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RESEARCH PAPER

# The effects of L-659,066, a peripheral α2-adrenoceptor antagonist, on dexmedetomidine-induced sedation and bradycardia in dogs

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## Abstract

**Objective** To investigate the influence of L-659,066, a peripheral α2-adrenoceptor antagonist, on dexmedetomidine-induced sedation and reduction in pulse rate (PR) in dogs.

**Study design** Randomized, cross-over.

**Animals** Six healthy laboratory Beagles.

**Methods** All animals received dexmedetomidine (5 μg $kg^{-1}$ IV, DEX) alone or in combination with L-659,066 (250 μg $kg^{-1}$ IV, DEX + L) with a 7-day rest period between treatments. Sedation was assessed using a composite sedation score and PRs were recorded. Atipamezole (50 μg $kg^{-1}$ IM, ATI) was administered to reverse the sedation. Overnight Holter-monitoring was carried out to obtain a minimum heart rate (MHR) at rest.

**Results** Bioequivalence was shown for clinical sedation between DEX and DEX + L. Heart rate was significantly higher with DEX + L during the period of sedation. Bioequivalence was demonstrated between MHR and PR in the DEX + L group during the period of sedation. Recoveries after ATI were uneventful.

**Conclusions** L-659,066 did not affect the quality of dexmedetomidine-induced sedation whilst it attenuated the reduction in PR. Thus, L-659,066 could prove a useful adjunct to reduce the peripheral cardiovascular effects attributed to dexmedetomidine in dogs.

**Clinical relevance** The clinical safety of α2-adrenoceptor agonists could be markedly improved with less peripheral cardiovascular effects.

*Keywords* atipamezole, dexmedetomidine, dog, heart rate, L-659,066, sedation.

## Introduction

While more novel and specific α2-adrenoceptor agonists have been developed in recent years, concern still remains over their cardiovascular effects (Murrell & Hellebrekers 2005). Dexmedetomidine, the active isomer of racemic medetomidine, is the latest and most specific compound licensed for use in dogs whilst the levo-isomer has little or no pharmacological activity (Kuusela et al. 2000). Briefly, the initial vasoconstriction mediated via α2-adrenoceptors located in vascular smooth muscle leads to an initial hypertension (Bloor et al. 1992). This sudden elevation in arterial blood

pressure results in an acute fall in pulse rate (PR) thought to be mediated mainly by the baroreflex. Bradycardia and decreased cardiac output follow, with further depression of cardiovascular function because of later central sympatholysis. These cardiovascular effects occur with lower doses than commonly used for sedation and thus reduce the clinical safety of α2-adrenoceptor agonists, especially in patients with cardiovascular compromise (Pypendop & Verstegen 1998).

In previous attempts to prevent or attenuate these cardiovascular effects, several studies on the use of anticholinergic drugs with α2-adrenoceptor agonists have been reported (Short 1991; Alibhai et al. 1996; Ko et al. 2000, 2001). The conclusion from these studies suggested that whilst anticholinergic agents attenuated medetomidine-induced bradycardia in dogs, they also accentuated the hypertension thus leading to a further increase in cardiac workload and myocardial oxygen consumption. Consequently, the routine use of anticholinergic drugs in conjunction with α2-adrenoceptor agonists remains controversial. Atipamezole, a central and peripheral α2-adrenoceptor antagonist reversed the cardiovascular effects of α2-adrenoceptor agonists, but as it also reversed the central effects, its use in clinical situations (e.g. during an invasive procedure) is somewhat challenging (Vainio 1990). However, promising results have been obtained when the peripheral cardiovascular effects of dexmedetomidine were prevented by pre-medicating dogs with L-659,066, a peripherally selective α2-adrenoceptor antagonist (Pagel et al. 1998). Further, when the two compounds were administered simultaneously, L-659,066 prevented completely the peripheral systemic hemodynamic effects of dexmedetomidine in sheep (Honkavaara et al. 2006). Thus, although there is a central component to the cardiovascular effects of α2-adrenoceptor agonists, L-659,066 could prove useful in preventing the initial vasoconstriction and improve the margin of safety of dexmedetomidine (or medetomidine).

However, in order for this concept to be clinically relevant, L-659,066s central antagonistic action in dogs should be minimal. While L-659,066 has been shown not to extensively cross the blood-brain–barrier of rats or marmosets (Clineschmidt et al. 1988), there are no published reports on its effects on α2-adrenoceptor agonists' central effects in dogs. Hence, the aim was to investigate the effects of L-659,066 on dexmedetomidine-induced sedation and its reversal by atipamezole in dogs. The PRs were also recorded.

## Methods

The present study was approved by the Laboratory Animal Ethics Committee of the Helsinki University. Six healthy Beagles aged from 9 to 11 years and weighing between 12 and 21 kg were used. No abnormalities were detected on clinical examination or routine laboratory analyses (complete blood counts and serum chemistry). The dogs were housed in groups and were fed a commercial diet which was withheld for 12 hours prior to the experiments but fresh water was provided *ad libitum*.

The dogs were randomly assigned into a cross-over design with a minimum period of 7 days between treatments. The cephalic vein was cannulated under local anaesthesia (5 mg lidocaine, lidocain 20 mg $mL^{-1}$, Orion Pharma, Turku, Finland) with a 22-SWG catheter (Optiva-2) and lactated Ringer's solution was infused (5 mL $kg^{-1}$ $hour^{-1}$) during the experiments. For the control treatment (DEX), 5 μg $kg^{-1}$ of dexmedetomidine (Dexdomitor 0.5 mg $mL^{-1}$, Orion Pharma) was diluted with sterile saline to a volume of 10 mL. On a separate occasion, 250 μg $kg^{-1}$ of L-659,066 (Merck, Sharpe & Dohme, PA, USA) was added to the diluted dexmedetomidine solution (DEX + L) just prior to administration. Drugs were administered intravenously over a 30-second period. Sedation was assessed subjectively by an investigator blinded to the treatment using a composite sedation score (CSS), (Kuusela et al. 2000), see Appendix 1. The CSS was assessed prior to (baseline) and 5, 10, 20 and 40 minutes after drug administration. Immediately after the 40 minute CSS assessment, 50 μg $kg^{-1}$ of atipamezole (Antisedan 5 mg $mL^{-1}$, Orion Pharma) was injected intramuscularly and the CSS was assessed for a further 20 minutes at 5 minute intervals. Pulse rates were counted by femoral artery palpation (30-second average) after each CSS. The time to onset of sedation (time to lateral recumbency) after the initial treatments was recorded. Recovery times after atipamezole (time to standing) were also recorded. Rectal temperature was measured prior to the first and after the last CSS. Several weeks after the experiments, an overnight Holter-monitoring (Hyvärinen et al. 2006) was carried out on all dogs to compare the PRs during rest and the treatment

  