min and at t = 5 min for the flank and perineal regions, respectively. At these time-points, the mean analgesia scores for the 30 and 10 μg/kg medetomidine doses were significantly lower (P < 0.05) when compared to those for the 10 and 20 μg/kg doses for the flank, and the 20 and 30 μg/kg doses for the perineum, respectively.

In all treatment groups, epidural injection of medetomidine caused a significant decrease (P < 0.05) of mean values of respiration rate, heart rate, arterial pressure and rectal temperature values within 5 min after injection. These effects persisted for the entire observational period of 180 min. The dose–time response and the pair-wise comparison of the various medetomidine treatments for the mean values of respiration rate, heart rate, arterial pressure and rectal temperature are summarized in Table 2.

Experimental surgeries

Laparotomies in 10 goats using 20 μg/kg of medetomidine lasted over 60 min (means 57.4 ± 15.7). Of the 10 surgeries, one was a laparohysterotomy and another a laparoruminotomy (Table 3). Analgesia at the skin, subcutaneous tissues, external and internal oblique muscles and transverse muscles was examined critically. All muscle layers displayed adequate surgical analgesia. Recovery at the end of the 180-min observational period was uneventful, and all animals were grazing normally. The details of the surgical procedures are shown in Table 3.

Discussion

Epidural administration of α2-adrenergic receptor agonists such as xylazine (Le Blanc et al., 1988; Zaugg and Nussbaum., 1990; Skarda and Muir, 1996a); detomidine (Skarda and Muir, 1994, 1996b) and medetomidine (Lin et al., 1998) has induced perineal and bilateral flank analgesia in many species, with cranial analgesia of variable extent. Our findings in goats were different from these reports. Lumbosacral epidural administration of medetomidine in goats induced generalized analgesia, dose-dependent sedation and lateral recumbency. Wittern et al. (1998) and Tiwari et al. (1998) also reported recumbency after epidural administration of detomidine and xylazine in horses and buffaloes, respectively. In the reported studies, 50 μg/kg of detomidine and 100 μg/kg of xylazine were used in horses and buffaloes. Our report also showed a relatively longer duration of analgesia after epidural injection of medetomidine than
Table 1. The mean analgesic score in response to needle pricks at the flank and perineal regions after lumbosacral epidural injection of three doses of medetomidine in goats

<table>
<thead>
<tr>
<th>Dose (µg/kg)</th>
<th>Time after treatments (min)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flank</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>2.67 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>2.83 ± 0.13**</td>
<td>2.83 ± 0.13**</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>3.00 ± 0.13**</td>
<td>2.83 ± 0.13**</td>
<td>2.67 ± 0.13**</td>
<td>2.67 ± 0.13**</td>
<td>2.16 ± 0.13**</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perineum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>2.67 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>2.80 ± 0.08**</td>
<td>2.80 ± 0.08**</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>3.00 ± 0.08**</td>
<td>2.83 ± 0.08a*</td>
<td>2.83 ± 0.08a*</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as means ± SEM adjusted to two decimal places (n = 6). *Values significantly different (P < 0.05) from the baseline data. Values in the same column and same region, which have different superscripts, are significantly different (P < 0.05).
Table 2. Effects of lumbosacral epidural injection of three doses (10, 20 and 30 μg/kg) of medetomidine on respiratory and heart rates, arterial blood pressure and rectal temperatures in goats

<table>
<thead>
<tr>
<th>Time after treatments (min)</th>
<th>RR</th>
<th>HR</th>
<th>MAP</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>26.7 ± 2.6** 20.0 ± 2.6** 20.3 ± 2.6**</td>
<td>82.3 ± 5.0** 71.7 ± 5.0** 72.0 ± 5.0**</td>
<td>108.0 ± 5.6** 90.3 ± 5.6** 92.2 ± 5.6**</td>
<td>38.5 ± 0.6** 38.8 ± 0.6** 38.9 ± 0.6**</td>
</tr>
<tr>
<td>5</td>
<td>19.2 ± 2.6* 19.2 ± 2.6* 19.2 ± 2.6*</td>
<td>63.0 ± 5.0** 59.5 ± 5.0** 54.5 ± 5.0**</td>
<td>80.4 ± 5.6** 82.9 ± 5.6** 84.2 ± 5.6**</td>
<td>37.9 ± 0.6** 37.8 ± 0.6** 37.8 ± 0.6**</td>
</tr>
<tr>
<td>10</td>
<td>17.7 ± 2.6** 13.0 ± 2.6** 13.3 ± 2.6**</td>
<td>54.5 ± 5.0** 57.0 ± 5.0** 56.8 ± 5.0**</td>
<td>82.7 ± 5.6** 83.3 ± 5.6** 83.9 ± 5.6**</td>
<td>38.9 ± 0.6** 38.8 ± 0.6** 38.8 ± 0.6**</td>
</tr>
<tr>
<td>15</td>
<td>14.8 ± 2.6** 13.3 ± 2.6** 12.3 ± 2.6**</td>
<td>57.0 ± 5.0** 59.7 ± 5.0** 59.2 ± 5.0**</td>
<td>83.9 ± 5.6** 84.0 ± 5.6** 84.0 ± 5.6**</td>
<td>39.0 ± 0.6** 38.9 ± 0.6** 38.9 ± 0.6**</td>
</tr>
<tr>
<td>20</td>
<td>12.6 ± 2.6 11.8 ± 2.6 11.2 ± 2.6 11.7 ± 2.6 12.2 ± 2.6 11.7 ± 2.6 13.2 ± 2.6 11.5 ± 2.6 12.7 ± 2.6 12.2 ± 2.6 12.7 ± 2.6 12.0 ± 2.6 12.8 ± 2.6</td>
<td>12.3 ± 2.6 11.8 ± 2.6 11.5 ± 2.6 11.7 ± 2.6 12.0 ± 2.6 12.8 ± 2.6</td>
<td>12.3 ± 2.6 11.8 ± 2.6 11.5 ± 2.6 11.7 ± 2.6 12.0 ± 2.6 12.8 ± 2.6</td>
<td>12.3 ± 2.6 11.8 ± 2.6 11.5 ± 2.6 11.7 ± 2.6 12.0 ± 2.6 12.8 ± 2.6</td>
</tr>
<tr>
<td>30</td>
<td>23.3 ± 1.8** 19.3 ± 1.8** 23.0 ± 1.8**</td>
<td>23.3 ± 1.8** 23.0 ± 1.8** 23.3 ± 1.8**</td>
<td>23.3 ± 1.8** 23.0 ± 1.8** 23.3 ± 1.8**</td>
<td>23.3 ± 1.8** 23.0 ± 1.8** 23.3 ± 1.8**</td>
</tr>
</tbody>
</table>

*Values significantly (P < 0.05) different from values recorded at base line (t=0). Values in same column, same region having same superscripts are not significantly different (P > 0.05). Data are expressed as mean ± SE; adjusted to one decimal place, (n = 6); PAR = parameters, RR = mean respiration rate (breaths/min), HR = mean heart rate (beats/min), MAP = mean arterial pressure (mmHg) and RT = rectal temperatures (°C).
Table 3. Type, onset and duration of surgical procedures following lumbosacral epidural injection of medetomidine (20 μg/kg body weight) in 10 goats

<table>
<thead>
<tr>
<th>ID no.</th>
<th>Sex</th>
<th>Body weight (kg)</th>
<th>Total dose (μg/kg)</th>
<th>Type of operation</th>
<th>Onset of procedure post-injection (min)</th>
<th>Duration of procedure (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIL</td>
<td>F</td>
<td>14.5</td>
<td>290</td>
<td>Laparotomy</td>
<td>18</td>
<td>56</td>
</tr>
<tr>
<td>NIL</td>
<td>M</td>
<td>13.0</td>
<td>260</td>
<td>Laparotomy</td>
<td>8</td>
<td>39</td>
</tr>
<tr>
<td>145</td>
<td>M</td>
<td>13.5</td>
<td>270</td>
<td>Laparotomy</td>
<td>15</td>
<td>45</td>
</tr>
<tr>
<td>144</td>
<td>F</td>
<td>15.5</td>
<td>310</td>
<td>Laparotomy</td>
<td>12</td>
<td>55</td>
</tr>
<tr>
<td>150</td>
<td>M</td>
<td>16</td>
<td>320</td>
<td>Laparotomy</td>
<td>10</td>
<td>86</td>
</tr>
<tr>
<td>143</td>
<td>M</td>
<td>14.5</td>
<td>290</td>
<td>Laparotomy</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>141</td>
<td>F</td>
<td>12</td>
<td>240</td>
<td>Laparotomy</td>
<td>15</td>
<td>73</td>
</tr>
<tr>
<td>149</td>
<td>F</td>
<td>13</td>
<td>260</td>
<td>Laparotomy</td>
<td>9</td>
<td>45</td>
</tr>
<tr>
<td>NIL</td>
<td>F</td>
<td>22</td>
<td>440</td>
<td>Laparohysterotomy</td>
<td>10</td>
<td>76</td>
</tr>
<tr>
<td>NIL</td>
<td>M</td>
<td>14</td>
<td>280</td>
<td>Laparoruminotomy</td>
<td>90</td>
<td>45</td>
</tr>
</tbody>
</table>

analgesia reported earlier after epidural administration of xylazine (Aithal et al., 1996, 1997; Mpanduji, 1998) and the traditional local analgesics (Fikes et al., 1989; Makady et al., 1991; Grubb et al., 1992). The longer duration of analgesia after lumbosacral epidural injection of medetomidine in goats concurred with the previous report by Lin et al. (1998). In that report, caudal epidural injection of 15 μg/kg of medetomidine induced perineal analgesia which lasted 412 ± 156 min in cattle. The differences in the duration and extent of analgesia in these animal species may be attributed firstly, to the highly lipophilic nature of medetomidine (Savola et al., 1986), and secondly, to the high affinity of medetomidine to α2-adrenergic receptor binding sites. A far greater relative α2/α1 ratio of 1620 has been reported for medetomidine than that of xylazine (160) or detomidine (260) (Virtanen et al., 1988; Virtanen, 1989). Thirdly, they may be attributed to species variations. Goats are reported to be more sensitive to α2-adrenergic receptor agonists than cattle and sheep (Yeboa and Huvos, 1980; Hall and Clarke, 1991).

Studies performed so far have shown that systemic administration of α2-adrenergic receptor agonists inhibit the neuronal firing at the locus coeruleus in the brain to induce sedation and analgesia (Cedarbaum and Aghajanian, 1977; Desarro et al., 1987). Furthermore, the α2-adrenergic receptor agonist xylazine is known to have local anaesthetic properties (Aziz and Martin, 1978; Chambers, 1993). The α2-adrenergic receptor agonist, medetomidine inhibits the spinal release of the neural transmitter ‘substance P’ at the spinal cord (Pernow, 1983) to induce analgesia, thereby attributing to the generalized analgesia and sedation encountered in the goats in this study.

All test doses of medetomidine exhibited an inhibitory effect on respiration rate, heart rate, mean arterial blood pressure and had variable effects on rectal temperature. These changes are in agreement with the previous reports in swine (Ko et al., 1992), horses (Skarda and Muir, 1994, 1996a,b), and cattle (Lin et al., 1998) and are believed to be attributed to the central effects of α2-adrenergic receptor agonists (Short, 1992).

Bloat of variable onset and magnitude developed after administration of all doses of medetomidine. Similar phenomena have been reported in goats (Mpanduji, 1998) and buffaloes (Tiwari et al., 1998) after epidural administration of xylazine and/or detomidine. The decrease of rumeno-reticular motility is reported to be common after α2-adrenergic receptor agonist medications in ruminants (Short, 1992).

A long-lasting paralysis was encountered in this study after epidural injection of 10 μg/kg of medetomidine in one goat. Anatomically, differences in caudal extension of the spinal cord in different animal species exist. In ruminants, the spinal cord ends at the lumbosacral region. The dura sheath extends caudally as the filum terminale, from which nerve fibres radiate...
forming the cauda equina (Dyce et al., 1987). From their anatomical positions, the possibility of traumatizing the conus medullaris and/or the cauda equina at the lumbosacral site with the needle in ruminants exists if the animal struggles during needle placement and injection. The paralytic effect, which was seen in the present study, may have been caused by trauma to the conus medullaris and/or the cauda equina as the animal struggled during the lumbosacral epidural injection.

From this study, the following conclusions can be drawn. Lumbosacral epidural administration of medetomidine at doses of 10, 20 and 30 μg/kg body weight induced adequate analgesia of the flank and perineum. Analgesia also extended to the thorax, forelimbs, neck and head of goats.

Epidurally administered medetomidine induced variable changes in the cardiopulmonary parameters and rectal temperature that are typical of α2-adrenergic receptor agonists, but were not detrimental to the animals.

When performing lumbosacral epidural injections, extreme care must be taken to avoid traumatizing the conus medullaris and/or cauda equina in goats.

Lumbosacral epidural administration of medetomidine at a dose of 20 μg/kg of body weight, diluted in 5 ml of sterile water, produced surgical analgesia of the flank for over 60 min and lateral recumbency for 136 min after drug administration in Small East African goats.

Acknowledgements
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administration of detomidine into the caudal epidural space in a horse. J. Am. Vet. Med. Assoc. 213,
516–518.