Comparison of Sedative and Analgesic/Anesthetic Effects Induced by Medetomidine, Acepromazine, Azaperone, Droperidol and Midazolam in Laboratory Pigs

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ABSTRACT. The sedative and analgesic/anesthetic effects of medetomidine, acepromazine, azaperone, droperidol and midazolam were compared in laboratory pigs. In these sedatives, medetomidine produced the most profound degree of sedation with greater drowsiness than was achieved by other sedatives tested. Medetomidine induced sedation accompanied with weak analgesia and muscle relaxation smoothly and quickly and depressed arousal reaction deeply as compared with other sedatives. Pigs given medetomidine were not aroused easily even by moderately rough stimulation for approximately 60 min after injection.—KEY WORDS: medetomidine, sedative, swine.


Due to anatomical and physiological similarities to humans, pigs are becoming used more widely in biomedical researches [8]. Recently pigs have also been used to replace dogs for many purposes. However, pigs are not easy to be handled because they vocalize extremely loudly and struggle hardly when restrained. Administration of a sedative might be needed for restraint to complete the minor or non-painful procedures and to induce general anesthesia smoothly.

On the basis of chemical structure, sedatives are divided into four major groups which are butyrophenones, phenothiazines, benzodiazepines and thiazines. Several drugs of these groups have been reported to be available for swine sedation [6]. Azaperone, a butyrophenone derivative, has been most widely used, and acepromazine (a phenothiazine derivative), droperidol (a butyrophenone derivative) and diazepam (a benzodiazepine derivative) have been reported to be available for sedation in pigs.

Recently we have reported that medetomidine, which is a newly developed thiazine derivative and an $\alpha_2$-adrenoreceptor agonist, induced the sedation accompanied with lateral recumbency and mild analgesia in pigs [9]. Medetomidine has a great advantage in its effect being smoothly and quickly reversed by a specific $\alpha_2$-adrenoreceptor antagonist [7]. However, there has been no comparative study of the sedative effects of these sedatives.

The purpose of this study was to compare qualitatively and quantitatively the sedative and analgesic/anesthetic effects of medetomidine with those of the sedatives described above or its derivative (azaperone, acepromazine, droperidol and midazolam) in laboratory pigs. Special attention was paid to evaluate the depressive abilities of the arousal reaction induced by sensory stimuli of these sedatives.

Six castrated mixed breed pigs (Sumichiku Co., Ltd., Japan) were repeatedly used at a weekly interval in this study. Their mean age was 12.2 weeks (range 9 to 15 weeks) and mean body weight was 20.8 kg (range 15.5 to 26.0 kg). During the period of stabilization (for more than a week), the pigs were fed a commercial ration once a day and given water ad libitum. The pigs were fasted for more than 12 hr before the experiments, and each animal was exposed to different drugs in a randomized block design.

The drugs and their dosages used in this study were as follows: acepromazine maleate (Acepromazine maleate injection, TechAmerica Veterinary Products, U.S.A.) at 2 mg/kg of body weight, azaperone (Stresnil, Sankyo Co., Ltd., Japan) at 8 mg/kg, droperidol (Droletan, Sankyo Co., Ltd., Japan) at 2 mg/kg, midazolam (Dormicum, Yamanouchi Pharmaceutical Co., Japan) at 2 mg/kg and medetomidine (Farmos Group Ltd., Finland) at 80 $\mu$g/kg. The dose of each drug except for midazolam was determined from the maximal-recommended or previously reported doses in pigs [3, 9, 13]. The dose of midazolam was one fourth of the maximal dose of diazepam [13] which has one fourth to a half degree of sedative effect of midazolam. All drugs were injected into the cervical muscle.

The experiments were performed in a quiet room with a controlled temperature at 24±1.5°C and humidity at 50±15%. The pigs were administrated one of the drugs tested, and were kept in solitary cages to keep the animals from disturbing each other. Sedative effects were repeatedly assessed before injections of the drugs, and 10, 20, 30, 40, 60, 90, 120, 180, 240, 360 and 480 min after dosing and/or until the complete recovery from sedation.

Effect of each drug was assessed by sedative character [4] and analgesic/anesthetic character and by induction time (time from injection of the drug until the animal became ventral recumbency), standing time (time from injection of the drug until the animal could stand) and total recovery time (time from injection of the drug until the animal could not be distinguished from untreated animals). Sedative character of each drug was totally evaluated from posture, response to noise, resistance to restraint and resistance to mouth open and to pull tongue outwards. Analgesic/anesthetic character was totally evaluated from response to nose-pinching and toe-pinching withdrawal response.

Posture of the pig was evaluated according to the following scale: score 0: normal; score 1: being able to stand or sit on their hind legs; score 2: keeping the position of ventral recumbency; score 3: lateral recumben-
cy with apparent spontaneous movement (head lifting or limb struggling); score 4: lateral recumbency with subtle spontaneous movement (ear and nose twitching or blink); score 5: lateral recumbency without any spontaneous movement. Response to noise (hand clapping) was assessed as follows: score 0: normal response; score 1: hears and moves; score 2: hears and twitches ear; score 3: no perception. Resistance of the pig against the restraint was scored as follows: score 0: strong resistance against being laid laterally recumbent; score 1: moderate resistance against being laid laterally recumbent; score 2: slight resistance against being laid laterally recumbent but moderate resistance against dorsally recumbent; score 4: no resistance against being laid laterally recumbent but moderate resistance against dorsally recumbent; score 5: no resistance against being laid laterally recumbent but moderate resistance against dorsally recumbent. Resistance against mouth open and pulling the tongue outwards was evaluated as follows: score 0: resistance against mouth opening (difficult to open) and pulling the tongue outwards; score 1: moderate resistance against mouth opening (possible to open) and pulling the tongue outwards; score 2: slight resistance against mouth opening (relaxed) and pulling the tongue outwards; score 3: no resistance against mouth opening and pulling the tongue outwards.

Response to nose (nasal septum)-pinching was assessed as follows: score 0: total body movement; score 1: raising the head; score 2: slight movement of the head; score 3: no response. Toe-pinch withdrawal response was scored as follows: score 0: normal response; score 1: weakened; score 2: only induced by an increased stimulus; score 3: no response. The scores of the individual parameters described above were summed up to evaluate each character.

Recovery condition and undesirable side effects were also observed throughout the experiment.

Differences in sedative effects between drugs at corresponding time were assessed by use of Kruskal-Wallis test and Williams Wilcoxon multiple comparison procedure. The data of induction time, standing time and total recovery time were analyzed by one-way analysis of variance and Duncan’s multiple comparison procedure. In all analyses, values were considered to be statistically significant when P<0.05.

Following the intramuscular injection of medetomidine, the pigs were smoothly induced to sedation and became ataxic and drowsy within a few min. The animals consistently became ventral recumbency in less than 15 min (Table 1), then became lateral recumbency and maintained this position for approximately 60 min. During being in lateral recumbency, these pigs were in deep sedation with losing consciousness. They did not respond to most of sensory stimuli and were not aroused when an observer approached the animals, clapped the hands, touched the body, pulled the extremity, pinched the nose or toe and restrained in lateral recumbency, however they resisted against restraint in dorsal recumbency. In addition, these pigs showed apparent muscle relaxation during this period and hardly resisted against mouth open. Mean total score used for evaluating sedative character of

Table 1. Induction time, standing time and total recovery time in pigs given medetomidine, azaperone, acepromazine, droperidol and midazolam

<table>
<thead>
<tr>
<th>Sedative</th>
<th>Mean induction time (min)</th>
<th>Mean standing time (min)</th>
<th>Mean total recovery time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>azaperone</td>
<td>13±4.94</td>
<td>177.3±82.6</td>
<td>648.9±107.3</td>
</tr>
<tr>
<td>droperidol</td>
<td>16.0±3.0</td>
<td>121.0±49.4</td>
<td>288.0±35.4</td>
</tr>
<tr>
<td>acepromazine</td>
<td>24.6±11.6</td>
<td>88.7±51.6</td>
<td>355.0±105.7</td>
</tr>
<tr>
<td>medetomidine</td>
<td>12.5±7.7</td>
<td>79.2±16.4</td>
<td>227.5±36.0</td>
</tr>
<tr>
<td>midazolam</td>
<td>7.8±4.8</td>
<td>39.3±26.0</td>
<td>185.8±58.4</td>
</tr>
</tbody>
</table>

a) Data were expressed as mean±standard deviation. A,B,C: Mean values with same superscripts are not significantly different (P>0.05).

Fig. 1. Effects of medetomidine (●), azaperone (○), acepromazine (□), droperidol (△) and midazolam (△) on sedative variables (—; full marks = 15) and analgesic/anesthetic (—; full marks = 6) variables. Each symbol represents the mean value of the total scores used for evaluating sedative character or analgesic/anesthetic character.

Table 2. Statistical analysis of the total scores used for evaluating sedative character

<table>
<thead>
<tr>
<th>Sedative</th>
<th>0</th>
<th>10</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>60</th>
<th>90</th>
<th>120</th>
<th>180</th>
<th>240</th>
<th>300</th>
<th>360</th>
<th>420</th>
<th>480</th>
</tr>
</thead>
<tbody>
<tr>
<td>medetomidine</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>AB</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>azaperone</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>AB</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>midazolam</td>
<td>A</td>
<td>AB</td>
<td>A</td>
<td>B</td>
<td>B</td>
<td>C</td>
<td>A</td>
<td>C</td>
<td>C</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>droperidol</td>
<td>A</td>
<td>C</td>
<td>BC</td>
<td>BC</td>
<td>B</td>
<td>BC</td>
<td>BC</td>
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<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>acepromazine</td>
<td>A</td>
<td>BC</td>
<td>C</td>
<td>C</td>
<td>B</td>
<td>C</td>
<td>AB</td>
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<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

a) Same alphabet (A, B, C) means that there is no significant difference in posture score between each group (P>0.05).
medetomidine maintained much higher values than those of other sedatives from 20 to 60 min after administration (Fig. 1). There were significant differences between the scores in pigs given medetomidine and those of all other sedatives at 30 and 40 min after injections of drugs (Table 2). There were also significant differences between the scores in pigs given medetomidine and those of azaperone, acepromazine and droperidol at 20 min after injection, between the scores in pigs given medetomidine and those of acepromazine, droperidol and midazolam at 60 min after injection (Table 2). In addition to the sedative character, medetomidine produced weak analgesic/anesthetic effects for short duration (Fig. 1). On the contrary, other sedatives produced no analgesic/anesthetic effects, and, there were significant differences between the total score used to monitor analgesic/anesthetic effects in pigs given medetomidine and those of other sedatives at 20, 30 and 40 min after administration. The pigs given azaperone were also smoothly induced to sedation and became ataxic and drowsy within a few min, but only 3 of the 6 pigs became lateral recumbency and the others maintained ventral recumbency. In these pigs, it took a longer time to reach maximum effects and similar sedative condition was maintained for longer duration. The mean total score used to sedative character in these pigs marked higher values than those in other sedatives 90 min after injection and thereafter (Fig. 1). There were significant differences between the scores in pigs given azaperone and those of all other sedatives 180 min after injections and thereafter (Table 2). However, even at the maximum action, azaperone did not exert an apparent muscle relaxant effect and did not depress the reaction to tactile and painful stimuli, though it moderately depressed the reaction to visual and auditory stimuli.

Induction of sedation with acepromazine was not as smooth and quick as medetomidine and azaperone (Table 1). The pigs given acepromazine repeated being ventral or sitting position and/or standing position until being in continuous ventral recumbency. Induction of sedation with droperidol was also not smooth, and one of the 6 pigs in this group did not become ventral recumbency and maintained standing position throughout the observation period. Acepromazine and droperidol produced light sedation and the mean total score used for evaluation of sedative character in these pigs were lower than that of azaperone throughout the observation period. These sedatives exerted mainly quieting and calming effects, and the pigs became lateral recumbency for short duration or did not become lateral recumbency and stood up in about 90 (acepromazine) and 120 min (droperidol) after administration in averages (Table 1). Furthermore, the animals showed no apparent muscle relaxation and responded to sensory stimuli normally or even in an exaggerated manner.

Administration of midazolam resulted in marked ataxia with struggling in their cages for 5 to 15 min. After that all the animals calmed down and 5 of 6 pigs became ventral recumbency and then lateral recumbency. However, the sedative effect of midazolam continued for short duration and the pigs stood up within 40 min after administration in an average (Table 1).

Recovery from sedation in pigs given medetomidine was quick and smooth without excitement and other unpleasant effects. The mean standing time and the mean total recovery time in these pigs were significantly and much shorter than those in azaperone. It took more than 12 hr for total recovery in 2 of the 6 pigs given azaperone. During the recovery phase, all the pigs given azaperone, 3 pigs given acepromazine and 2 pigs given droperidol continued to lick and gnaw the inside of their cages until they recovered completely, among which the pigs given azaperone showed severer behavior which caused in much salivation and bleeding from their oral cavity.

For the sedation of pigs as experimental animals, losing consciousness and arousal reaction induced by sensory stimulation is essential even for minor handling. And it is also desired to induce the animals to sedation quickly and smoothly with the rapid recovery after completion of the procedures or examinations.

In this study, administration of medetomidine induced satisfactory and the most profound degree of sedation with greater drowsiness than was achieved with other sedatives tested. One of the most apparent differences between medetomidine and other sedatives was the effect on arousal reaction induced by sensory stimulation such as visual, auditory, tactile or painful stimuli. This reaction was depressed in pigs given medetomidine, while that in pigs given other sedatives were not influenced so much. It has been known that sensory stimuli activate locus coeruleus in the pons of the upper brainstem [5]. The sedative action of medetomidine is generally ascribed to inhibition of locus coeruleus, which contains pathways involved in the maintenance of vigilance, mediated through presynaptic α2-adrenoceptors [1, 12], and this mechanism might also reduce the reactivity to sensory stimuli [2]. In addition, medetomidine has been also reported to activate postsynaptic α2-adrenoceptors in the brain, and both mechanisms induce an extraordinary potent ability of medetomidine. Although this depressive effect might not be strong enough to avoid any arousal reaction by sensory stimuli caused by manipulation and restraint, medetomidine has the most suitable sedative effect among the drugs tested in this study as a chemical restraint agent in laboratory pigs.

In addition, medetomidine was thought to be suitable as a chemical restraint agent for laboratory pigs because its onset and recovery from sedation was quick and smooth as compared with other sedatives. The pigs given medetomidine were induced to sedation without any apparent adverse effects and totally recovered from sedation much earlier than pigs given azaperone. This is caused by a high affinity and selectivity at α2-adrenoceptors and a short elimination half-time of medetomidine [10]. Although the duration of valuable sedative action of medetomidine was shorter than that in azaperone, its duration might be long enough for most of practical uses.
Pigs given azaperone, acepromazine and droperidol showed the strange behavior such as persistent licking or gnawing during recovery phase. It has been known that these drugs produce their sedative effects by antagonism of dopamine as a neurotransmitter which also causes extrapyramidal side effects characterized by abnormal motions [11]. These abnormal behavior observed in this study may be related to this neurological side effect.

Although diazepam has been reported to produce sedation in pigs, we tested midazolam instead of diazepam in this study. Recently diazepam has been widely replaced by midazolam in human medicine, because midazolam has a greater advantage to diazepam; potent effects, short half-life and water-solubility [11]. Administration of midazolam in this study resulted in marked ataxia and struggling for a certain time, however its duration of valuable sedation was too short. Furthermore, injection volume of midazolam for sedation was relatively large (8 ml for a pig of 20 kg of body weight) with a higher cost and its administration caused pain and head shaking. Thus, midazolam might find little clinical support as a sole agent for sedation or chemical restraint. However, benzodiazepines are more important or valuable as adjuncts to other anesthetics or opioids in veterinary practice [13]. Furthermore, it has been reported that the combination of midazolam and metoclopramide or droperidol showed synergistic effects and produced good sedation in pigs [3]. Further investigation for the combined use of midazolam at lower dose with other sedatives such as medetomidine was thought to be valuable for development of more suitable sedation in laboratory pigs.

In conclusion, among the sedatives tested in this study, medetomidine produces the most potent sedative effects in laboratory pigs, and its sedative character is most suitable for a chemical restraint agent as compared with those of azaperone, acepromazine, droperidol and midazolam.

REFERENCES