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THE USE OF ATROPINE TO CONTROL HEART RATE RESPONSES DURING DETOMIDINE SEDATION IN HORSES

By

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SHORT, C. E., J.-J. STAUFFER, G. GOLDBERG and O. VAINIO: *The use of atropine to control heart rate responses during detomidine sedation in horses.* Acta vet. scand. 1986, 27, 548—559. — Detomidine is a sedative-analgesic which has a pharmacological profile similar to xylazine. There is evidence that the sedative effects are mediated through alpha-2 adrenoceptors.

Cardiopulmonary responses were determined using detomidine as the principal agent and as a preanesthetic prior to the induction of general anesthesia. Compatibility with guaifenesin, sodium thiamylal and halothane were determined.

As in the case of xylazine, detomidine produces a slowing of heart rates. This was found to be either sinus bradycardia or heart block. There may be a corresponding increase in systolic blood pressures. The respiratory pattern is altered through the arterial blood gases and pH data supported evidence of adequate ventilation. The heart rate response to detomidine without anticholinergic treatment was transient and related to he duration of drug action.

Atropine sulfate, 0.02 mg/kg i.v. was effective in preventing or treating bradycardia or heart block from detomidine. Heart rates also increased during the administration of guaifenesin and sodium thiamylal when given 50 min post-detomidine.

equine anesthesia; cardiac function; ventilation; halothane; guaifenesin; sodium thiamylal; analgesia.

One of the problems associated with equine anesthesia is the selection of medications to be used for anesthesia for standing procedures or for prolonged surgical procedures requiring injectable medications rather than inhalant anesthetic approaches. Various combinations which might suffice for this purpose have

included tranquilizers and narcotics to produce neuroleptanalgesia. Included in this group of agents have been combinations of acepromazine and methadone, acepromazine and meperidine, xylazine and morphine (*Klein & Baetjer* 1974, *Muir et al.* 1979, *Kalpravidh et al.* 1984a) and a host of others (*Klein & Baetjer* 1974, *Robertson et al.* 1981, *Kerr et al.* 1982, *Kalpravidh et al.* 1984a, *Kalpravidh et al.* 1984b). Such combinations should provide adequate analgesia to allow the performance of minor surgical procedures and at the same time maintain a horse that is calm and easily handled. When standing procedures were not considered appropriate, combinations of preanesthetic agents followed by agents such as ketamine or combinations of muscle relaxants and barbiturates including sodium thiamylal and guaifenesin have been used for induction of general anesthesia. Supplemental dosages, either intermittently or by continuous i.v. drop have been used to prolong such anesthesia for surgical procedures lasting more than 5—10 min. The need continues both for profound analgesic agents which will facilitate safe standing surgical procedures or analgetic combinations which can preceed the administration of safe and effective field anesthesia.

Observations of the responses in laboratory animals (*Virtanen et al.* 1985) and in horses (*Clarke & Hall* 1969, *Robertson et al.* 1981) to a new analgetic/sedative injectable (detomidine hydrochloride)* showed profound relaxation and analgesia, but with subjective changes of cardiovascular function. The responses were related to those observed with xylazine (*Kerr et al.* 1972, *Hsu* 1981) but more profound sedation due to activation of alpha-2 adrenoceptors (*Delbarre & Schmitt* 1971, *Delini-Stula et al.* 1979, *Clough & Hatton* 1981, *Vainio* 1983, *van Zwieten et al.* 1983, *Virtanen et al.* 1985).

Early investigations of the use of detomidine in the horse revealed the development of bradycardia with or without associated heart block (*Short et al.* 1986). The occurrence of the slowing of the heart was within seconds to 5 min after the intravenous administration of the detomidine and might occur at a wide range of dosages from 20—60 µg/kg of intravenous detomidine. The duration of bradycardia appeared to be somewhat dose-related; however, this was not always the case. The ob-

* Domosedan® Injection. Farmos Group Ltd, Turku 10, Finland.

servance of bradycardia following detomidine administration in the horse was not unexpected since a similar phenomenon had been observed following the administration of xylazine. Xylazine and detomidine are both members of the alpha-adrenergic agonist family of medications and it was therefore predictable that the side effect of detomidine might be similar to that of xylazine. In addition, detomidine was discovered by the developers of this product during their efforts to develop a clonidine-like product for the control of cardiovascular responses.

Since this response was observed, it was appropriate to determine if the administration of an anticholinergic agent such as atropine sulfate could be used for prevention or control of the bradycardia with or without heart block (*Alitalo et al.* 1986). Atropine was not effective in the initial studies when administered at 0.01 mg/kg (*Alitalo et al.* 1986). Atropine is the anticholinergic approved in a large number of countries. Since responses may be dose related, we chose to use the same drug at twice the dosage in this study. It was anticipated that similar responses for use of anticholinergics to correct or prevent bradycardia during detomidine in horses could be expected from either atropine or glycopyrrolate if an equipotent dosage were used.

MATERIALS AND METHODS

The animals used in this study were mature female horses. Previously the carotid artery had been exteriorized for collection of arterial blood samples. The horses had been shown to be in excellent physical condition. Four horses were used for the 20 μg/kg administration, and 4 additional horses for 40 μg/kg detomidine administration. The heart rates and ECG tracings were made utilizing a Physio Control Monitoring and Recording System and indirect blood pressure measurements were made using a Dynamap Non-invasive blood pressure measuring system (produced by Critikon). The arterial blood gases and pH analyses were made utilizing a blood gas analysis system (Radiometer).

The experimental design consisted of administration of 20 μg/kg i.v. of detomidine to each of 4 horses to determine if bradycardia, with or without heart block, would occur. Following the development of bradycardia, 0.02 mg/kg i.v. atropine was administered to correct the bradycardia. After a minimum time

delay of 1 week, the same 4 horses were used with the administration of 0.02 mg/kg i.v. atropine administered prior to detomidine to determine if the atropine would prevent the occurrence of bradycardia and/or heart block in the same 4 horses. Four additional horses were used with 40 μg/kg i.v. detomidine administered in a similar manner as with the previous 4 horses. Arterial blood samples were taken 10 and 20 min after detomidine administration in each case. This provided information on arterial blood gases and pH at 10 and 20 min post-detomidine with atropine premedication and a differential of blood gas and pH analysis after detomidine alone and 10 min after detomidine

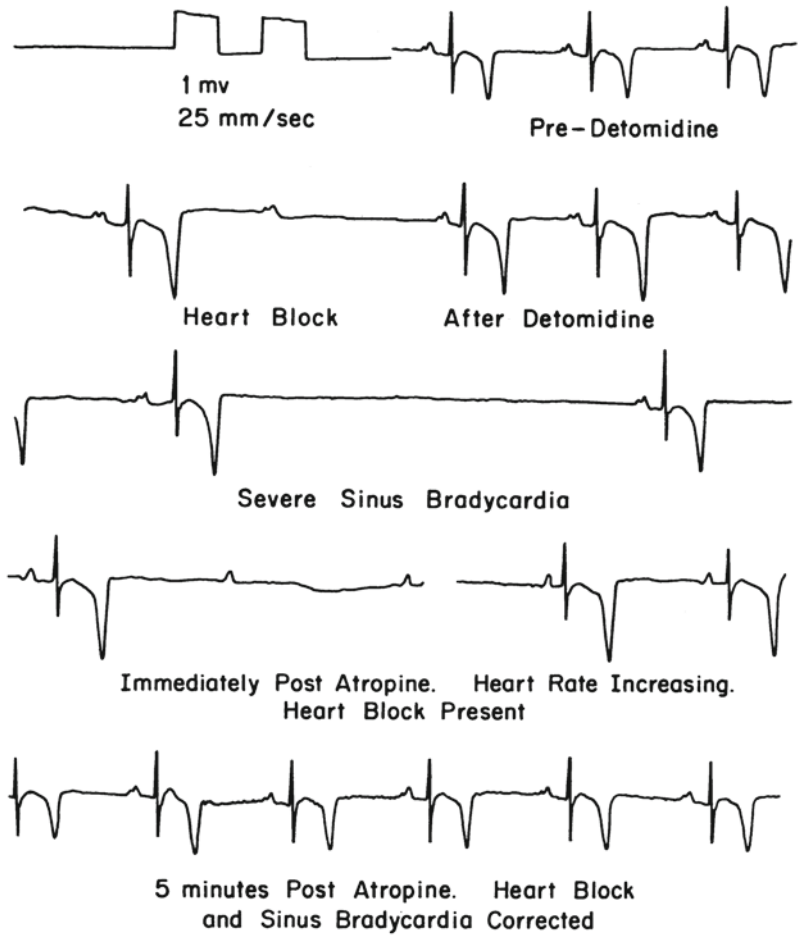

Figure 1. ECG response to atropine treatment of detomidine (20 μg/kg) induced bradycardia and heart block.

and atropine. The heart rates, respiratory rates and arterial blood pressures were determined at 5 min intervals up to 40 min after the administration of the detomidine. This included the period of time in which the most pronounced effect to detomidine and atropine on the cardiovascular system was demonstrated.

RESULTS

Bradycardia occurred within 30 s to 2 min in each of the horses administered detomidine without premidication with atropine. The characteristic ECG pattern as shown in Fig. 1 for 20 μg/kg detomidine and in Fig. 2 for 40 μg/kg detomidine were observed. The most severe drop in heart rate occurred within 2 min, but slow heart rates were still in existence at 5 min. The heart rate responses are shown in Fig. 3. Atropine was effective in correcting the reduced heart rate in each of the 4 horses at both 20 and 40 μg/kg detomidine.

Neither bradycardia nor heart block occurred in horses receiving atropine as a premedication prior to the administration

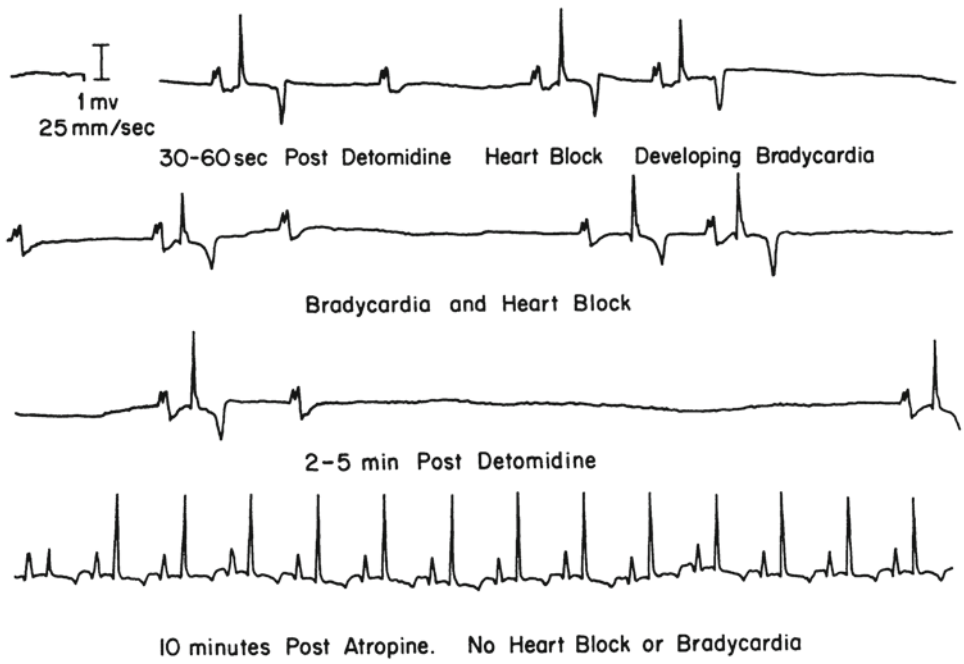

Figure 2. ECG responses to atropine treatment of detomidine (40 μg/kg) induced bradycardia and heart block.

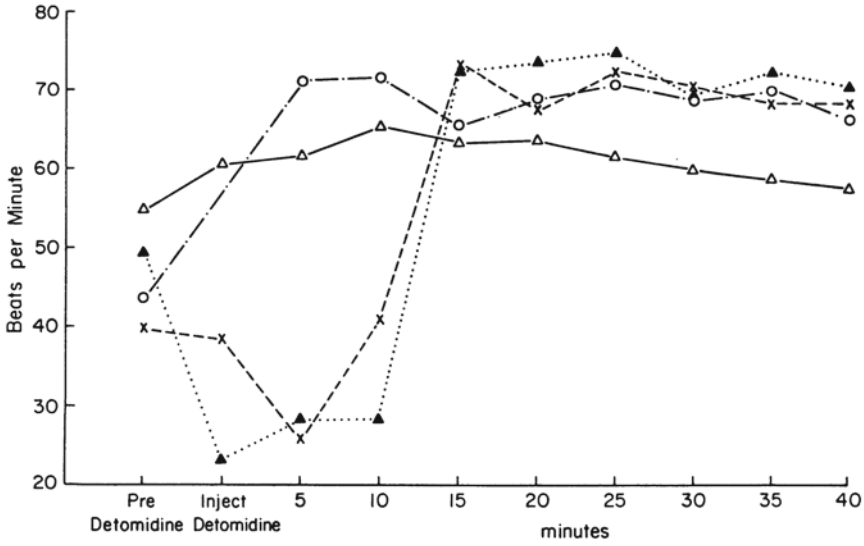

Figure 3. Heart rate responses during detomine.
○ 20 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine premed.
× 20 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine treatment.
△ 40 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine premed.
▲ 40 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine treatment.

of detomidine. Heart rates were accelerated above normal indicating a sinus tachycardia in some horses, but abnormal electrocardiographic wave patterns were not observed in any horse.

Respiratory rates, as shown in Fig. 4, were stable in both of the experimental groups. Arterial blood pH was within normal limits in all groups as was $PaCO_2$. PaO_2 levels were in acceptable levels for awake horses without oxygen supplementation (Tables 1 and 2). It should be of note that $PaCO_2$ levels were lower in most groups when atropine was used as a premedication. Blood pressure responses are shown in Figs. 5, 6, and 7. Systolic blood pressures were stable or elevated with the exception of the 40 μg/kg group which had a brief period of reduced systolic blood pressure. Systolic blood pressure increased in all horses while under the influence of detomidine. This is characteristic of detomidine in the horse. The blood pressure responses also indicate a rise in diastolic pressure. Mean arterial pressure did not increase as rapidly as did systolic pressure. However, after 15 min post-detomidine, mean pressures increased and after 30 min began to fall.

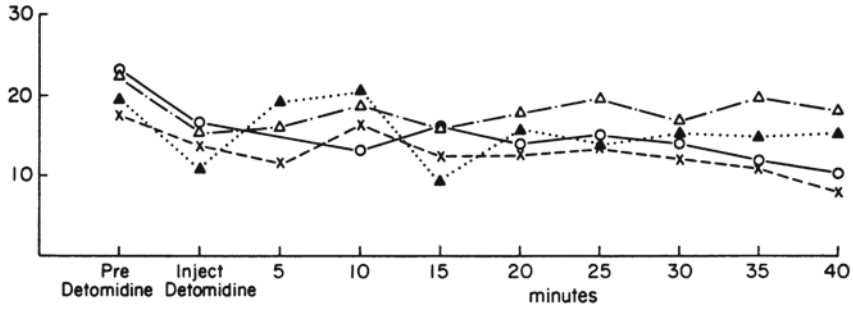

Figure 4. Respiratory rate responses during detomidine.
○ 20 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine premed.
× 20 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine treatment.
△ 40 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine premed.
▲ 40 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine treatment.

Each of the horses showed the characteristic outward signs of sedation and analgesia with both 20 and 40 μg/kg of detomidine as had been shown in previous studies.

DISCUSSION

Atropine as a representative of the anticholinergic group was effective as both a preventative of bradycardia and heart block during 20 and 40 μg/kg dosage levels of detomidine in the horse. It was also effective in the correction of bradycardia and heart

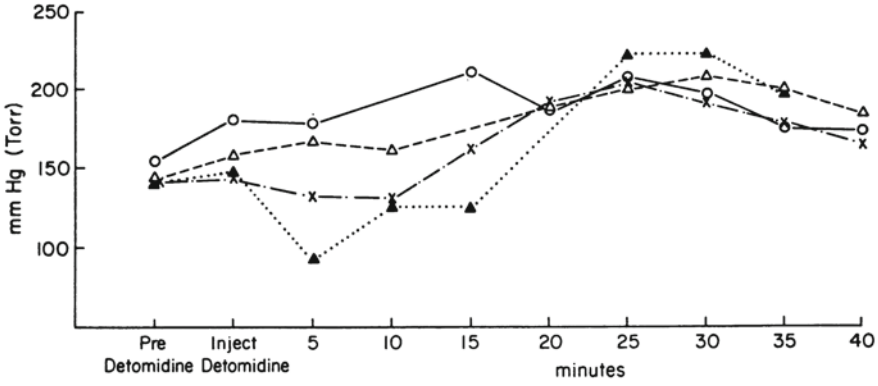

Figure 5. Systolic blood pressure response to detomidine.
○ 20 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine premed.
× 20 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine treatment.
△ 40 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine premed.
▲ 40 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine treatment.

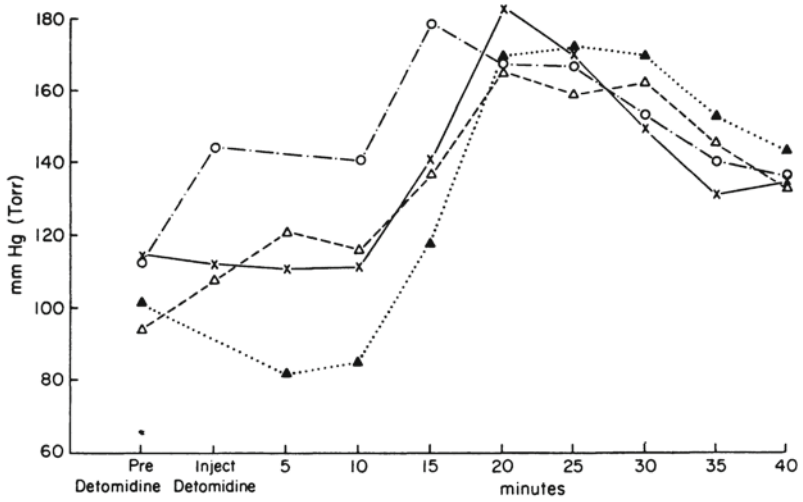

Figure 6. Mean arterial blood pressure response to detomidine.
○ 20 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine premed.
× 20 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine treatment.
△ 40 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine premed.
▲ 40 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine treatment.

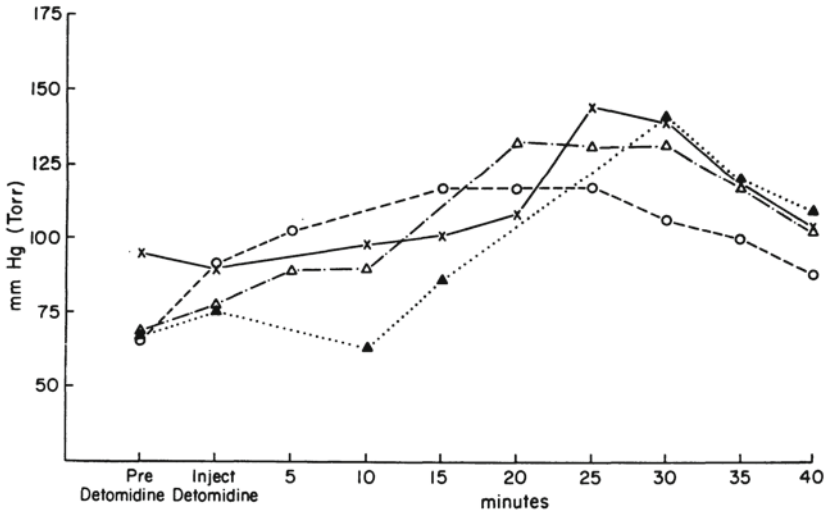

Figure 7. Diastolic blood pressure responses to detomidine.
○ 20 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine premed.
× 20 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine treatment.
△ 40 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine premed.
▲ 40 μg/kg i.v. detomidine with 0.02 mg/kg i.v. atropine treatment.

Table 1. Arterial blood gas and pH responses during detomidine (20 μg/kg).

Time	pH	$PaCO_2$ (mmHg)	$PaCO_2$ (mmHg)
A Detomidine plus 10 min	7.395 ± 0.025	43.3 ± 1.5	70.0 ± 2.4
B Detomidine and atropine premed plus 10 min	7.432 ± 0.017	39.0 ± 2.9	81.0 ± 7.3
C Detomidine and atropine treatment plus 10 min	7.430 ± 0.026	40.5 ± 1.7	78.5 ± 5.0
D Detomidine and atropine premed plus 20 min	7.433 ± 0.022	39.3 ± 3.5	84.8 ± 4.8

A: Control values. Detomidine only.
B: Control values. Detomidine administered 10 min after atropine
C: Atropine (0.02 mg/kg i.v.) administered 10 min after detomidine (Group A with atropine treatment).
D: Group B 10 min later.

Table 2. Arterial blood gas and pH responses during detomidine (40 μg/kg).

Time	pH	$PaCO_2$ (mmHg)	$PaCO_2$ (mmHg)
A Detomidine plus 10 min	7.448 ± 0.017	36.3 ± 1.5	86.3 ± 5.3
B Detomidine and atropine premed plus 10 min	7.448 ± 0.017	39.0 ± 2.9	81.5 ± 8.9
C Detomidine plus atropine treatment plus 10 min	7.458 ± 0.021	38.0 ± 3.7	89.0 ± 13.3
D Detomidine and atropine premed plus 20 min	7.448 ± 0.049	38.8 ± 3.3	79.8 ±9.6

A: Control values. Detomidine only.
B: Control values. Detomidine administered 10 min after atropine
C: Atropine (0.02 mg/kg i.v.) administered 10 min after detomidine (Group A with atropine treatment).
D: Group B 10 min later.

block when they occurred and anticholinergics had not been used as preanesthetic prior to the administration of the detomidine. The heart rates following the administration of atropine were closer to control levels in horses receiving 40 μg/kg of detomidine. Heart rates in animals receiving 20 μg/kg of detomidine showed elevations which were excessive. This in conjunction with the increase in blood pressures would increase the myocardial oxygen demands since elevated heart rates and systolic pressures will increase the rate pressure product, an index of myocardial oxygen demands. The arterial blood pH, CO_2 and oxygen levels were very acceptable for awake horses without oxygen supplementation. There was not, however, a highly significant increase in oxygen availability in animals with elevated heart rates and evidence of arterial hypertension. As a result, it would be potentially advantageous to consider a lower dose of 0.01 mg/kg i.v. atropine to correct or prevent bradycardia if only 20 μg/kg body weight detomidine is used. This should reduce the incidence of sinus tachycardia and increased oxygen demand. The heart rates did not elevate as high during 40 μg/kg detomidine and as a result, the myocardial O_2 demands did not increase in a similar manner as the 20 μg/kg group.

CONCLUSION

The results of this study indicate that anticholinergics are effective against the occurrence of bradycardia and heart block produced by detomidine and that they can also be effectively utilized to correct the presence of existing bradycardial heart block during detomidine effects. This study provides strong evidence that this is an effective method of correcting this side effect of the alpha-adrenergic agonist group of medications on the control of heart rate. We would have concern to avoid the possibilities of myocardial hypoxia if heart rates were overstimulated in the presence of low normal oxygen levels with the spontaneous breathing of atmospheric air. As a result, higher doses of atropine than used in this study should be used with appropriate professional care.

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SAMMANFATTNING

Användning av atropin för att kontrollera hjärtfrekvensen vid detomidinbehandling på häst.

Detomidin är ett sedativt analgetikum med en farmakologisk profil lik xylazinets. De sedativa effekterna medieras uppenbarligen genom alfa-2 adrenoreceptorer.

De kardiopulmonära effekterna av detomidin studerades med detomidin som den principiella faktorn och som ett preanestetikum före induktion av allmän anestesi med guaifenesin, natrium thiamylal och halotan.

I likhet med xylazin förorsakar detomidin bradykardi, vilken befanns vare antingen sinus-bradykardi eller hjärtblock. En motsvarande ökning i systoliskt blodtryck kan inträffa. Respirationen kan vara förändrad även om arteriella blodgaser och pH tyder på adekvat ventilation. Effekten på hjärtfrekvensen av detomidin utan antikolinergisk behandling var tillfällig och berodde på längden av detomidinets verkan.

Intravenös applicering av atropinsulfat, 0,02 mg/kg, förhindrade effektivt den av detomidin förorsakade bradykardin eller hjärtblocket. Hjärtfrekvensen ökade också efter administrering av guaifenesin och natrium thiamylal 30 min efter detomidin.

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