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# Cardiovascular and Pulmonary Effects of a New Sedative/Analgesic (Medetomidine) as a Preanaesthetic Drug in the Dog

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**Bergström, K.: Cardiovascular and pulmonary effects of a new sedative/analgesic (Medetomidine) as a preanaesthetic drug in the dog. Acta vet. scand. 1988, 29, 109-116.** - Cardiovascular and pulmonary effects of a new sedative/analgesic (medetomidine) as a preanaesthetic drug in the dog. A study was carried out to investigate the possible usefulness of medetomidine (Farnos Group, Turku, Finland) for premedication prior to general anaesthesia with thiopental sodium and halothane. The main emphasis was laid on the circulatory and respiratory effects of medetomidine. Dogs treated with xylazine (2 mg/kg) or placebo (physiological saline solution) served as controls. Medetomidine caused a decrease in blood pressure, heart rate and respiratory rate at all dose levels tested. These decreases were essentially dose-dependent, but there were great individual variations. It is concluded that the drug can be useful for premedication at the lowest dose level tested (10 µ/kg). The sedative effect, however, is so strong that an even lower dose might be sufficient for the present purpose.

anaesthesia; sedation; analgesia; thiopental.

## Introduction

The use of different sedatives as preanaesthetic drugs in animals is today worldwide and has been adopted from human medicine. Within the latter discipline one of the most important reasons for such premedication is to moderate the patient's anxiety about the general anaesthesia and the following operation. This aspect is in most cases of no current interest in veterinary medicine and it is therefore important to consider the need for premedication prior to a general anaesthesia in each individual case.

One specific situation in veterinary medicine is when deep sedation has been produced for an examination (e.g. an X-ray) and the results indicate a need for general anaesthesia.

This unfortunate situation demands good knowledge of the sedative and its effects on the circulation and respiration.

The usefulness of medetomidine, an alpha-adrenoreceptor agonist (*Savola et al.* 1986), as a sedative/analgesic for diagnostic and therapeutic procedures that do not require general anaesthesia is currently being studied by other investigators.

In the present study medetomidine was tested as a preanaesthetic drug in the dog. Dogs treated with physiological saline solution (placebo) or xylazine served as controls. Xylazine is known as a sedative in the dog and its cardiopulmonary effects have been studied (*Klide et al.* 1975). Xylazine is also used as a preanaesthetic drug and the

amount of barbiturate needed to induce anaesthesia is then reduced (Walter 1985).

### Materials and methods

#### Animals

The study comprised 25 healthy experimental beagles, 22 females and three males. The mean age of 23 of the 25 dogs was 11.8 months (range 8 to 20 months). Two dogs were excluded from the calculation of the mean age because of their high age, 6 and 9 years, respectively. The mean weight of the 25 dogs was 10.95 kg, (range 8 to 14 kg).

#### Preparation of the dog

After infiltration anaesthesia (lidocaine with adrenaline 1%<sup>1</sup>) in the awake dog, the left femoral artery was punctured and a teflon catheter was introduced into the aorta using the Seldinger technique (Seldinger 1953).

The length of the catheter was about 15 cm and its outer diameter was 1.05 or 1.25 mm. In a few cases when the first arterial puncture failed, the right femoral artery was used instead of the left.

#### Tested drugs

The dogs were divided randomly into 5 groups with 5 dogs in each, which were given the following treatment:

Group 1 Placebo – physiological saline – as a preanaesthetic drug, 2 ml/dog irrespective of body weight. Control group.

Group 2 Xylazine (Rompun<sup>®2</sup>) 2 mg/kg. Control group.

Group 3 Medetomidine<sup>3</sup>, 10 µg/kg.

Group 4 Medetomidine, 30 µg/kg.

Group 5 Medetomidine, 60 µg/kg.

The sedative, control drug and placebo were administered intramuscularly (i.m.; M. triceps brachii) 20 min before induction of general anaesthesia.

Two dogs from each group (except for the xylazine group) were selected randomly for a separate test 2 weeks before the main test which was performed identically except that atropine (Atropin<sup>®4</sup>) 0.05 mg/kg was injected i.m. 10 min before the sedative (or placebo).

#### General anaesthesia

General anaesthesia was induced with 2.5% thiopental sodium (Pentothal<sup>®5</sup> Natrium<sup>5</sup>) given intravenously. After intubation the anaesthesia was maintained with halothane (Halothan<sup>®6</sup>) and nitrous oxide mixed with 50% oxygen. The halothane concentration varied according to the individual reaction of each dog (variation 0-1%). The flow of oxygen and nitrous oxide was maintained at 2 l/min each.

#### Schedule of the recording performed

After the preparations described, the dog was placed in right lateral recumbency, and two recordings of the variables studied (see below) were made prior to the sedation and the atropine injection, respectively. If the dog was given atropine, 1 or 2 recordings were made 5 and/or 10 min after the atropine injection (before the injection of the sedative). A recording was made 10 and 20 min after the sedation. Further recordings were performed immediately after the thiopental injection and intubation and every 15 min during the 1 h general anaesthesia.

1 Xylacain<sup>®</sup> adrenalin 1 % Astra, Södertälje, Sweden.

2 Rompun<sup>®</sup> 20 mg/ml Bayer, Leverkusen, West Germany.

3 Medetomidine 1 mg/ml Farnos group, Turku, Finland.

4 Atropin<sup>®</sup> 0.5 mg/ml ACO, Solna, Sweden.

5 Pentothal Natrium<sup>®</sup> 2.5 g Abbott, North Chicago, Illinois, USA.

6 Halothan<sup>®</sup> Hoechst, Frankfurt (M), West Germany.

Recordings at 15 min intervals were continued during the first hour of the post-anaesthetic period, and then 2, 3, 6 and 20 h after termination of the general anaesthesia. Finally, the dogs once again underwent a routine clinical examination, as prior to the test. The investigator tried to keep the anaesthesia deep enough for surgical procedures by following it in a conventional way with the help of the reflex pattern.

After the one-hour general anaesthesia, administration of the inhalation anaesthetic was ceased and the dogs were allowed to recover, breathing air.

#### *Variables recorded*

**Objective recordings:** ECG and blood pressure (systolic, mean and diastolic) were recorded on an ink-jet recorder (Mingograf 34, Siemens-Elema, Solna, Sweden). Lead II, CR was used to measure the heart rate and a pressure transducer (EMT 311, Siemens-Elema) recorded the blood pressure via the artery catheter. The blood pressure mentioned in the results is the mean blood pressure.

The respiratory rate was calculated by observing respiratory chest expansion.

Blood gas-analysis was performed on arterial blood samples drawn through the artery catheter. All blood samples were collected anaerobically into heparinized 2 ml plastic syringes. The samples were analysed within 5 min after collection, using a standard electrode technique (ABL 3 Radiometer, Copenhagen, Denmark). Blood-gas values were corrected according to the rectal temperature.

**Subjective recordings:** Response to pain stimuli (pin prick sensation, reaction to pinch in the coronary border).

Degree of sedation (e.g. response to sound, ability to stand, calmness).

Depth of the general anaesthesia (reflexes and response to pain stimuli – see above).

Colour of mucous membranes, capillary refill time, pulse quality and type of respiration.

#### **Results**

##### *Blood pressure*

Interindividual variations of the mean arterial blood pressure occurred in the groups receiving sedatives without prior atropine injection. In fact the dog with the lowest mean blood pressure value (after the sedation and during the general anaesthesia) belonged to the group premedicated with medetomidine 10 µg/kg (Fig. 1). In a few dogs the blood pressure was recorded continuously during the first 10 min of the sedation period. This check, however, did not give any further information.

In the sedated dogs premedicated with atropine (10 min prior to the injection of the sedative), the blood pressure rose markedly during the sedation period. The increase was most pronounced in the groups receiving medetomidine 10 and 60 µg/kg. The mean values in these groups reached 175 and 210 mmHg, respectively.

Fifteen minutes after the thiopental injection, the blood pressure in these atropine groups had dropped to the initial level (125–150 mm Hg) or were even lower. During the course of the general anaesthesia the pressure decreased slightly further.

The placebo dogs treated with atropine behaved differently. The blood pressure did not change considerably during the course of the test.

Note! The dogs in the xylazine group were not tested with atropine.

##### *Heart rate*

The heart rate and the blood pressure recordings showed an essentially similar pattern,

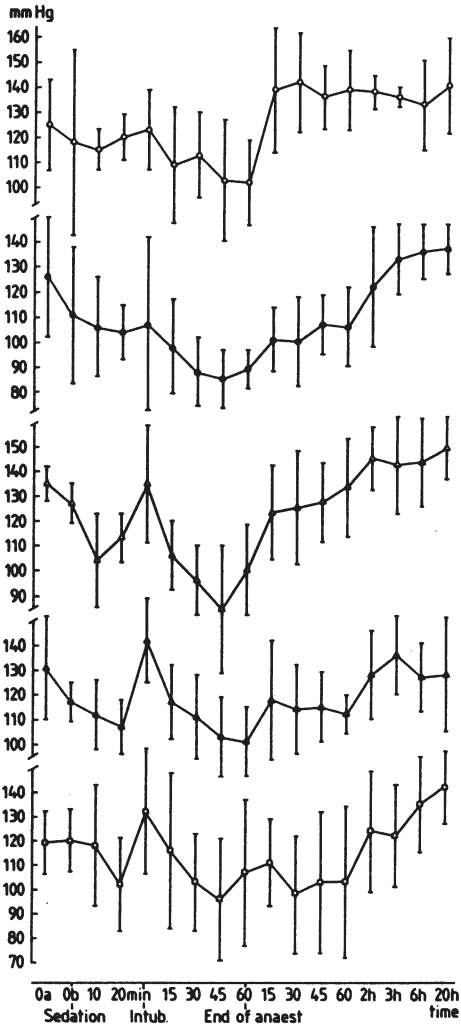


Figure 1. The mean arterial blood pressure in dogs given sedation prior to general anaesthesia. Five groups with 5 dogs in each. Mean value and standard deviation.

- Placebo
- Rompun
- △ Medetomidine 10 µg/kg
- ▲ Medetomidine 30 µg/kg
- Medetomidine 60 µg/kg

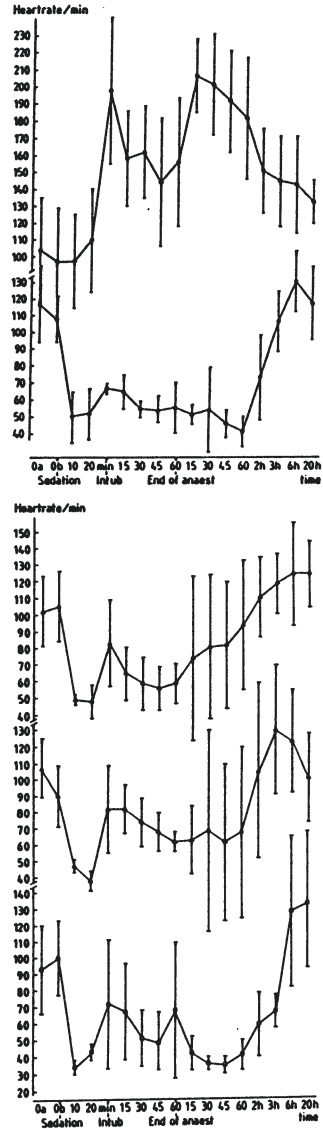


Figure 2 a-b. The heart rate in dogs given sedation prior to general anaesthesia. Five groups with 5 dogs in each. Mean value and standard deviation.

- Placebo
- Rompun
- △ Medetomidine 10 µg/kg
- ▲ Medetomidine 30 µg/kg
- Medetomidine 60 µg/kg

except in the placebo group (Figs. 2a and 2b).

In 2 of the atropine-premedicated groups (medetomidine 60  $\mu\text{g}/\text{kg}$  and placebo) the heart rate increased during the first 10 min after the atropine injection. In the other 2 groups (medetomidine 10 and 30  $\mu\text{g}/\text{kg}$ , respectively) the increase occurred within 10 min after administration of the sedative (i.e. 20 min after the atropine injection). Maximum values for all groups were reached 10 min after sedation, with the following mean values: placebo, 263 beats/min; medetomidine 10 and 60  $\mu\text{g}/\text{kg}$ , 225/min; and medetomidine 30  $\mu\text{g}/\text{kg}$ , 146/min. During the later part of the sedation, the heart rate started to drop in all groups given atropine (including the placebo group), and continued to decrease during anaesthesia, though less in the placebo group than in the others (placebo: about 150 beats/min; remaining groups: 80-120/min).

Post-anaesthetically the curves for the atropine and non-atropine groups showed the same appearance.

### ECG

The ECG recordings did not differ between the groups. Nor did they diverge from other ECGs in general during this form of anaesthesia.

### Respiration

During sedation the respiratory frequency decreased and the breathing became deeper (Fig. 3).

The respiratory rate in the atropine groups was similar to that in the groups not treated with atropine before sedation.

### Temperature

The rectal temperature fell during general anaesthesia, but less markedly in the placebo and medetomidine 60  $\mu\text{g}/\text{kg}$  groups. The

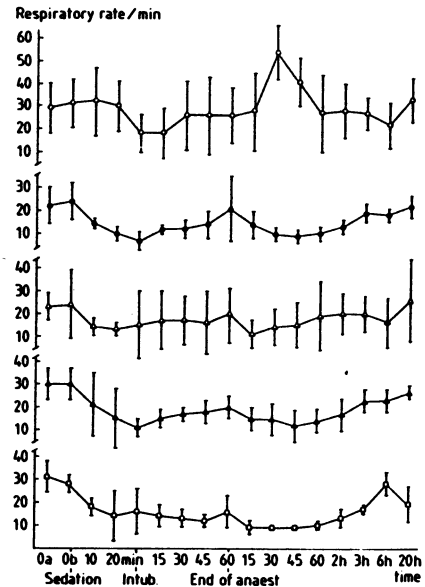


Figure 3. The respiratory rate in dogs given sedation prior to general anaesthesia. Five groups with 5 dogs in each. Mean value and standard deviation.

- Placebo
- Rompun
- △ Medetomidine 10  $\mu\text{g}/\text{kg}$
- ▲ Medetomidine 30  $\mu\text{g}/\text{kg}$
- Medetomidine 60  $\mu\text{g}/\text{kg}$

temperature in the placebo group regained the normal level about 1 h after the end of anaesthesia. In the other groups (including medetomidine 60  $\mu\text{g}/\text{kg}$ ), a normal temperature was attained after 3-6 h.

### Blood-gas analysis

$\text{PaO}_2$  generally decreased slightly (in all groups) after administration of thiopental (from about 13 kPa to 8-11 kPa) and then increased markedly during general anaesthesia (to 40-50 kPa).

Normal  $\text{PaO}_2$  values were reached within the first 15 min after the anaesthetic gas had been turned off.

$\text{PaCO}_2$  rose temporarily after the induction

of anaesthesia and the intubation (from about 5 kPa to 5.5-7 kPa).

In all groups there was a slight decrease in base excess during anaesthesia (about 1-2 mmol/l). Irregular values were observed during the post-anaesthetic period in the groups premedicated with xylazine and medetomidine 60 µg/kg.

### *Sedation*

Dogs pretreated with atropine are not described separately.

The degree of sedation differed between the groups.

The placebo dogs were calm, but totally un-sedated and their response to pain stimuli was the same as prior to the injections.

The dogs of the xylazine group were moderately to profoundly sedated after 10-20 min, and there was obvious pain depression, though not so strong as in the medetomidine 30 and 60 µg/kg groups. One of the xylazine-treated dogs started to wave her head up and down about 10 min after the injection, and did not stop until thiopental was given.

A second dog in this group developed a slight spasm in the limbs 5 min after the injection, and a third dog began to perform trot-like movements with the forelimbs 20 min after injection of the sedative (just prior to induction of the general anaesthesia).

The third group (medetomidine 10 µg/kg) showed slight sedation 10 min after the injection and moderate sedation after about 20 min, except for 1 dog, which became very profoundly sedated - actually more than those receiving 60 µg/kg. The pain depression in these dogs was slight, except in the profoundly sedated dog mentioned above (this dog also showed lower values of blood pressure, heart rate and respiratory rate than the others).

In the fourth group (medetomidine 30 µg/kg), the dogs displayed moderate to profound sedation after 3-5 min. The analgesia was moderate. In 3 of the dogs in this group (1 with atropine, 2 without), the mucous membranes appeared a little pale after sedation, compared with the colour prior to sedation.

The dogs of the last group (medetomidine 60 µg/kg) were profoundly sedated within 10 min after injection of the drug. One dog, however, was excited for 3-10 min after the injection, and 2 dogs showed a slight spasm in their limbs from time to time during the sedation period. In these dogs the mucous membranes were also slightly paler than prior to sedation. The dogs in this group exhibited very little response to painful stimuli. The profoundly sedated dogs were unable to stand, and did not react to loud sounds. In many of the sedated dogs (especially at higher dose levels) the nictitating membrane covered a considerable part of the eye. The reflexes of the moderately to profoundly sedated dogs were obviously reduced.

### *Induction of anaesthesia*

In all the sedated groups a lower dose of thiopental sodium was needed for intubation compared with the placebo group (Table 1).

### *Post-anaesthetic period*

The interval between the end of inhalation and the moment of extubation was shortest in the placebo group (mean value 6.75 min) and longest in the group receiving medetomidine 30 and 60 µg/kg (18.1 and 17.5 min, respectively). The other 2 groups were intermediate with respect to this interval (8 min for xylazine and 12.5 min for medetomidine 10 µg/kg).

Table 1. Amount of thiopental needed for intubation in dogs given a sedative prior to general anaesthesia. Five groups with 5 dogs in each.

(x = the most profoundly sedated dog in the whole study)  
(♂ = male dogs, the others were females)

Drug	Thiopental sodium mg/kg					$\bar{x}$
Placebo	28.6 ♂	18.2	17.2	13.5	13.1	18.0
Xylazine						
2 mg/kg	7.6	5.5	4.2	5.4	9.1 ♂	6.4
Medetomidine						
10 µg/kg	10.5	7.1	2.5*	8.3	7.6	7.2
Medetomidine						
30 µg/kg	7.5	6.6	4.6	6.6	10.4 ♂	7.1
Medetomidine						
60 µg/kg	5.7	3.4	3.2	8.3	5.7	5.2

No dog showed excitation during the post-anaesthetic period, but the unsedated dogs shivered during awakening (not longer than 1 h post-anaesthetically).

No vomiting was observed during the experiments, but on the other hand the dogs had not been fed for 12 h prior to the tests.

### Discussion

Regarding the course of the general anaesthesia following sedation, there was no fundamental difference between the two drugs tested (medetomidine and xylazine). In comparison with the placebo group, there was constantly a higher degree of reflex depression, arterial hypotension, bradycardia and respiratory depression, and more prolonged awakening in the sedated dogs. The degree of these effects, however, was mainly dose-dependent. The effects were less apparent and of shorter duration in the groups receiving medetomidine at the lowest dose level (10 µg/kg), but large individual variations occurred. In fact, the greatest hypotension during anaesthesia was noted in a dog premedicated with medetomidine at this lowest dose level.

The depth of the general anaesthesia was difficult to judge because of fluctuations in the degree of reflex depression during the course of the anaesthesia (this held for all groups except the placebo group). A consequence of this was an increased risk of apnoea when anaesthesia was induced with thiopental after sedation with the drugs investigated. On the other hand, a lower dose of thiopental was required after sedation of the dogs and this effect was dose-dependent.

In the dogs which received atropine prior to sedation, the circulatory effects were reversed. Even during the course of the general anaesthesia and post-anaesthetic period, the dogs in the atropine groups showed a relatively higher blood pressure and heart rate.

On the basis of the above observations, the author would like to make the following recommendations for the use of medetomidine for premedication prior to general anaesthesia.

At a low dosage (10 µg/kg), the drug can be useful as a pre-anaesthetic drug, provided that the dogs are in a good general condition and that the anaesthesia is administered in an animal hospital or a clinic where the surgeons and their assistants are trained in managing unexpected apnoea. Even lower doses of medetomidine than the lowest one tested in the present study (10 µg/kg) ought to be tried for premedication purposes, since the sedative effect of the drug is very potent. Animals with a deteriorated general condition should not be premedicated at all, since the advantage of the lowered dose of thiopental does not necessarily balance the possible disadvantage of the negative effect of medetomidine (as well as of xylazine) on the circulation and respiration. It should be emphasized that thiopental used alone has a fairly moderate negative effect on the circulation and its obvious depressing effect on the respiration is easily controllable, in distinc-

tion from the cardiovascular effects of the sedatives.

Atropine prior to sedation cannot be recommended on the basis of the present experience, as it is not known how the effect of atropine, with tachycardia and arterial hypertension, affects the risks of the anaesthesia.

#### Acknowledgements

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#### References

- Klide A M, Calderwood H W, Soma L R*: Cardiopulmonary Effects of Xylazine in Dogs. *Amer. J. vet. Res.* 1975, 36, 931-935.
- Seldinger S I*: Catheter replacement of the needle in percutaneous arteriography. *Acta Radiol.* 1953, 39, 368-376.
- Savola J M, Ruskocho H, Puurunen J, Salonen J S, Körki N T*: Evidence for medetomidine as a selective and potent agonist at  $\alpha_2$ -adrenoreceptors. *J. Auton. Pharmac.* 1986, 5, 275-284.
- Walter H H*: Effects of atropine on xylazine-pentobarbital anaesthesia in dogs: Preliminary study. *J. Amer. vet. Res.* 1985, 46, 856-858.

#### Sammenfatning

*Effekt på blodcirkulation och respiration av ett nytt sedativum/analgetikum (medetomidin) som preanestetikum till hund.*

Undersökningens syfte var att fastställa om medetomidin (Farnos group, Turku, Finland) kan användas till premedicinering inför allmän anestesi med tiopentalnatrium och halotan. Framför allt undersöktes medetomidinets cirkulatoriska och respiratoriska effekter. Hundar behandlade med xylazin (2 mg/kg) respektive placebo (fysiologisk koksaltlösning) användes som kontroller.

Medetomidin orsakade sänkning av blodtryck, hjärtfrekvens, och andningsfrekvens vid alla doseringar som testades. Dessa effekter var principiellt dosberoende, men det fanns stora individuella skillnader.

Medetomidin kan användas för premedicinering i den lägsta testade doseringen (10 µg/kg). Den sedativa effekten är emellertid så stark att en ännu lägre dos eventuellt skulle kunna vara tillräcklig för ändamålet.

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