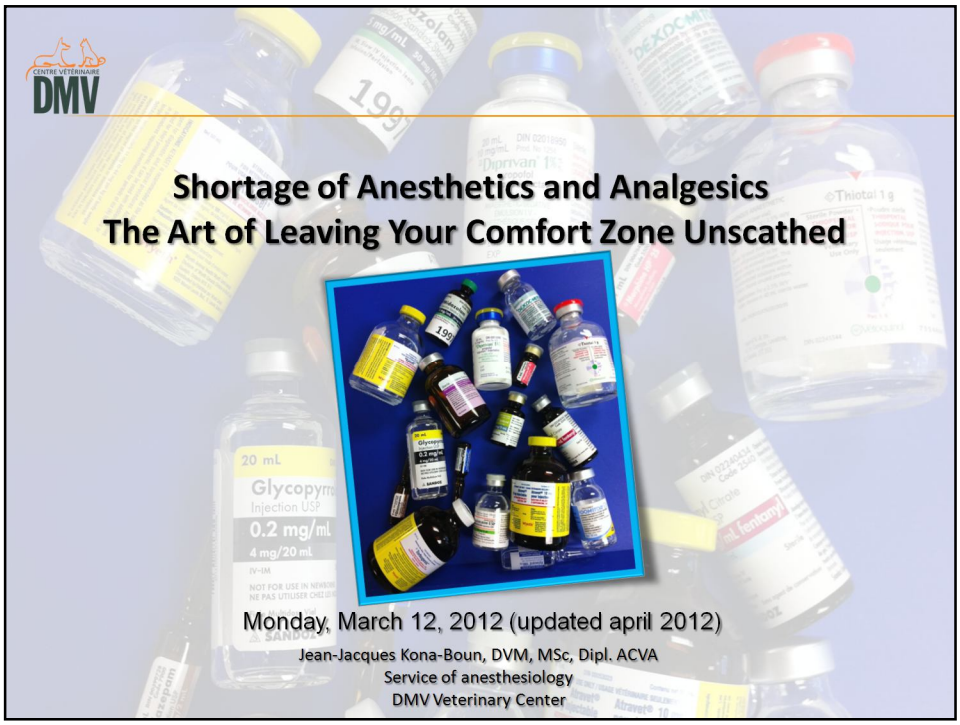


The drug shortage that has been affecting the veterinary and human medical communities in past little while is a serious one, and it extends beyond Canada's borders. Just the same, it is far from inescapable.

As in any other crisis situation, this is forcing us to develop our ability to adapt and to move out of our comfort zone.

Although people generally stay within a limited number of protocols that they are comfortable with, there is not just one way to do things; there is not just one truth.

This time of shortage affords a good opportunity to confirm the adage that there are no safe anesthetic drugs or safe anesthetic procedures, but only safe anesthesiologists. In other words, there are a number of suitable anesthesia and analgesia protocols for achieving the same objectives, and the main thing that makes them safe is how – properly or improperly – we use them.

Before discussing the drugs affected by the shortage and their alternatives, we should briefly review the most common pharmacologic classes available for the different steps before, during and after anesthesia.

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.

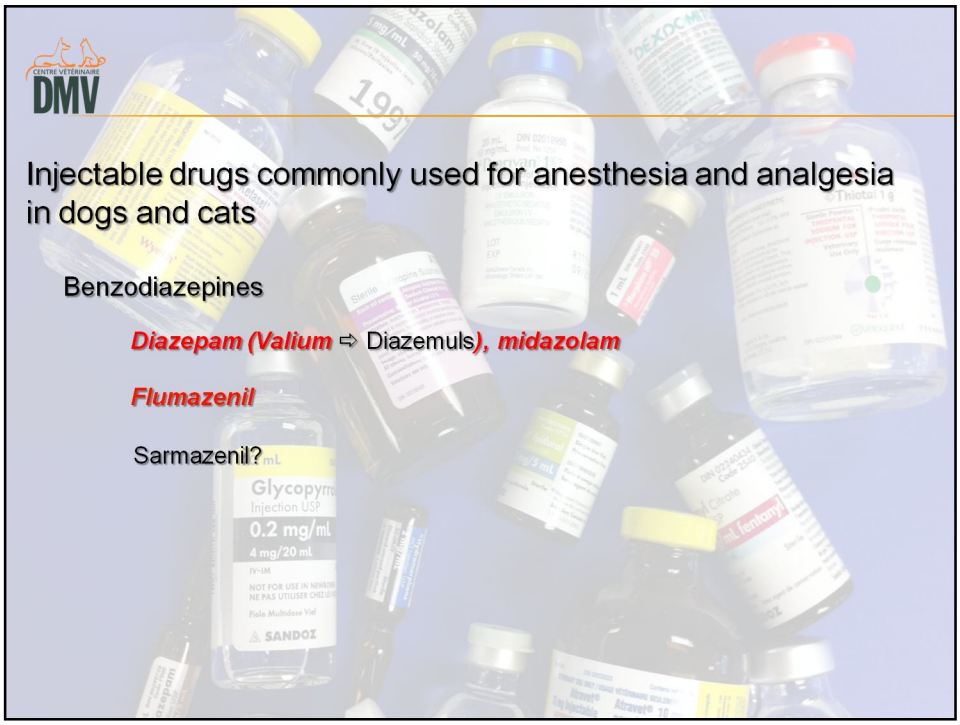
However, even with the possibility of a more or less quiet return of some of these drugs for which there is currently a problem, a discussion of the alternatives to their use is relevant, if only to open our minds to the diversity of anesthesia and analgesia protocols, and because there is presently nothing by which we can determine how sustainable this possible return to the market will be.

There is an alternative to Valium, and some have already purchased it: Diazemuls, which is diazepam in a lipid emulsion instead of as a suspension in propylene glycol. The emulsifying lipid is Intralipid, the same substance used for propofol and parenteral nutrition.

However, it would appear that Diazemuls was recently reserved for the human sector.

Climazolam: an injectable benzodiazepine approved in Europe for anesthesia in dogs and cats, for example, as premedication with an opioid or for induction with ketamine.

Climazolam is a possible alternative to midazolam, but its use will require a relaxing of the import regulations by Health Canada and of the minimum practice standards of the OMVQ (which encourages the use of approved drugs), since it is not approved in Canada.



The benzodiazepine antagonist commonly used in Canada is flumazenil, which is manufactured by Sandoz. However, there is an alternative supply source.

Sarmazenil is a benzodiazepine antagonist approved in Europe for dogs and cats. If there are no alternative supply sources for flumazenil, sarmazenil would be an alternative to it. However, its use would require a relaxing of the import regulations by Health Canada and of the minimum practice standards of the OMVQ (which encourages the use of approved drugs), since sarmazenil is not approved in Canada.

Possible alternative suppliers for morphine, hydromorphone and fentanyl: to be confirmed.

Alternatives could theoretically be found in two other opioids:

- One was commonly used in dogs and cats until recently in Canada: oxymorphone (see below).
- The other is still commonly used at this time in dogs and cats, but in other countries (mainly in Europe): methadone (see below).

The problem with these two opioids is twofold:

- The complexity of the import process: oxymorphone ⇨ Health Canada would have to relax the import regulations.
- Not approved in Canada for dogs and cats: methadone (but is nonetheless available in Canada, although it is used in humans) ⇨ the minimum practice standards would have to be relaxed by the OMVQ (which encourages the use of approved drugs).

The main opioid antagonist for dogs and cats, and for humans is naloxone, which is also affected by the shortage. However, an alternative supply source of naloxone (compounding) might be available.

Options:

• Partially antagonize with butorphanol, carefully dosing to effect by i.v. injection: acceptable if the condition is not critical. Preserves a certain level of analgesia.

• Fully antagonize with naltrexone: if the condition is critical and there is a need to eliminate any potential depressive effect (e.g., during CPR in a patient that has received one or more opioids).

Naltrexone is an antagonist of potent opioids used in wild animals (e.g., etorphine and carfentanil). Longer duration of action (about twice as long) than that of naloxone (30-60 minutes → 60-120 minutes) ⇨ smaller risk of renarcosis.

There is very little in the literature about naltrexone in dogs and cats, but one reported dose in cats is 0.3-0.6 mg/kg (Vet Anaesth Analg 2011, 38, 594-597). Nothing regarding dogs ⇨ Reserve for emergency antagonism during critical conditions and carefully dose to effect (?).

Medetomidine and dexmedetomidine play a very important role in perioperative and intraoperative anesthesia and analgesia.


Injectable drugs commonly used for anesthesia and analgesia in dogs and cats
α_2-adrenergic agonists
Medetomidine, dexmedetomidine
NSAIDs
Meloxicam, deracoxib, carprofen, ketoprofen, tolfenamic acid

Injectable drugs commonly used for anesthesia and analgesia in dogs and cats

Anticholinergics (antimuscarinics)

Atropine, ***glycopyrrolate***

Injectable drugs commonly used for anesthesia and analgesia in dogs and cats

Barbiturates

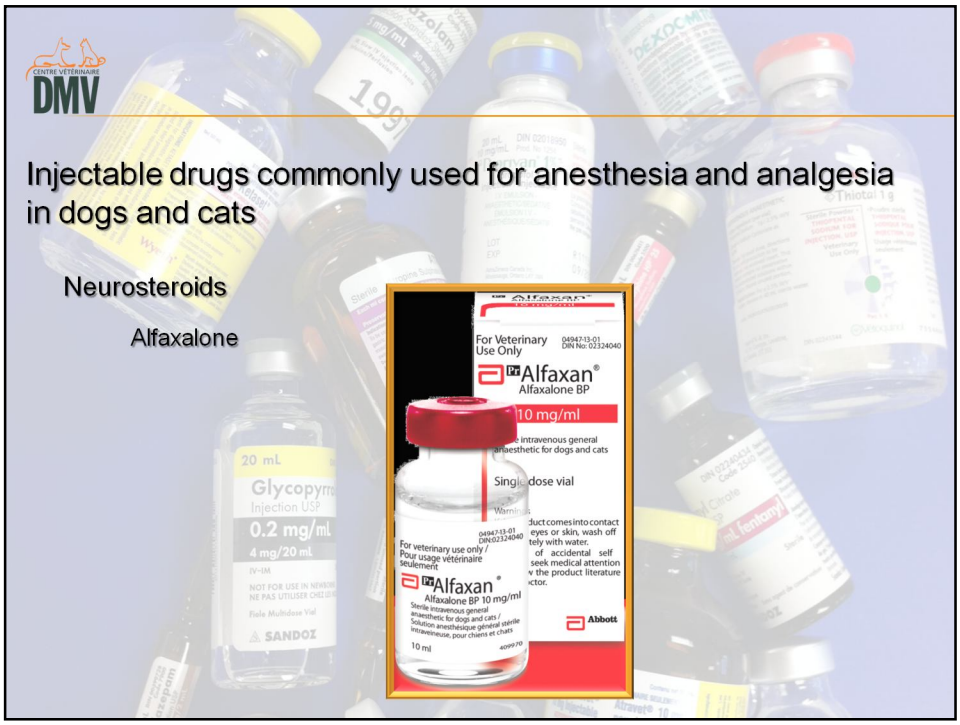
Thiopental

Propofol, in the same lipid emulsion as the currently available formulation of diazepam, Diazemuls.

Injectable drugs commonly used for anesthesia and analgesia in dogs and cats

Cyclohexamines (dissociative anesthetics)

Ketamine



Alfaxalone arrived in Canada barely a year ago.

Actually, it is not a new drug. It was used from the 1970s in combination with alfadolone (another neurosteroid) in what was called Saffan. However, the excipient, castor oil, sometimes caused potentially fatal anaphylactic reactions.

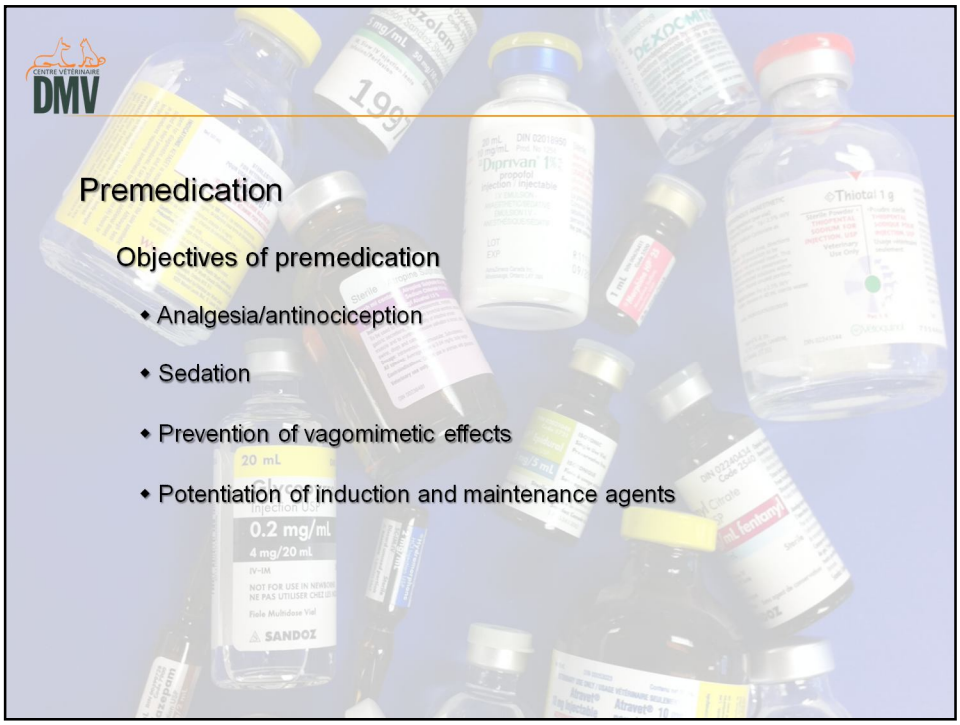
Alfaxan is only alfaxalone, and the excipient is a cyclodextrin, which solubilizes the hydrophobic steroid but does not cause the anaphylactic effects associated with castor oil, which was used in the old formulation.

Alfaxalone exhibits a good level of respiratory and cardiovascular safety (higher than that exhibited by propofol, especially cardiovascular safety), provided it is injected slowly, over about 60 seconds. Its therapeutic index is 3 to 4 times that of propofol.

Induction is rapid, and the duration of action is very short (less than 10 minutes).

Otherwise, alfaxalone is fairly similar to propofol in terms of its anesthetic effects. In cats, emergence is potentially faster because it is not a phenol derivative and therefore does not undergo glucuronic acid conjugation (deficient metabolic pathway in cats).

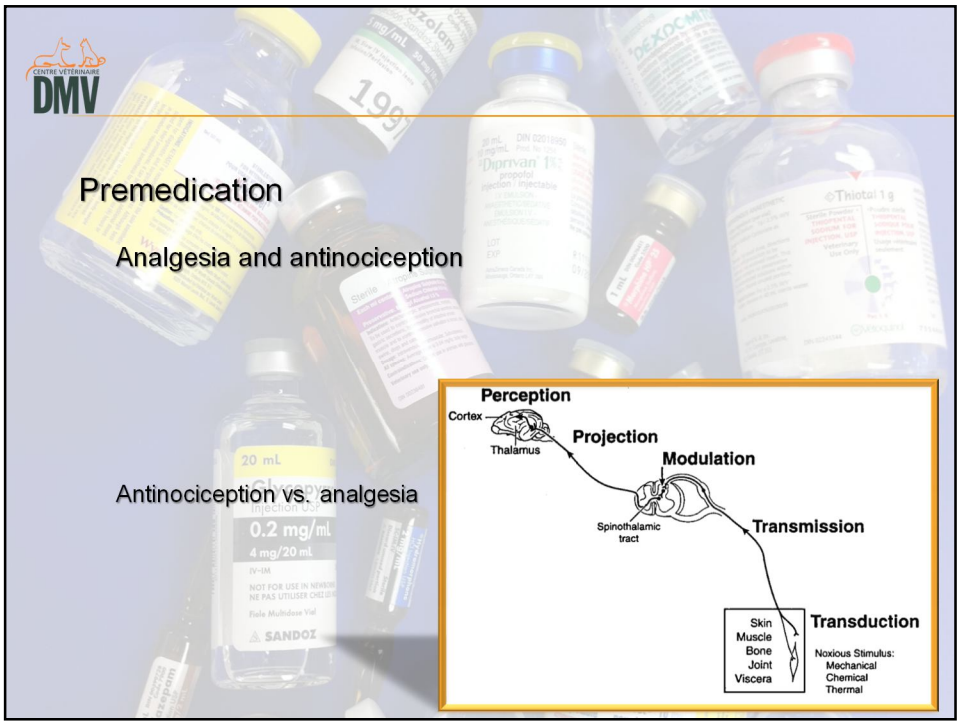
Ropivacaine is used in veterinary medicine and has effects similar to those of bupivacaine, in particular, in terms of the onset and duration of action. Main advantages: better differential block (motor block less pronounced and better sensory block than with bupivacaine), as well as less cardiotoxicity.



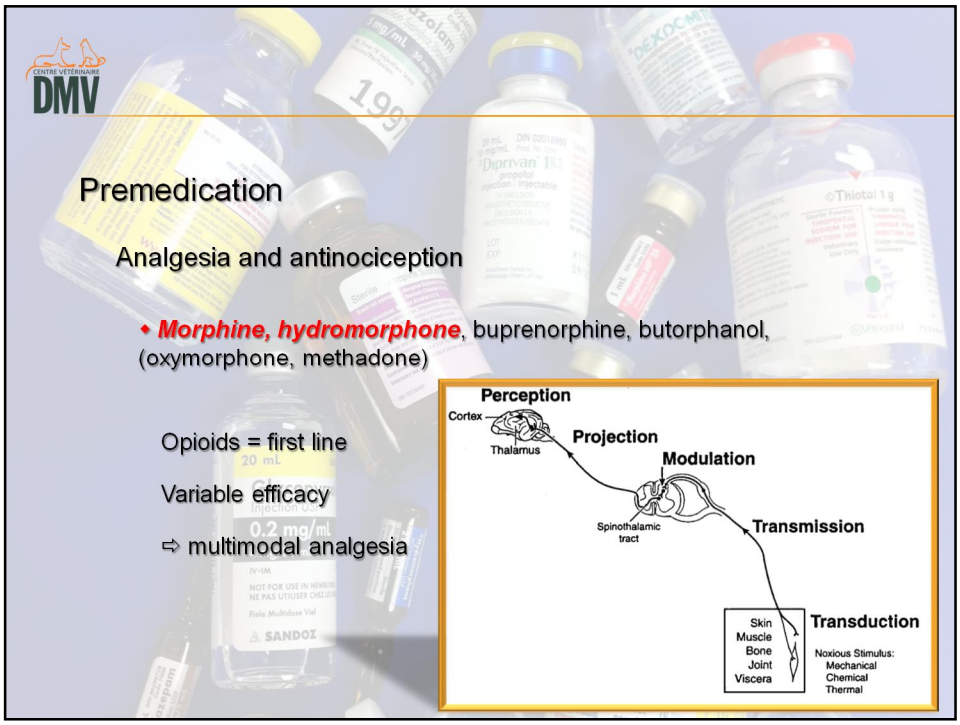
We have done a quick review of the different injectable drugs used for anesthesia and analgesia.

We identified those for which there is a problem, i.e., reduced or no availability.

The next step in our discussion, before identifying alternative drugs, is to determine the objectives we wanted to achieve previously with the drugs whose availability is now a problem. This is going to determine the properties that we expect to find in the replacement drugs.



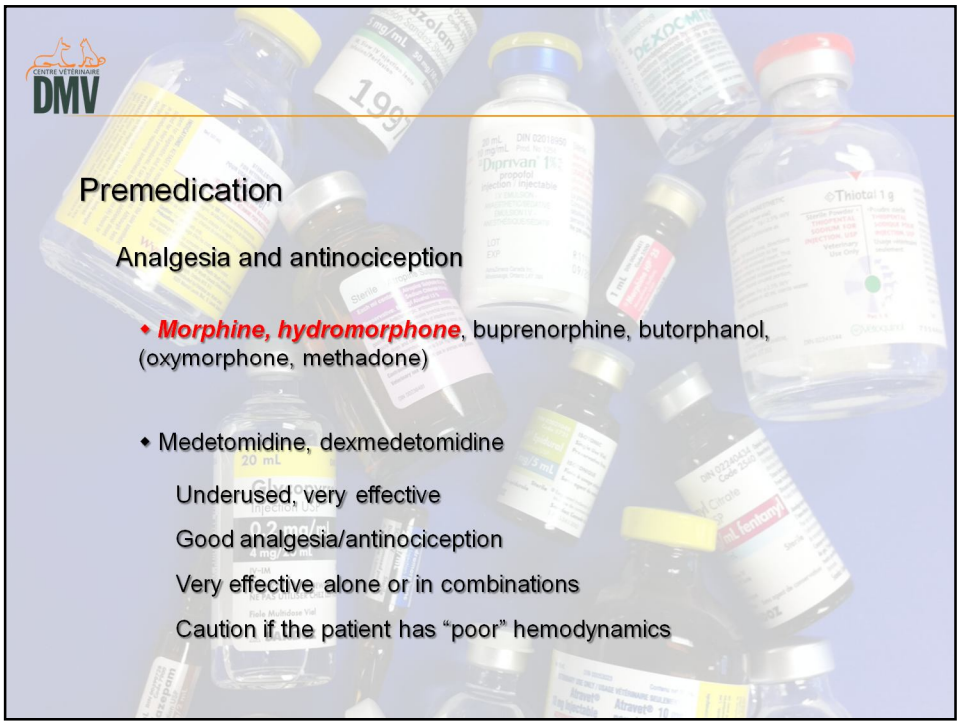
Analgesia and, ideally, antinociception. Antinociception is the interruption of nociceptive nerve conduction (that is, nerve conduction resulting from nociceptor activation) along the different segments where the signal being transmitted will eventually result in pain, this pain being associated with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



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

They do not all have the same efficacy for all pain intensities (e.g., hydromorphone and morphine vs. butorphanol and buprenorphine for severe pain).

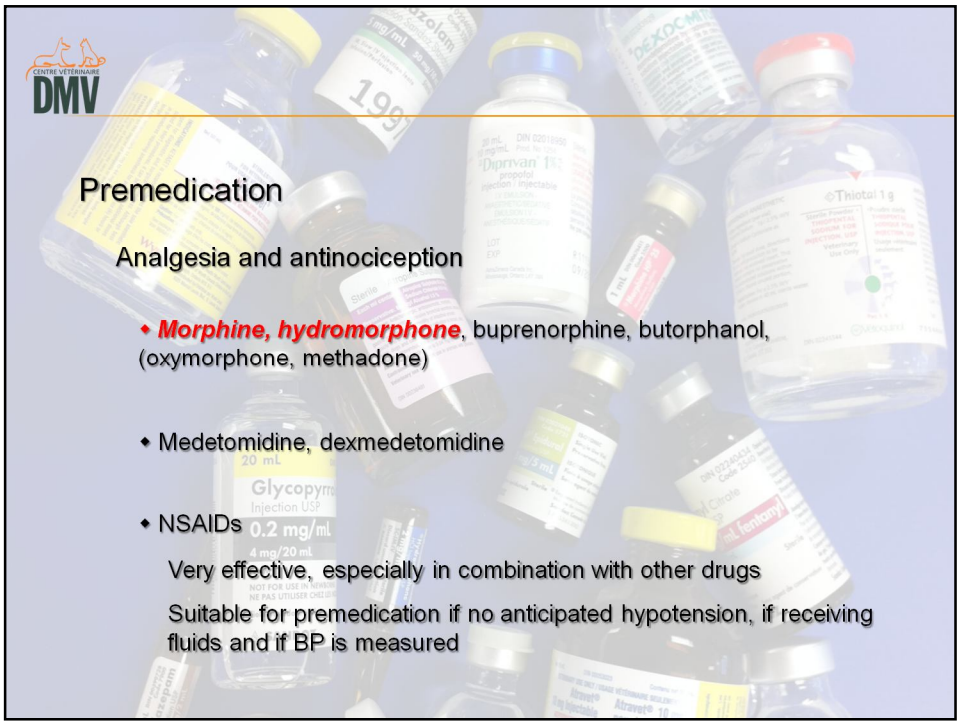
However, we should not consider the effect of an analgesic administered alone, which may be suboptimal. Instead, it should be incorporated into a context of multimodal analgesia, where it would be acceptable, thanks to its synergistic or at least additive effect, acting through mechanisms different from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



α_2-adrenergic agonists are very good but largely underutilized analgesics/antinociceptives. Very effective in combination with or even in place of an opioid. They are also antagonizable (atipamezole, mainly in dogs and cats, in the case of medetomidine and dexmedetomidine).

On the other hand, they have greater hemodynamic repercussions than opioids and should therefore be used with caution in patients with certain hemodynamic conditions (e.g., hypovolemia, mitral valve insufficiency with significant regurgitation, dilated cardiomyopathy or any condition causing poor myocardial contractility), mainly because of the initial, transient increase in afterload.

Dex/medetomidine do not seem to be a problem for certain heart conditions, e.g., cats with hypertrophic cardiomyopathy associated with a dynamic obstruction of the left ventricular outflow tract.

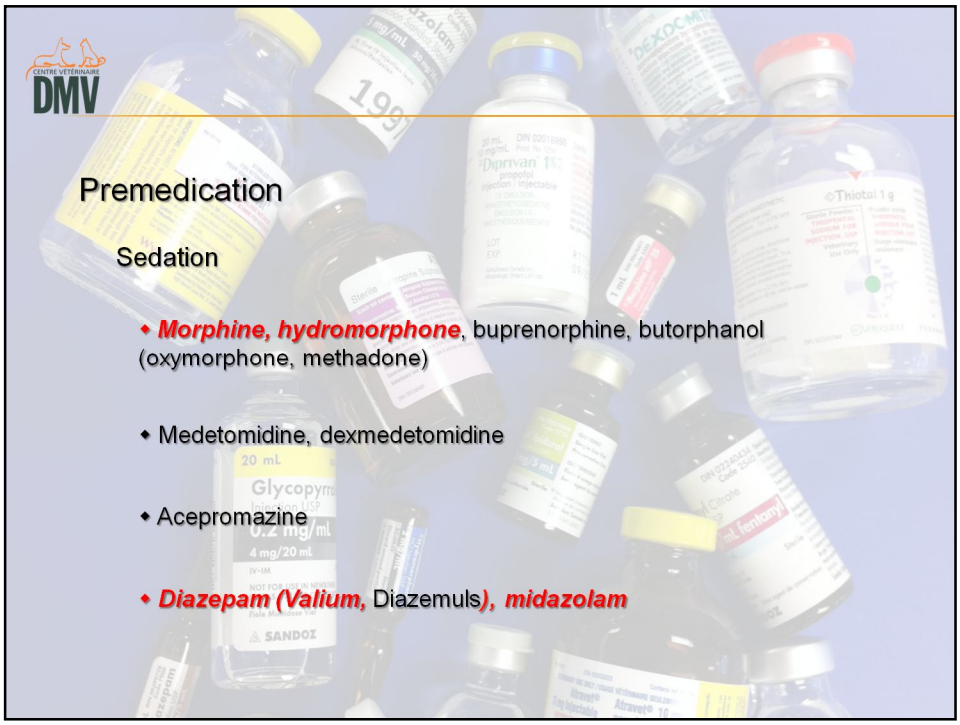


Administering NSAIDs as premedication is suitable in patients who are not too young if hypotension is not anticipated, if the patient receives i.v. fluids and if its blood pressure is measured regularly to prevent a combination of hypotension and a blockage of PGE_2 and PGI_2 synthesis in the kidneys.

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).

Ideally, 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.

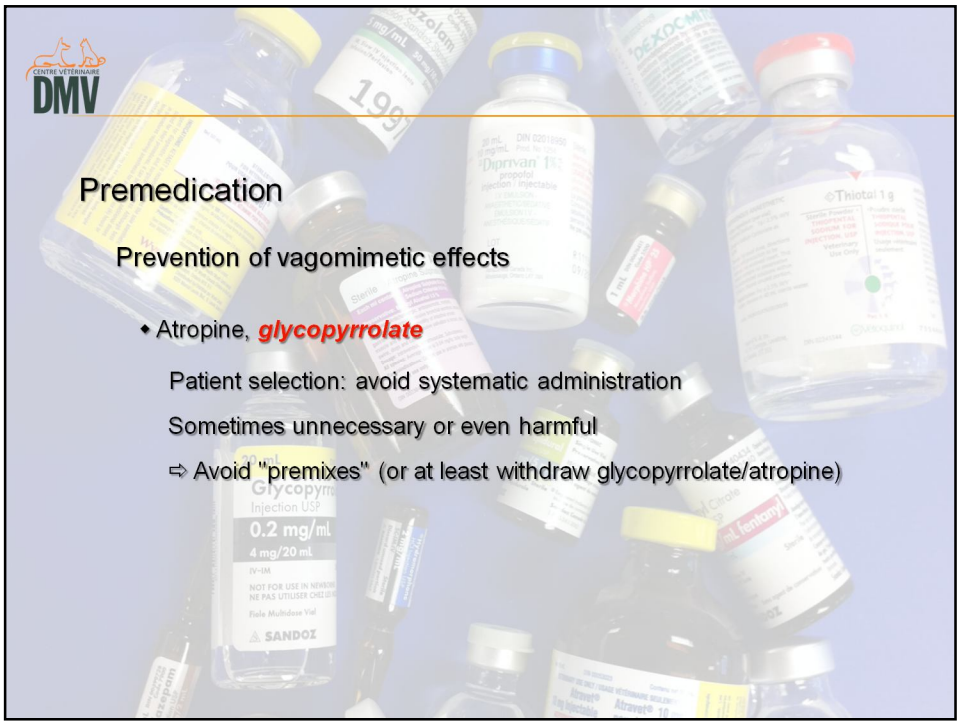


With the appropriate doses and routes of administration, opioids can produce good sedative effects (variable efficacy), especially when administered intravenously, so much so that they are sometimes used alone for premedication in patients that are not overly excited or stressed.

α_2-adrenergic agonists have significant sedative and anxiolytic effects, in addition to being good analgesic/antinociceptive agents. They can also be used alone or in combination with opioids.

Diazepam and midazolam: in this time of shortage, they should be reserved for patients that truly require them (for example, epileptic patients and very young or very old patients) or for which the adverse effects of acepromazine or α_2-adrenergic agonists could be harmful.

Diazemuls would be an alternative to Valium, although it would seem that our access to it is blocked at this time (see below).



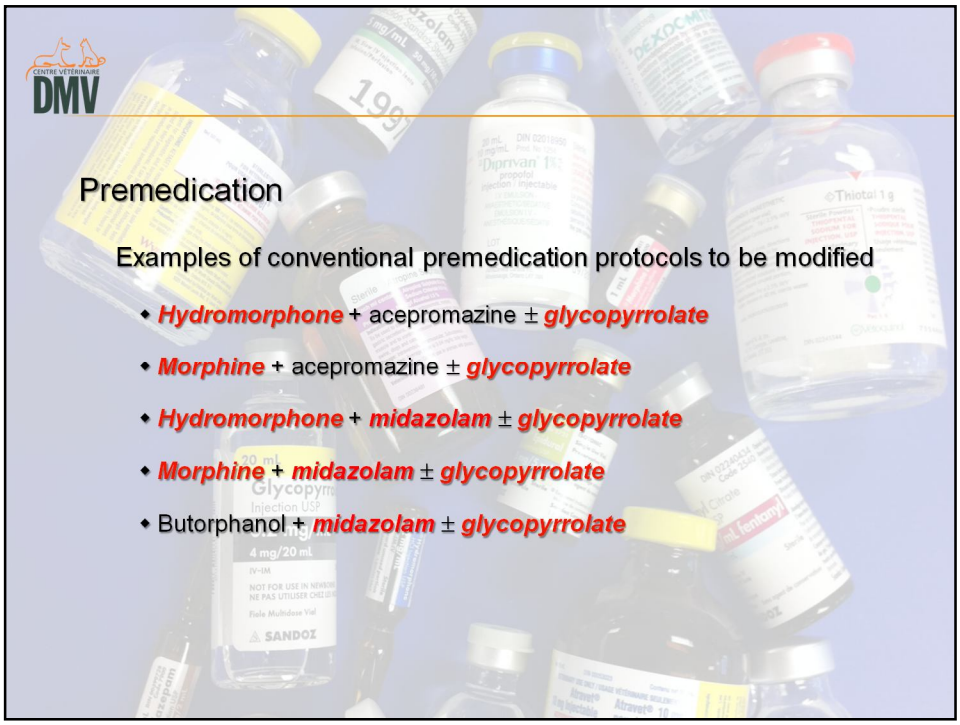
Anticholinergics should be reserved for patients that truly require them. This is true not only for glycopyrrolate, which is affected by the shortage, but also for atropine, even if it is not affected.

Avoid administering them systematically as premedication. Not only is this not always useful, but it can even sometimes be harmful, especially if combined with ketamine (e.g., BAGK or HAGK in cats), because of their positive chronotropic effects – which are in addition to those of ketamine – in a patient that is potentially already stressed ⇨ increase in myocardial O_2 consumption with, at the same time, a decrease in myocardial perfusion.

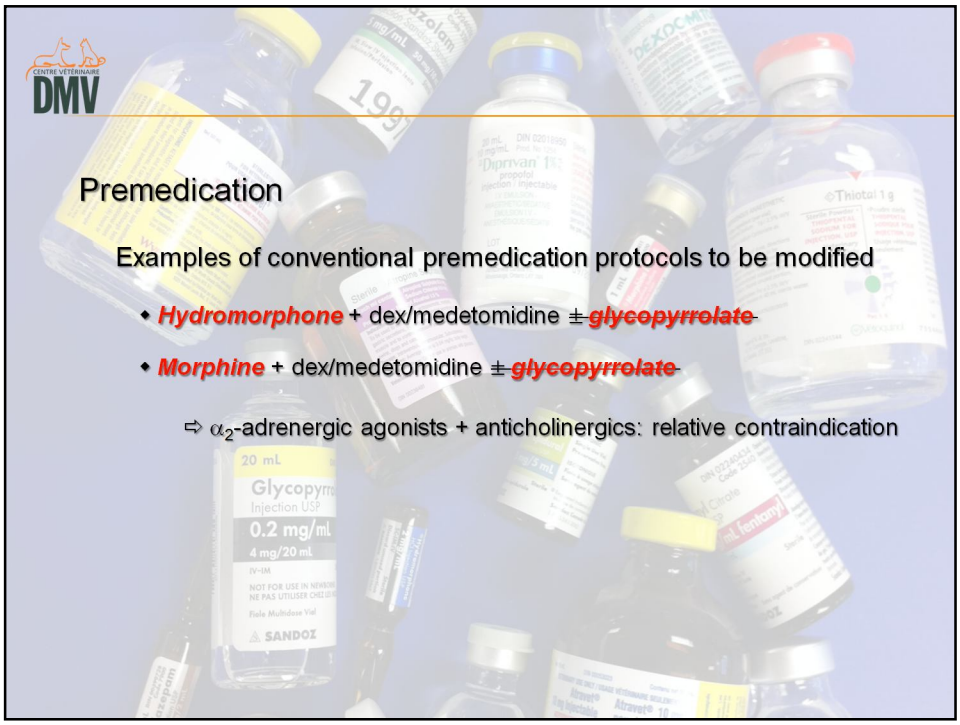
The anticholinergic + ketamine combination has been associated with deaths – due to the development of myocardial infarction – in young cats undergoing routine surgical procedures.

⇨ forget about "premixes" or at least eliminate glycopyrrolate from them (this applies to atropine as well) and administer it only if warranted by the patient's condition.

Atropine is a good alternative to glycopyrrolate. It was used in place of glycopyrrolate several years ago when there was a shortage of it.



This is not an exhaustive list but rather some of the main protocols commonly used in dogs and cats.

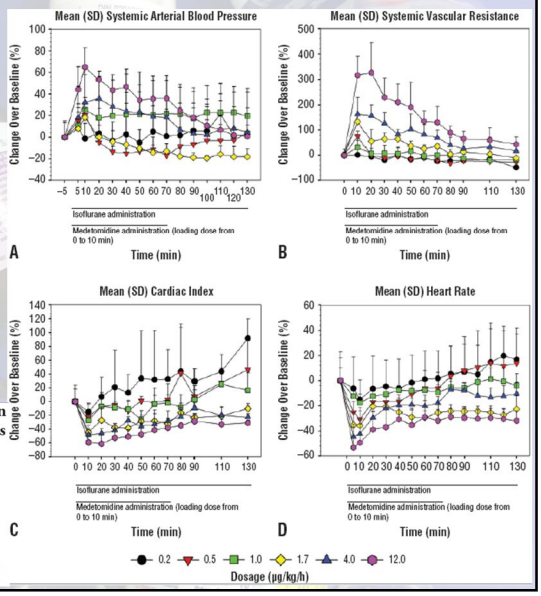


Relative contraindication for the administration of glycopyrrolate/atropine with dex/medetomidine for countering the reflex bradycardia that occurs during the initial, transient phase of vasoconstriction.

Premedication

α_2-adrenergic agonists

- Treatment of bradycardia?



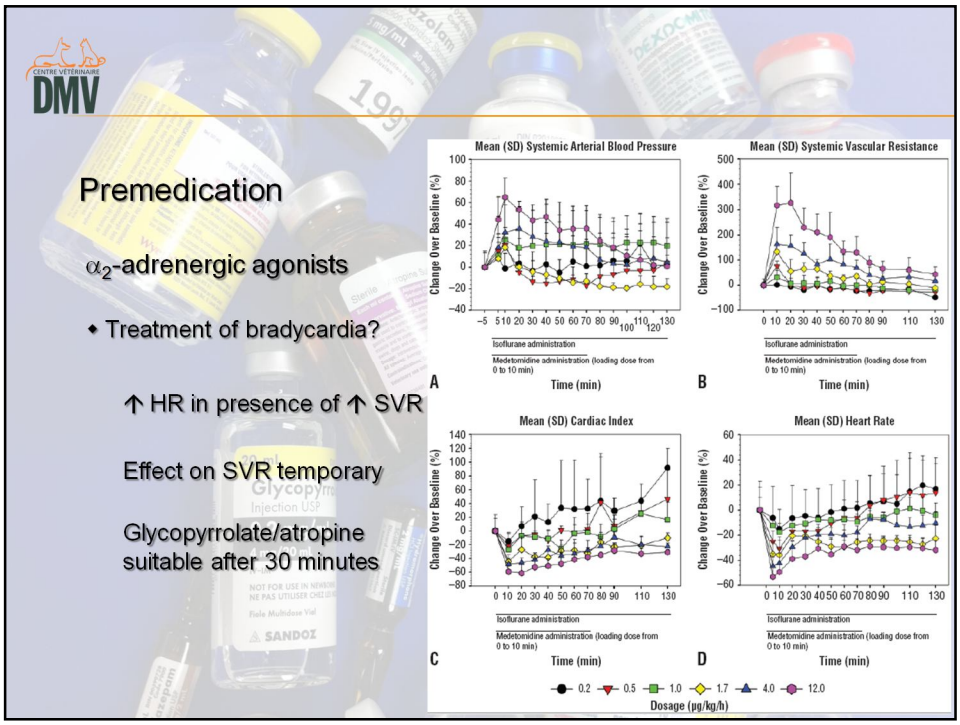
Hemodynamic Effects of an Intravenous Infusion of Medetomidine at Six Different Dose Regimens in Isoflurane-Anesthetized Dogs*,†

Johanna M. Kaartinen, DVM[a,b]
Daniel S. J. Pang, BVSc, MSc, DACVA, DECVAA, MRCVS[a,b,c]
Maxim Moreau, MSc[a]
Outi M. Vainio, DVM, PhD, DECVPT[d]
Francis Beaudry, PhD, PChem[e]
Jérôme R. E. del Castillo, DMV, MSc, PhD[a]
Leigh A. Lamont, DVM, MS, DACVA[c]
Sophie G. Cuvelliez, DVM, MS, DACVA, DECVAA[b]
Eric Troncy, DV, MSc, PhD, DUa[a,f]

Vet Ther 11(1), 2010

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

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

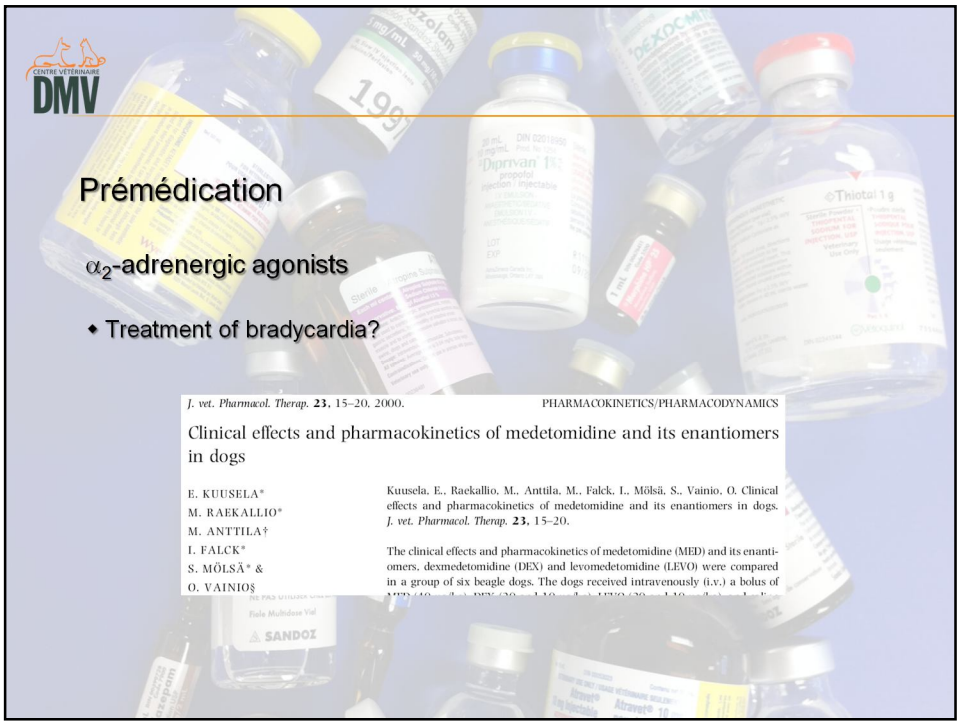


If HR ↑ in the presence of high systemic vascular resistance (and therefore in the presence of a high afterload) ⇨ ↑ in myocardial workload and oxygen consumption while at the same time a ↓ in myocardial perfusion. This is not a problem if the heart is in good health, but it can lead to heart failure.

If the initial bradycardia associated with vasoconstriction is truly worrisome, 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.

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.



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 before administering atropine / glycopyrrolate is adequate after similar doses of dex/medetomidine by i.m route.

Prémédication

α_2-adrenergic agonists

- Treatment of 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

Prémédication

α_2-adrenergic agonists

- Treatment of bradycardia?

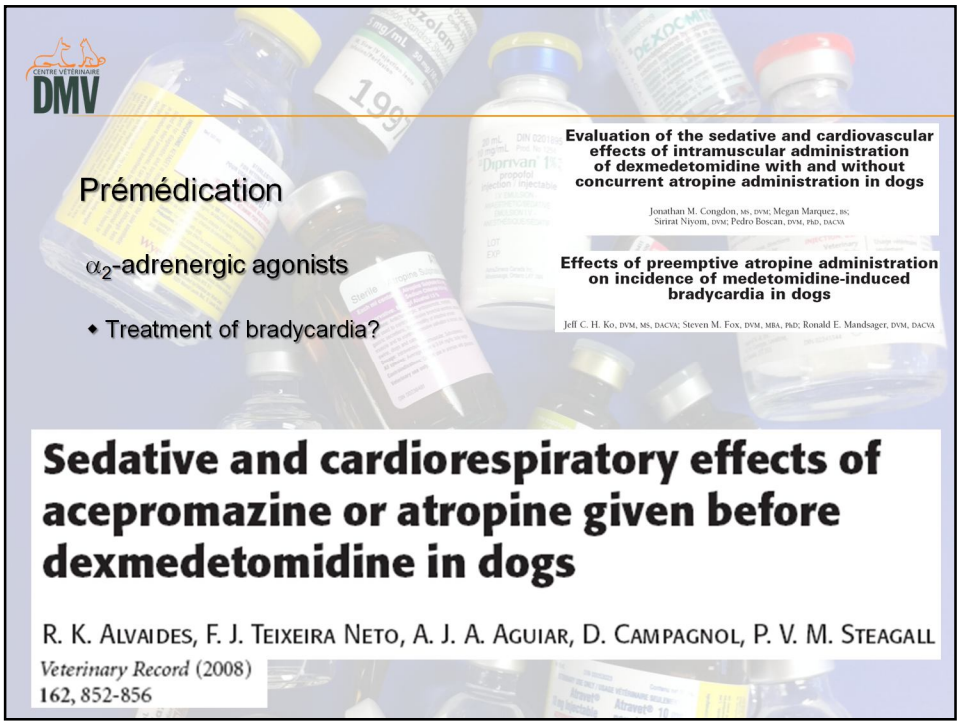
Evaluation of the sedative and cardiovascular effects of intramuscular administration of dexmedetomidine with and without concurrent atropine administration in dogs

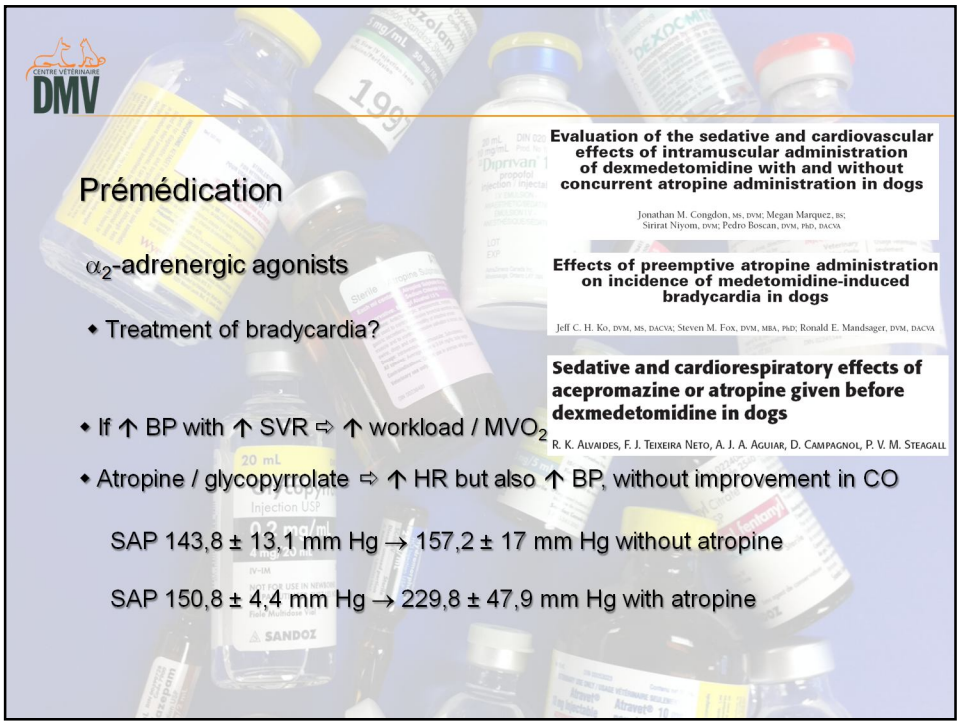
Jonathan M. Congdon, MS, DVM; Megan Marquez, BS; Sirirat Niyom, DVM; Pedro Boscan, DVM, PhD, DACVA

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

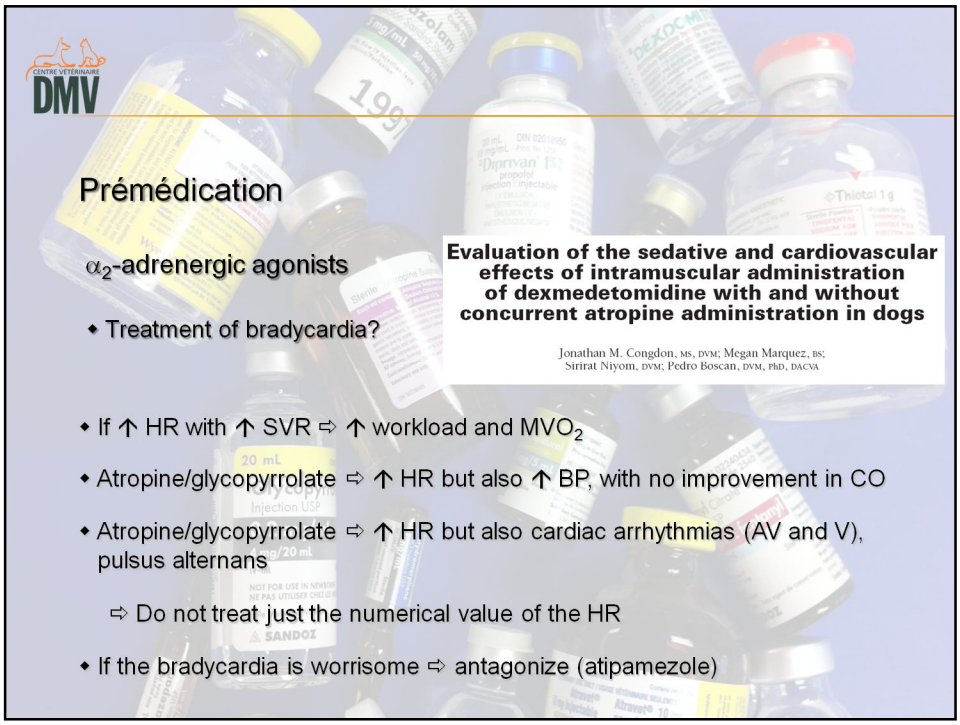
(*J Am Vet Med Assoc* 2001;218:52–58)


DMV
Prémédication
α_2-adrenergic agonists
Treatment of 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



Atropine or glycopyrrolate during the initial phase of vasoconstriction ⇨ ↑ HR but at the cost of BP ↑ even more, without improvement in cardiac output.

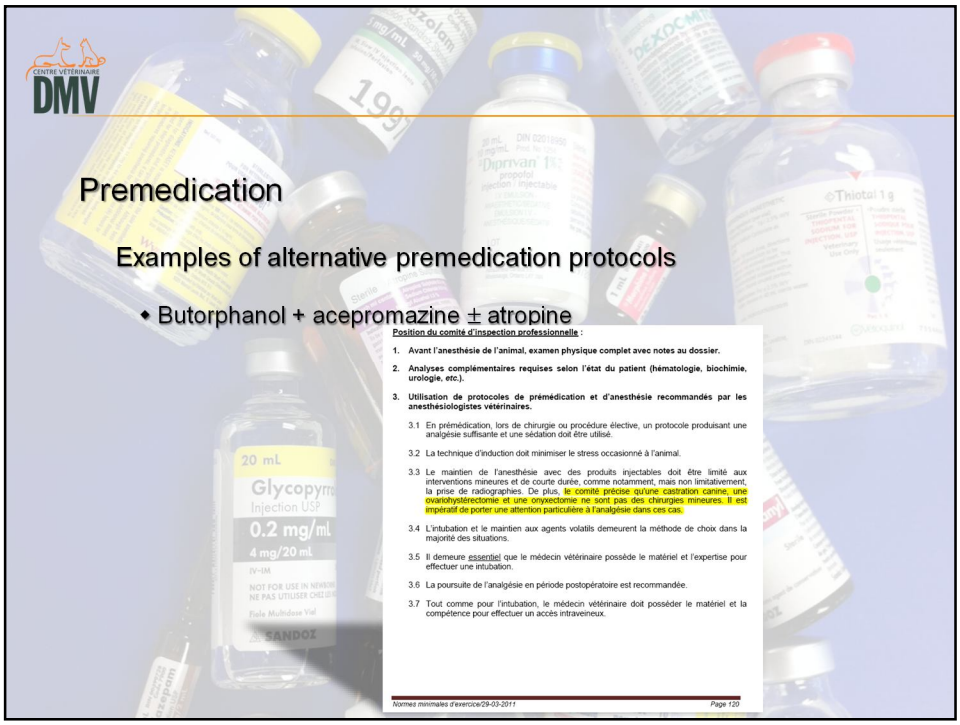
Study in JAVMA 2011 (Congdon et coll.): SAP 143,8 ± 13,1 mm Hg → 157,2 ± 17 mm Hg without atropine and 150,8 ± 4,4 mm Hg → 229,8 ± 47,9 mm Hg with atropine.



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.

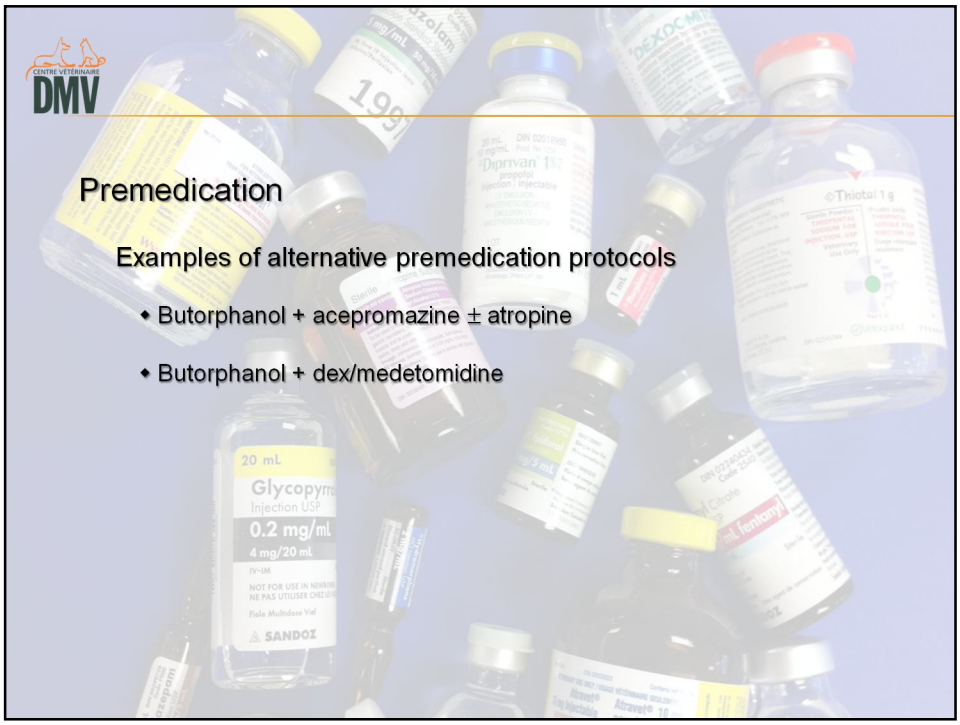
If the initial bradycardia associated with vasoconstriction is very worrisome (not just because of its numerical value, but also in light of the other clinical signs), many recommend antagonizing (atipamezole) rather than administering a positive chronotropic drug (e.g., atropine or glycopyrrolate).

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



Butorphanol is generally known not to be effective against more intense pain ⇨ BAG is not considered sufficient for surgery if this is the only analgesic.

As for routine surgeries, based on the update of the OMVQ's minimum practice standards (March 2011), neutering, spaying and declawing are not considered minor surgeries. Therefore, it is important to pay close attention to analgesia in these cases.



On the other hand, butorphanol might be acceptable in an additive or synergistic combination in a multimodal analgesia protocol: NSAIDs, locoregional anesthesia, α_2-adrenergic agonists, etc.

Buprenorphine is a partial μ-opioid receptor agonist. It is very popular in small animal veterinary medicine in different European countries (especially the United Kingdom). As with butorphanol, the analgesia provided by buprenorphine reaches a plateau ⇨ is considered marginally effective or not effective at all when used alone for severe pain. Furthermore, because of buprenorphine's strong affinity for μ-opioid receptors, it may be difficult to dislodge it with more effective opioids. Buprenorphine would appear to provide better analgesia in cats than in dogs. In any event, buprenorphine, like butorphanol, is acceptable for severe pain if it is used in combination in multimodal analgesia protocols: NSAIDs, locoregional anesthesia, α_2-adrenergic agonists, etc.

One advantage of buprenorphine over other opioids is its duration of action: reportedly about 6-12 hours, but probably closer to 6. On the other hand, there is a long delay to peak action, being up to 1 hour, even after i.v. injection ⇨ subcutaneous administration is not recommended. This delay can be a drawback if a rapid analgesic/antinociceptive effect is sought, for example, if pain is present upon emergence after extubation. One possible solution would be to administer an α_2-adrenergic agonist intravenously (if not contraindicated) while waiting for the buprenorphine to exert its full effect. Another advantage is that oral transmucosal administration seems as efficacious as i.v. administration in cats. Cat saliva has an alkaline pH, which promotes the absorption of buprenorphine, a weak base with a high pK_a (promotes the predominance of the nondissociated, nonionized and therefore fat-soluble form in an alkaline environment). Lastly, buprenorphine causes little or no vomiting or hyperthermia.

Premedication

Examples of alternative premedication protocols

- Buprenorphine + acepromazine ± atropine
- Buprenorphine + dex/medetomidine

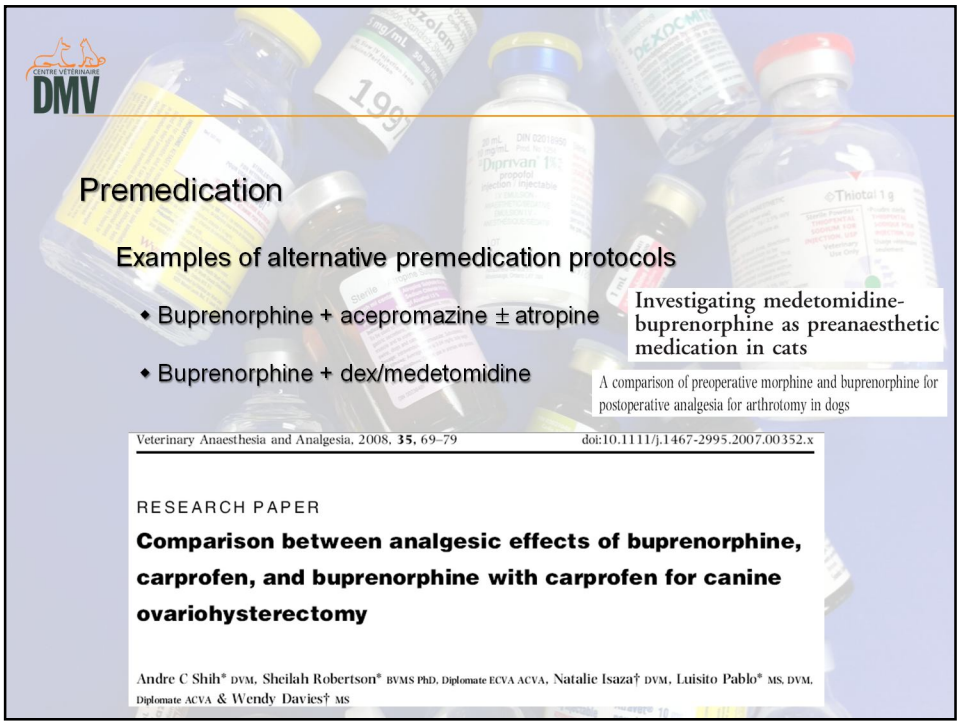
Investigating medetomidine-buprenorphine as preanaesthetic medication in cats

J. vet. Pharmacol. Therap. **20**, 284–289, 1997. SYSTEMIC PHARMACOLOGY

A comparison of preoperative morphine and buprenorphine for postoperative analgesia for arthrotomy in dogs

D.C. BRODBELT
P.M. TAYLOR &
G.W. STANWAY*

Brodbelt, D.C., Taylor, P.M., Stanway, G.W. A comparison of preoperative morphine and buprenorphine for postoperative analgesia for arthrotomy in dogs. *J. vet. Pharmacol. Therap.* **20**, 284–289.



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.

Premedication

Examples of alternative premedication protocols

- Buprenorphine + acepromazine ± atropine
- Buprenorphine + dex/medetomidine

Investigating medetomidine-buprenorphine as preanaesthetic medication in cats

A comparison of preoperative morphine and buprenorphine for postoperative analgesia for arthrotomy in dogs

Veterinary Anaesthesia and Analgesia, 2010, **37**, 417–424 doi:10.1111/j.1467-2995.2010.00555.x

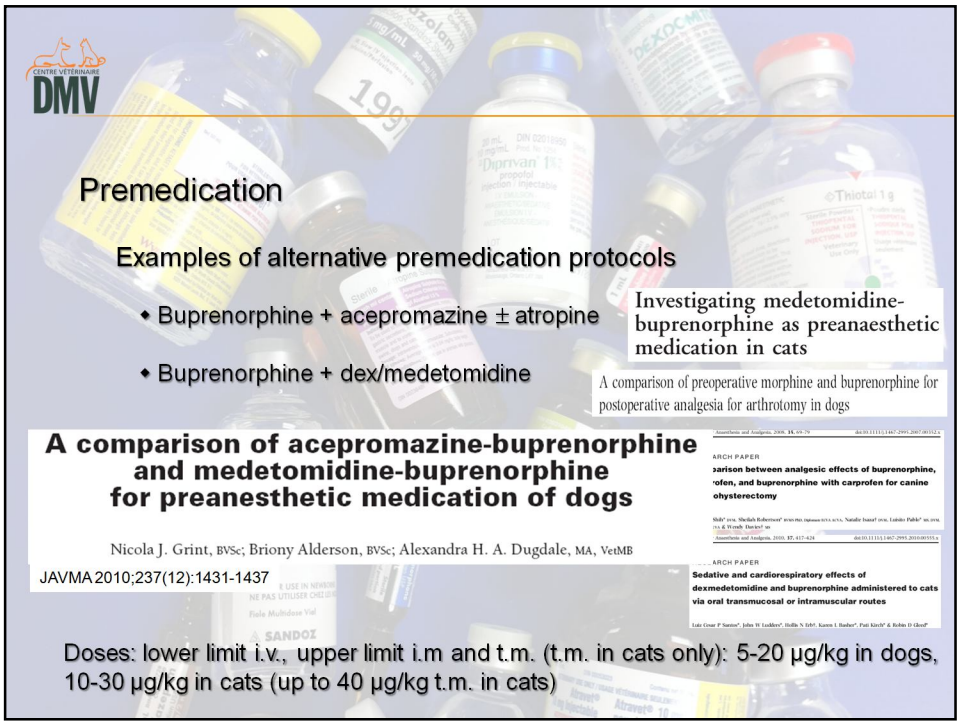
RESEARCH PAPER

Sedative and cardiorespiratory effects of dexmedetomidine and buprenorphine administered to cats via oral transmucosal or intramuscular routes

Luiz Cesar P Santos*, John W Ludders*, Hollis N Erb†, Karen L Basher*, Pati Kirch* & Robin D Gleed*

RESEARCH PAPER

Comparison between analgesic effects of buprenorphine, carprofen, and buprenorphine with carprofen for canine ovariohysterectomy



Doses: lower limit i.v. (although not approved for i.v. administration), upper limit i.m and t.m. (t.m. in cats only): 5-20 µg/kg in dogs, 10-30 µg/kg in cats (up to 40 µg/kg t.m. in cats).

Oxymorphone has similar efficacy to hydromorphone and morphine. It used to be available in Canada and was commonly used for analgesia in small animals before the arrival of hydromorphone about 12 years ago. It is very effective but was more expensive than hydromorphone and morphine.

Premedication

Examples of alternative premedication protocols

- Oxymorphone + acepromazine ± atropine
- Oxymorphone + dex/medetomidine

Comparison of the analgesic efficacy of hydromorphone and oxymorphone in dogs and cats: a randomized blinded study

J. vet. Pharmacol. Therap. **31**, 580–583, doi: 10.1111/j.1365-2885.2008.00987.x. SHORT COMMUNICATION

Pharmacokinetics and behavioral effects of oxymorphone after intravenous and subcutaneous administration to healthy dogs

B. KUKANICH*
B. K. SCHMIDT†
L. A. KRUGNER-HIGBY†
S. TOERBER* &
L. J. SMITH†

Premedication

Examples of alternative premedication protocols

- Oxymorphone + acepromazine ± atropine
- Oxymorphone + dex/medetomidine

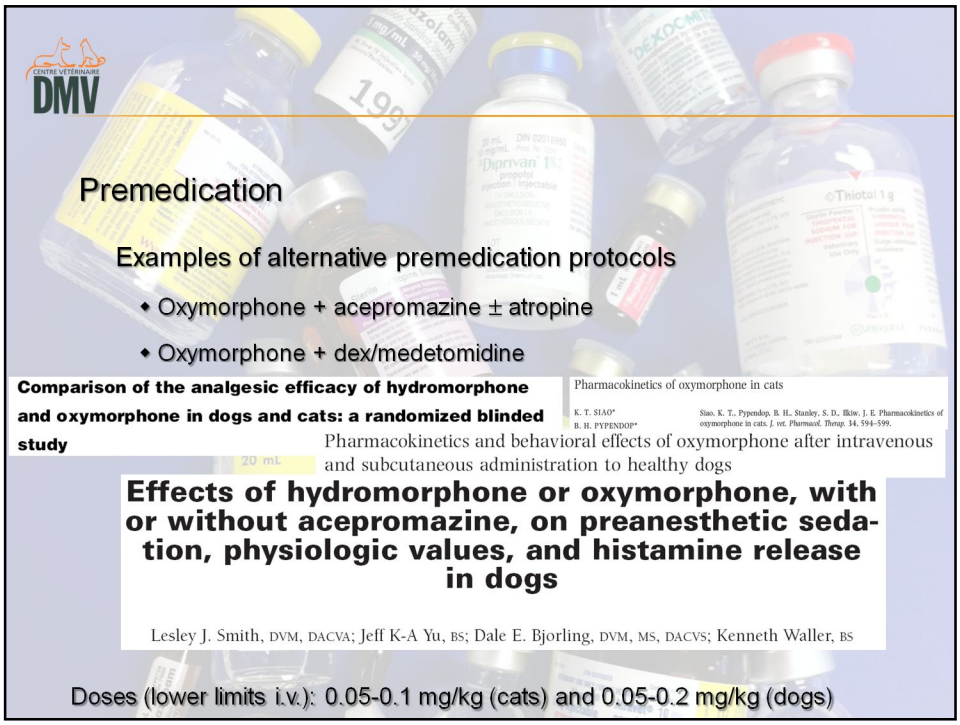
Comparison of the analgesic efficacy of hydromorphone and oxymorphone in dogs and cats: a randomized blinded study

Pharmacokinetics and behavioral effects of oxymorphone after intravenous and subcutaneous administration to healthy dogs

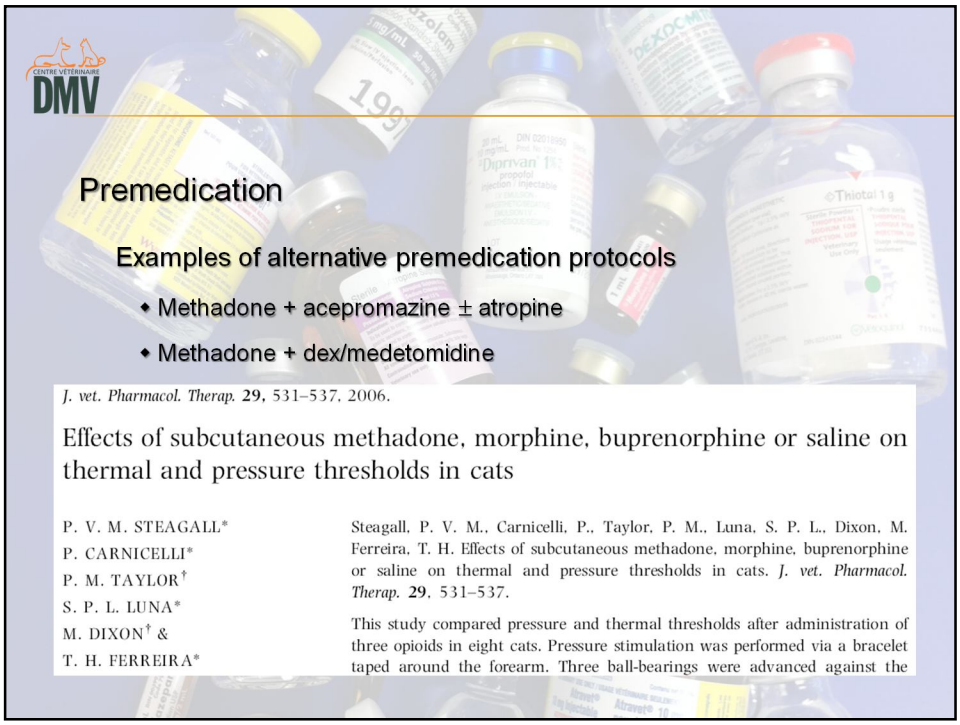
Pharmacokinetics of oxymorphone in cats

K. T. SIAO*
B. H. PYPENDOP*

Siao, K. T., Pypendop, B. H., Stanley, S. D., Ilkiw, J. E. Pharmacokinetics of oxymorphone in cats. *J. vet. Pharmacol. Therap.* 34, 594–599.



Doses (lower limits i.v.): 0.05-0.1 mg/kg (cats) and 0.05-0.2 mg/kg (dogs).



Methadone is an opioid similar to morphine because of its agonist effects on μ-opioid receptors.

It also acts by antagonizing NMDA receptors, which would theoretically make it similar to ketamine and amantadine, an advantage in the fight against CNS sensitization and the development of pathological pain.

Methadone is an opioid commonly used for analgesia in small animals in a number of countries, mainly in Europe.

It is also used in humans in Canada and several other countries as a replacement drug in withdrawal therapies for drug addicts (as is buprenorphine) and to treat severe pain, especially cancer pain.

Premedication

Examples of alternative premedication protocols

- Methadone + acepromazine ± atropine
- Methadone + dex/medetomidine

J. vet. Pharmacol. Therap. 29, 531–537, 2006.

Effects of subcutaneous methadone, morphine, buprenorphine or saline on thermal and pressure thresholds in cats

Veterinary Anaesthesia and Analgesia, 2009, **36**, 158–161 doi:10.1111/j.1467-2995.2(

SHORT COMMUNICATION

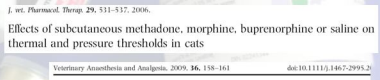
Effects of medetomidine, L-methadone, and their combination on arterial blood gases in dogs

Marja R Raekallio* DVM, PhD, Maija P Räihä† DVM, Maarit H Alanen‡ DVM, Nina M Sarén§ DVM & Tove A Tuovio¶ DVM

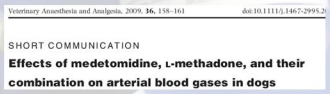
Premedication

Examples of alternative premedication protocols

- Methadone + acepromazine ± atropine
- Methadone + dex/medetomidine


J. vet. Pharmacol. Therap. 29, 531–537, 2006.

Effects of subcutaneous methadone, morphine, buprenorphine or saline on thermal and pressure thresholds in cats


Veterinary Anaesthesia and Analgesia, 2009, 36, 158–161 doi:10.1111/j.1467-2995.2

SHORT COMMUNICATION

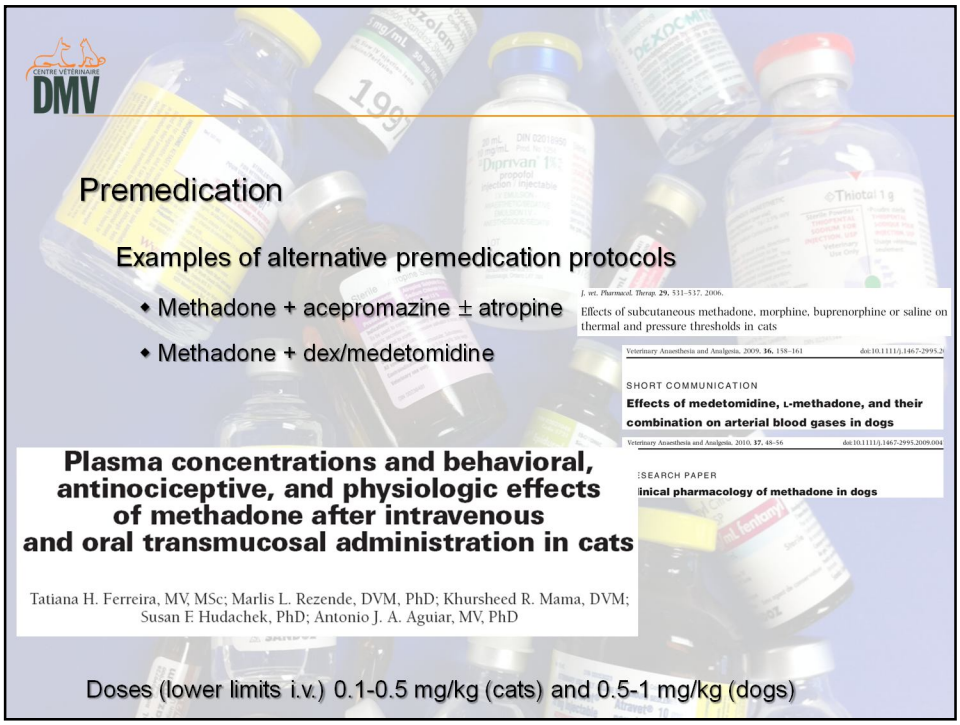
Effects of medetomidine, L-methadone, and their combination on arterial blood gases in dogs


Veterinary Anaesthesia and Analgesia, 2010, **37**, 48–56 doi:10.1111/j.1467-2995.2009.004

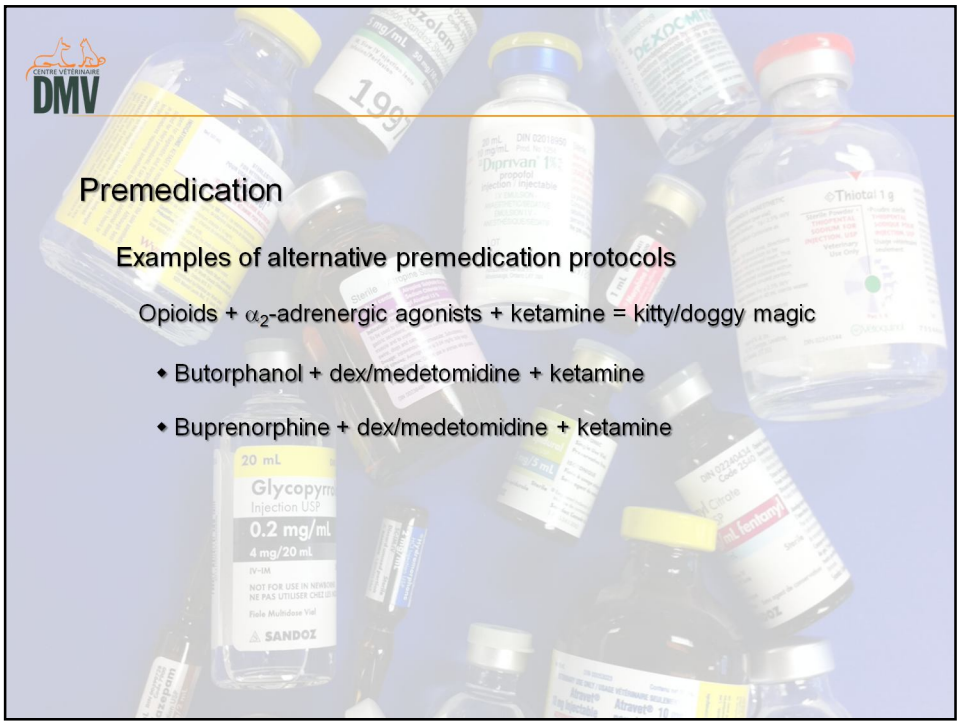
RESEARCH PAPER

Clinical pharmacology of methadone in dogs

Carina Ingvast-Larsson*, Anja Holgersson*, Ulf Bondesson†, Anne-Sofie Lagerstedt‡ & Kerstin Olsson§



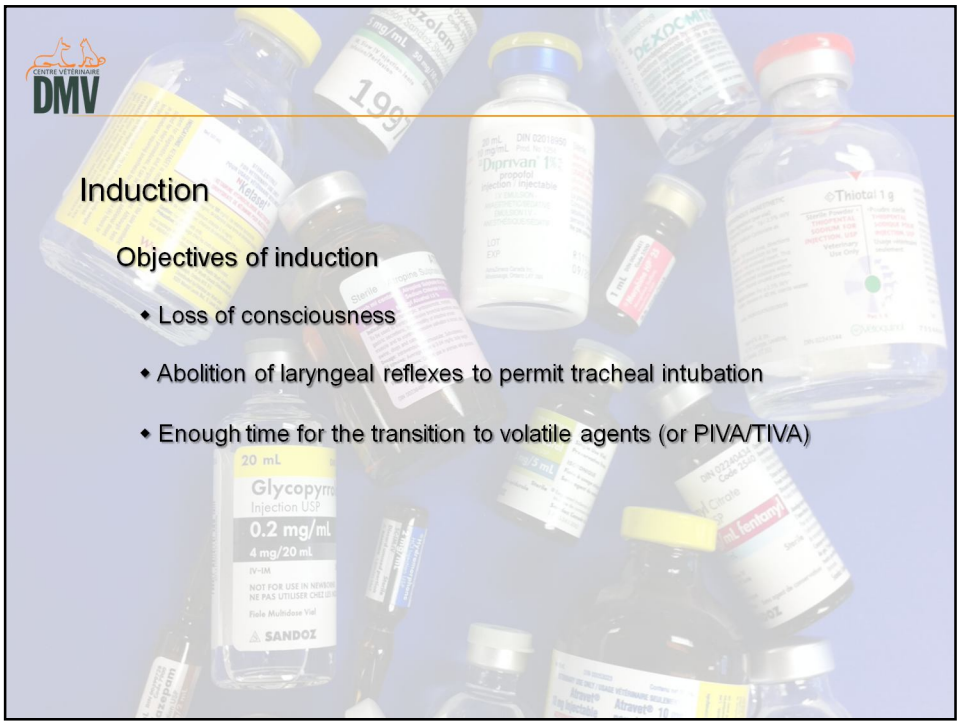
Doses (lower limits i.v.), similar to those for morphine: 0.1-0.5 mg/kg (cats) and 0.5-1 mg/kg (dogs).

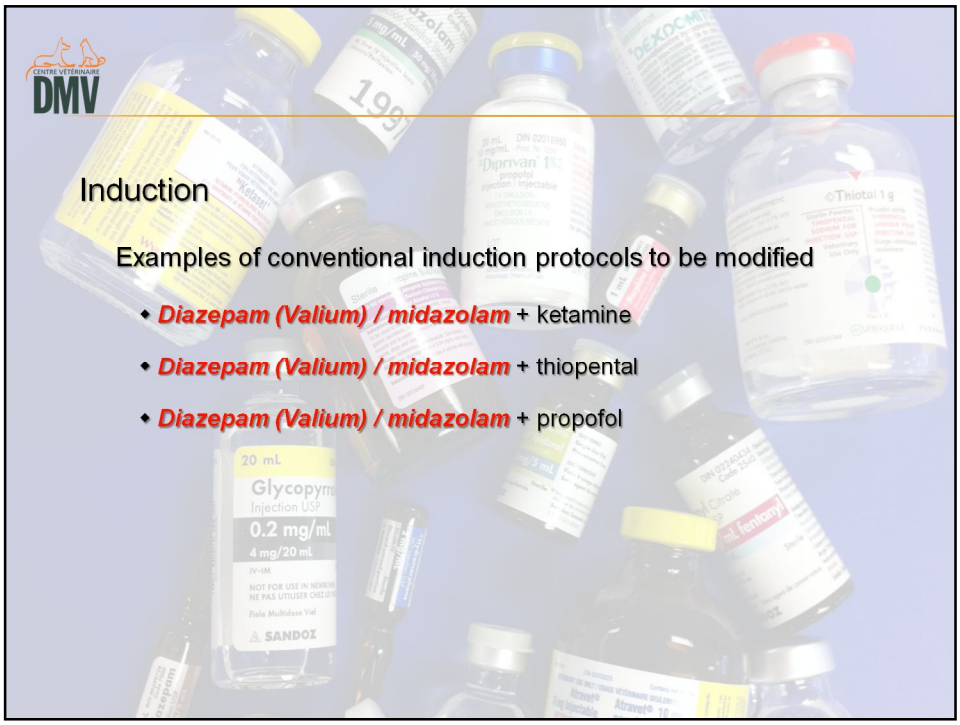


These are injectable-only protocols for short, minimally to moderately invasive procedures in dogs and cats.

Or

Premedication for particularly aggressive patients.

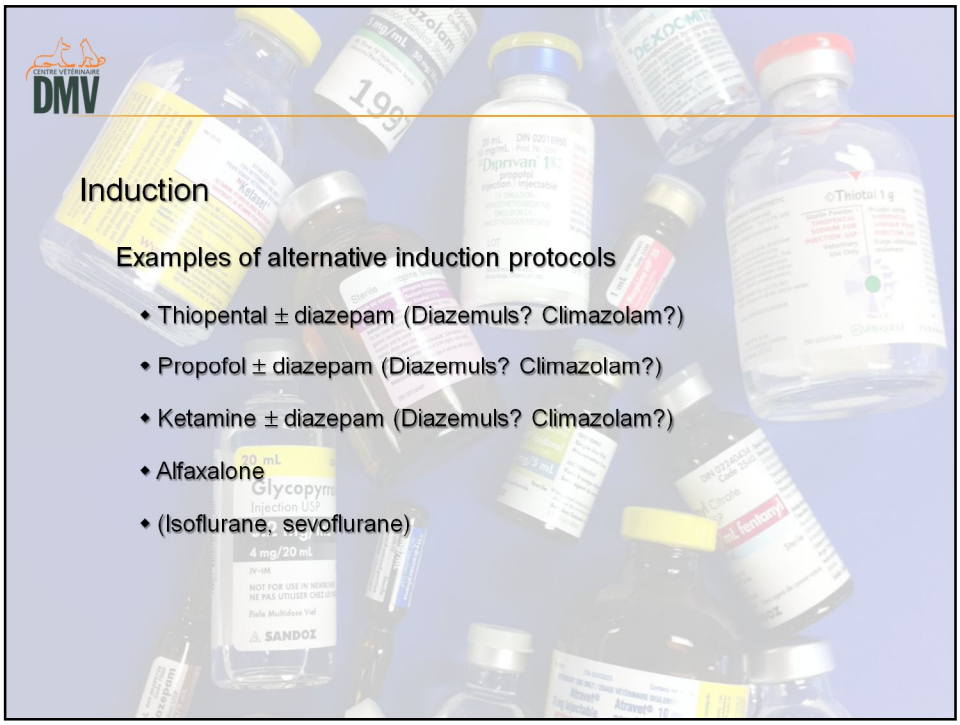

Induction
Objectives of induction
• Loss of consciousness
• Abolition of laryngeal reflexes to permit tracheal intubation
• Enough time for the transition to volatile agents (or PIVA/TIVA)



In Canada, the most commonly used injectable drugs for inducing anesthesia in dogs and cats are ketamine, thiopental, propofol and alfaxalone.

All can be combined with a coinduction agent, usually a benzodiazepine (e.g., diazepam or midazolam) or an opioid (e.g., fentanyl, which can be the main induction agent in patients in critical condition that already have an impaired level of consciousness from the outset).

Even in the absence of a benzodiazepine, induction can be done with ketamine if the premedication is effective enough and provides good myorelaxation, in addition to good sedation, as is the case, for example, with an α_2-adrenergic agonist (medetomidine or dexmedetomidine) in combination with (ideally) or not with an opioid.



Since most veterinarians do not use a coinduction agent (with the exception of those who use diazepam-ketamine), induction protocols are not affected very much by the shortage. Concerning ketamine-diazepam: Diazemuls is not compatible with other drugs ⇨ do not mix (however, this also used to be true for Valium).

If climazolam were approved in Canada (it is approved in Europe for dogs and cats), it could replace diazepam or midazolam in combination with ketamine or other induction agents.

Doses for alfaxalone: 2 mg/kg i.v. in dogs and 5 mg/kg i.v. in cats.

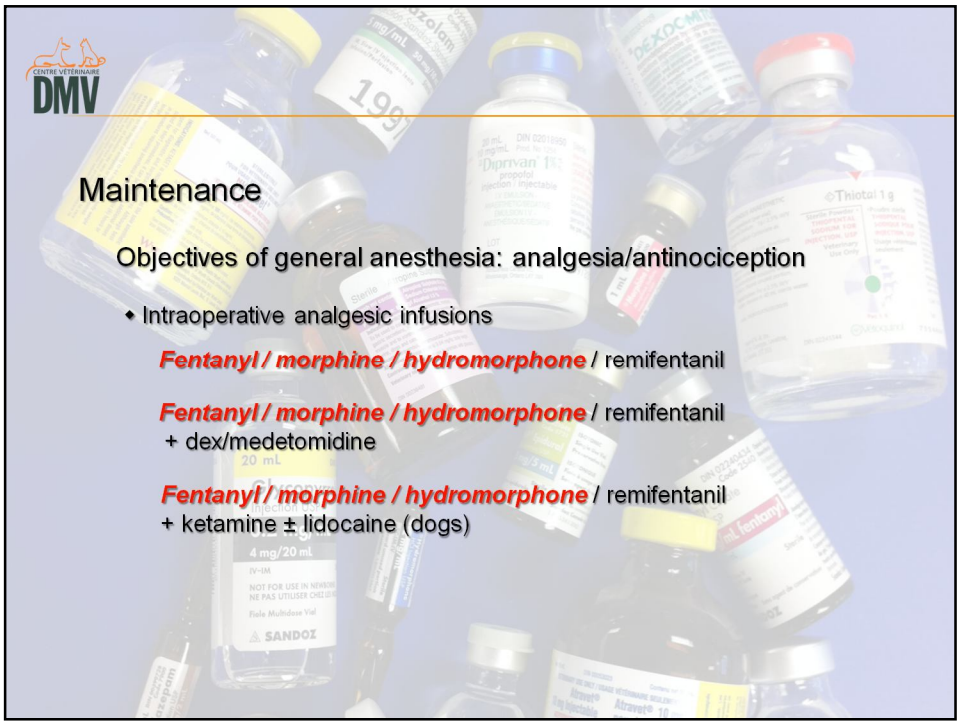
Induction with volatile agents: mentioned here even if they are not injectables, since this technique is used by some veterinarians.

Induction with volatile agents is, at best, acceptable in certain specific circumstances, but it is not recommended as a routine practice.

In addition, halogenated hydrocarbons contribute to pollution, not only of the work space, but also to atmospheric pollution for many years: destructive effect on the ozone layer (especially isoflurane, one of the volatile agents commonly used in Canada) and a greenhouse effect much greater than that of CO_2 (all the volatile agents presently used in Canada).

Emphasis on analgesia/antinociception, since of the agents used during the maintenance of anesthesia to achieve these effects are some of the drugs most affected by the shortage.

However, other injectables can be used, as a bolus or, ideally, as an infusion, to contribute to the maintenance of general anesthesia (PIVA, TIVA), in particular, via narcosis: propofol, alfaxalone, etc.



The main advantage of remifentanil is its ultrashort duration of action and its half-life of a few minutes after the infusion is stopped, regardless of the duration of administration.

Remifentanil is broken down by nonspecific hydrolysis by tissue and plasma esterases rather than by intrahepatocytic metabolism ⇨ the reduction in its activity does not depend on the liver or kidneys, unlike with other opioids:
⇨ very little accumulation;
⇨ rapid emergence once the infusion is stopped, even after several hours of infusion;
⇨ ideal in cases involving an infusion of long duration or in the presence of hepatic or renal dysfunction.


Maintenance
Objectives of general anesthesia: analgesia/antinociception
• Locoregional anesthesia for declawing, dental procedures and others
Lidocaine, bupivacaine, ropivacaine

Drugs other than the conventional combinations of morphine + bupivacaine and morphine + lidocaine can be administered by the epidural route, with varying efficacy and kinetics.

However, not all of these other drugs are necessarily available in formulations appropriate for epidural injection: fentanyl and hydromorphone, which are affected by the shortage, but also buprenorphine, dex/medetomidine, methadone, etc.

Epidural doses (possibly ↓ if used in a combination)

Fentanyl: 2-20 µg/kg in dogs, 4 µg/kg in cats.

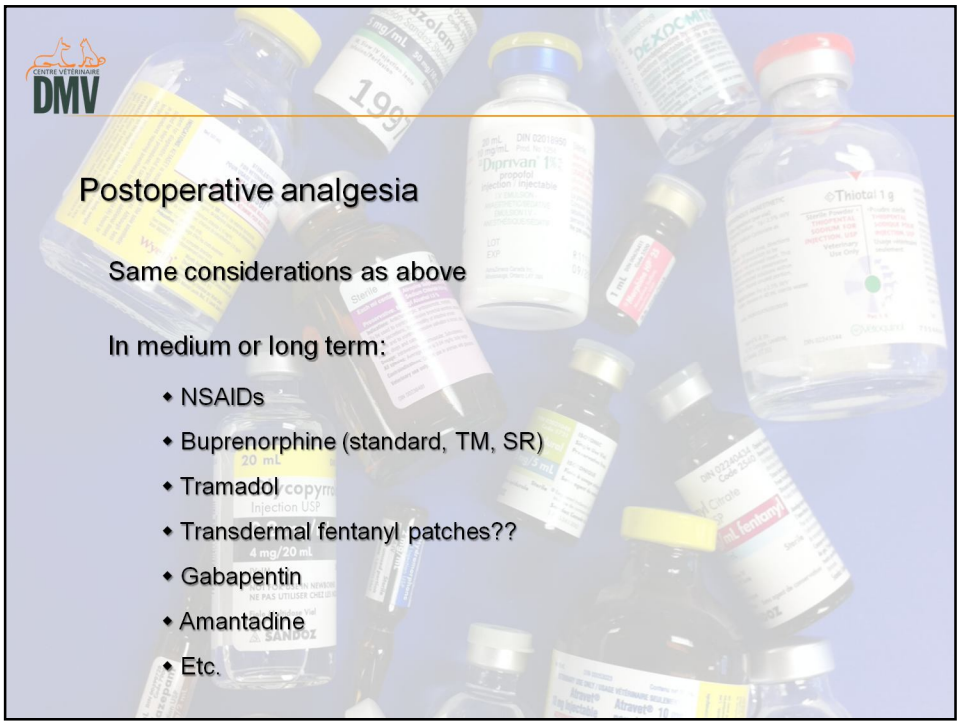
Hydromorphone: 0.03-0.05 mg/kg, also 0.1-0.2 mg/kg.

Buprenorphine (see articles): 4-40 µg/kg in dogs, 4-20 µg/kg in cats.

Medetomidine: 1-5 (also 5-15) µg/kg in dogs, 2-10 µg/kg in cats.

Dexmedetomidine (see article concerning cats): 4 µg/kg.

Methadone (see article concerning dogs): 0.3 mg/kg.



Examples of injectable drugs are provided here, but we should not forget other, nonpharmacologic therapies, such as acupuncture.

Buprenorphine TM (transmucosal) or SR (slow release)

Dose of buprenorphine SR: dog = 0.12-0.27 mg/kg s.c, cat = 0.12 mg/kg s.c. The SR formulation (which is a compounded formulation) is administered by the s.c route and releases buprenorphine during approximately 3 days ⇨ 0.12 mg/kg (= 120 µg/kg) similar to 20 µg/kg BID x 3 days with the regular injectable formulation.

Fentanyl patches are not affected by the shortage; only the injectable form is. Efficacy highly variable, random effects, wide variability between individuals.

Other drugs used in anesthesiology are affected by the production stoppage at Sandoz.

The decrease in their availability is not as critical outside specialized centres because most veterinarians make little or no use of them.

Vasopressin: treatment of refractory hypotension associated with vasoplegia (e.g., septic shock) and used in addition to or even in place of adrenaline during CPR.

Noradrenaline: treatment of refractory hypotension associated with vasoplegia (e.g., septic shock).

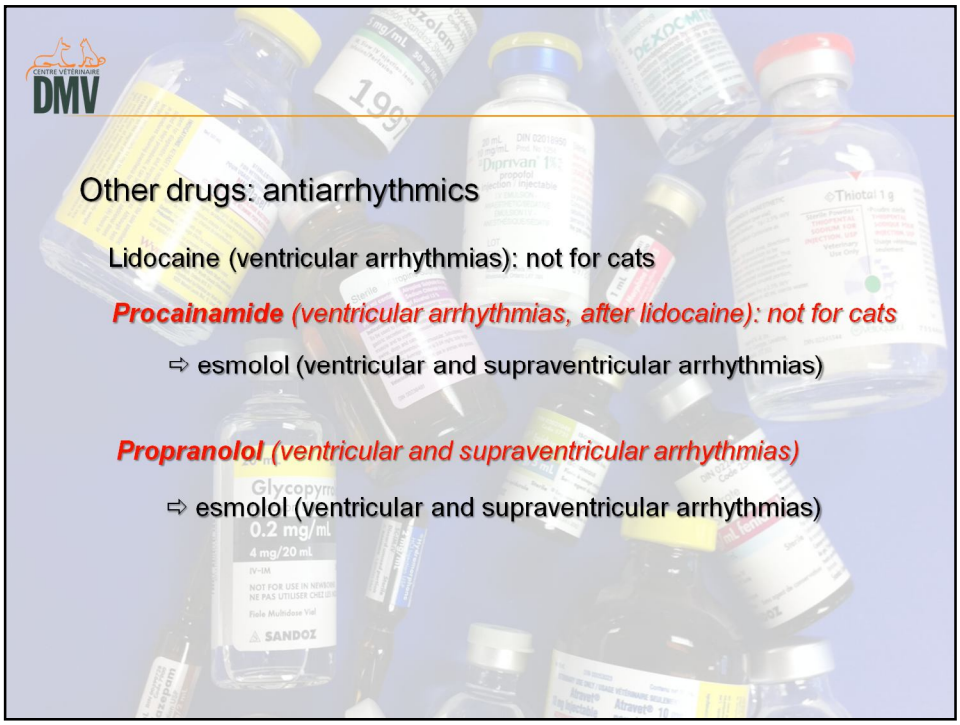
Ephedrine: cardiotonic and vasopressor support (direct α- and β-adrenergic agonist effects and indirect effects due to the release of norepinephrine).

Phenylephrine: systemic vasopressor support (α-adrenergic agonist) and reduction in bleeding when applied topically (e.g., epistaxis following rhinoscopy).

Dobutamine: positive inotropic agent (β_1-agonist, among other things). Dose: 1-10 µg/kg/min in dogs and cats.

Dopamine: similar to dobutamine (identical inotropic doses), even if dobutamine is often considered to have a better positive inotropic effect.

Vasopressor effect at high doses (> 10 µg/kg/min).



Procainamide: second-line drug for the treatment of lidocaine-refractory ventricular arrhythmias in dogs.

⇨ possible to try esmolol.

Esmolol = first-line treatment of ventricular arrhythmias in cats.

Propranolol: the shortage is not posing a problem in the case of propranolol because esmolol is preferred over it and esmolol is still available.

Esmolol = selective β_1-blocker (unlike propranolol, which is a mixed β_1/β_2 blocker) and has a rapid onset of action and an ultrashort duration of action ⇨ preferably administered as an infusion.

Sotalol, too, but it is not available as an injectable. Consequently, it has little application in anesthesia.

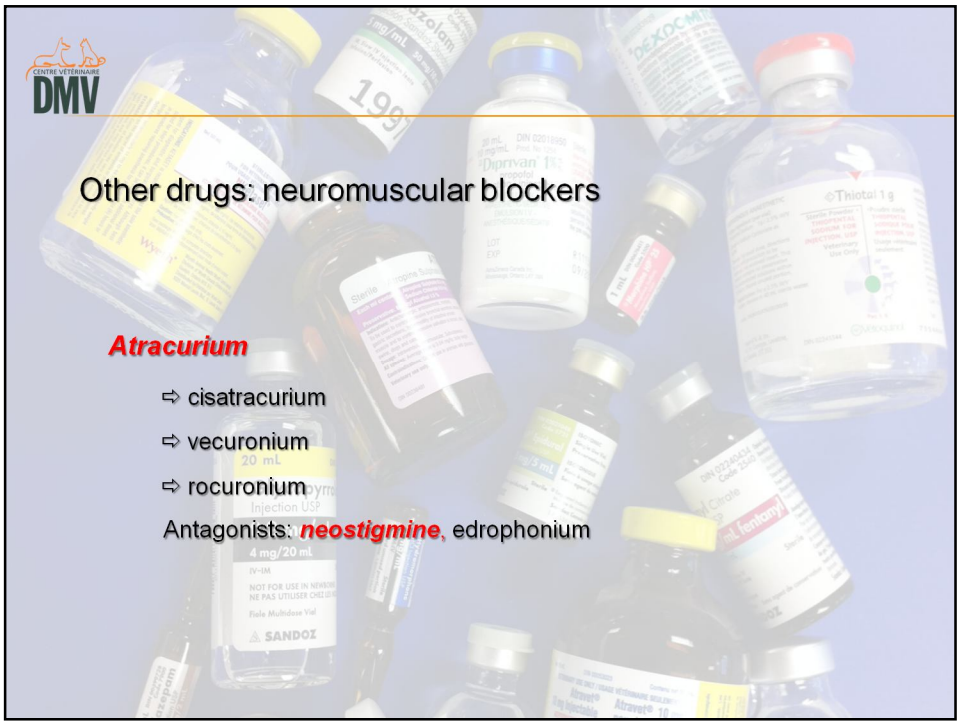
Doses for esmolol:

- Repeated boluses: 0.05-0.1 mg/kg i.v. over 2 minutes, repeatable every 5 minutes up to a maximum of 0.5 mg/kg.
- Infusion: 0.25-0.5 mg/kg i.v. over 2 minutes, then 10-200 µg/kg/min.

Diphenhydramine used to be the injectable H_1-antihistamine of first choice for anaphylactic reactions. There might be an alternative supply source.

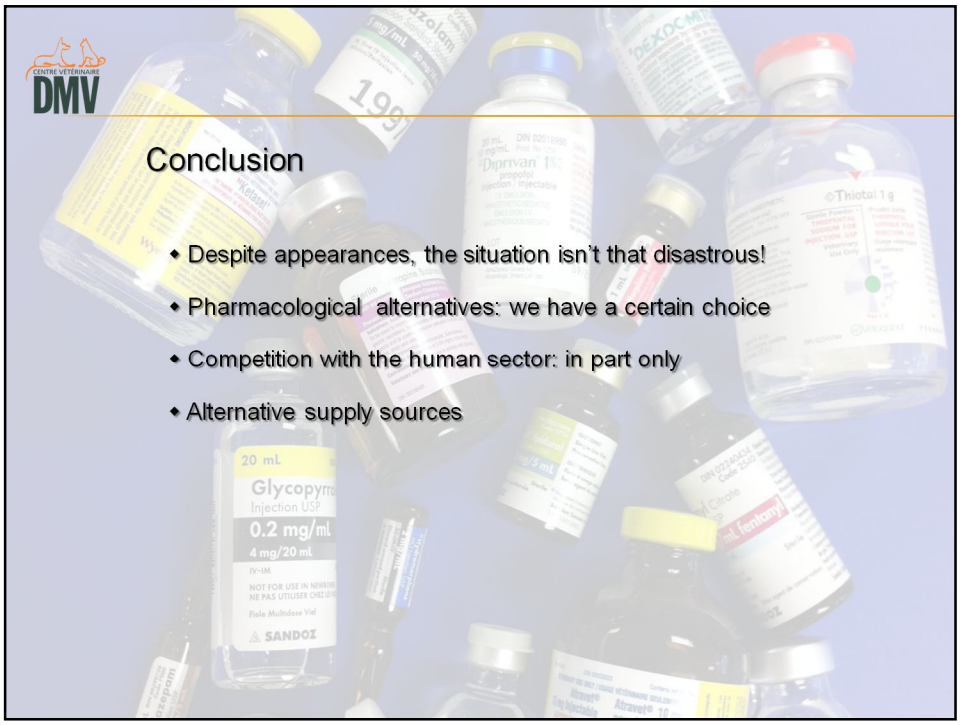
One possible alternative would be dimenhydrinate, which is manufactured by Sandoz but for which there might be an alternative supply source. It is an H_1-antihistamine used in dogs and cats, mainly for its antiemetic effect and to prevent motion sickness.

Dimenhydrinate is related to diphenhydramine, since it is a salt consisting of a diphenhydramine molecule and a molecule of 8-chlorotheophyllinate (a chlorinated form of theophylline, which is added to counter the drowsiness caused by diphenhydramine). Dimenhydrinate has to be broken down in the body into diphenhydramine before it can exert its effects. This is why they occur later than those of diphenhydramine.



Because of atracurium's short duration of action, it is often not necessary to antagonize it. This is not the case with certain alternative neuromuscular blockers.

Antagonists = acetylcholinesterase inhibitors: neostigmine, which was affected by the shortage but recently available through an alternate supplier, edrophonium (also used for diagnosing myasthenia gravis), pyridostigmine (no injectable formulation available?) and physostigmine (?).

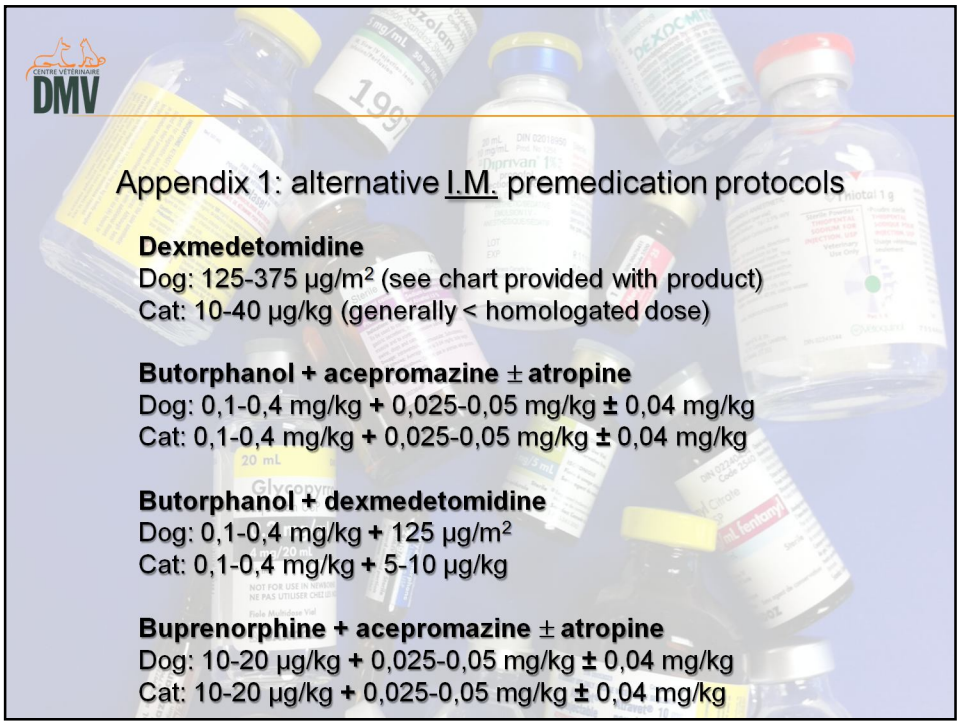


In conclusion, there is no need to panic. Although far from optimal, the situation is not as disastrous as it seems. The outcome of this crisis will depend in large part on how flexible we are and on our ability to adapt.

This is also an excellent opportunity to broaden our knowledge of the pharmacology of the drugs used for anesthesia and analgesia. In improving our knowledge of anesthetic pharmacology, we learn that there are more options than we tend to think when we are used to a routine that works well for us.

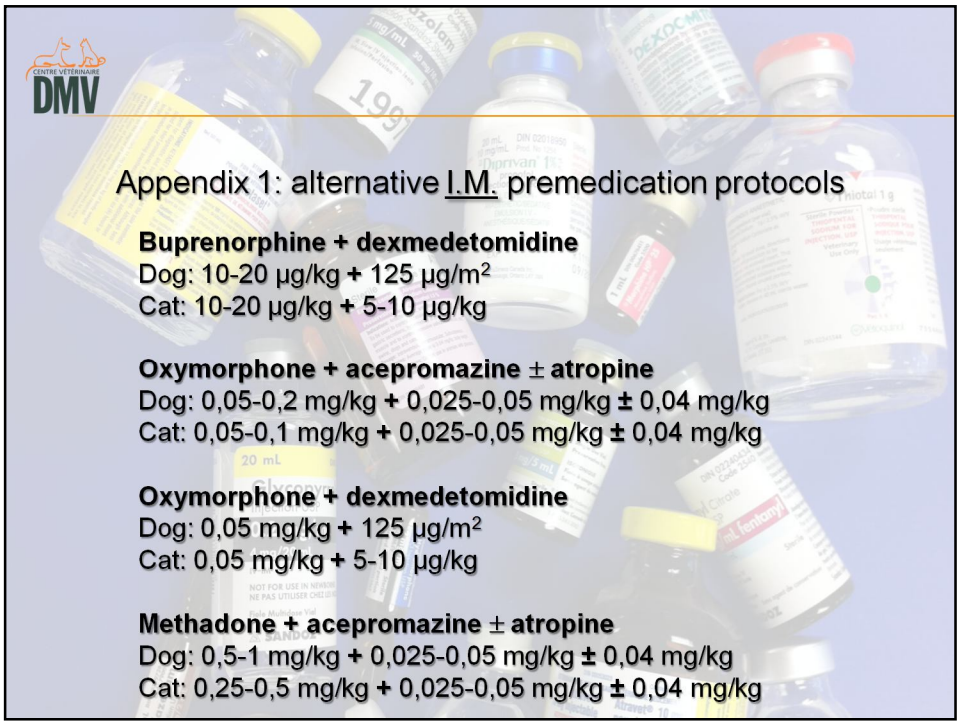
The fear of getting only the scraps left over from human medicine is only partly justified when we realize the diversity of the anesthesia and analgesia protocols available to us, which do not exclusively involve drugs that are highly coveted by the human sector at this time.

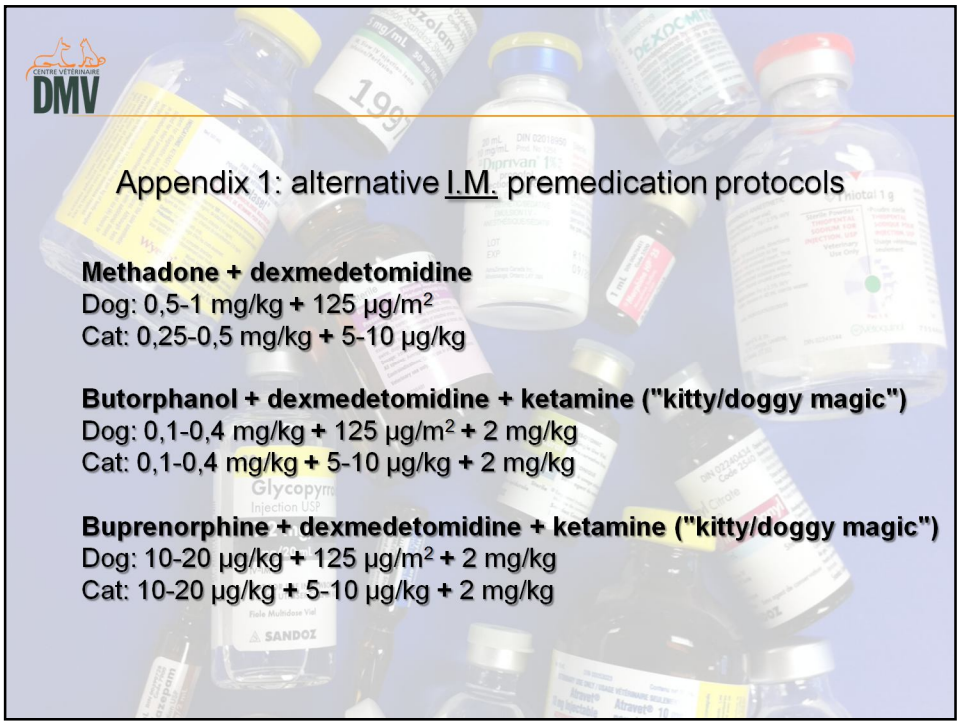
The fact that there are not only pharmacological alternatives to the drugs affected by the shortage but also possible alternative supply sources for these drugs suggests that we should not expect our reserves of anesthetic and analgesic drugs to run out in the near future.

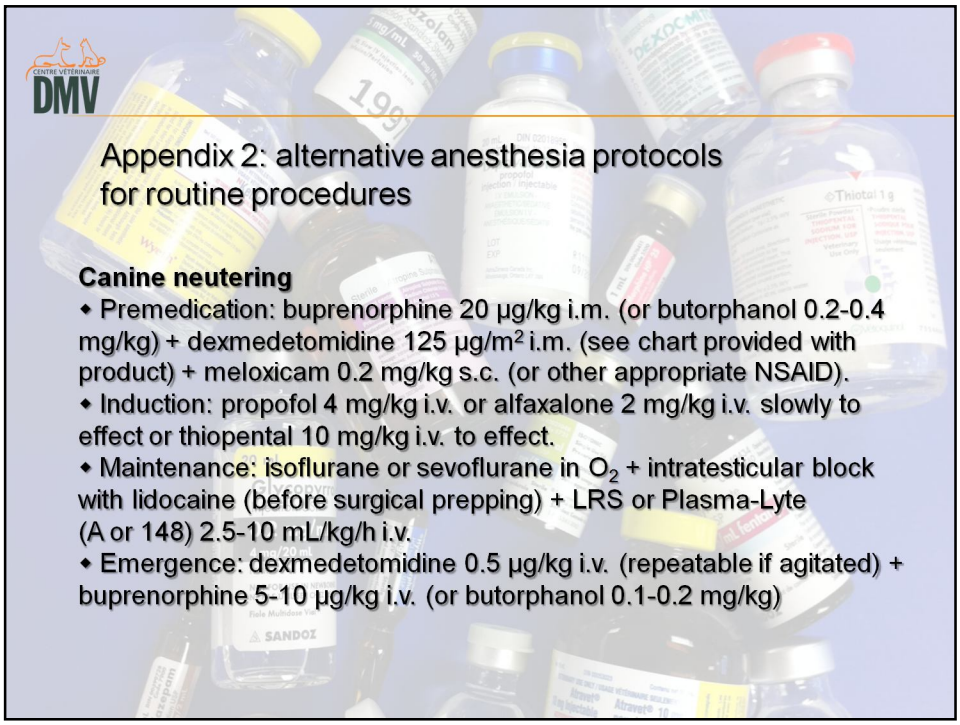


Appendix 1: these are merely suggestions for alternative protocols. They are provided as information only.

Use lower doses i.v. and possibly higher doses i.m, for especially stressed or aggressive patients or for more painful procedures.

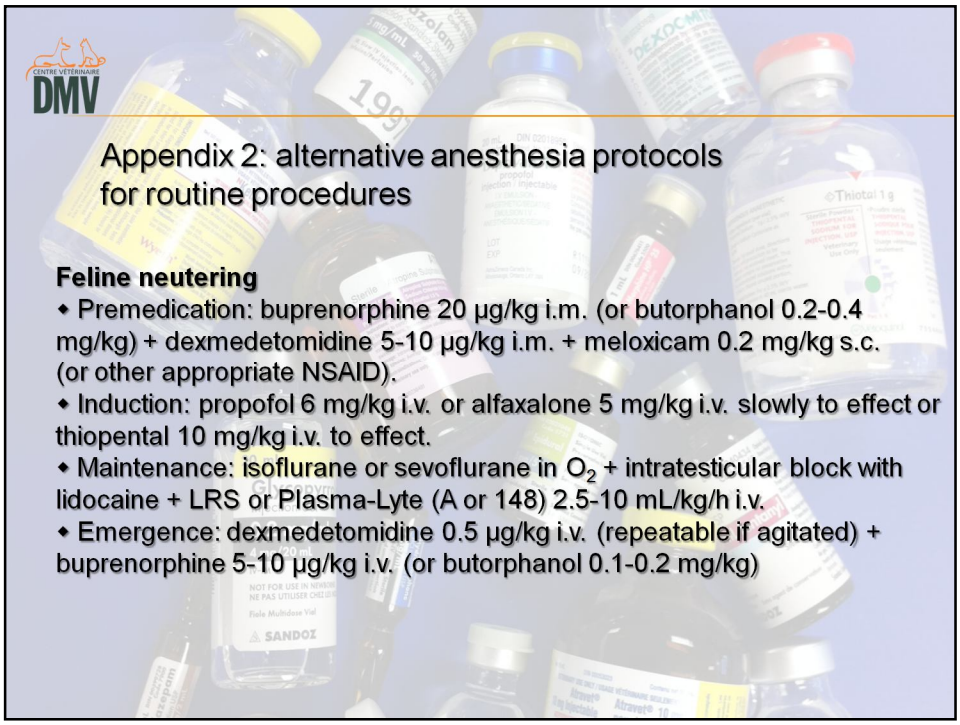

DMV
Appendix 1: alternative I.M. premedication protocols
Buprenorphine + dexmedetomidine
Dog: 10-20 µg/kg + 125 µg/m²
Cat: 10-20 µg/kg + 5-10 µg/kg
Oxymorphone + acepromazine ± atropine
Dog: 0,05-0,2 mg/kg + 0,025-0,05 mg/kg ± 0,04 mg/kg
Cat: 0,05-0,1 mg/kg + 0,025-0,05 mg/kg ± 0,04 mg/kg
Oxymorphone + dexmedetomidine
Dog: 0,05 mg/kg + 125 µg/m²
Cat: 0,05 mg/kg + 5-10 µg/kg
Methadone + acepromazine ± atropine
Dog: 0,5-1 mg/kg + 0,025-0,05 mg/kg ± 0,04 mg/kg
Cat: 0,25-0,5 mg/kg + 0,025-0,05 mg/kg ± 0,04 mg/kg


DMV
Appendix 1: alternative I.M. premedication protocols
Methadone + dexmedetomidine
Dog: 0,5-1 mg/kg + 125 µg/m²
Cat: 0,25-0,5 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



Appendix 2: these are merely suggestions for alternative protocols. They are provided as information only.

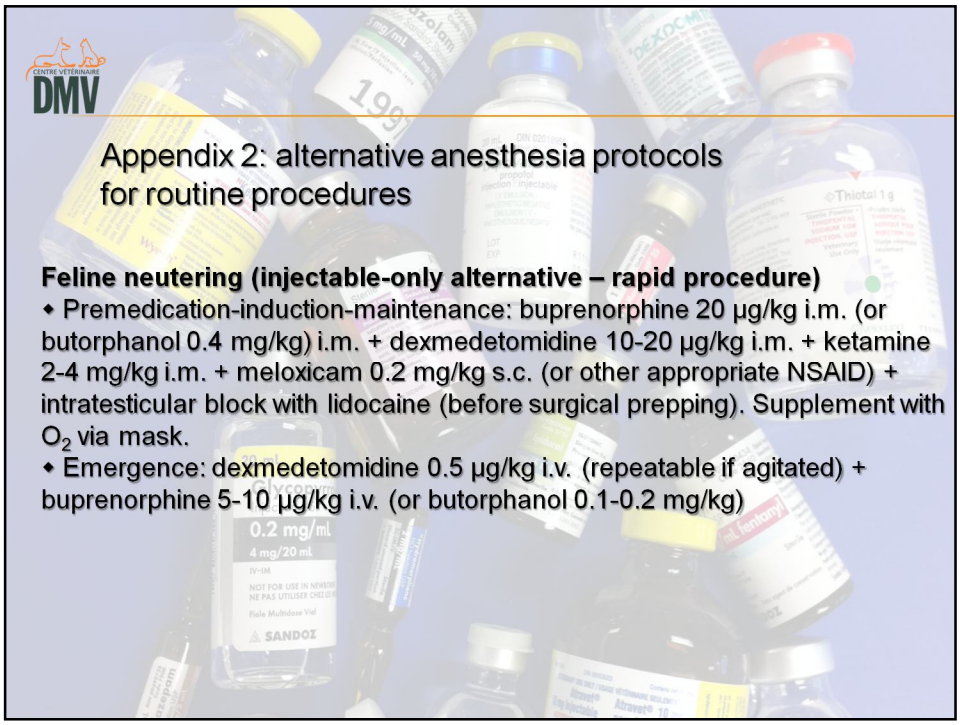
Use lower doses i.v. and possibly higher doses i.m. for especially stressed or aggressive patients or for more painful procedures. Do not use NSAIDs as premedication if hypotension is anticipated, if the animal is not receiving i.v. fluids and if its blood pressure is not being measured.



Appendix 2: alternative anesthesia protocols for routine procedures

Feline neutering

- Premedication: buprenorphine 20 µg/kg i.m. (or butorphanol 0.2-0.4 mg/kg) + dexmedetomidine 5-10 µg/kg i.m. + meloxicam 0.2 mg/kg s.c. (or other appropriate NSAID).
- Induction: propofol 6 mg/kg i.v. or alfaxalone 5 mg/kg i.v. slowly to effect or thiopental 10 mg/kg i.v. to effect.
- Maintenance: isoflurane or sevoflurane in O_2 + intratesticular block with lidocaine + LRS or Plasma-Lyte (A or 148) 2.5-10 mL/kg/h i.v.
- Emergence: dexmedetomidine 0.5 µg/kg i.v. (repeatable if agitated) + buprenorphine 5-10 µg/kg i.v. (or butorphanol 0.1-0.2 mg/kg)


DMV
Appendix 2: alternative anesthesia protocols for routine procedures
Feline neutering (injectable-only alternative – rapid procedure)
◆ Premedication-induction-maintenance: buprenorphine 20 µg/kg i.m. (or butorphanol 0.4 mg/kg) i.m. + dexmedetomidine 10-20 µg/kg i.m. + ketamine 2-4 mg/kg i.m. + meloxicam 0.2 mg/kg s.c. (or other appropriate NSAID) + intratesticular block with lidocaine (before surgical prepping). Supplement with O_2 via mask.
◆ Emergence: dexmedetomidine 0.5 µg/kg i.v. (repeatable if agitated) + buprenorphine 5-10 µg/kg i.v. (or butorphanol 0.1-0.2 mg/kg)

Appendix 2: alternative anesthesia protocols for routine procedures

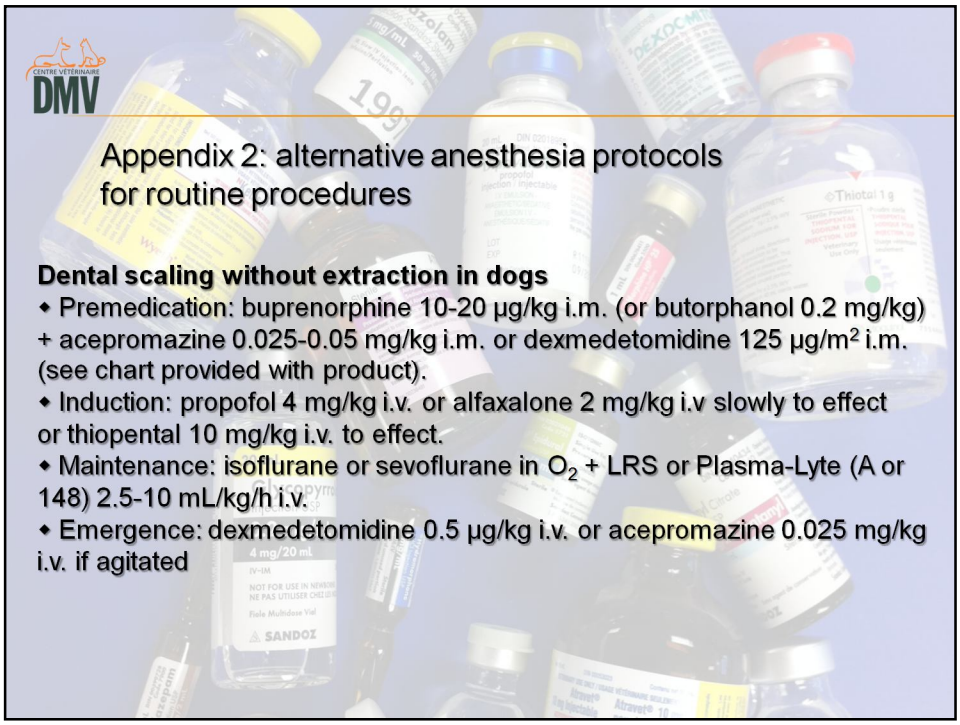
Canine spaying

- Premedication: buprenorphine 20 µg/kg i.m. (or butorphanol 0.2-0.4 mg/kg) + dexmedetomidine 125 µg/m^2 i.m. (see chart provided with product) + meloxicam 0.2 mg/kg s.c. (or other appropriate NSAID).
- Induction: propofol 4 mg/kg i.v. or alfaxalone 2 mg/kg i.v. slowly to effect or thiopental 10 mg/kg i.v. to effect.
- Maintenance: isoflurane or sevoflurane in O_2 + LRS or Plasma-Lyte (A or 148) 2.5-10 mL/kg/h i.v. Dexmedetomidine as a bolus (0.25-0.5 µg/kg i.v) if reaction to the surgical manipulation or via infusion (0.5 µg/kg followed by 0.5-2 µg/kg/h).
- Emergence: dexmedetomidine 0.5 µg/kg i.v. (repeatable if agitated) + buprenorphine 5-10 µg/kg i.v. (or butorphanol 0.1-0.2 mg/kg)

Appendix 2: alternative anesthesia protocols for routine procedures

Feline spaying

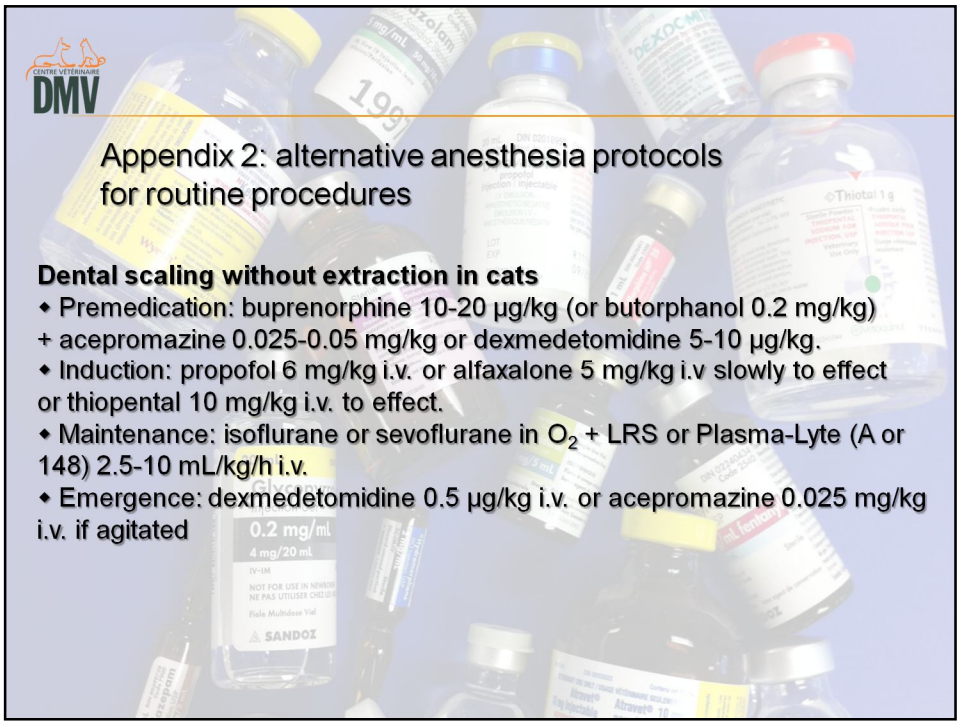
- Premedication: buprenorphine 20 µg/kg i.m. (or butorphanol 0.2-0.4 mg/kg) + dexmedetomidine 5-10 µg/kg i.m. + meloxicam 0.2 mg/kg s.c. (or other appropriate NSAID).
- Induction: propofol 6 mg/kg i.v. or alfaxalone 5 mg/kg i.v. slowly to effect or thiopental 10 mg/kg i.v. to effect.
- Maintenance: isoflurane or sevoflurane in O_2 + LRS or Plasma-Lyte (A or 148) 2.5-10 mL/kg/h i.v. Dexmedetomidine as a bolus (0.25-0.5 µg/kg i.v) if reaction to the surgical manipulation or via infusion (0.5 µg/kg followed by 0.5-2 µg/kg/h).
- Emergence: dexmedetomidine 0.5 µg/kg i.v. (repeatable if agitated) + buprenorphine 5-10 µg/kg i.v. (or butorphanol 0.1-0.2 mg/kg)



Appendix 2: alternative anesthesia protocols for routine procedures

Dental scaling without extraction in dogs

- Premedication: buprenorphine 10-20 µg/kg i.m. (or butorphanol 0.2 mg/kg) + acepromazine 0.025-0.05 mg/kg i.m. or dexmedetomidine 125 µg/m^2 i.m. (see chart provided with product).
- Induction: propofol 4 mg/kg i.v. or alfaxalone 2 mg/kg i.v slowly to effect or thiopental 10 mg/kg i.v. to effect.
- Maintenance: isoflurane or sevoflurane in O_2 + LRS or Plasma-Lyte (A or 148) 2.5-10 mL/kg/h i.v.
- Emergence: dexmedetomidine 0.5 µg/kg i.v. or acepromazine 0.025 mg/kg i.v. if agitated



Appendix 2: alternative anesthesia protocols for routine procedures

Dental scaling without extraction in cats

- Premedication: buprenorphine 10-20 µg/kg (or butorphanol 0.2 mg/kg) + acepromazine 0.025-0.05 mg/kg or dexmedetomidine 5-10 µg/kg.
- Induction: propofol 6 mg/kg i.v. or alfaxalone 5 mg/kg i.v slowly to effect or thiopental 10 mg/kg i.v. to effect.
- Maintenance: isoflurane or sevoflurane in O_2 + LRS or Plasma-Lyte (A or 148) 2.5-10 mL/kg/h i.v.
- Emergence: dexmedetomidine 0.5 µg/kg i.v. or acepromazine 0.025 mg/kg i.v. if agitated

Appendix 2: alternative anesthesia protocols for routine procedures

Dental scaling with extraction in dogs

- Premedication: buprenorphine 20 µg/kg i.m. (or butorphanol 0.2-0.4 mg/kg) + dexmedetomidine 125 µg/m^2 i.m. (see chart provided with product) + meloxicam 0.2 mg/kg s.c. (or other appropriate NSAID).
- Induction: propofol 4 mg/kg i.v. or alfaxalone 2 mg/kg i.v. slowly to effect or thiopental 10 mg/kg i.v. to effect.
- Maintenance: isoflurane or sevoflurane in O_2 + dental block with bupivacaine + LRS or Plasma-Lyte (A or 148) 2.5-10 mL/kg/h i.v. Dexmedetomidine as a bolus (0.25-0.5 µg/kg i.v.) if reaction to the surgical manipulation or via infusion (0.5 µg/kg followed by 0.5-2 µg/kg/h).
- Emergence: dexmedetomidine 0.5 µg/kg i.v. (repeatable if agitated) + buprenorphine 5-10 µg/kg i.v. (or butorphanol 0.1-0.2 mg/kg).

Appendix 2: alternative anesthesia protocols for routine procedures

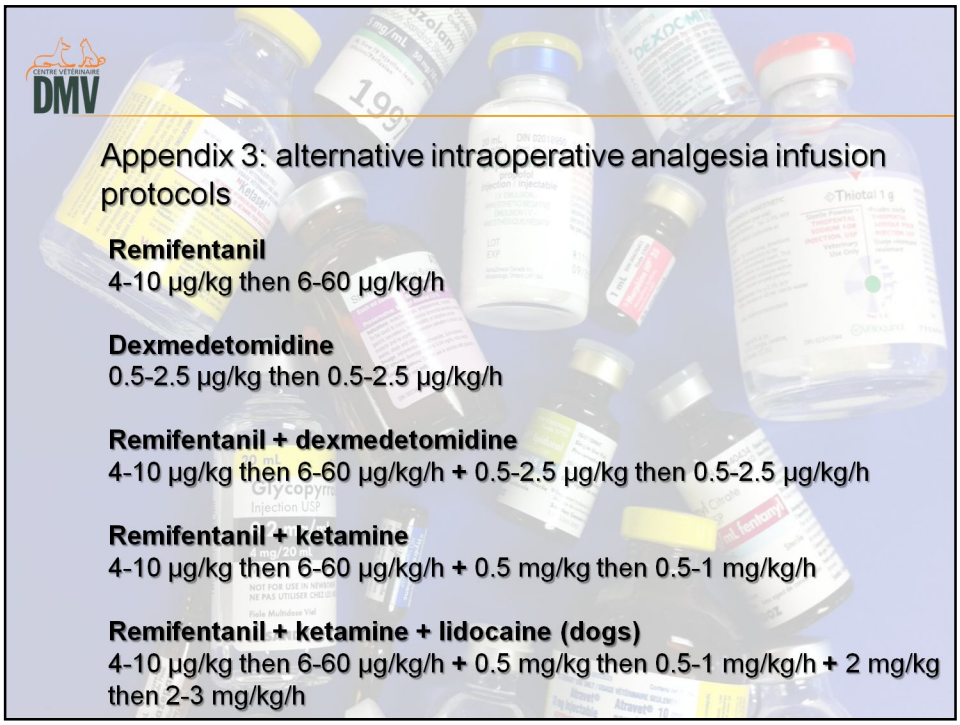
Dental scaling with extraction in cats

- Premedication: buprenorphine 20 µg/kg i.m. (or butorphanol 0.2-0.4 mg/kg) + dexmedetomidine 5-10 µg/kg i.m. + meloxicam 0.2 mg/kg s.c. (or other appropriate NSAID).
- Induction: propofol 6 mg/kg i.v. or alfaxalone 5 mg/kg i.v slowly to effet or thiopental 10 mg/kg i.v. to effect.
- Maintenance: isoflurane or sevoflurane in O_2 + dental block with bupivacaine + LRS or Plasma-Lyte (A or 148) 2.5-10 mL/kg/h i.v. Dexmedetomidine as a bolus (0.25-0.5 µg/kg i.v.) if reaction to the surgical manipulation or via infusion (0.5 µg/kg followed by 0.5-2 µg/kg/h).
- Emergence: dexmedetomidine 0.5 µg/kg i.v. (repeatable if agitated) + buprenorphine 5-10 µg/kg i.v. (or butorphanol 0.1-0.2 mg/kg).

Appendix 2: alternative anesthesia protocols for routine procedures

Declawing in cats

- Premedication: buprenorphine 20 µg/kg (or butorphanol 0.2-0.4 mg/kg) + dexmedetomidine 5-10 µg/kg i.m. + meloxicam 0.2 mg/kg s.c. (or other appropriate NSAID).
- Induction: propofol 6 mg/kg i.v. or alfaxalone 5 mg/kg i.v. slowly to effect or thiopental 10 mg/kg i.v. to effect.
- Maintenance: isoflurane or sevoflurane in O_2 + ring block with bupivacaine + LRS or Plasma-Lyte (A or 148) 2.5-10 mL/kg/h i.v. Dexmedetomidine as a bolus (0.25-0.5 µg/kg i.v.) if reaction to the surgical manipulation or via infusion (0.5 µg/kg followed by 0.5-2 µg/kg/h).
- Emergence: dexmedetomidine 0.5 µg/kg i.v. (repeatable if agitated) + buprenorphine 5-10 µg/kg i.v. (or butorphanol 0.1-0.2 mg/kg).



Appendix 3: these are merely dosage suggestions for alternative intraoperative analgesic infusion protocols. They are provided as information only. The effective dose will vary according to the intensity of the pain to be prevented or treated.


DMV
Acknowledgement
Translation department of Pfizer Animal Health
Pfizer
Animal Health