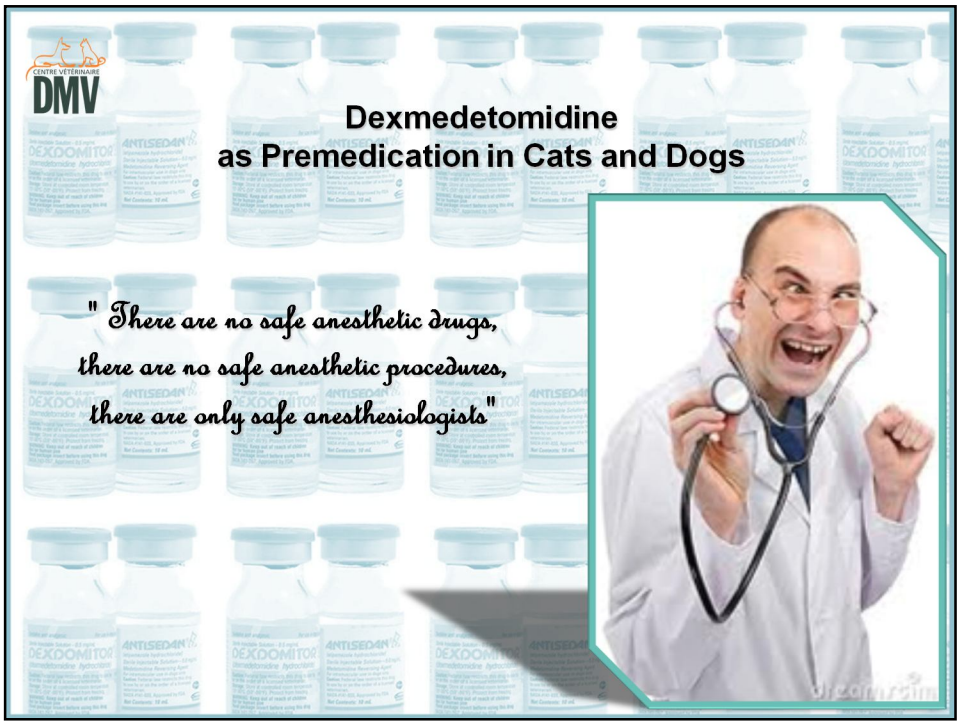
Dexmedetomidine is the latest addition to the class of α_2-adrenergic agonists.

This drug is largely underutilized, mainly because of a lack of familiarity among veterinarians and the persistent fear of adverse effects, especially cardiovascular adverse effects.

However, when properly used, it is a very useful tool in the anesthesia and analgesia pharmacopeia, and it is even more essential in the current context of drug shortage at the national and international level.



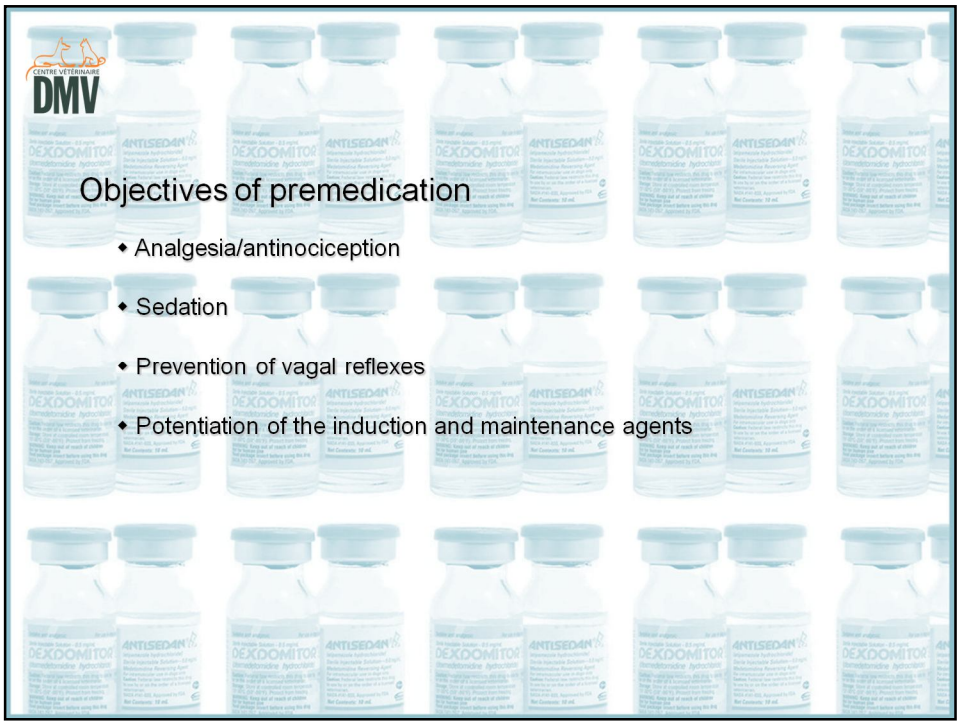
It is very possible to use dexmedetomidine safely and effectively on a regular basis, if you know how to use it, but it is also to possible to experience catastrophes with the "good old" BAG if not used properly.

Acepromazine, too, is associated with many adverse effects, especially hemodynamic ones.

Most anesthetic induction agents cause hypotension, which is due to vasodilatation and myocardial depression, and respiratory depression.

The worst of all, in terms of hemodynamic and respiratory repercussions – and whose doses we would like to decrease as much as possible – are volatile anesthetic agents.

⇨ consequently, there is great interest in significantly reducing the doses of all these drugs and, as a result, their depressant effects by using potent, potentiating sedative/analgesic agents.



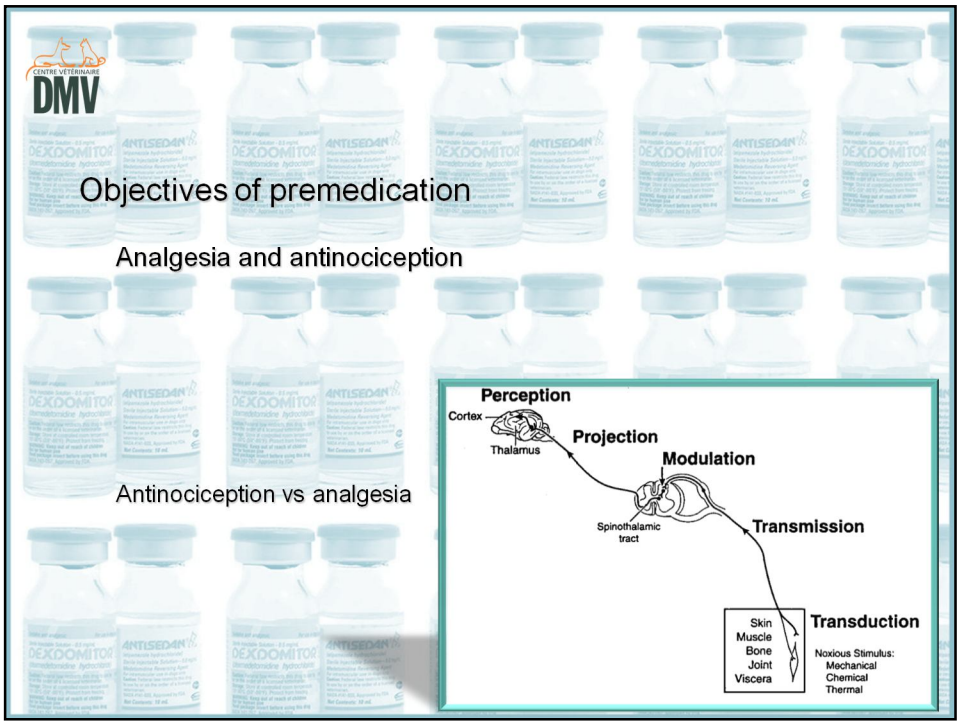
When done properly, anesthesia involves several steps even before thinking of putting a patient to sleep.

◆ Preanesthetic preparation: physical exam, relevant diagnostic tests (labs, imaging, ECG, etc.), stabilizing conditions that could adversely interact with the anesthesia, preanesthetic fasting (if applicable), etc.

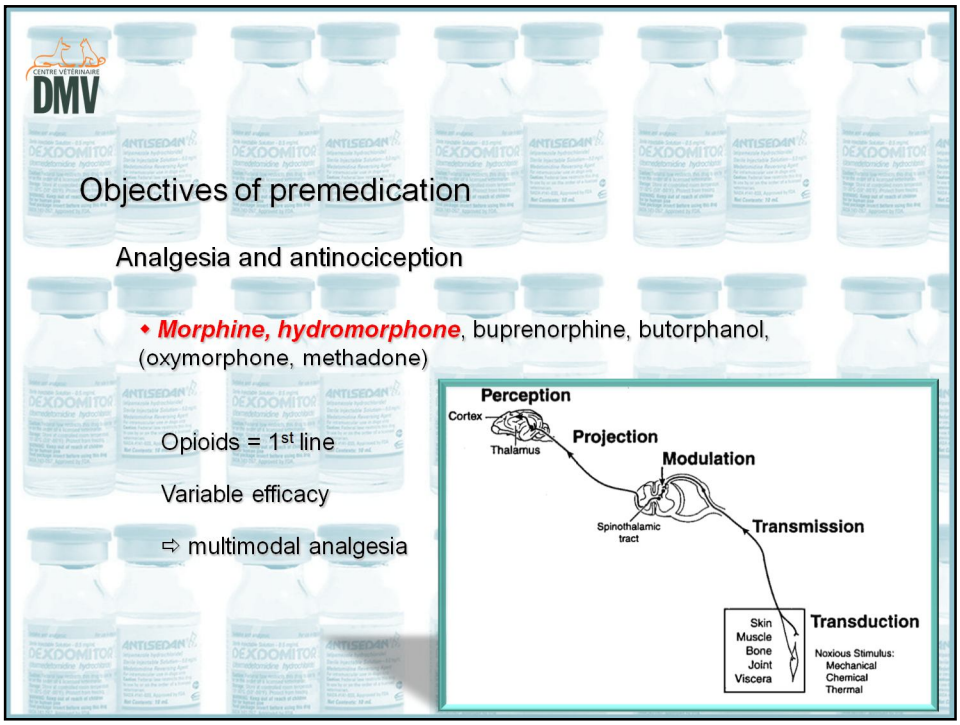
◆ Premedication, unless the patient's pathological condition or certain treatments currently in progress make it unnecessary.

The usefulness of premedication goes far beyond simply making it easier to handle the patient before putting it to sleep and to insert an i.v. catheter.

The beneficial effects of premedication have an impact not only on induction, but also during maintenance and possibly up until recovery. It all depends on the duration of action of the premedication and the duration of the general anesthesia.



Analgesia and, ideally, antinociception. Antinociception is the interruption of nociceptive nerve conduction (that is, nerve conduction resulting from nociceptor activation) along the different segments where the signal being transmitted will eventually result in pain, this pain being associated with the conscious perception of nociception after the signal is integrated in the higher nervous centres (thalamus, cortex).



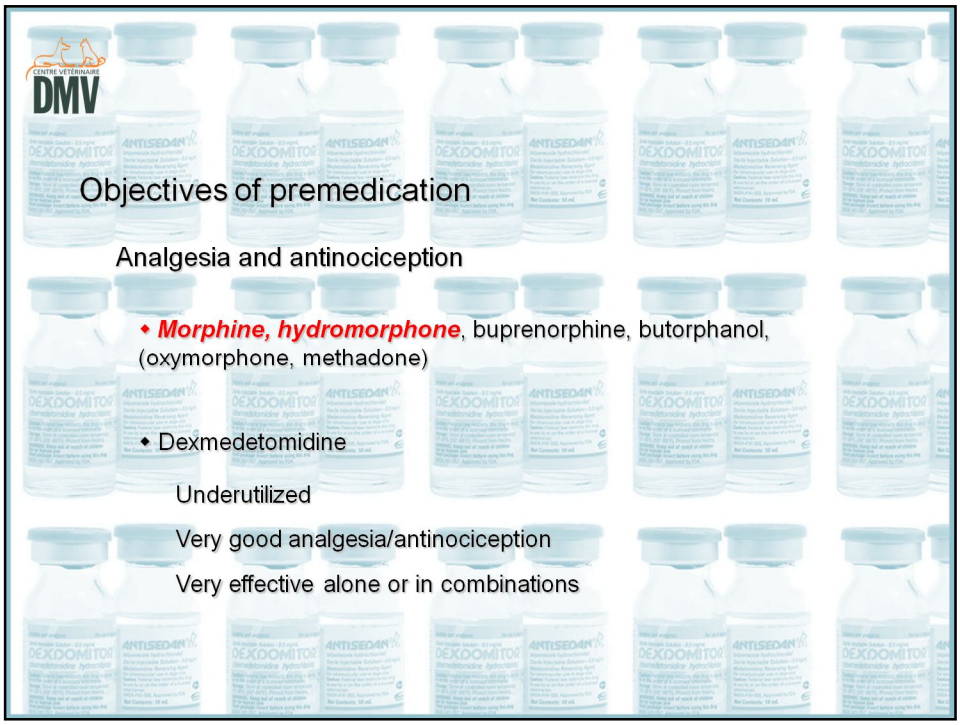
The drugs affected by the production stoppage at Sandoz are in red. Nonetheless, the availability of some of these critical drugs might possibly be maintained, thanks to measures taken by other pharmaceutical companies or by compounding pharmacies.

Opioids are still the first-line agents in anesthesia to provide analgesia, both in humans and animals.

They do not all have the same efficacy for all pain intensities (e.g., hydromorphone, oxymorphone, morphine and methadone as opposed to butorphanol and buprenorphine for severe pain).

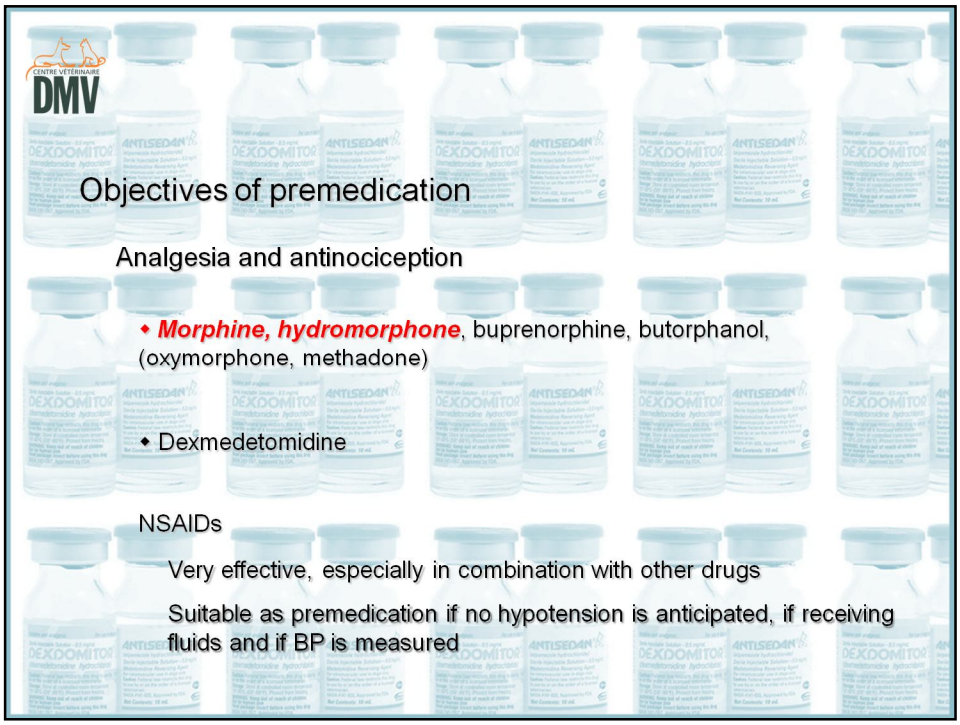
However, we should not consider the effect of an analgesic administered alone, which may be suboptimal. Instead, it should be incorporated into a context of multimodal analgesia, where it would be acceptable, thanks to its synergistic or at least additive effect, acting through mechanisms different from those of the coadministered analgesics or at different levels in the nociceptive signal transmission pathway.

When we talk about potentiating the analgesic/antinociceptive effect of opioids as premedication, α_2-adrenergic agonists come to the fore, together with NSAIDs.



Dexmedetomidine is a very good, but underutilized, analgesic/antinociceptive agent.

It is very effective for analgesia/antinociception in combination with or in place of an opioid.

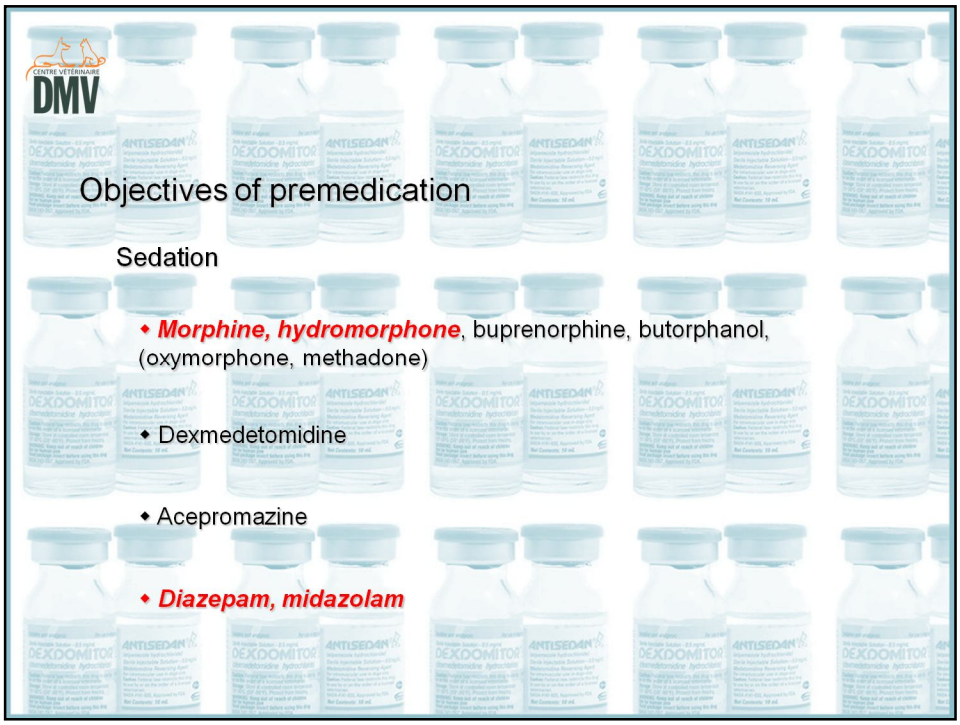


Administering NSAIDs as premedication is suitable in patients who are not too young and if hypotension is not anticipated, if the patient receives i.v. fluids and if its blood pressure is measured regularly to prevent a combination of hypotension and a blockage of PGE_2 and PGI_2 synthesis in the kidneys.

COX-1 or COX-2 selectivity is not an absolute guarantee of renal safety. Like COX-1, COX-2 is constitutive to the kidneys, and its expression increases during hypotension and renal ischemia.

Therefore, eicosanoids derived from COX-2 also play a physiological and protective role in the kidneys (eicosanoids are compounds derived from eicosatetraenoic acid, also known as arachidonic acid. In this case, they are PGE_2 and PGI_2).

NSAIDs are administered as soon as possible in order to minimize the amount of proinflammatory eicosanoids (e.g., PGE_2), which cause peripheral and central sensitization. They have excellent efficacy in combination with opioids or α_2-adrenergic agonists.

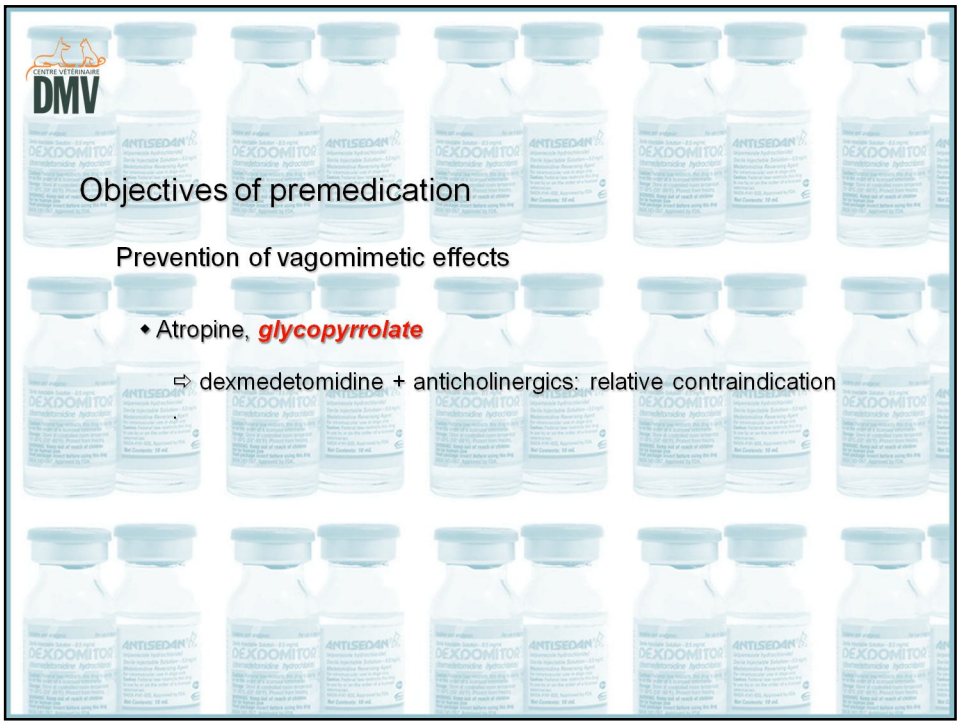


With the appropriate doses and routes of administration, opioids can produce good sedative effects (variable efficacy), especially when administered intravenously, so much so that they are sometimes used alone for premedication in patients that are not overly excited or stressed.

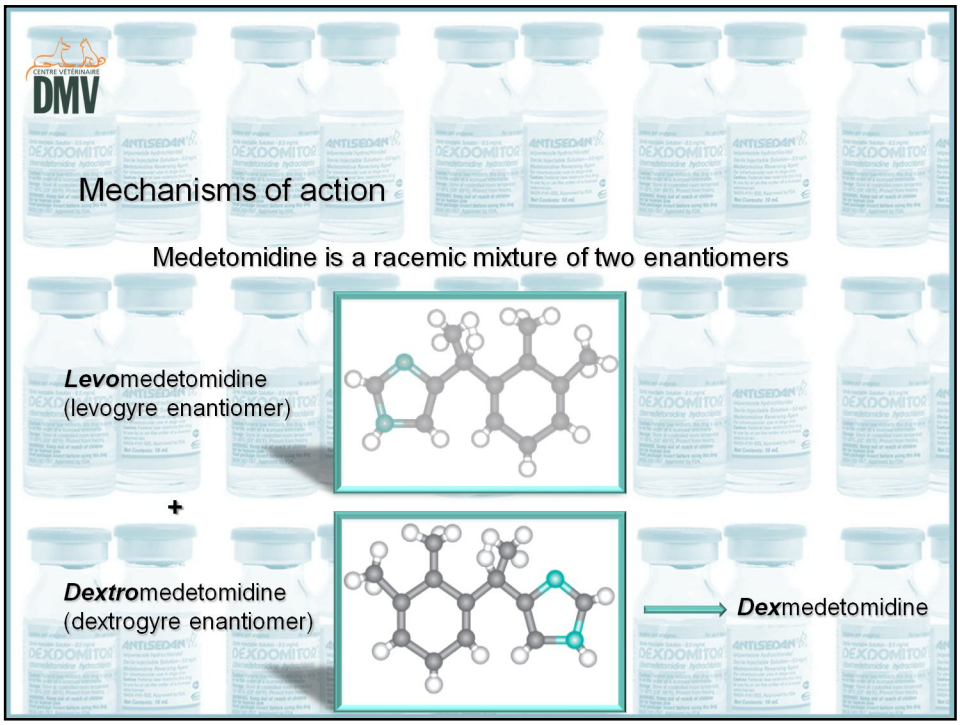
Dexmedetomidine has significant sedative and anxiolytic effects, in addition to being a very good analgesic/antinociceptive agent. It can be administered alone or in combination with opioids.

Acepromazine: relatively good sedation but no antinociception.

Diazepam, midazolam: lighter sedation in general (more efficient in the very young or old patients, or those having an altered level of consciousness), sometimes paradoxical excitation, no antinociception.



Relative contraindication for the administration of glycopyrrolate/atropine with dex/medetomidine for countering the reflex bradycardia that occurs during the initial, transient phase of vasoconstriction (see below).



Medetomidine is a racemic mixture of two enantiomers (i.e., optical isomers, being mirror images of each other and having at least one asymmetrical carbon atom and rotating the plane of polarized light in opposite directions):

- Levomedetomidine (rotates the plane of polarized light toward the left, or counterclockwise). This enantiomer is considered inactive, at the clinical doses, from the standpoint of the desirable pharmacological properties.

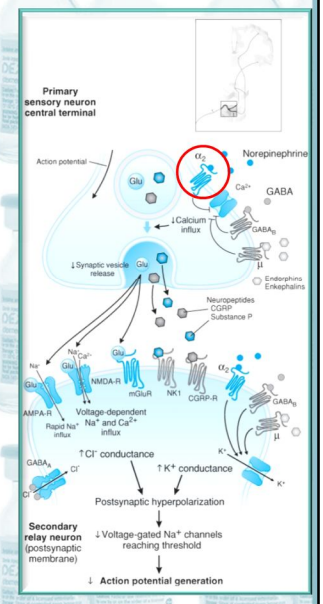
- Dextromedetomidine (= dexmedetomidine; rotates the plane of polarized light toward the right, or clockwise). This is the active enantiomer.

Mechanisms of action

CNS effects (α_2-adrenergic receptors)

- Presynaptic non-noradrenergic neurons

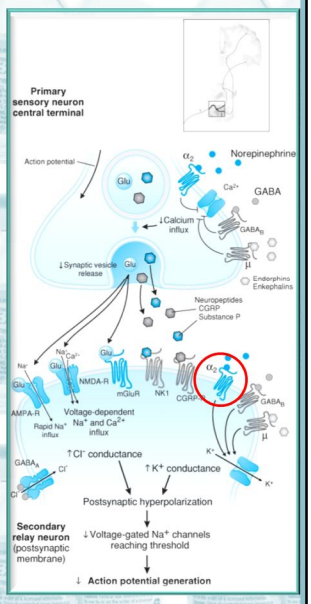
  ⇨ ↓ release of excitatory pronociceptive neurotransmitters

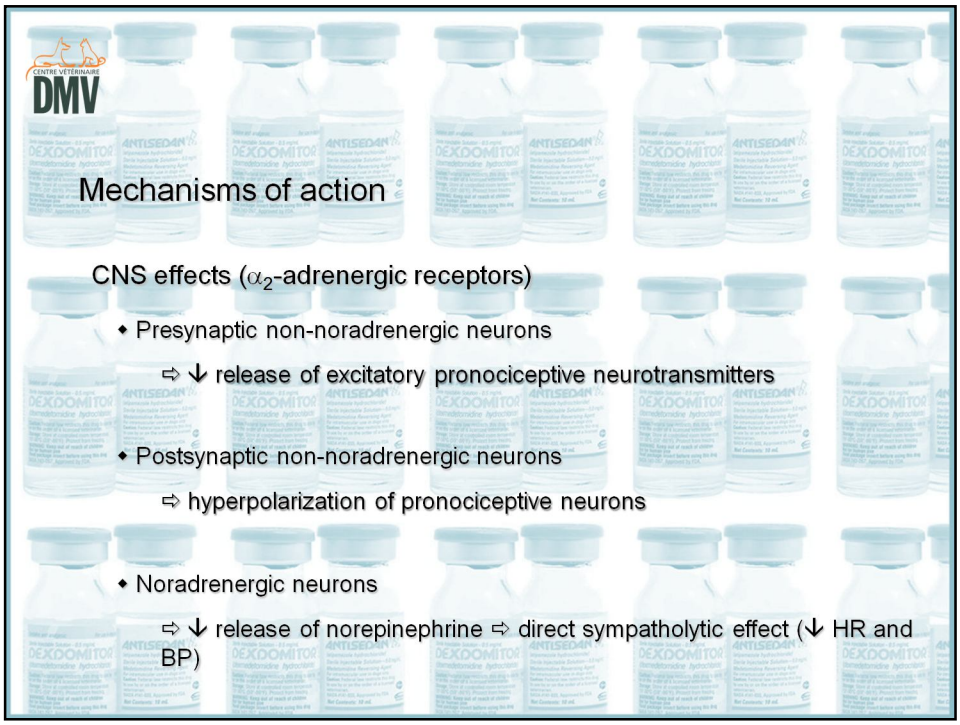


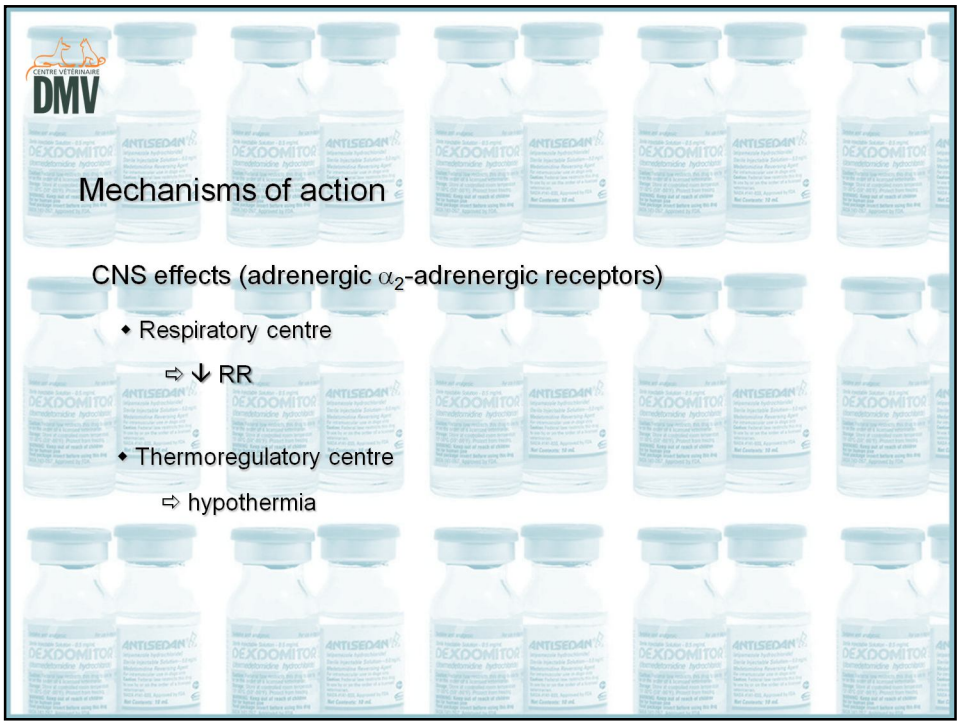
Mechanisms of action

CNS effects (α_2-adrenergic receptors)

- Presynaptic non-noradrenergic neurons
  - ⇨ ↓ release of excitatory pronociceptive neurotransmitters
- Postsynaptic non-noradrenergic neurons
  - ⇨ hyperpolarization of pronociceptive neurons

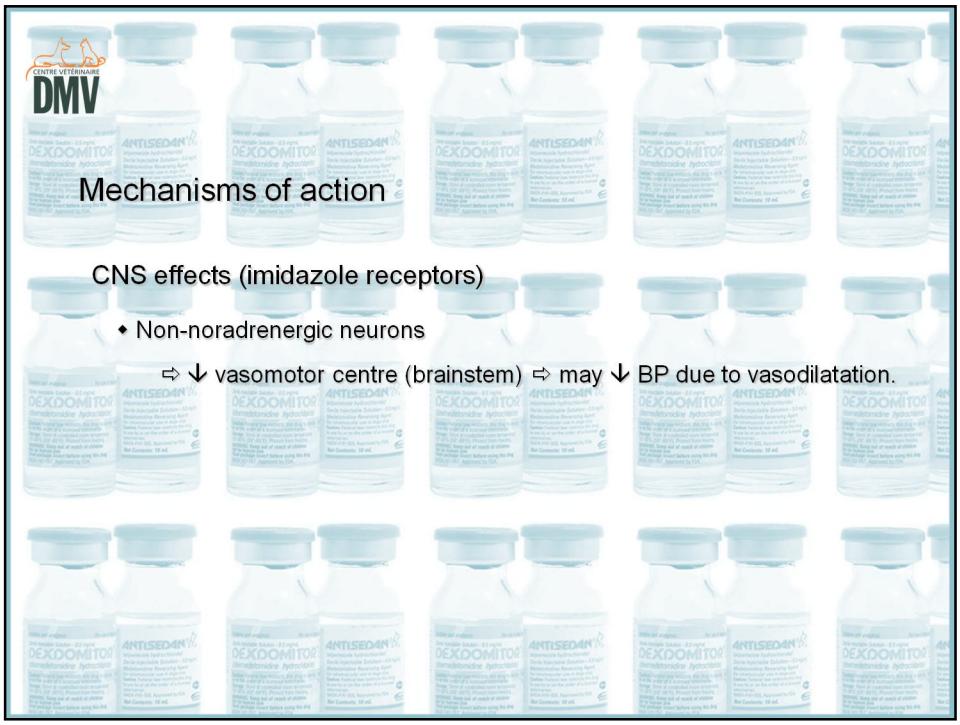



Mechanisms of action
CNS effects (α_2-adrenergic receptors)
Presynaptic non-noradrenergic neurons
⇨ ↓ release of excitatory pronociceptive neurotransmitters
Postsynaptic non-noradrenergic neurons
⇨ hyperpolarization of pronociceptive neurons
Noradrenergic neurons
⇨ ↓ release of norepinephrine ⇨ direct sympatholytic effect (↓ HR and BP)

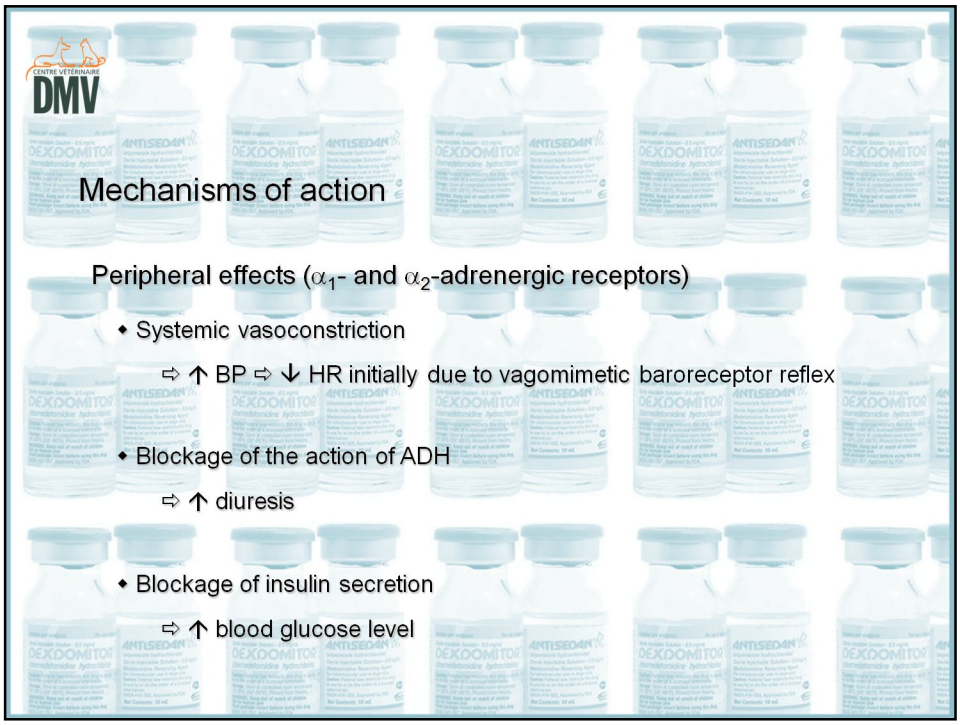


Dexmedetomidine's respiratory depressant effect results mainly in a lower RR, but typically not in a lower tidal volume, which can even increase ⇨ blood gas values maintained within normal limits.

However, during deep sedation, it is advisable to administer oxygen by mask.



Dexmedetomidine also interacts with imidazoline receptors = non-noradrenergic receptors located in the CNS, particularly in the vasomotor centre ⇨ ↓ vascular tone ⇨ vasodilatation.

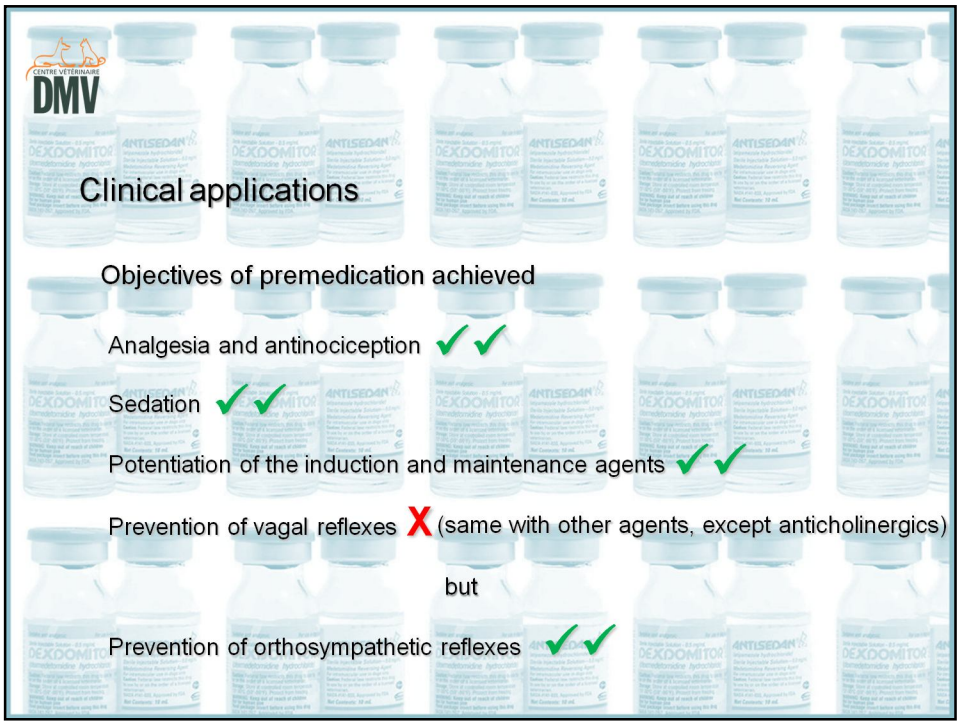


Vagomimetic baroreceptor reflex following the initial, transient vasoconstriction ⇨ bradycardia and bradydysrythmias: 1st- and 2nd-degree atrioventricular blocks (rarely 3rd-degree atrioventricular block or sinus pause).

Blockage of the action of ADH and ↑ diuresis = problem only if the patient is dehydrated/hypovolemic, hypotensive and not receiving fluids.

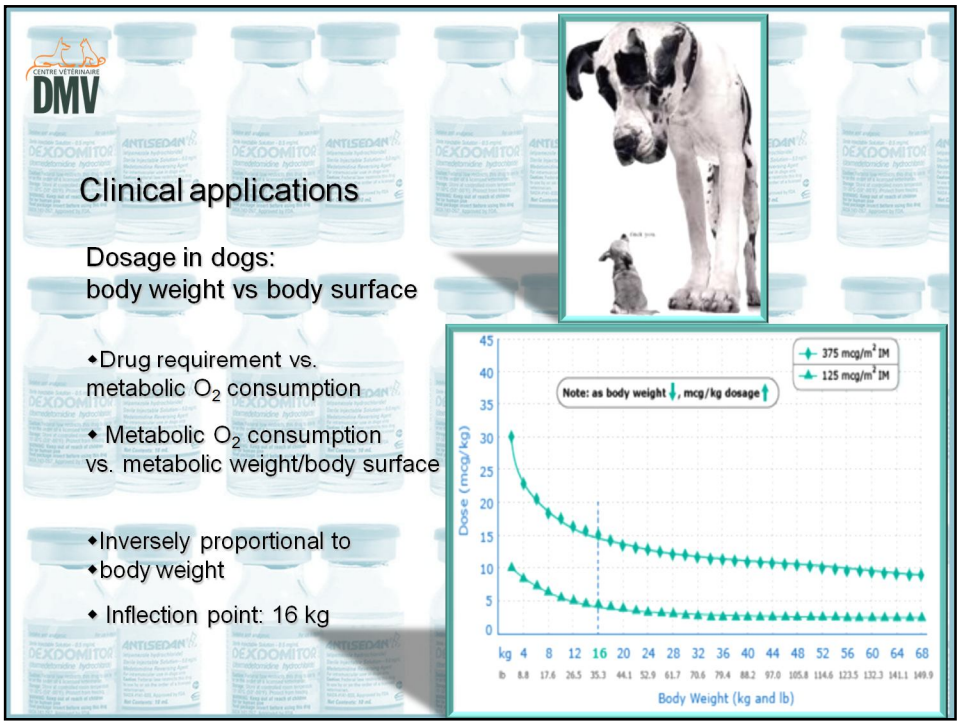
⇨ consider emptying the bladder before recovery if the patient is receiving a large quantity of fluids and/or is at risk for urinary retention because of a pathological condition or because of treatment (epidural anesthesia).

Blockage of insulin secretion is theoretically a problem only in the presence of diabetes: clinical significance unclear.



Most of the objectives of premedication are met with dexmedetomidine.

Prevention of orthosympathetic reflexes: The decrease in orthosympathetic hyperactivity caused by surgical stimulation (due to the direct sympatholytic effect and to analgesia/ antinociception) is beneficial for the heart, as it decreases its O_2 consumption and promotes coronary perfusion.

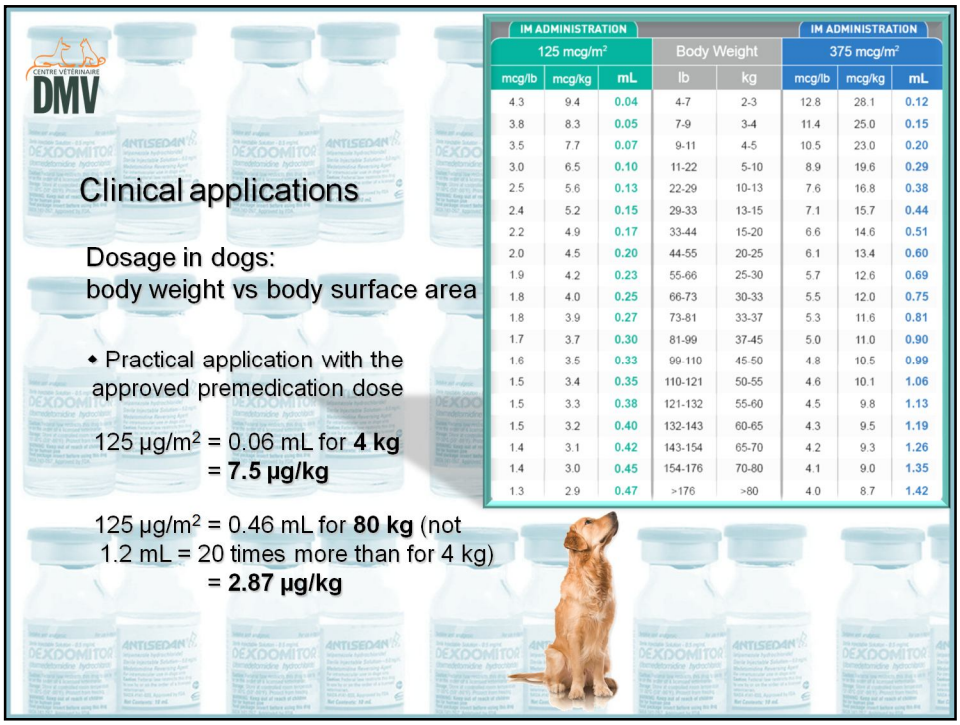


The required dose of a drug varies somewhat like basal metabolic O_2 consumption: the relationship with body weight is not linear and is best correlated with body surface area (m^2) or metabolic weight ($weight^{0.75}$).

The larger the animal, the lower the basal metabolic O_2 consumption per unit of body weight (mL/kg/min). Similarly, the dose of a drug per unit of body weight (e.g., µg/kg) is lower in a large animal than in a smaller one.

Consequently, the dosage for dexmedetomidine in dogs is better expressed in $µg/m^2$ than in µg/kg, because of the wide variation in possible sizes in this species. The purpose of this is to avoid overdosing a large dog and underdosing a small one with a fixed dose in µg/kg.

The inflection point in the dose curve (µg/kg) as a function of body weight (kg) suggests that a body weight of 16 kg is a critical value below which the dexmedetomidine requirement increases significantly.



The backward calculation from µg/m² to µg/kg clearly illustrates the risk of underdosing in a small animal and of overdosing in a large animal with a fixed dose of 5 µg/kg, for example.

Clinical applications

Dosage in dogs:
body weight vs body surface area

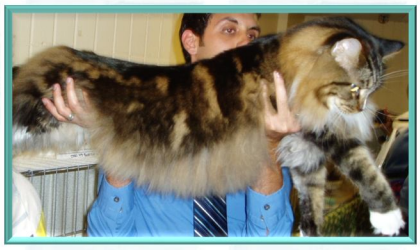
- Practical application with the approved premedication dose

375 µg/m² = 0,175 ml for **4 kg**
= **21,87 µg/kg**

375 µg/m² = 1,385 ml for **80 kg** (not 3,5 ml = 20 times more than for 4 kg)
= **8,65 µg/kg**

IM ADMINISTRATION					IM ADMINISTRATION		
125 mcg/m²			Body Weight		375 mcg/m²		
mcg/lb	mcg/kg	mL	lb	kg	mcg/lb	mcg/kg	mL
4.3	9.4	0.04	4-7	2-3	12.8	28.1	0.12
3.8	8.3	0.05	7-9	3-4	11.4	25.0	0.15
3.5	7.7	0.07	9-11	4-5	10.5	23.0	0.20
3.0	6.5	0.10	11-22	5-10	8.9	19.6	0.29
2.5	5.6	0.13	22-29	10-13	7.6	16.8	0.38
2.4	5.2	0.15	29-33	13-15	7.1	15.7	0.44
2.2	4.9	0.17	33-44	15-20	6.6	14.6	0.51
2.0	4.5	0.20	44-55	20-25	6.1	13.4	0.60
1.9	4.2	0.23	55-66	25-30	5.7	12.6	0.69
1.8	4.0	0.25	66-73	30-33	5.5	12.0	0.75
1.8	3.9	0.27	73-81	33-37	5.3	11.6	0.81
1.7	3.7	0.30	81-99	37-45	5.0	11.0	0.90
1.6	3.5	0.33	99-110	45-50	4.8	10.5	0.99
1.5	3.4	0.35	110-121	50-55	4.6	10.1	1.06
1.5	3.3	0.38	121-132	55-60	4.5	9.8	1.13
1.5	3.2	0.40	132-143	60-65	4.3	9.5	1.19
1.4	3.1	0.42	143-154	65-70	4.2	9.3	1.26
1.4	3.0	0.45	154-176	70-80	4.1	9.0	1.35
1.3	2.9	0.47	>176	>80	4.0	8.7	1.42

Clinical applications



Dosage in cats

- Less variation in body weight ⇨ dose based on body weight
- Dose approved for i.m. premedication = 40 µg/kg

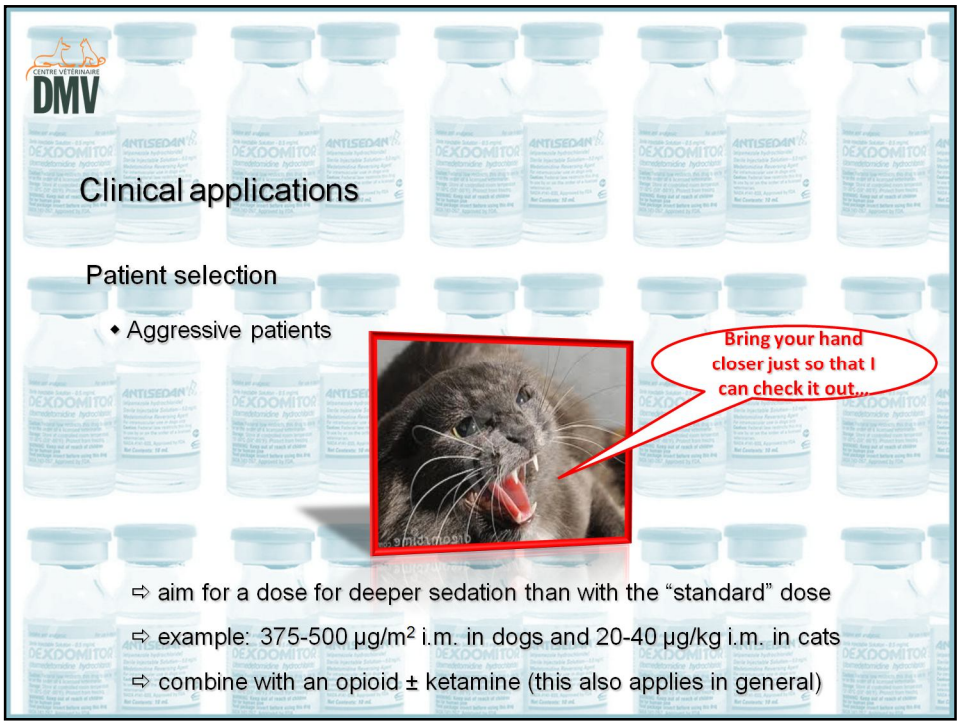
⇨ common doses are lower, especially if combined with opioids

⇨ dose adjustment principle based on body weight still valid for extreme weights (e.g., a large Maine Coon vs a small Siamese)

Clinical applications

Patient selection

- Dexmedetomidine = good choice for **all** patients, if no contraindications
- Not only for agitated or aggressive patients, although it is particularly useful for them
  - ⇨ adjust the dose according to the animal's temperament and the required level of sedation/analgesia



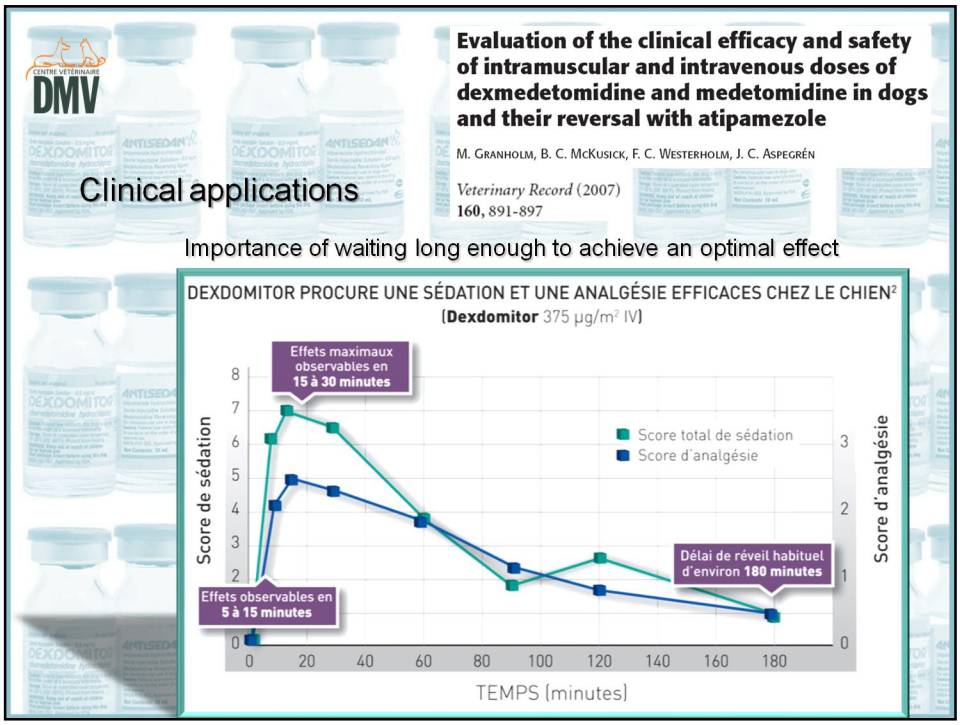
Very stressed or aggressive patients can exhibit greater resistance to sedation with dexmedetomidine and, in general, with α_2-adrenergic agonists. This applies to other sedation agents as well.

Combining with other sedation/restraining agents is often more effective than excessively increasing the dexmedetomidine dose, which increases the duration of the effects more than their intensity.

Two factors that are often responsible for the mistaken perception of poor efficacy:

- Environment not conducive to sedation (too many tactile, visual and auditory stimuli).

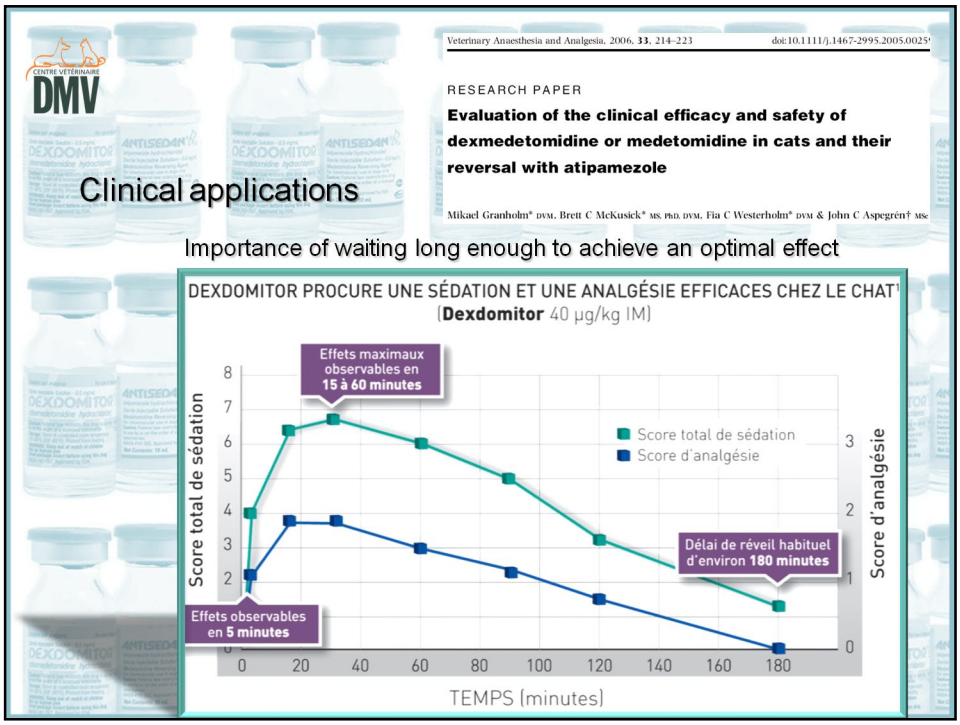
- Mainly a lack of patience ⇨ wait until the optimal effect is reached before handling an agitated, stressed or aggressive patient.



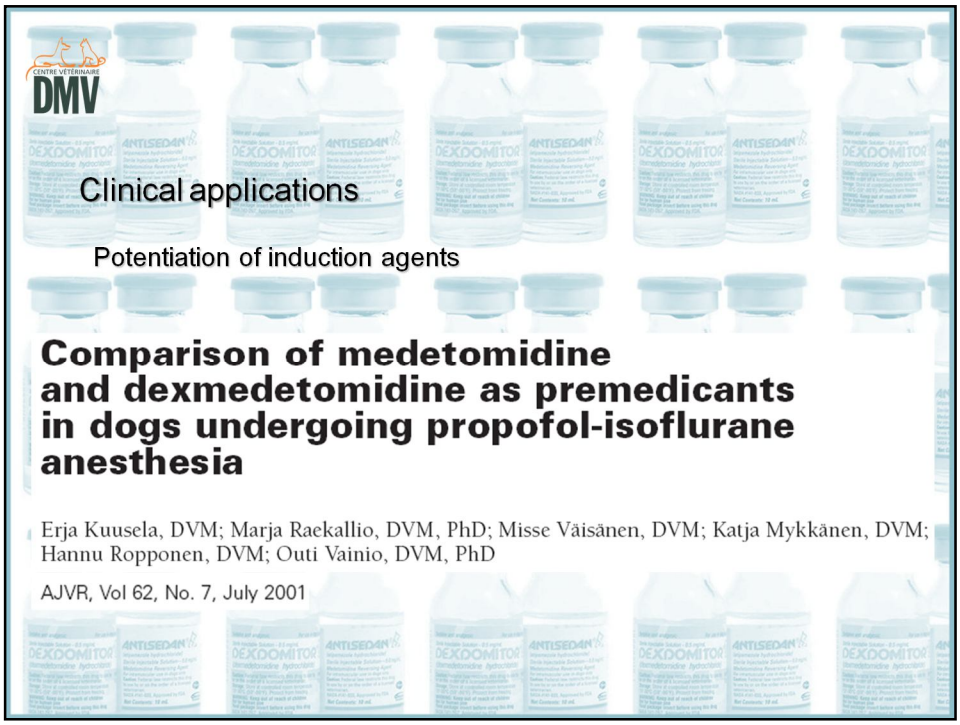
Importance of waiting long enough before concluding that the premedication is not effective: peak of action within 15-30 min after i.v. injection, 30 min after i.m. injection.

Often, a patient will not appear calmed at all after several minutes, but it will end up going down after just a few extra minutes of waiting.

This is also true for other premedication agents, in particular, acepromazine: onset of action after i.m. injection in dogs = 15 minutes; peak of action = 30 minutes.

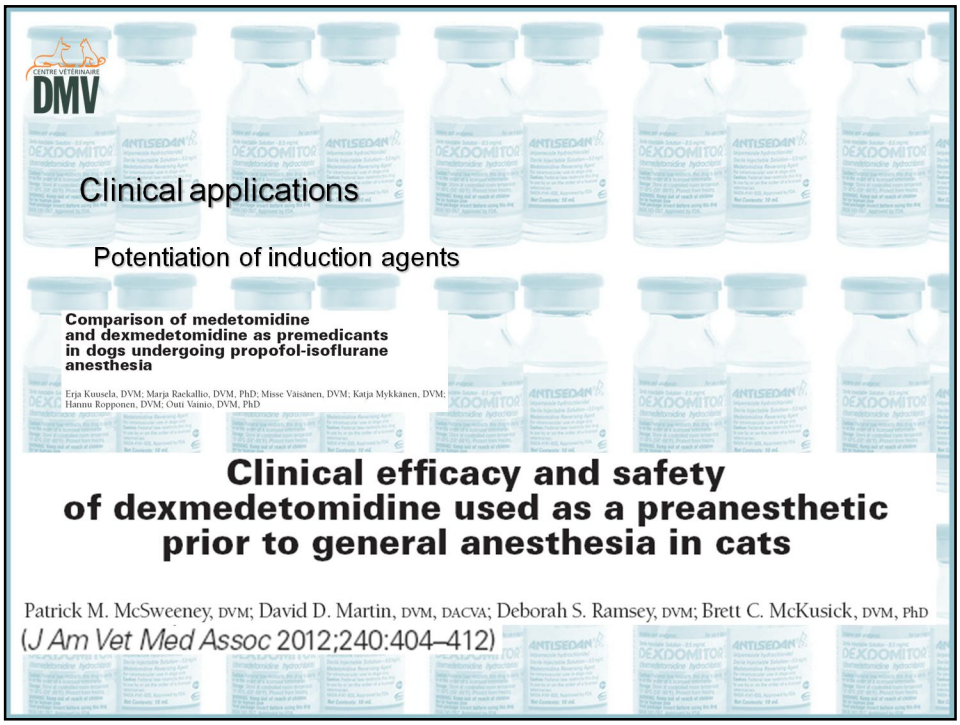


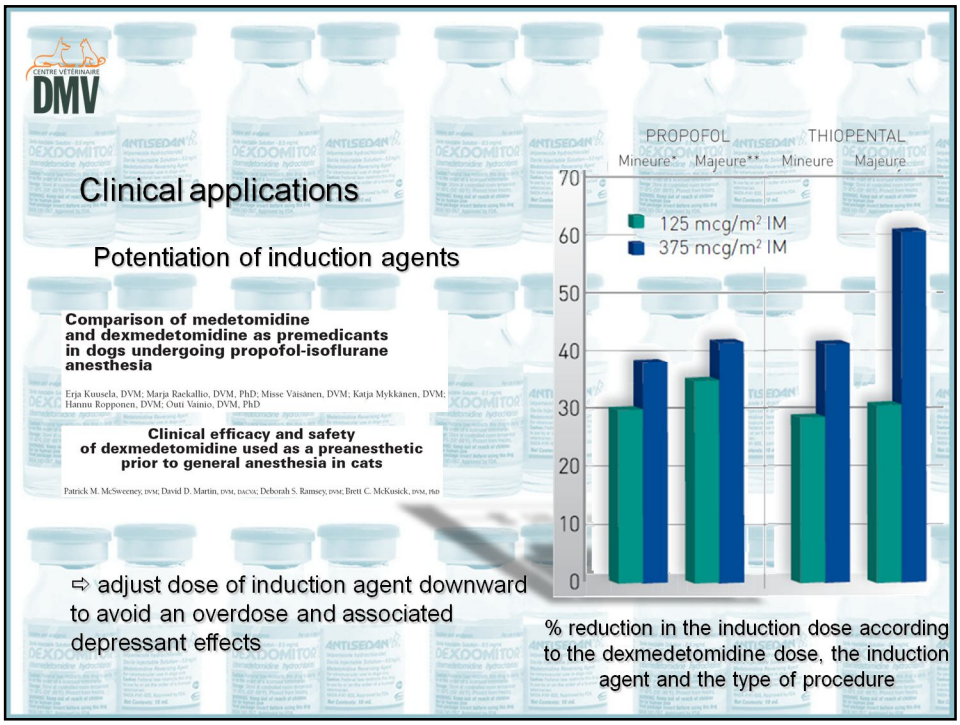
Same in cats. Peak of action up to 60 min.



Dexmedetomidine has a pronounced potentiating effect on anesthetic induction agents.

In spite of the shortage affecting some benzodiazepines (diazepam, midazolam), anesthetic induction with ketamine is still possible without combining it with these molecules, provided that the sedation and myorelaxation caused by the premedication are adequate (JAVMA 2012;240: 404-412). An appropriate dose of dexmedetomidine, combined or not with an opioid, allows to meet these objectives.

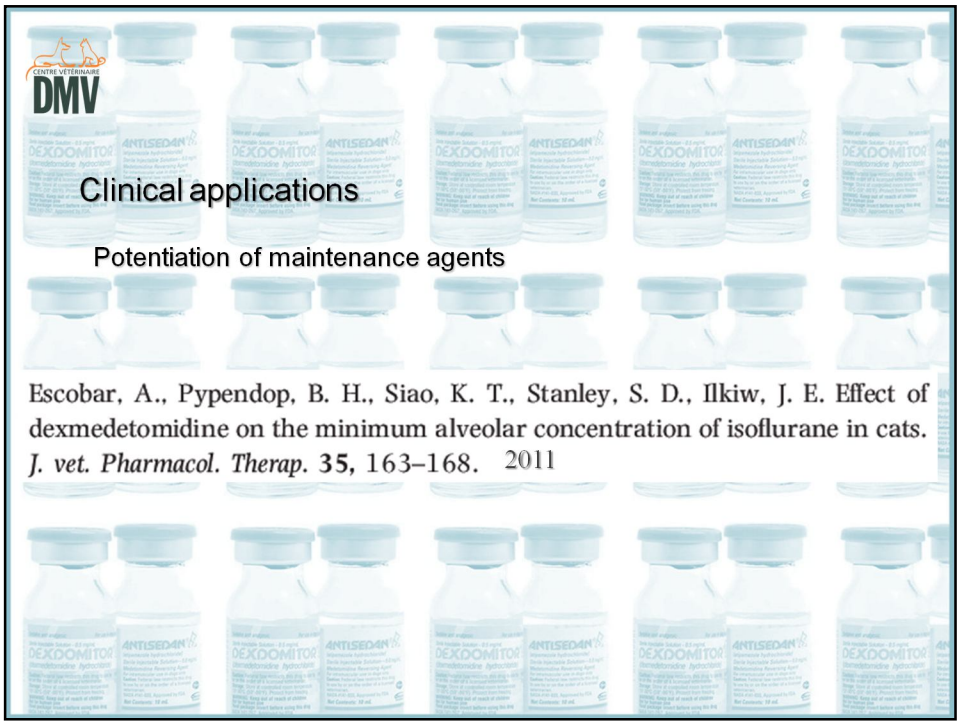

DMV
Clinical applications
Potentiation of induction agents
Comparison of medetomidine and dexmedetomidine as premedicants in dogs undergoing propofol-isoflurane anesthesia
Erja Kuusela, DVM; Marja Raekallio, DVM, PhD; Misse Väisänen, DVM; Katja Mykkänen, DVM; Hannu Ropponen, DVM; Outi Vainio, DVM, PhD
Clinical efficacy and safety of dexmedetomidine used as a preanesthetic prior to general anesthesia in cats
Patrick M. McSweeney, DVM; David D. Martin, DVM, DACVA; Deborah S. Ramsey, DVM; Brett C. McKusick, DVM, PhD
(J Am Vet Med Assoc 2012;240:404–412)



Because of dexmedetomidine's strong potentiating effect on the efficacy of induction agents, the quantity of these agents to be administered has to be adjusted to avoid an overdose.

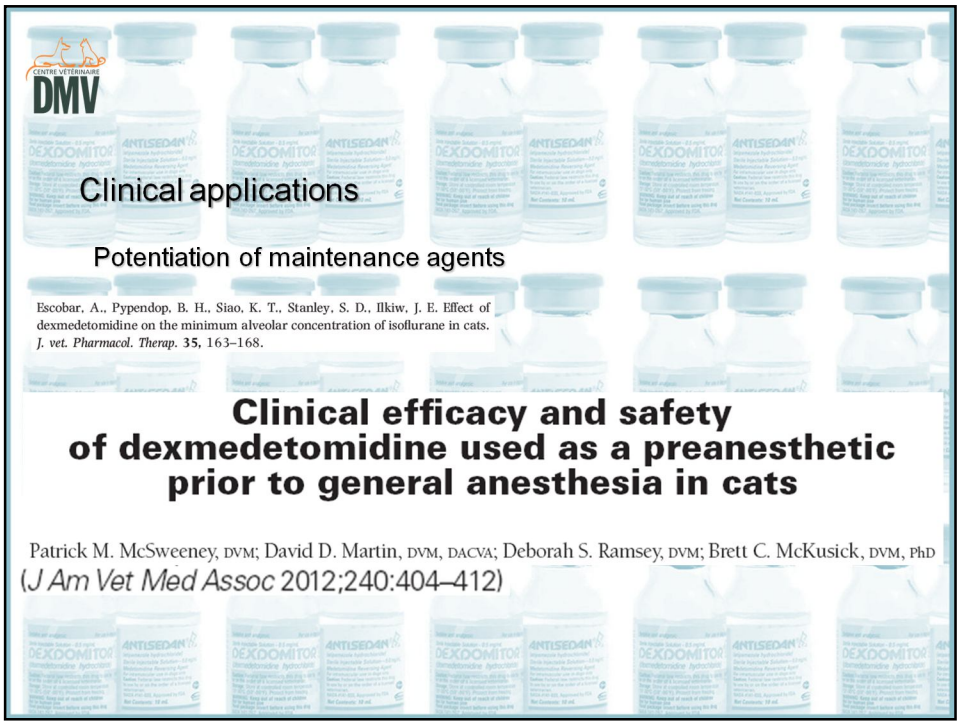
The exact relationship between dexmedetomidine and the percent decrease in the dose of induction agent is not known, since it depends on many other factors, such as the patient's temperament, its susceptibility/resistance (influenced by its pharmacogenetics, its disease, etc.), the combination with one or more other premedication agents, etc.

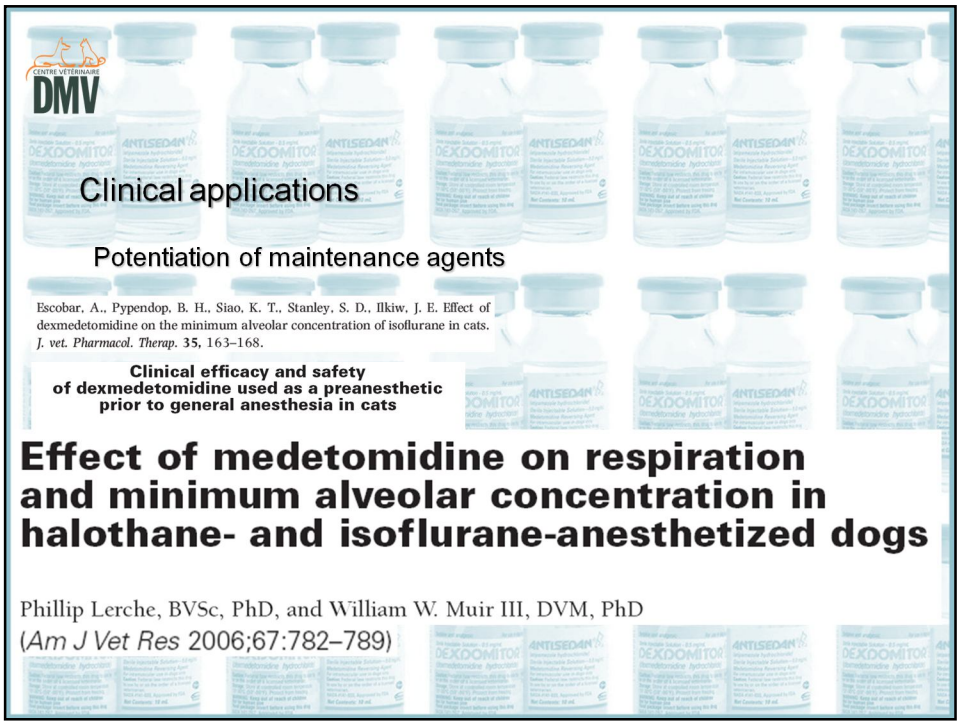
In any event, the injectable induction agent is administered to effect, and the injection is stopped when the desired effects are achieved. If it turns out that tracheal intubation is not possible, injecting the induction agent is resumed until the desired effect is achieved.



Dexmedetomidine administered as premedication has a pronounced potentiating effect on anesthetic and maintenance agents.

Clinical illustration of this effect: patient under general anesthesia with isoflurane at an adequate level of anesthesia woke up right after the administration of atipamezole. One of the objectives of maintaining general anesthesia, which consisted in narcosis, was achieved to a large extent because of the α_2-adrenergic agonist.


DMV
Clinical applications
Potentiation of maintenance agents
Escobar, A., Pypendop, B. H., Siao, K. T., Stanley, S. D., Ilkiw, J. E. Effect of dexmedetomidine on the minimum alveolar concentration of isoflurane in cats. J. vet. Pharmacol. Therap. 35, 163–168.
Clinical efficacy and safety of dexmedetomidine used as a preanesthetic prior to general anesthesia in cats
Patrick M. McSweeney, DVM; David D. Martin, DVM, DACVA; Deborah S. Ramsey, DVM; Brett C. McKusick, DVM, PhD
(J Am Vet Med Assoc 2012;240:404–412)


DMV
Clinical applications
Potentiation of maintenance agents
Escobar, A., Pypendop, B. H., Siao, K. T., Stanley, S. D., Ilkiw, J. E. Effect of dexmedetomidine on the minimum alveolar concentration of isoflurane in cats. J. vet. Pharmacol. Therap. 35, 163–168.
Clinical efficacy and safety of dexmedetomidine used as a preanesthetic prior to general anesthesia in cats
Effect of medetomidine on respiration and minimum alveolar concentration in halothane- and isoflurane-anesthetized dogs
Phillip Lerche, BVSc, PhD, and William W. Muir III, DVM, PhD
(Am J Vet Res 2006;67:782–789)

Clinical applications

Potentiation of maintenance agents

Escobar, A., Pypendop, B. H., Siao, K. T., Stanley, S. D., Ilkiw, J. E. Effect of dexmedetomidine on the minimum alveolar concentration of isoflurane in cats. *J. vet. Pharmacol. Therap.* **35**, 163–168.

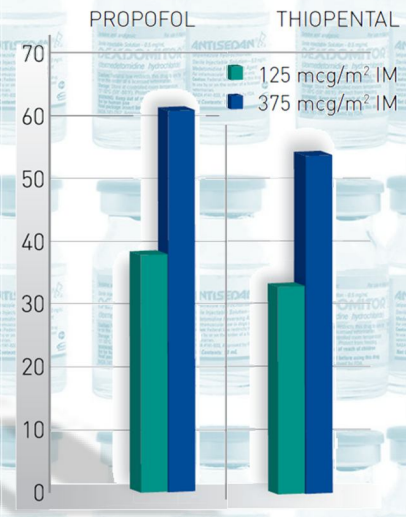
Clinical efficacy and safety of dexmedetomidine used as a preanesthetic prior to general anesthesia in cats

Patrick M. McSweeney, DVM; David D. Martin, DVM, DACVA; Deborah S. Ramsey, DVM; Brett C. McKusick, DVM, PhD

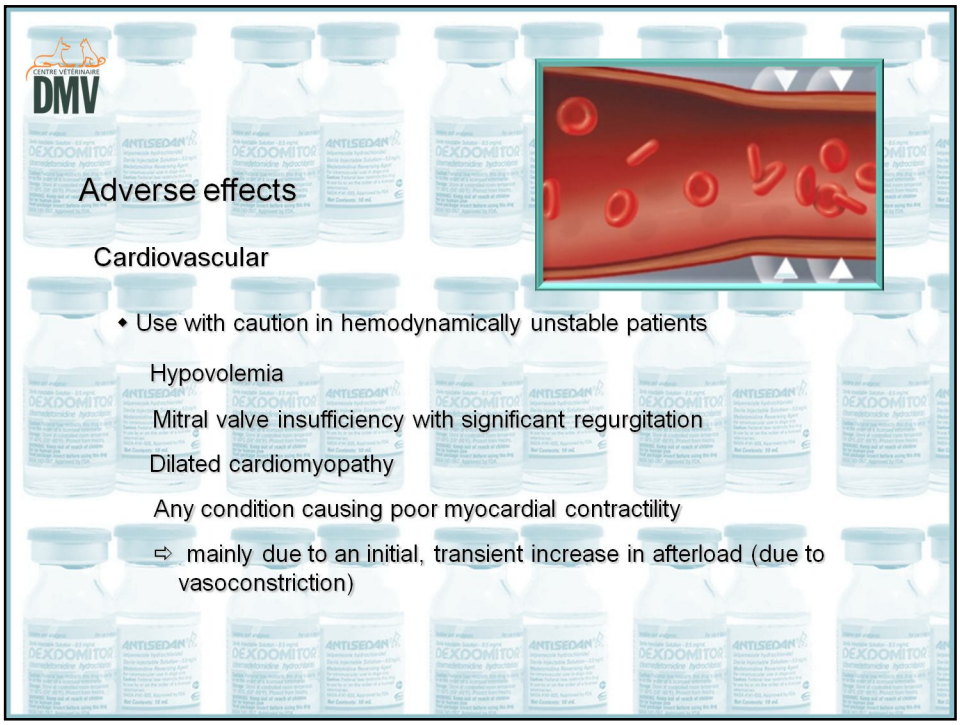
Effect of medetomidine on respiration and minimum alveolar concentration in halothane- and isoflurane-anesthetized dogs

Phillip Lerche, BVSc, PhD, and William W. Muir III, DVM, PhD

⇨ adjust dose of maintenance agent downward to avoid an overdose and associated depressant effects



% reduction in the isoflurane concentration according to the dexmedetomidine dose and the induction agent



Dexmedetomidine should be used with caution or even avoided in certain hemodynamically unstable patients:

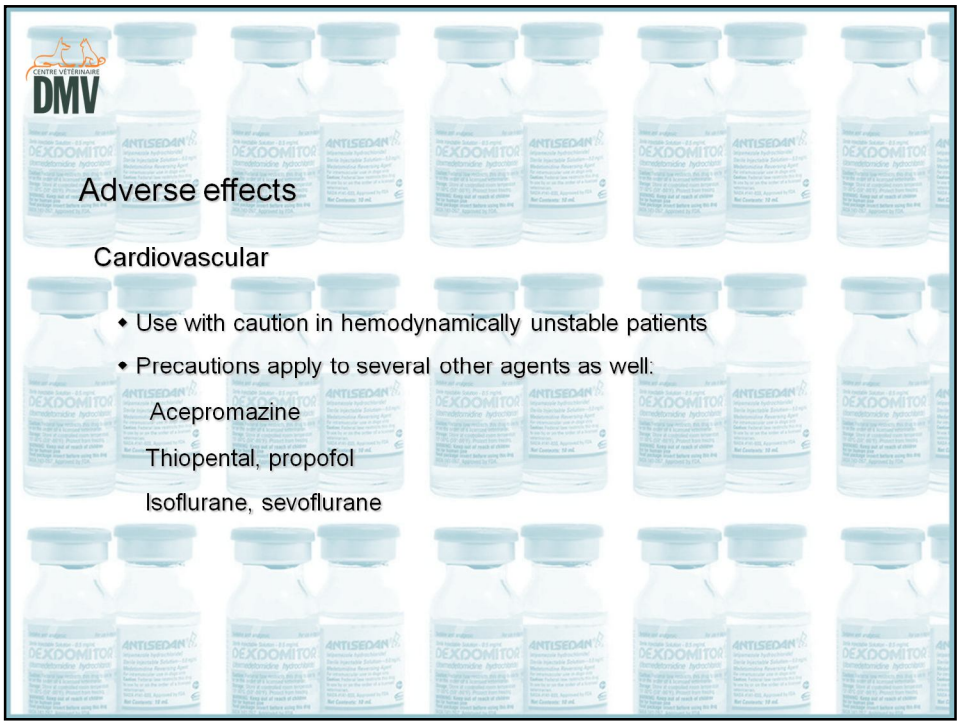
- hypovolemia ⇨ ↓ preload and then ↓ stroke volume, consequently ↓ cardiac output, which can ↓ even more due to the ↑ afterload;
- mitral valve insufficiency with significant regurgitation: initial ↑ afterload ⇨ ↑ regurgitation;
- dilated cardiomyopathy: ↓ stroke volume if afterload ↑;
- any condition causing poor myocardial contractility.

These precautions and contraindications stem mainly from the initial, transient increase in afterload due to vasoconstriction.

Even if the vasoconstriction is transitory, it can have deleterious consequences in this short time for some patients.

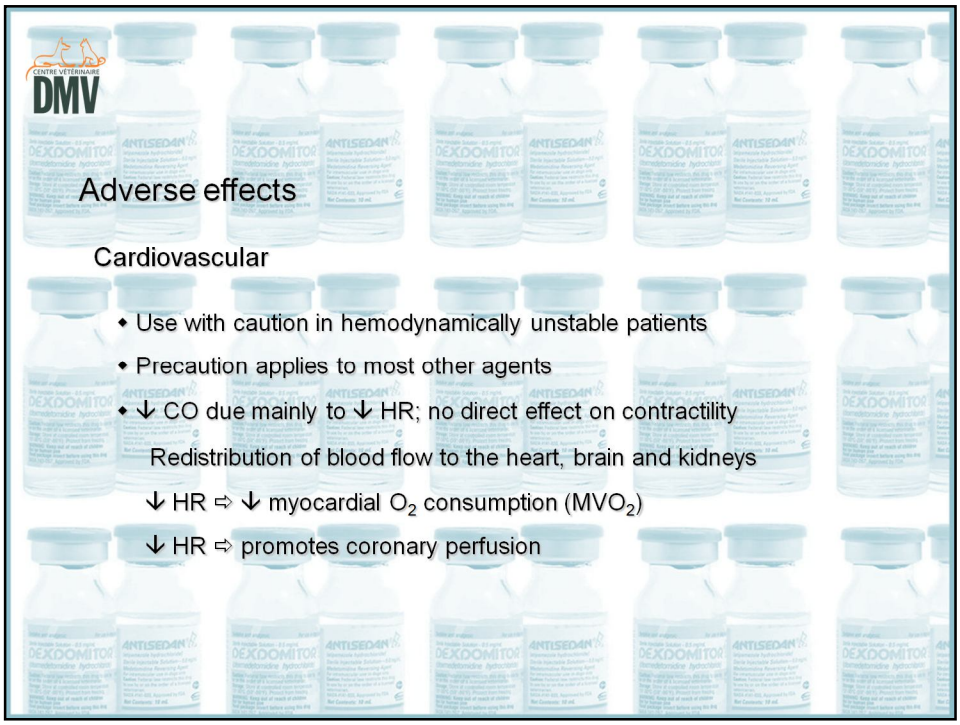
If the vasoconstriction is still present at the time of anesthetic induction, it may be counterbalanced, at least partly, by the vasodilatating effect of the induction agents (except dissociative agents) and of the maintenance agents (volatile).

The initial vasoconstriction sometimes makes i.v catheterization difficult, particularly in small patients.



However, these precautions also apply to other agents commonly used as premedication (acepromazine), for induction (thiopental and propofol) and during maintenance (isoflurane and sevoflurane).

These agents, too, can have serious hemodynamic repercussions, even in patients that are seemingly in good health. Furthermore, they do not have any antinociceptive effects and are not antagonizable.



The decrease in cardiac output is due mainly to bradycardia, not to a direct depressive effect on the myocardium.

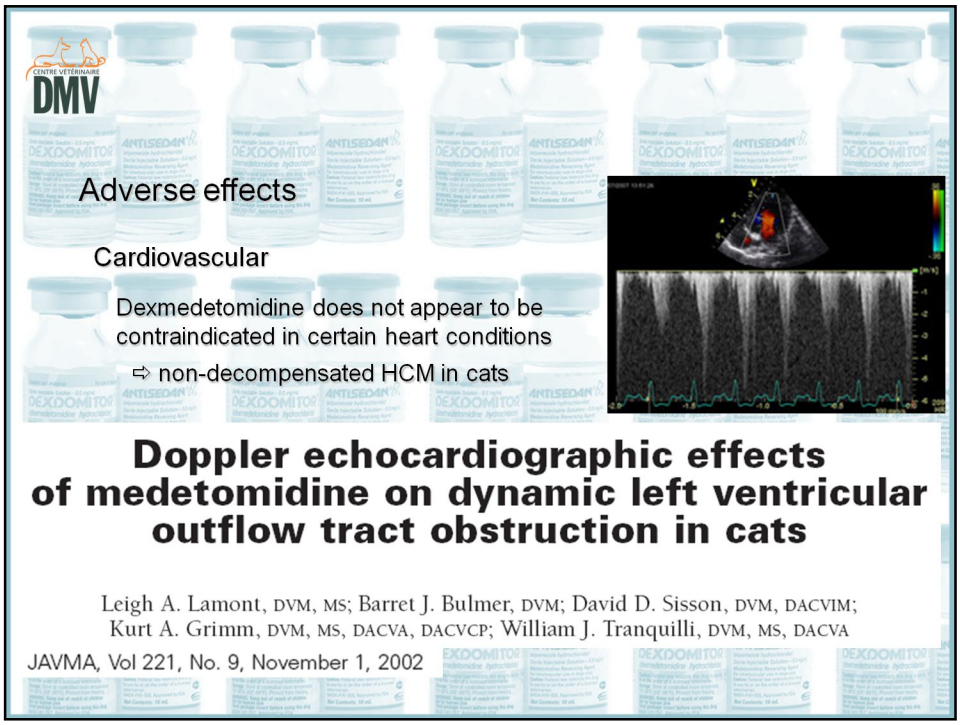
Despite this decrease in cardiac output, blood flow to the heart, brain and kidneys is maintained by redistribution from less vital tissues and organs.

Furthermore, ↓ in HR ⇨ ↓ myocardial O_2 consumption, while coronary system perfusion (which occurs mainly during diastole) is improved.

The reluctance to use dexmedetomidine as premedication out of fear that its depressant effects may be augmented by those of other anesthetic agents is unfounded.

On the other hand, because of its potentiating effect, one can substantially reduce the doses of these agents and, consequently, their depressant effects.

Despite the potential adverse effects, dexmedetomidine is often used (administered as a bolus or by CRI) in humans as a sedation agent for patients in intensive care.



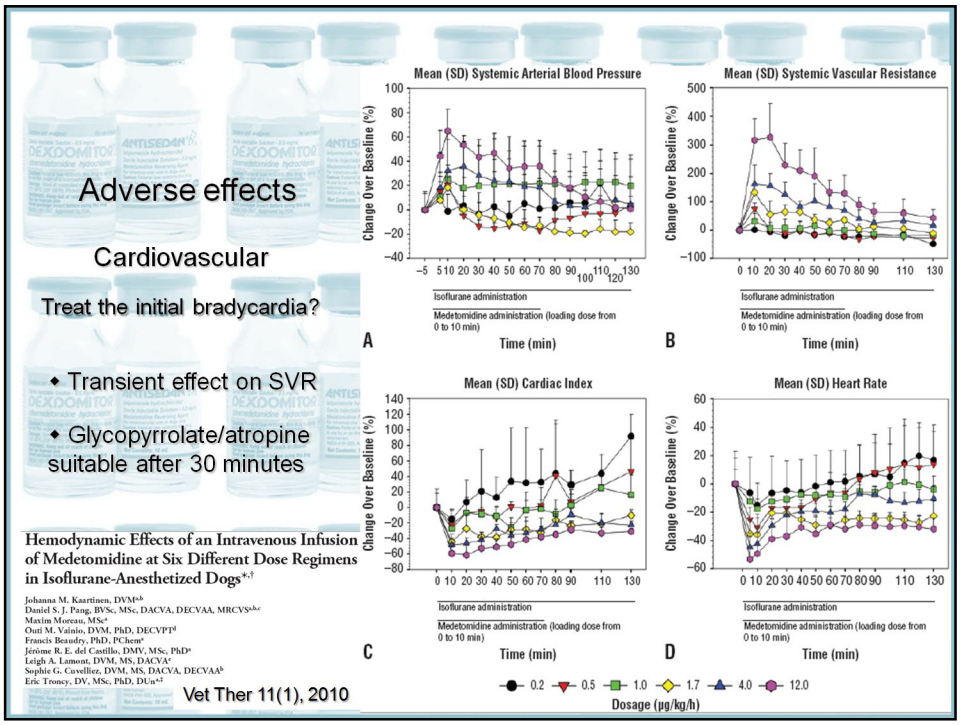
Dexmedetomidine does not appear to be harmful for certain heart conditions, provided there is no failure or cardiogenic shock: e.g., cats with hypertrophic cardiomyopathy associated with dynamic left ventricular outflow tract obstruction (JAVMA 2002, 221(9), 1276-1281).

Proposed mechanisms by which dexmedetomidine could have a beneficial effect on the heart in this situation:

- The creation, by vasoconstriction, of a left aortoventricular hydrostatic pressure gradient that promotes better systolic ejection by ↓ the dynamic obstuction.
- ↓ HR ⇨ ↓ MVO_2.

In addition, ↓ HR ⇨ ↑ coronary perfusion and therefore ↑ in O_2 supply to the myocardium.

However, when in doubt (particularly in the absence of a thorough echocardiographic evaluation), it is probably best to avoid to use dexmedetomidine in these patients.

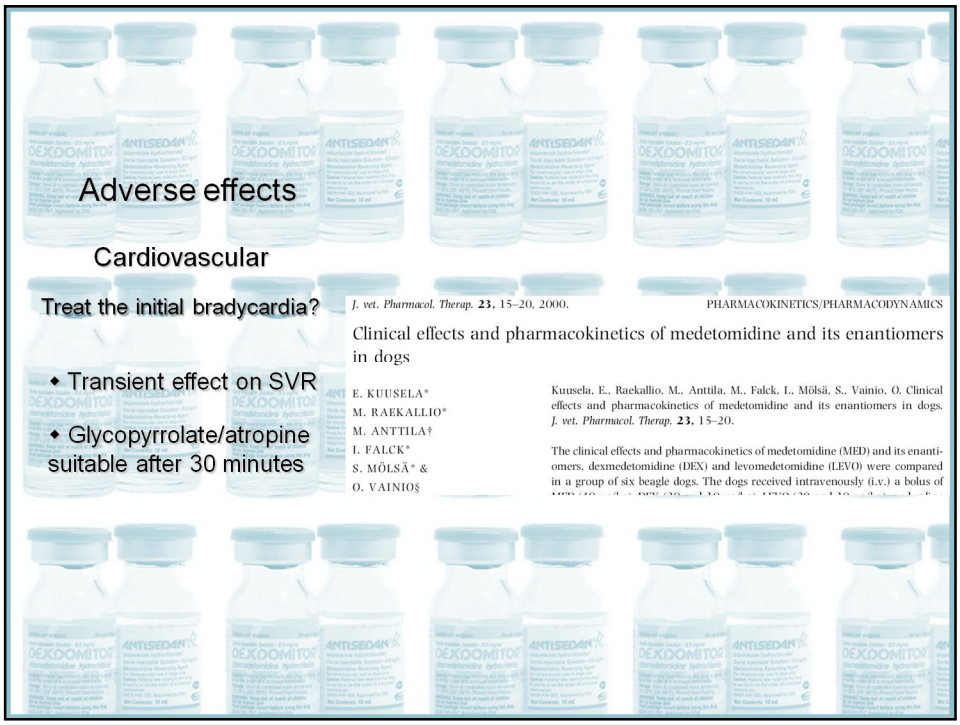


The initial bradycardia following injection is caused by a vagomimetic baroreceptor reflex in response to the vasoconstriction. Later bradycardia is due to a direct orthosympatholytic effect and is not associated with an increase in afterload or vascular resistance.

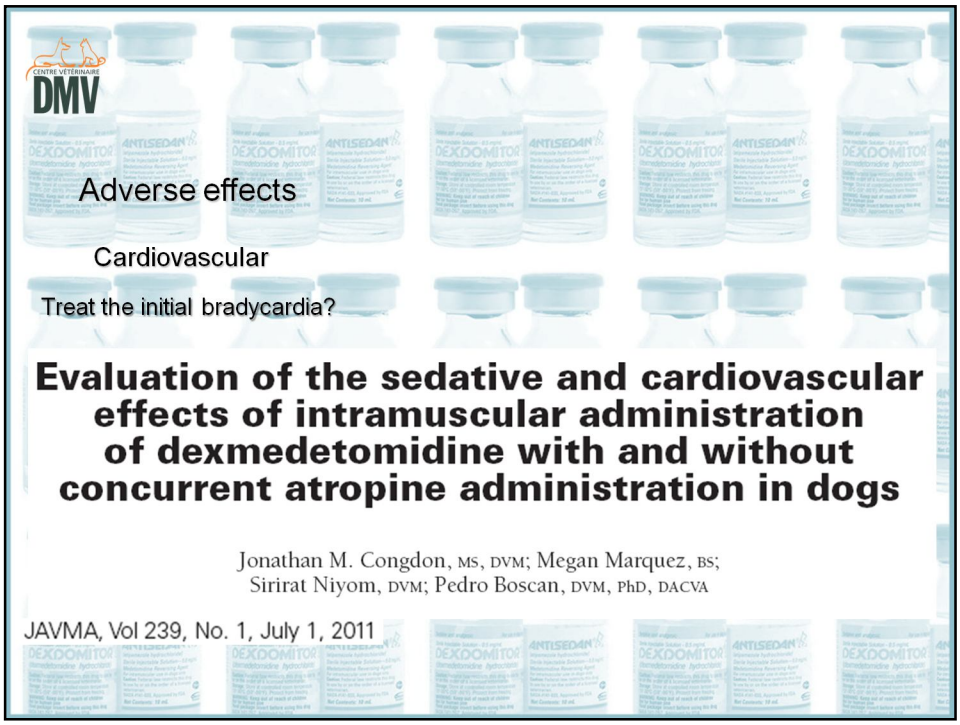
Study of medetomidine in dogs (Vet Ther 2010): loading dose 0.2/0.5/1/1.7/4/12 µg/kg i.v. over 10 minutes, followed by an infusion at 0.2/0.5/1/1.7/4/12 µg/kg/h. Significant effects on systemic vascular resistance and blood pressure only during the first 10-20 minutes with 0.2/0.5/1/1.7 µg/kg/h and up to 70 minutes with 4 µg/kg/h ⇨ glycopyrrolate or atropine is generally suitable after this period for the commonly used doses of medetomidine. It is substantially the same thing for dexmedetomidine.

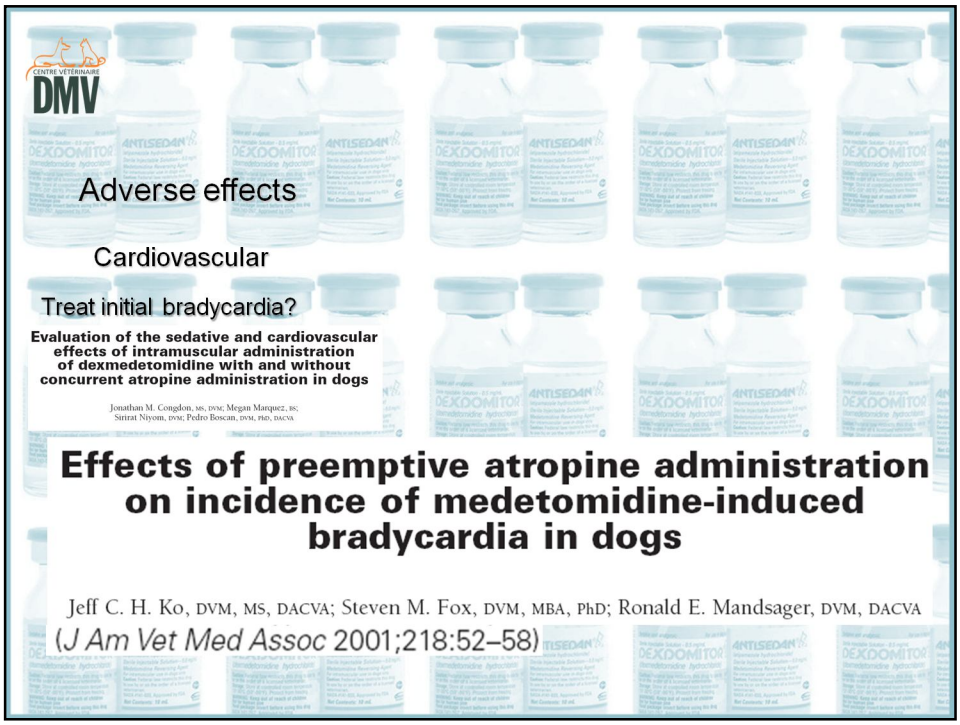
By the time the animal is under general anesthesia (if the delay to maximal effect of dexmedetomidine has been respected), the initial vasopressor effect of dexmedetomidine should have decreased sufficiently so that the treatment of bradycardia is no longer a problem.

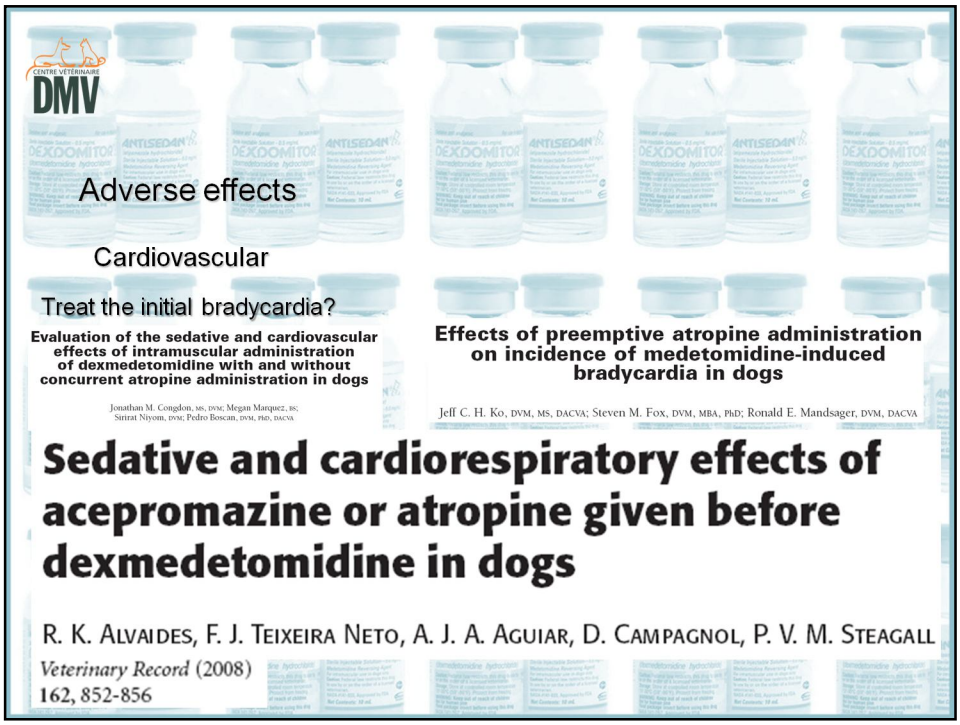
The initial hypertension seems to be less pronounced in cats, despite an increase in systemic vascular resistance (AJVR 2001, 62(11), 1745-1749).

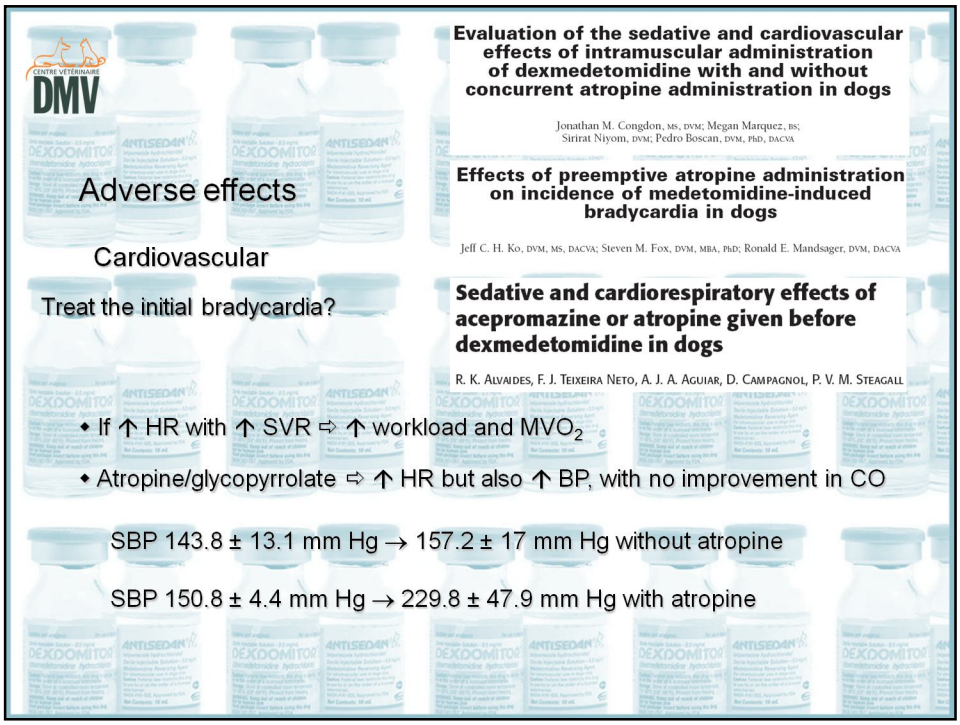


Study in J Vet Pharmacol Therap 2000: after dexmedetomidine 10 and 20 µg/kg i.v or medetomidine 40 µg/kg i.v, BP returned to normal values in 15-30 minutes ⇨ suggests that a delay of 30 minutes or more before administering atropine / glycopyrrolate is adequate after similar doses of dex/medetomidine by the i.m route.


Adverse effects
Cardiovascular
Treat the initial bradycardia?
Evaluation of the sedative and cardiovascular effects of intramuscular administration of dexmedetomidine with and without concurrent atropine administration in dogs
Jonathan M. Congdon, MS, DVM; Megan Marquez, BS;
Sirirat Niyom, DVM; Pedro Boscan, DVM, PhD, DACVA
JAVMA, Vol 239, No. 1, July 1, 2011


Adverse effects
Cardiovascular
Treat initial bradycardia?
Evaluation of the sedative and cardiovascular effects of intramuscular administration of dexmedetomidine with and without concurrent atropine administration in dogs
Jonathan M. Congdon, MS, DVM; Megan Marquez, BS; Sirirat Niyom, DVM; Pedro Boscan, DVM, PhD, DACVA
Effects of preemptive atropine administration on incidence of medetomidine-induced bradycardia in dogs
Jeff C. H. Ko, DVM, MS, DACVA; Steven M. Fox, DVM, MBA, PhD; Ronald E. Mandsager, DVM, DACVA
(J Am Vet Med Assoc 2001;218:52–58)

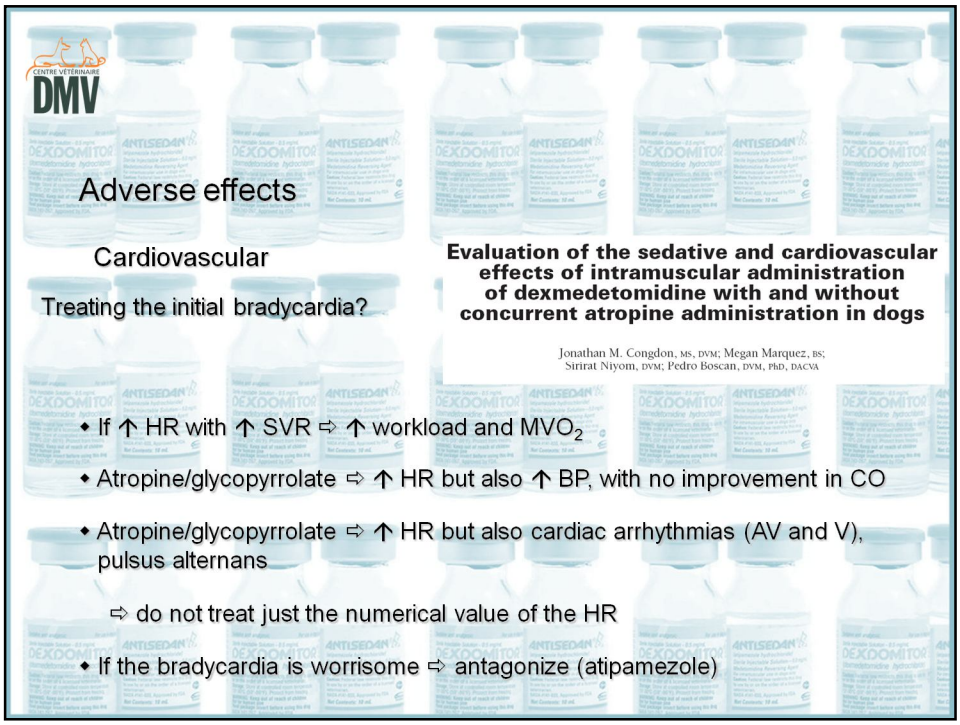

DMV
Adverse effects
Cardiovascular
Treat the initial bradycardia?
Evaluation of the sedative and cardiovascular effects of intramuscular administration of dexmedetomidine with and without concurrent atropine administration in dogs
Jonathan M. Congdon, MS, DVM; Megan Marquez, BS; Sirirat Niyom, DVM; Pedro Boscan, DVM, PhD, DACVA
Effects of preemptive atropine administration on incidence of medetomidine-induced bradycardia in dogs
Jeff C. H. Ko, DVM, MS, DACVA; Steven M. Fox, DVM, MBA, PhD; Ronald E. Mandsager, DVM, DACVA
Sedative and cardiorespiratory effects of acepromazine or atropine given before dexmedetomidine in dogs
R. K. Alvaides, F. J. Teixeira Neto, A. J. A. Aguiar, D. Campagnol, P. V. M. Steagall
Veterinary Record (2008)
162, 852-856



If HR ↑ in the presence of high systemic vascular resistance (and, therefore, in the presence of a high afterload) ⇨ ↑ workload and MVO_2. It is usually not a problem if the heart is in good health, but it can cause failure.

If atropine or glycopyrrolate ↑ HR during the initial phase of vasoconstriction, it is at the expense of a further ↑ BP, with no improvement in cardiac output.

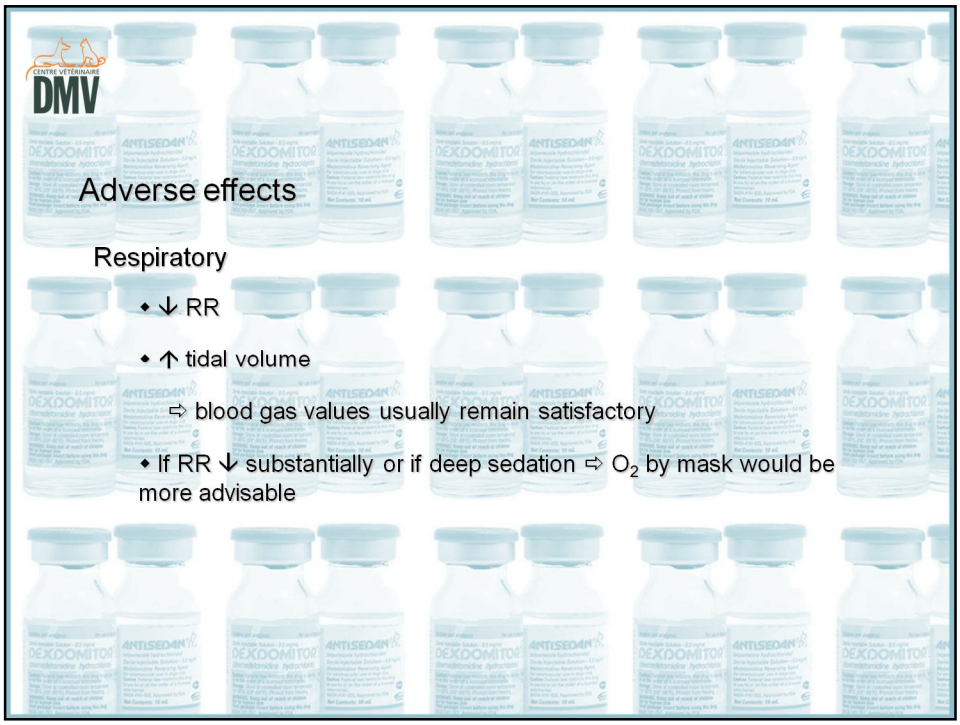
Study published in JAVMA 2011 (Congdon et al.): SBP 143.8 ± 13.1 mm Hg → 157.2 ± 17 mm Hg without atropine and 150.8 ± 4.4 mm Hg → 229.8 ± 47.9 mm Hg with atropine.



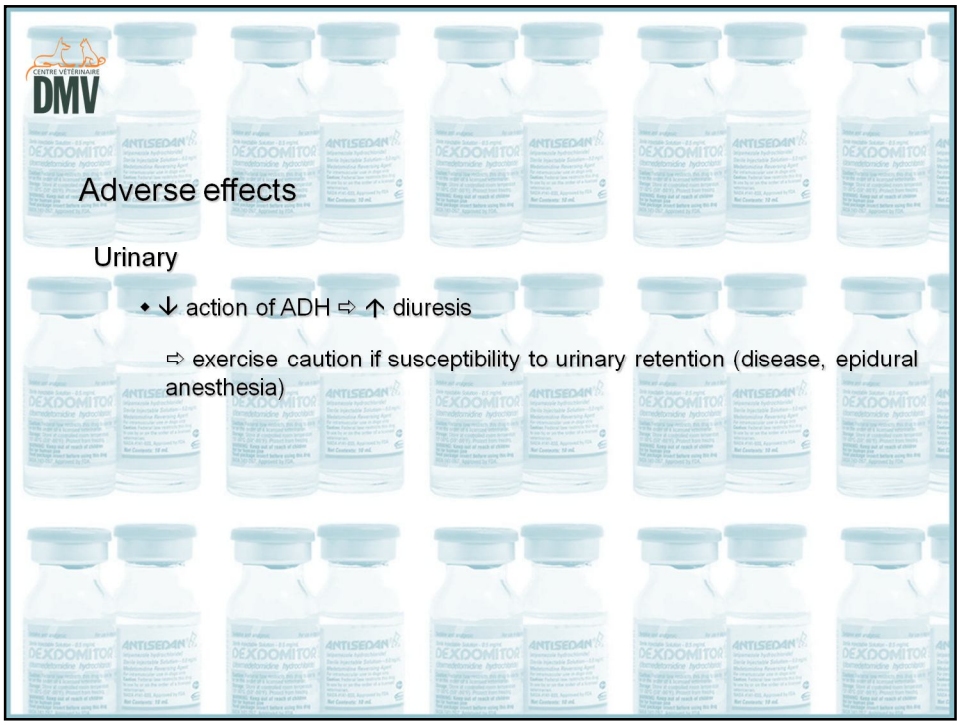
Atropine or glycopyrrolate ⇨ ↑ HR during the initial phase of vasoconstriction, but at the risk of cardiac arrhythmias developing, particularly ventricular arrhythmias, and pulsus alternans (suggesting a left ventricular systolic dysfunction), all this with no improvement in cardiac output.

If the initial bradycardia (associated with vasoconstriction) is very worrisome (not just because of its numerical value, but also in light of the other clinical signs), many recommend antagonizing (atipamezole) rather than administering a positive chronotropic drug (e.g., atropine or glycopyrrolate).

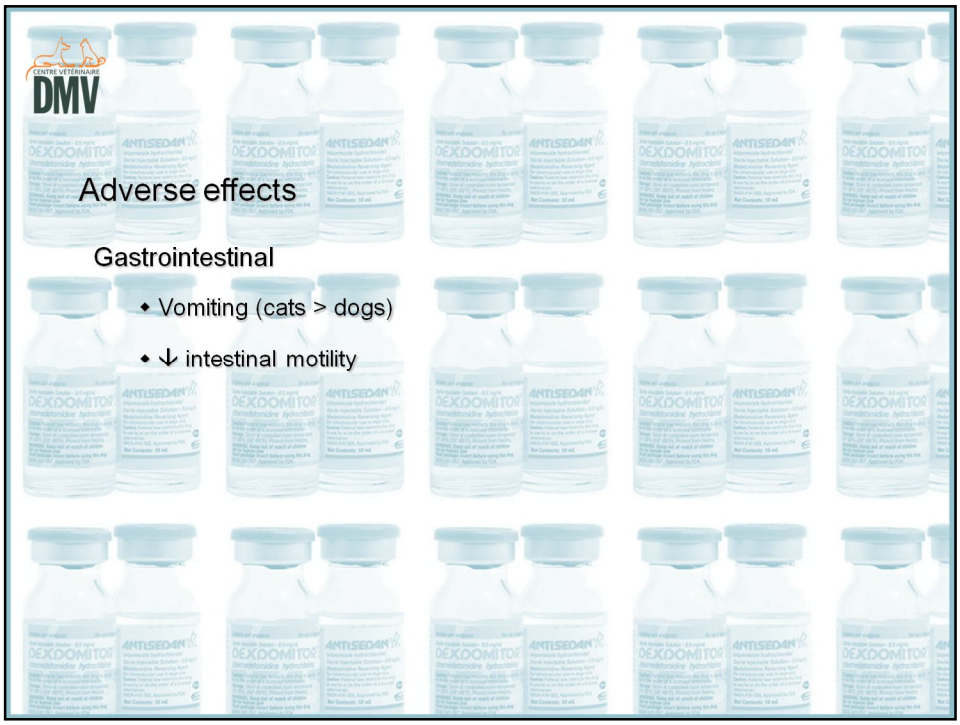
Exercise caution when antagonizing, as the desired effects (e.g., analgesia and sedation) will be antagonized as well, partially or completely.


Adverse effects
Respiratory
• ↓ RR
• ↑ tidal volume
⇨ blood gas values usually remain satisfactory
• If RR ↓ substantially or if deep sedation ⇨ O_2 by mask would be more advisable


Adverse effects
Homeothermia
↓ body temperature


DMV
Adverse effects
Urinary
↓ action of ADH ⇨ ↑ diuresis
⇨ exercise caution if susceptibility to urinary retention (disease, epidural anesthesia)

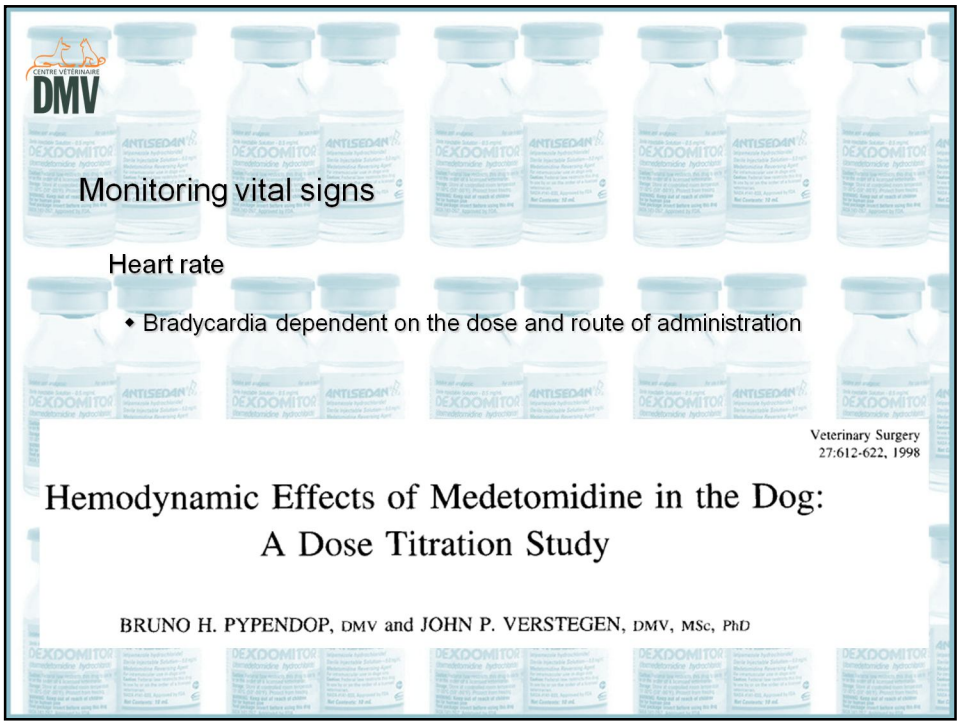
Blockage of insulin secretion is theoretically a problem only in the presence of diabetes: clinical significance unclear.



Incidence of vomiting in cats > 50% with medetomidine at 80 µg/kg i.m and dexmedetomidine at 40 µg/kg i.m.

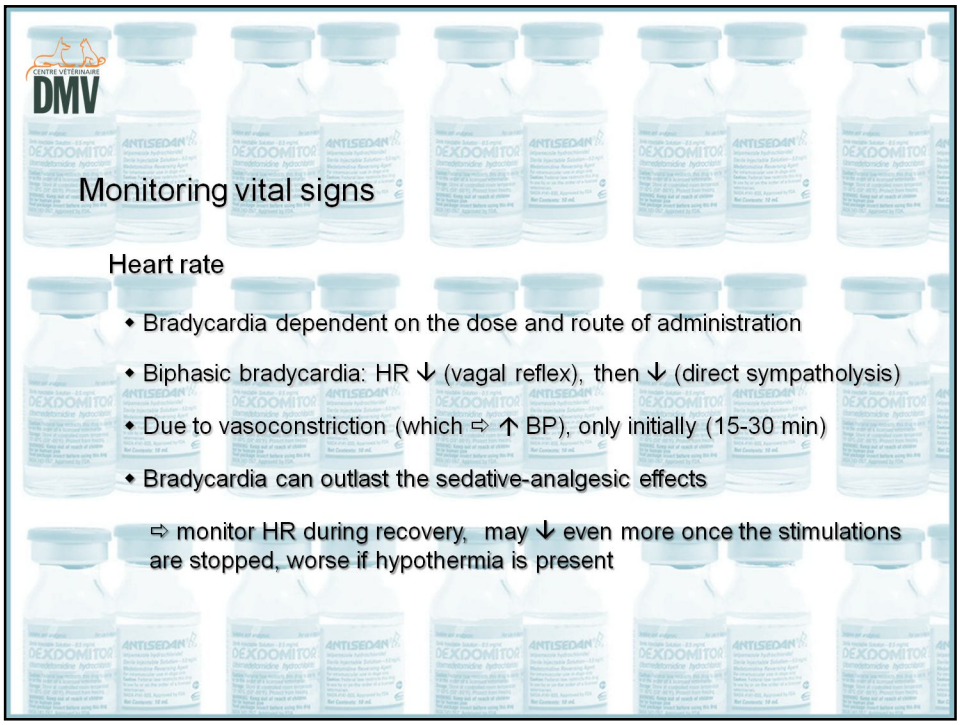
Incidence of vomiting in dogs ~ 10% with medetomidine at 40 µg/kg i.m.

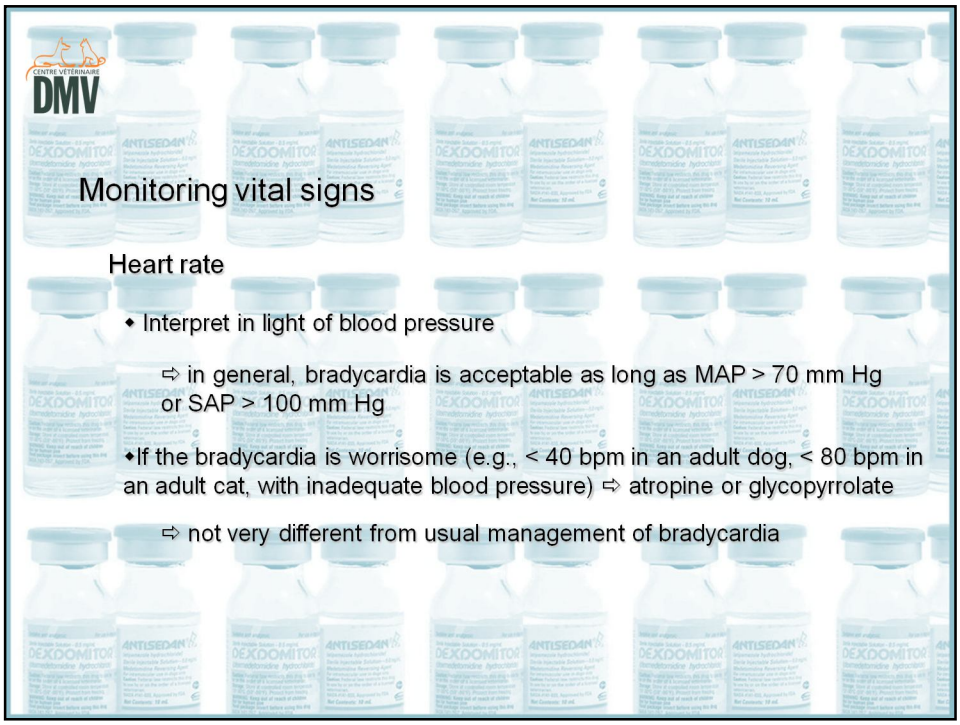
↓ gastro-intestinal motility: less of a problem in the dog/cat than in large species (horse, cattle).



Bradycardia is dose dependant but after a certain dose, the intensity of effects does not increase anymore but the duration of action instead.

Study in Vet Surg 1998 (Pypendop et al.): medetomidine i.v at 1/2/5/10/20 µg/kg (equivalent to dexmedetomidine i.v at 0.5/1/2.5/5/10 µg/kg) ⇨ hemodynamic effects almost maximal at 5 µg/kg medetomidine (equivalent to 2.5 µg/kg dexmedetomidine), and ↑ dose doesn't cause significantly more hemodynamic effects but prolong the duration of action instead.

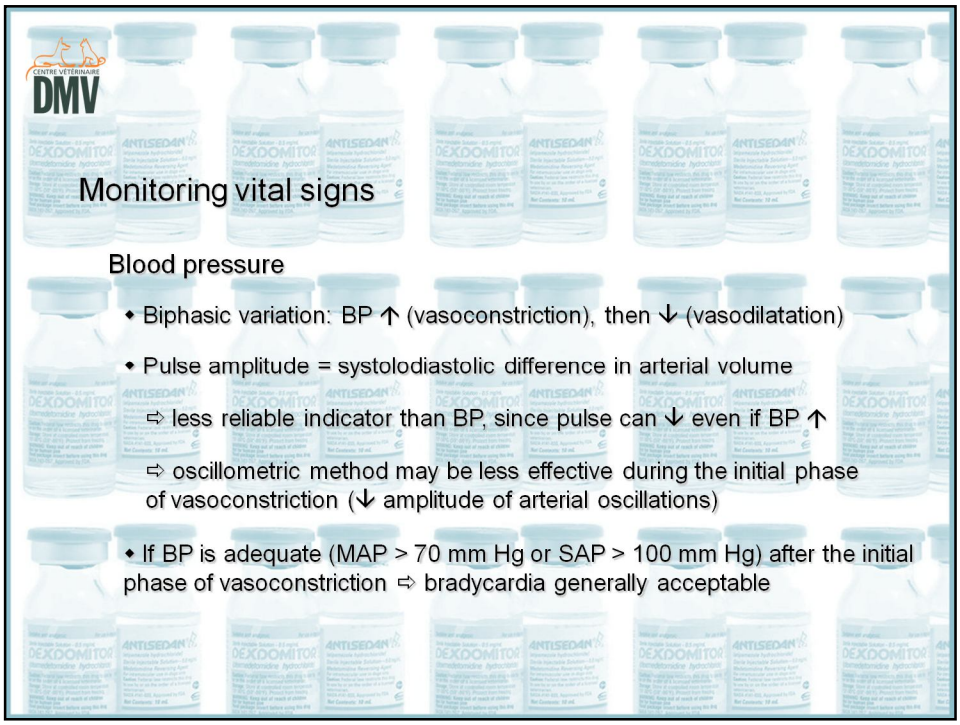

Monitoring vital signs
Heart rate
• Bradycardia dependent on the dose and route of administration
• Biphasic bradycardia: HR ↓ (vagal reflex), then ↓ (direct sympatholysis)
• Due to vasoconstriction (which ⇨ ↑ BP), only initially (15-30 min)
• Bradycardia can outlast the sedative-analgesic effects
⇨ monitor HR during recovery, may ↓ even more once the stimulations are stopped, worse if hypothermia is present



Criteria for defining bradycardia:

• Not merely an absolute value. Depends on the species (cat vs dog), the breed (large vs small breeds of dogs, brachycephalic breeds with a higher vagal tone) and age: 40 bpm in an adult dog and 80 bpm in an adult cat if the associated BP is inadequate (MAP < 70 mm Hg or SAP < 100 mm Hg).

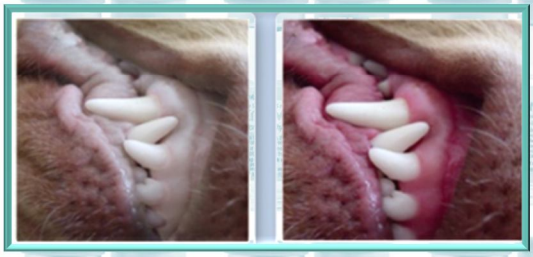
• Take into account the % ↓ from the baseline HR, bearing in mind that this baseline value can itself be ↑ because of stress/nervousness/pain.



The initial hypertension appears to be less pronounced in cats, despite an increase in systemic vascular resistance (AJVR 2001, 62(11), 1745-1749).

Monitoring vital signs

Colour of the oral mucosa



- Initial vasoconstriction ⇨ oral mucosa pale and cold, ↑ CRT
- Later vasodilatation ⇨ oral mucosa pink and warm, ↓ CRT

Monitoring vital signs

Colour of the oral mucosa

Effects of preemptive atropine administration on incidence of medetomidine-induced bradycardia in dogs

Jeff C. H. Ko, DVM, MS, DACVA; Steven M. Fox, DVM, MBA, PhD; Ronald E. Mandsager, DVM, DACVA

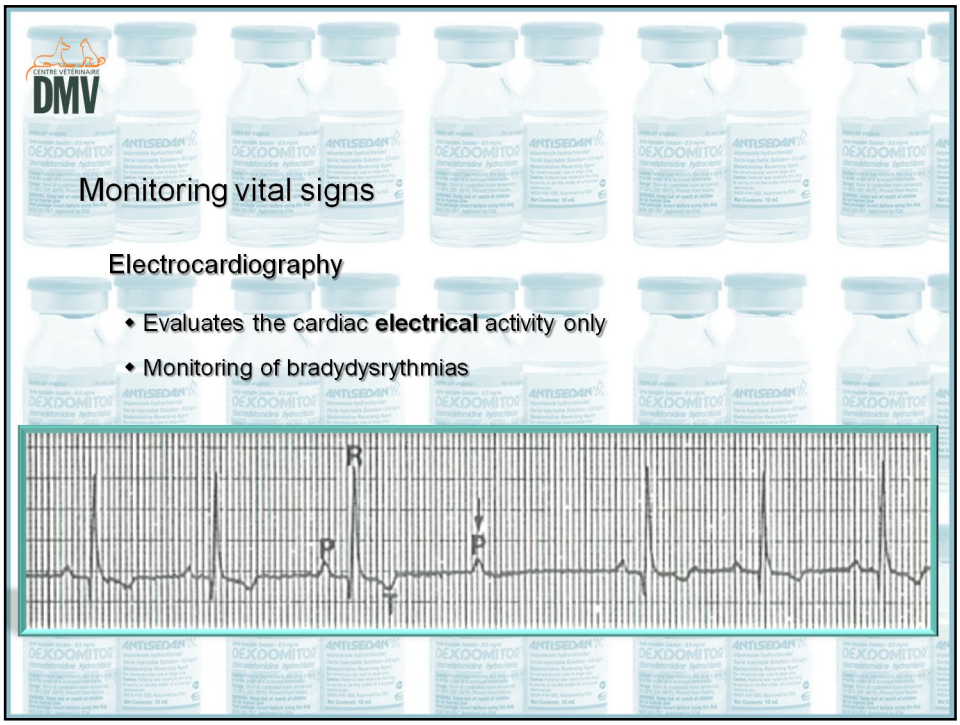
(*J Am Vet Med Assoc* 2001;218:52–58)

- Initial vasoconstriction ⇨ oral mucosa pale and cold, ↑ CRT
- Later vasodilatation ⇨ oral mucosa pink and warm, ↓ CRT
- ↓ HR and slowing of blood flow locally ⇨ ↑ O_2 extraction
  ⇨ tongue cyanosis in some cases, despite satisfactory blood gas values

Monitoring vital signs

Pulse oximetry

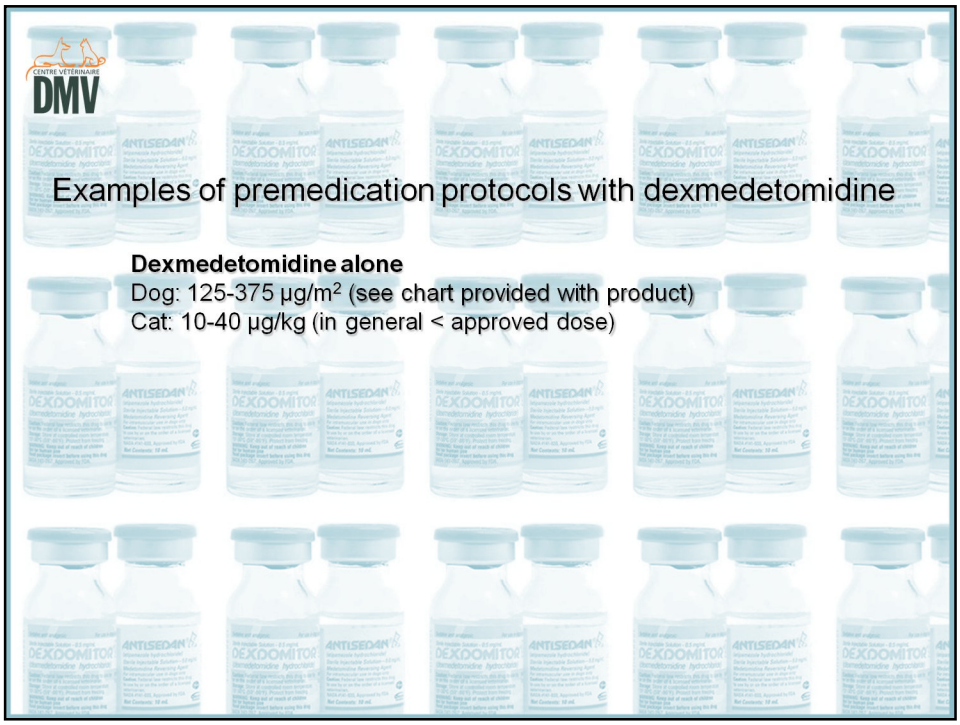
- Requires the detection of a sufficiently strong pulse
- Pulse signal ↓ during the initial phase of vasoconstriction
  - ⇨ S_pO_2 possibly less reliable during this transient phase



ECG allows the monitoring of cardiac rhythm (electrical activity only, no indication of mechanical activity):

- sinus bradycardia;

- other bradydysrythmias: 1st and 2nd degree atrioventricular blocks (rarely 3rd degree and sinus arrest).

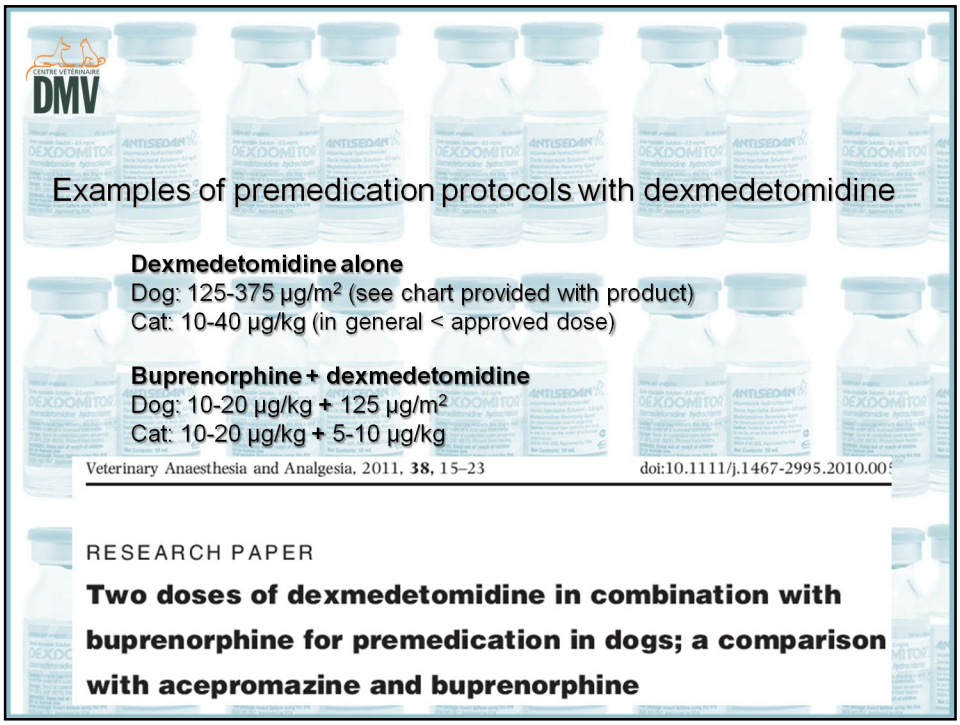


These are merely suggestions for premedication protocols with dexmedetomidine. They are provided as information only.

Use lower doses i.v. or when combined with other analgesic/sedative drugs.

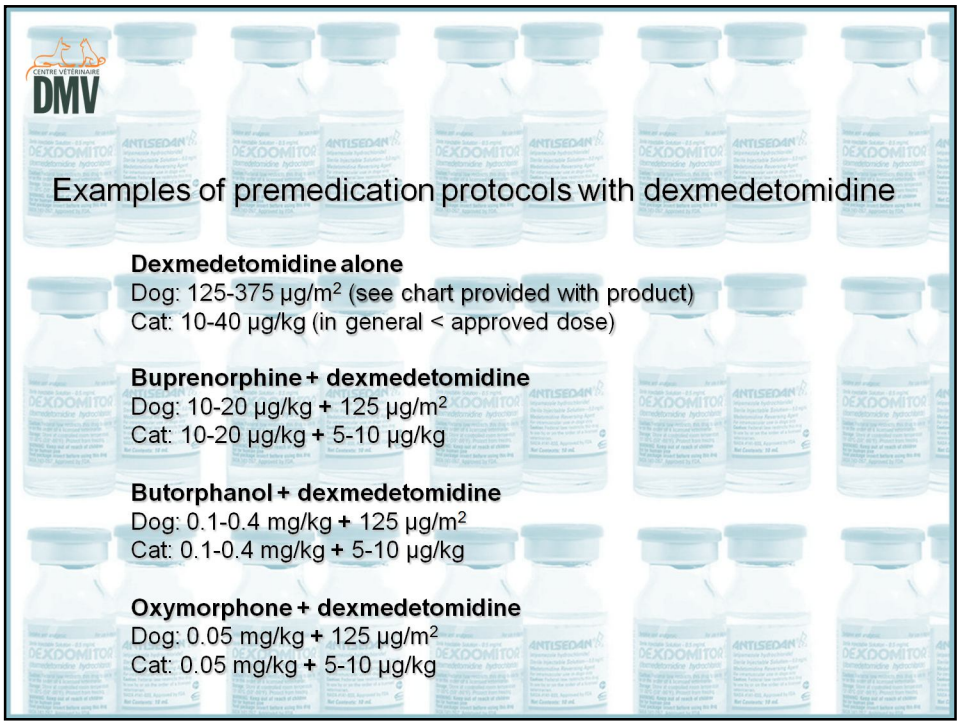
Use higher doses i.m. or for particularly stressed or aggressive patients or for more painful procedures.

In general, the dose of dexmedetomidine, even alone, in cats < approved premedication dose.



Buprenorphine-dexmedetomidine combination:

Given the long delay of buprenorphine to reach its maximal action (up to 60 minutes après i.m injection), it is advised to administer buprenorphine 20-30 minutes before dexmedetomidine (whose delay to peak of action can reach 30 minutes after i.m injection), instead of simultaneously.

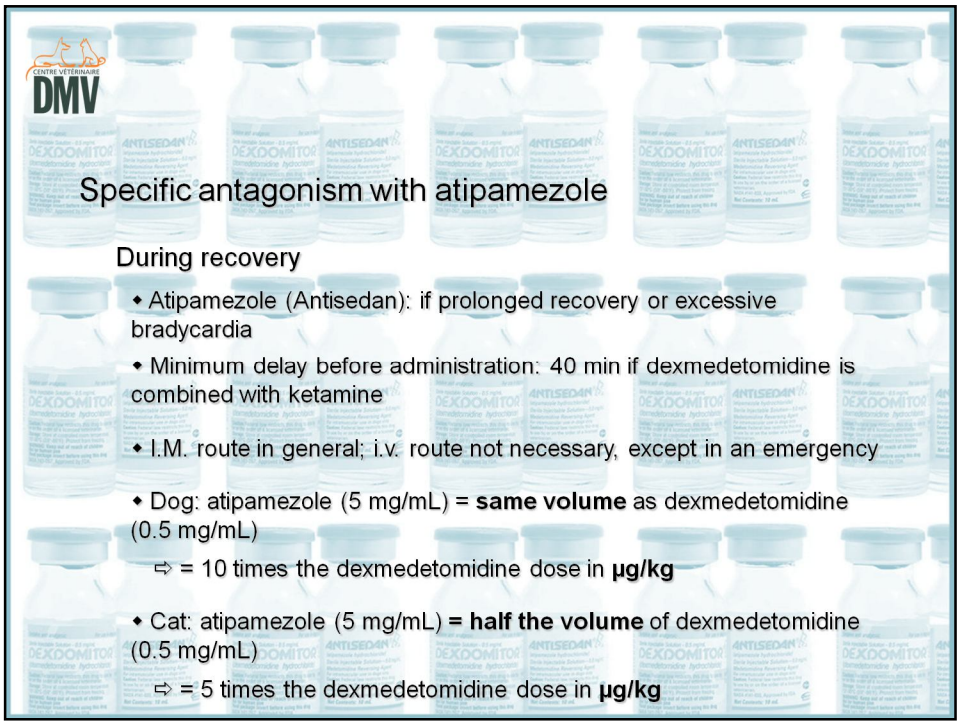

DMV
Examples of premedication protocols with dexmedetomidine
Dexmedetomidine alone
Dog: 125-375 µg/m² (see chart provided with product)
Cat: 10-40 µg/kg (in general < approved dose)
Buprenorphine + dexmedetomidine
Dog: 10-20 µg/kg + 125 µg/m²
Cat: 10-20 µg/kg + 5-10 µg/kg
Butorphanol + dexmedetomidine
Dog: 0.1-0.4 mg/kg + 125 µg/m²
Cat: 0.1-0.4 mg/kg + 5-10 µg/kg
Oxymorphone + dexmedetomidine
Dog: 0.05 mg/kg + 125 µg/m²
Cat: 0.05 mg/kg + 5-10 µg/kg

Examples of premedication protocols with dexmedetomidine

Methadone + dexmedetomidine
Dog: 0.5 mg/kg + 125 µg/m²
Cat: 0.25 mg/kg + 5-10 µg/kg

Butorphanol + dexmedetomidine + ketamine ("kitty/doggy magic")
Dog: 0.1-0.4 mg/kg + 125 µg/m² + 2 mg/kg
Cat: 0.1-0.4 mg/kg + 5-10 µg/kg + 2 mg/kg

Buprenorphine + dexmedetomidine + ketamine ("kitty/doggy magic")
Dog: 10-20 µg/kg + 125 µg/m² + 2 mg/kg
Cat: 10-20 µg/kg + 5-10 µg/kg + 2 mg/kg



The time to complete recovery after the administration of dexmedetomidine in a normal animal can be as long as 3 hours if it is not antagonized. This is more than the average length of many procedures ⇨ antagonism may be necessary in cases of prolonged recovery.

There is no minimum waiting time for antagonizing dexmedetomidine, unless it was administered in combination with a dissociative anesthetic agent. For example, dexmedetomidine-ketamine ⇨ ideally, do not antagonize for at least 40 min, this to prevent the development of the psychomimetic and catatonic effects of ketamine, which remains alone at the time of recovery.

Usually, atipamezole is administered intramuscularly; no need to administer it intravenously.

An overdose of atipamezole can cause hyperexcitability and tachycardia.


DMV
Specific antagonism with atipamezole
During recovery
Time to complete recovery = 5-15 min
Evaluation of the clinical efficacy and safety of intramuscular and intravenous doses of dexmedetomidine and medetomidine in dogs and their reversal with atipamezole
M. Granholm, B. C. McKusick, F. C. Westerholm, J. C. Aspegrén
Veterinary Record (2007)
160, 891-897

Specific antagonism with atipamezole

During recovery

- Time to complete recovery = 5-15 min

Evaluation of the clinical efficacy and safety of intramuscular and intravenous doses of dexmedetomidine and medetomidine in dogs and their reversal with atipamezole

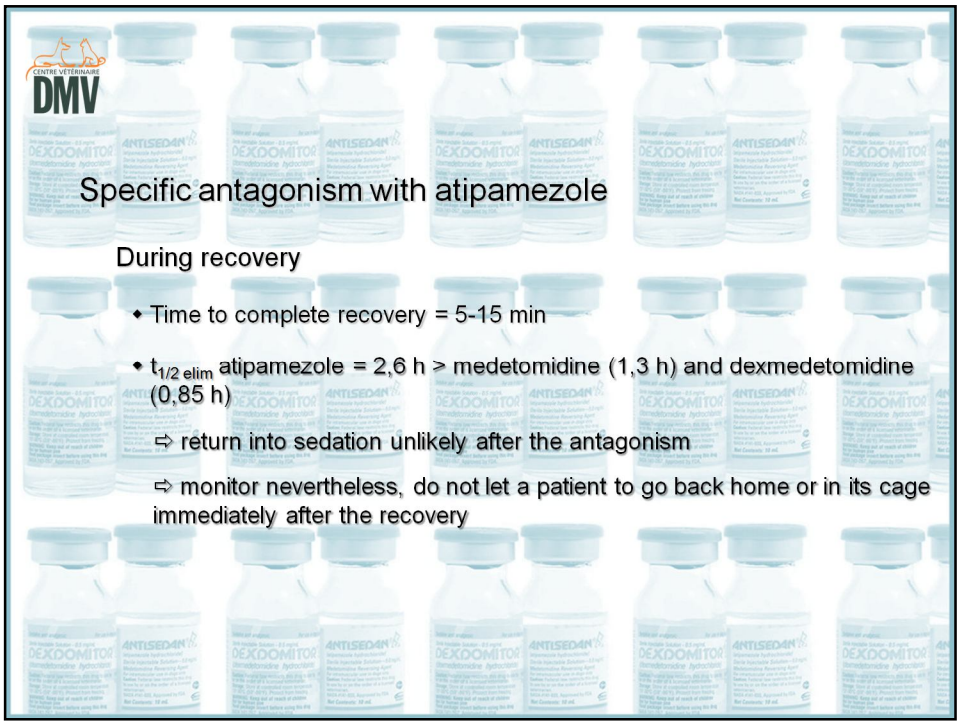
M. Granholm, B. C. McKusick, F. C. Westerholm, J. C. Aspegrén

Veterinary Anaesthesia and Analgesia, 2006, **33**, 214–223 doi:10.1111/j.1467-2995.2005.0025

RESEARCH PAPER

Evaluation of the clinical efficacy and safety of dexmedetomidine or medetomidine in cats and their reversal with atipamezole

Mikael Granholm* DVM, Brett C McKusick* MS, PhD, DVM, Fia C Westerholm* DVM & John C Aspegrén† MSc

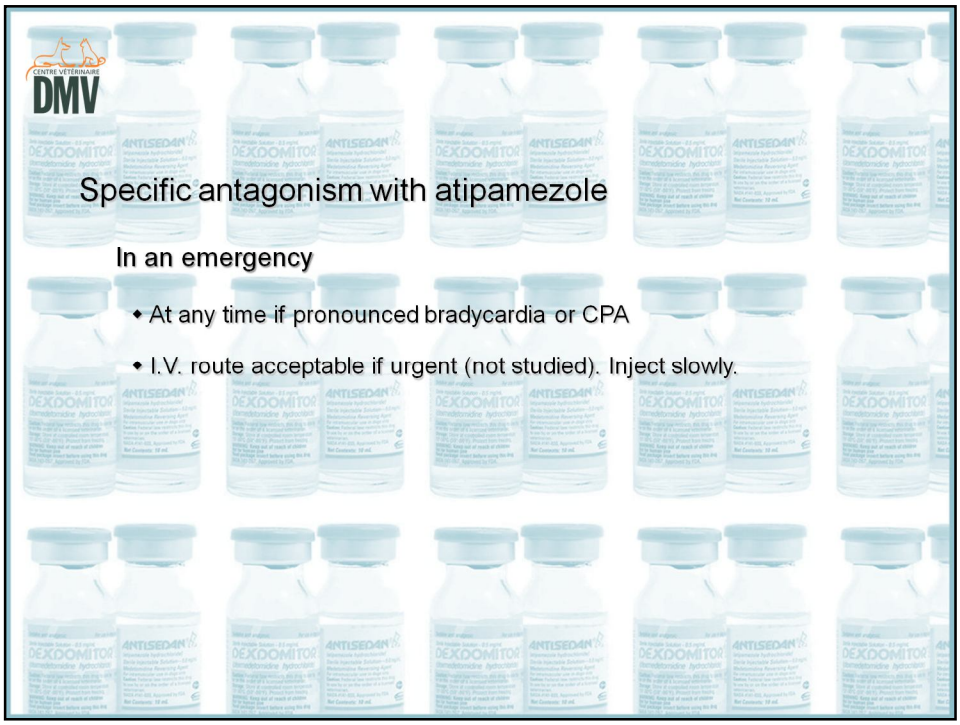


Even though the antagonism can occur quickly in certain patients, one should not conclude that it is ineffective until after several minutes.

The time to complete recovery after antagonism by atipamezole = 5 to 15 min ⇨ be patient.

The elimination half-life of atipamezole = 2,6 h ⇨ longer than for medetomidine (1,3 h) and dexmedetomidine (0,85 h)

⇨ return into sedation unlikely after the antagonism, nevertheless it is advised to monitor the patient during several minutes before letting him go back home or to its cage.



In case of an emergency (e.g., pronounced bradycardia or cardiopulmonary arrest), it is acceptable to administer atipamezole intravenously (although such off-label use has not been studied).

In case of an emergency, antagonism is warranted, even if the minimal waiting period of 40 minutes has not passed since the dexmedetomidine-ketamine combination was administered.

Quantity of atipamezole: same volume as for dexmedetomidine for the dog, half the volume for the cat, but also 5-20 µg/kg i.v. over several minutes (Compendium Continuing Education for Veterinarians 31 (1A), Jan 2009).

References

Alvaides RK, Teixeira Neto FJ, Aguiar AJA et al. Sedative and cardiorespiratory effects of acepromazine or atropine given before dexmedetomidine in dogs. *Vet Rec* 2008, 162, 852-856

Bell AM, Auckburally A, Pawson P et al. Two doses of dexmedetomidine in combination with buprenorphine for premedication in dogs: a comparison with acepromazine and buprenorphine. *Vet Anaesth Analg* 2011, 38, 15-23

Biermann K, Hungerbühler S, Mischke R et al. Sedative, cardiovascular, haematologic and biochemical effects of four different drug combinations administered intramuscularly in cats. *Vet Anaesth Analg* 2012, 39, 137-150

Congdon JM, Marquez M, Niyom S et al. Evaluation of the sedative and cardiovascular effects of intramuscular administration of dexmedetomidine with and without concurrent atropine administration in dogs. *J Am Vet Med Assoc* 2011, 239(1), 81-89

References

Escobar A, Pypendop BH, Siao KT et al. Effect of dexmedetomidine on the minimum alveolar concentration of isoflurane in cats. *J Vet Pharmacol Therap* 2011, 35, 163-168

Gómez-Villamandos RJ, Palacios C, Benítez A. Dexmedetomidine or medetomidine premedication before propofol-desflurane anaesthesia in dogs. *J Vet Pharmacol Therap* 2006, 29, 157-163

Granholm M, McKusick BC, Westerholm FC et al. Evaluation of the clinical efficacy and safety of dexmedetomidine or medetomidine in cats and their reversal with atipamezole. *Vet Anaesth Analg* 2006, 33, 214-223

Granholm M, McKusick BC, Westerholm FC et al. Evaluation of the clinical efficacy and safety of intramuscular and intravenous doses of dexmedetomidine and medetomidine in dogs and their reversal with atipamezole. *Vet Rec* 2007, 160, 891-897

References

Kaartinen JM, Pang DSJ, Moreau M et al. Hemodynamic effects of an intravenous infusion of medetomidine at six different dose regimens in isoflurane-anesthetized dogs. *Vet Ther* 2010, 11(1), E11-E16

Ko JCH, Fox SM, Mandsager RE. Effects of preemptive atropine administration on incidence of medetomidine-induced bradycardia in dogs. *J Am Vet Med Assoc* 2001, 218, 52-58

Ko JCH, Raffe MR, Knesl O et al. Making the switch from medetomidine to dexmedetomidine. *Comp Cont Educ Vet* 2009, 31(1A)

Kuusela E, Raekallio M, Anttila M et al. Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. *J Vet Pharmacol Therap* 2000, 23, 15-20

References

Kuusela E, Raekallio M, Väisänen M et al. Comparison of medetomidine and dexmedetomidine as premedicants in dogs undergoing propofol-isoflurane anesthesia. *Am J Vet Res* 2001, 62(7), 1073-1080

Lamont LA, Bulmer BJ, Grimm KA et al. Cardiopulmonary evaluation of the use of medetomidine hydrochloride in cats. *Am J Vet Res* 2001, 62(11), 1745-1749

Lamont LA, Bulmer BJ, Sisson DD et al. Doppler echocardiographic effects of medetomidine on dynamic left ventricular outflow tract obstruction in cats. *J Am Vet Med Assoc* 2002, 221(9), 1276-1281

Lerche P, Muir WW. Effect of medetomidine on respiration and minimum alveolar concentration in halothane- and isoflurane-anesthetized dogs. *Am J Vet Res* 2006, 67, 782-789

References

McSweeney PM, Martin DD, Ramsey DS et al. Clinical efficacy and safety of dexmedetomidine used as a preanesthetic prior to general anesthesia in cats. *J Am Vet Med Assoc* 2012, 240, 404-412

Murrell JC, Hellebrekers, LJ. Medetomidine and dexmedetomidine : a review of cardiovascular effects and antinociceptive properties in the dog. *Vet Anaesth Analg* 2005, 32, 117-127

Pypendop BH, Verstegen JP. Hemodynamic effects of medetomidine in the dog: a dose titration study. *Vet Surg* 1998, 27, 612-622

Riker RR, Shehabi Y, Bokesch PM. Dexmedetomidine vs midazolam for sedation of critically ill patients - A randomized trial. *J Am Medic Assoc* 2009, 301(5), 489-499

References

Selmi AL, Mendes GM, Lins BT et al. Evaluation of the sedative and cardiorespiratory effects of dexmedetomidine, dexmedetomidine-butorphanol, and dexmedetomidine-ketamine in cats. *J Am Vet Med Assoc* 2003, 222(1), 37-41


DMV
Acknowledgement
Translation department of Pfizer Animal Health
Pfizer
Animal Health