IMPROVING PATIENT OUTCOMES WITH α–2 AGONISTS

Worth it.

zoetis

The Aims of Premedication and Sedation

The **aims of premedication** are:

1. To provide **sedation and anxiolysis** in the patient to facilitate handling and reduce stress for the patient and the veterinary team;
2. To contribute to **balanced anaesthesia,** reducing doses required of induction and maintenance agents, reducing undesirable side effects also;
3. To provide **pre-emptive analgesia,** the first step in **preventative analgesia,** to minimise maladaptive pain response and sensitisation of pain pathways to maximise patient comfort;
4. To help **smooth** the **induction, maintenance** and **recovery** phases of anaesthesia;
5. To **reduce side effects** of other medications and/or reduce unwanted autonomic reflexes;
6. To induce **muscle relaxation** to facilitate gentle manipulation of the patient[1-3].

The **aims of sedation** do not differ greatly from those of pre-medication (with the exclusion of anaesthetic induction and maintenance).

In some cases, a **deeper level of sedation** may be required, depending on the procedure being performed. **Reversibility** is a desirable addition also[1-6].

No single medication fulfils all these aims in their entirety, so a **combination of agents** is generally recommended.

Because patient needs and procedural requirements vary and veterinary practitioners have differing preferences, the combination for either premedication or sedation should be **tailored for every case**, generally a sedative/tranquiliser with an opioid[1-6].

The α–2 Adrenoceptor Agonists

When clinically appropriate for the patient, the **α–2 adrenoceptor agonists** (aka 'α–2 agonists') are an excellent choice to include in **premedication or sedative** regimes for many patients as they fulfil many of these aims in themselves and are compatible with – and in some cases, synergistic with – other premedicant agents[1–3].

The most commonly used α–2 agonists in cats and dogs are **medetomidine** (found in both **Domitor**® and **Medetate**®) and **dexmedetomidine** (found in **Dexdomitor**®).

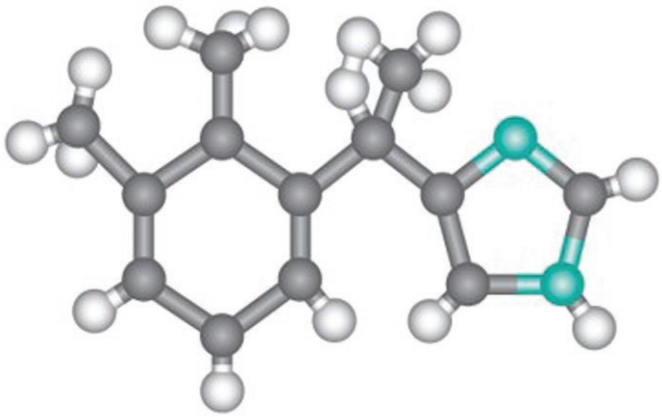
Medetomidine is an equal mixture of two isomers, **dexmedetomidine** and **levomedetomidine**, which are mirror images of one another[2,7,8].

The **dexmedetomidine** component is **active**, whilst levomedetomidine is considered to be pharmacologically inactive. It may, however, be involved in drug interactions and still requires hepatic metabolism to be cleared from the body[2,7,8].

Dexmedetomidine alone is a '**purified**' form, containing only the active component, leading to a reduction in the metabolic burden on the patient's liver[2,7,8].

Levomedetomidine: inactive

Dexmedetomidine: active



The dose strength of medetomidine in Domitor and Medetate is 1mg/mL and dexmedetomidine in Dexdomitor is 0.5mg/mL. The dose volumes for approximately equipotent effects are similar*, with only minor differences in terms of clinical effects noted between the two[1–11].

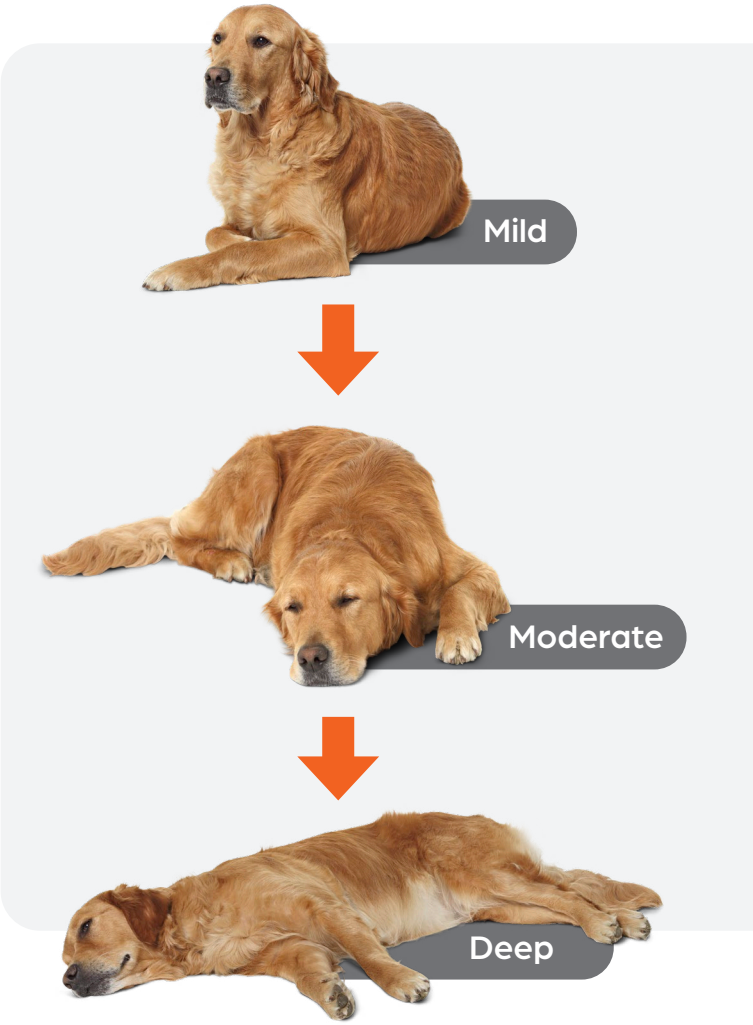
*When administered IM in cats, for approximately equipotent effects, the dose volume of dexmedetomidine is the same as that of medetomidine; when administered IM/IV in dogs, medetomidine is dosed on a bodyweight basis, while dexmedetomidine is dosed on a body surface area basis.

The Benefits of α–2 Agonists

When incorporated into anaesthesia or sedation protocols in cats and dogs, there are many desirable effects of α–2 agonists, helping fulfil the aims of premedication and sedation. These include:

Predictable, dose–dependent sedation:

- The **dose** and resulting **level** of **sedation** provided by α–2 agonists can be **carefully tailored** for the patient and the procedure, from **mild to moderate to deep sedation**[1–5].
  - > The level of sedation induced by α–2 agonists is reported to be more predictable than that of benzodiazepines or phenothiazines[5].
- α–2 agonists are **synergistic** with **opioids**, enabling greater sedative efficacy at lower doses when administered together[1].
- **The level of sedation plateaus** at higher dose rates and the **duration is extended**, rather than the animal becoming more deeply sedated. Side effects also increase with a dose increase[2,6–8].
- Note that the **sedative effects** of α–2 agonists are **longer lasting** than **analgesic** effects[1,2,7,8].



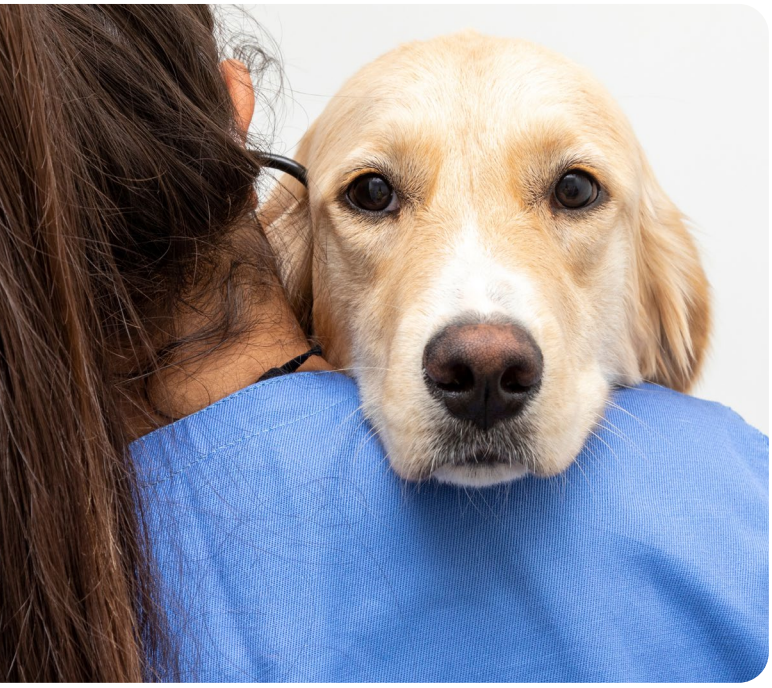
Following IM injection, medetomidine has a slightly faster onset of action than dexmedetomidine, a longer duration of action and a higher sedative efficacy in dogs[2,8–10]. In cats, no significant differences in sedation are noted between the two[8,11].

Profound analgesia, ideally suited to a multi–modal approach:

- α–2 agonists are **synergistic** with **opioids**, enabling greater analgesic efficacy at lower doses when administered together[1].
- The **analgesia** provided by α–2 agonists is relatively **short–lived** and should not be used as a sole source of pain relief for painful procedures[1,2].
- α–2 agonists provide good **visceral analgesia**[1], making them an excellent choice for soft tissue surgeries, such as speys and castrations, in conjunction with an opioid.
  - > Neither phenothiazines nor benzodiazepines provide any analgesia[1–5].

In dogs, the analgesic effects of dexmedetomidine are slightly longer lasting than medetomidine[7,10]. In cats, no significant differences in analgesia are noted between the two[8,11].

The Benefits of α–2 Agonists (continued)



Anxiolysis:

- Both medetomidine and dexmedetomidine produce **anxiolysis**[1,4], which is important for pets, their owners and veterinary staff, especially in terms of **fear–free** techniques and promoting a positive in–clinic experience. This is particularly important for **highly bonded pet owners** and will help to build their relationship with the veterinary team[12].

Muscle Relaxation:

- Both medetomidine and dexmedetomidine have **excellent muscle relaxation** properties, which facilitate handling of the patient and gentle manipulation to, for example, place IV catheters or position the patient for x–rays[1–3,6].

Drug sparing effects on other peri–anaesthetic medications:

- α–2 agonists have been found to **reduce the required induction or maintenance** agent doses by **up to 70%**. They are significantly more dose–sparing then either phenothiazines or benzodiazepines[1,2,5].

Reversibility:

- Both medetomidine and dexmedetomidine are equally well antagonised by **atipamezole** (found in both **Antisedan**® and **Antipam**), at the same dose rate, with both the sedative and analgesic effects being reversed[1–6,8,10,11].

Effects of α–2 Agonists to be Aware of

Bi–phasic effect on blood pressure: initially hypertension, followed by hypotension ~20–30 minutes later, later returning to normotension[1–5]	Bradycardia due to the baroreceptor response to initial hypertension; HR can decrease to 45–60 bpm in dogs and 100–115 bpm in cats[1–5]
Reduction in GI tract motility and blood flow[1,2], with vomiting commonly noted (cats > dogs)[1,–3,5]	Reduced insulin release, leading to hyperglycaemia[1–3]
Depression of thermoregulatory centre, but partially offset by peripheral vasoconstriction, to reduce the degree of body heat loss[1–3,5]	Minimal respiratory effects, with a slight reduction in respiratory rate offset by an increase in tidal volume[1,2,5]
Modification of uterine contractility[1–3,5]	Reduced anti–diuretic hormone release, leading to diuresis[1–5]
Decrease in ACTH secretion for reduced cortisol and a reduced stress response[1]	Reduced hepatic blood flow and rate of metabolism of drugs by the liver[2]
Reduction in intracranial pressure[1–3]	Reduction in intraocular pressure[1–3]

See product labels for further information.

Using α–2 Agonists in your Patients

α–2 agonists are generally recommended for use in **ASA Status Classification I–II patients**[3]. They provide **excellent dose–dependent sedation, anxiolysis, muscle relaxation** and **analgesia,** which is augmented when co–administered with **opioids,** due to **synergism** between the two medication classes, enabling a reduction in the dose required, and the side effects produced[1–3,5].

Their **reversibility** makes them an outstanding choice for sedation, as the patient can be sent home to their family promptly following the procedure, without grogginess or unsteadiness[1–3].

α–2 agonists are *not* recommended for patients with significant cardiovascular disease, hepatic disease, renal disease, hypotension or shock or in geriatrics, neonates, diabetics, debilitated patients or pregnant patients[1–3,5].

Circulation time is increased with α–2 agonist use, so when used as a premedication, it is critical to **administer induction agents** (such as Alfaxan®) **slowly** and assess the depth of anaesthesia during induction, remembering the profound **dose–sparing** effect of α–2 agonists[1,2].

The Zoetis range of α–2 agonists and accompanying reversal agents provides you with choice: choice of the agent, medetomidine (**Domitor** and **Medetate**) or dexmedetomidine (**Dexdomitor**); choice of the pioneer product (**Domitor, Dexdomitor, Antisedan**) or a high–quality Australian–made version to support local manufacturing (**Medetate, Antipam**).

Zoetis also provides you with a comprehensive suite of other peri–anaesthetic agents to accompany the α–2 agonists, from opioids [**Methadyne**™ (methadone), **Buprelieve**® (buprenorphine) and **Butordyne**® (butorphanol)] to induction agents (**Alfaxan**® **Multidose** and **Alfaxan**® injection) and maintenance agents (**Isoflo**®).

All are available now through Zoetis Direct!

References: 1. Dugdale AHA et al. Chapter 4 Sedation and Premedication: Small Animals. In: Veterinary Anaesthesia: Principles to Practice. 2nd Edition 2020, © Wiley-Blackwell; 55-76. **2.** Duke-Novakovski T et al. BSAVA Manual of Canine and Feline Anaesthesia and Analgesia 3rd Edition 2016. **3.** Murrell J. Premedicants in cats and dogs: which one should you choose and when? In Practice 2022;44(4):205-213. **4.** Rankin DC. Chapter 10 Sedatives and Tranquillizers. In: Grimm et al. Lumb and Jones Veterinary Anaesthesia and Analgesia 5th Edition 2015. © John Wiley and Sons; 196-206. **5.** Pawson P. Chapter 6 Sedatives. In: Small Animal Pharmacology 2nd Edition 2008, © Elsevier Ltd;113-125. **6.** Robertson SA et al. AAFP Feline Anesthesia Guidelines. JFMS 2018;20:602-634. **7.** Kuusela E et al. Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. J Vet Pharmacol Therap 2000;23 15-20. **8.** Bennett RC et al. Dexmedetomidine or medetomidine: which should veterinary surgeons select? Companion Animal 2016;21(3): 128-137. **9.** Kuusela E et al. Comparison of medetomidine and dexmedetomidine as premedicants in dogs undergoing propofol-isoflurane anesthesia. AJVR 2001;62(7):1073-1080. **10.** Granholm M 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 Record 2007;160:891-897. **11.** Granholm M 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(4):214-223. **12.** Zoetis International HABRI Survey – The Veterinarian Perspective, 2023, data on file.