Strathprints Institutional Repository

A comparison of medetomidine and its active enantiomer dexmedetomidine when administered with ketamine in mice

Wesley M. Burnside, Aurélie Thomas, Angus I. Cameron & Paul A. Flecknell
Comparative Biology Centre, Newcastle University, Framlington Place, Newcastle upon Tyne NE2 4HH, UK

Introduction

Medetomidine-ketamine (MK) and dexmedetomidine-ketamine (DK) are widely used to provide general anesthesia, yet have only been compared in the golden-headed lion tamarin.[1] Similarly, medetomidine and dexmedetomidine alone have only been compared in the dog[2] and rat[3].

Ketamine rapidly induces dissociative anesthesia while also providing analgesia; its side effects include minimal tachycardia, dysphoria, and muscle rigidity.

Medetomidine, a 1:1 racemic mixture of stereoisomers levomedetomidine and dexmedetomidine, is an α_2 agonist sedative and analgesic; its side effects include bradycardia, hypotension, respiratory depression, and diuresis. Dexmedetomidine is the active enantiomer of medetomidine.[2] Reversibility by atipamezole is a major advantage of these drugs.

The objectives of this study were to compare the effects of MK and DK, administered IP or SC, on the 1) loss of the righting reflex (LORR); 2) tail-pinch reflex; 3) pedal reflex; 4) heart rate (HR); 5) respiratory rate (*fr*); 6) peripheral oxygen saturation (S_pO_2), and 7) regain of the righting reflex (RORR)over time in mice.

Methods

Animals: Male (n = 10) and female (n = 10) C57BL/6N mice[a], weighing 21 ± 2.3 g at the time of the study, were previously acclimated in a ventilated closed system for two weeks.

Experimental Design: The mice underwent 4 anesthetic treatments in a randomized crossover design with ≥ 48 hours between treatments; ketamine[b] (75 mg kg^{-1}) was combined with medetomidine[c] (1 mg kg^{-1}) or dexmedetomidine[d] (0.5 mg kg^{-1}) and injected IP or SC.

Procedure: The LORR was recorded. Mice were placed on a heating pad without supportive oxygen. Tail-pinch and pedal reflexes, HR, *fr*, and S_pO_2 were monitored for 89 minutes from 5 minutes post-induction at 7-minute intervals with the pulse oximeter[e] probe on the thigh. Atipamezole[f] (5 mg kg^{-1}) was administered to reverse anesthesia (same route as induction). The RORR was recorded.

Statistical Analysis: General linear models were used to analyze LORR and RORR times. The presence of tail-pinch and pedal reflexes were evaluated with binomial generalized linear models. The HR, *fr*, and S_pO_2 were examined with generalized additive mixed effects models which accounted for individual random variation among mice (Fig. 1).

[a] Charles River UK Ltd., Margate, UK
[b] Ketalar™ Injection, Pfizer Ltd., Sandwich, UK
[c] Domitor®, Janssen Animal Health, Basingstoke, UK
[d] Dexdomitor®, Janssen Animal Health, Basingstoke, UK
[e] MouseOx®, Starr Life Sciences Corp., Oakmont, PA, USA
[f] Antisedan®, Janssen Animal Health, Basingstoke, UK

Results & Discussion

There were no significant differences in LORR or RORR times ($p \geq 0.077$; Fig. 2). Anesthetic depth was monitored by tail-pinch and pedal reflexes. Loss of the tail-pinch reflex always occurred by 12 minutes post-induction and was not affected by treatment (p = 0.359; Fig. 3). Pedal reflex loss was not consistently achieved by either drug, but was more frequent with MK than DK over time (p = 0.021; Fig. 3). In rats, medetomidine and dexmedetomidine alone did not induce sustainable pedal reflex loss.[3]

Heart rate was not affected by treatment (Fig. 1a), but covaried with time and *fr* ($p \leq 0.002$; Fig. 4a,b). Bradycardic effects were apparent for approximately 26 minutes post-induction; the HR increased thereafter. In the conscious dog, HR was similarly affected by medetomidine and dexmedetomidine alone.[2] In tamarins, MK-treated individuals had a significantly higher HR over time.[1]

The *fr* was significantly higher with MK than DK (Fig. 1b; $p < 0.001$), and increased as S_pO_2 decreased (Fig. 4b,c; $p < 0.001$). On observation, the depth of breath appeared more shallow over time; this may account for the increase in *fr* over time. No difference was seen in *fr* in conscious dogs treated with medetomidine or dexmedetomidine alone, but significantly reduced *fr* overall.[2]

Mice injected IP had a significantly higher S_pO_2 (Fig. 1c; p = 0.040), but hypoxia was still evident. The S_pO_2 was positively correlated with bodyweight (p = 0.006) and significantly lower in males than females (p = 0.008). The S_pO_2 was negatively correlated with HR (p = 0.001), *fr* ($p < 0.001$), and time ($p < 0.001$; Fig. 4c).

Hypoxia is a significant cause of mortality in anesthetized mice, yet supportive oxygen is not commonly used.[4] Hypoxia was marked within 5 minutes post-induction (83.8 ± 6.7 % S_pO_2) and S_pO_2 decreased severely to 66.7 ± 7.5 % by 89 minutes (Fig. 4c).

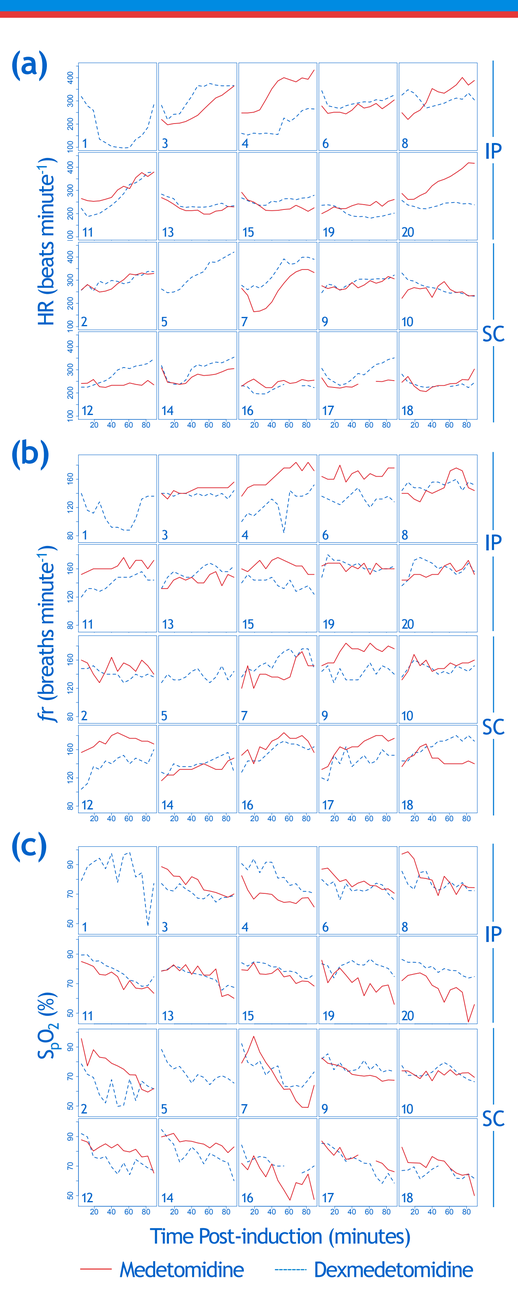

Figure 1. Individual plots by mouse for (a) HR, (b) *fr* and (c) peripheral oxygen saturation (S_pO_2) by drug-ketamine combination and administration route (IP or SC) over time post-induction used for statistical analysis.

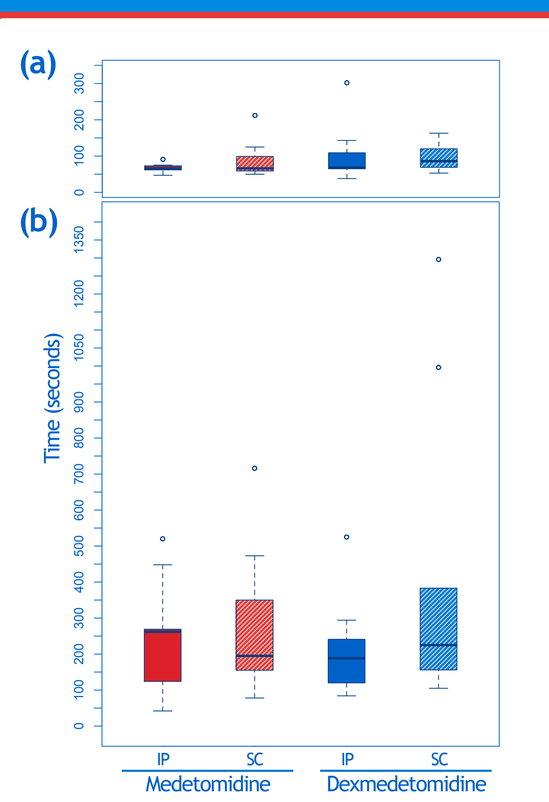

Figure 2. Mean (a) loss of righting reflex (LORR) and (b) regain of righting reflex times (RORR) times by drug-ketamine combination and administration route.

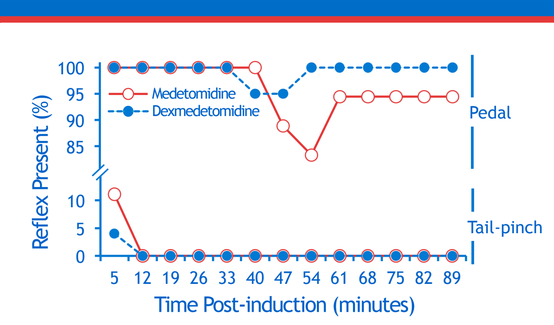

Figure 3. Pedal and tail-pinch reflex presence by drug-ketamine combination and administration route over time post-induction.

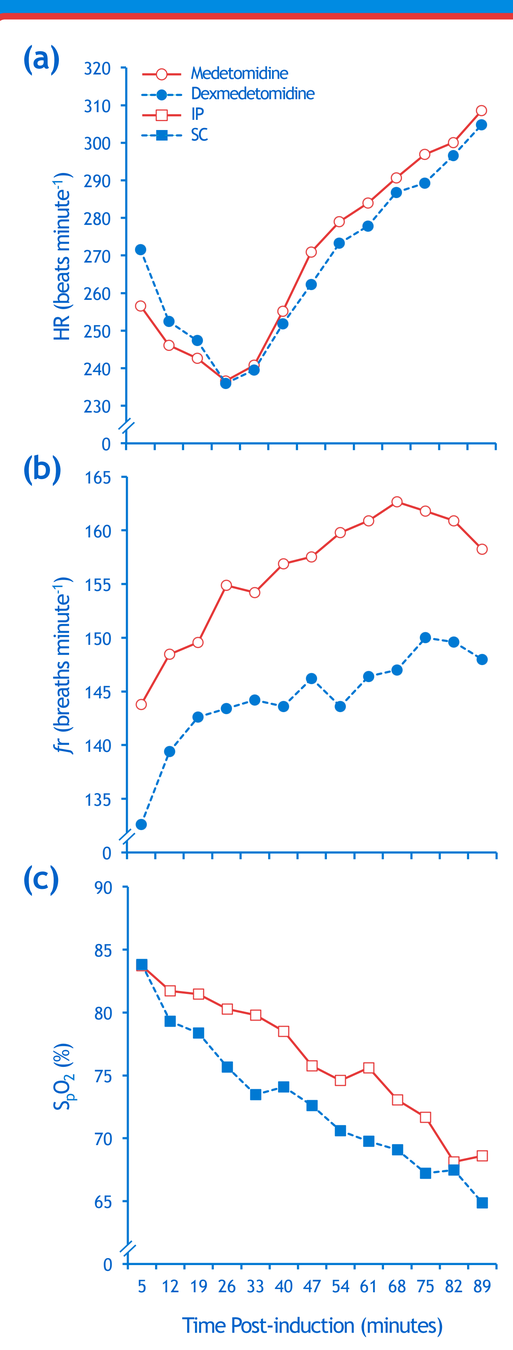

Figure 4. Mean (a) HR and (b) *fr* by drug-ketamine combination, and (c) peripheral oxygen saturation (S_pO_2) by administration route, over time post-induction.

Conclusions

- There were no clinical advantages of dexmedetomidine over medetomidine in this study.
- The doses of MK and DK administered in this study do not appear to have provided appropriate anesthetic depth for surgical procedures.
- There were no clinical advantages of IP over SC administration as the onset and anesthetic depth were similar; therefore, the SC route is favorable to prevent damage to internal organs that may occur IP.
- All mice were markedly or severely hypoxic throughout this study. Always provide oxygen to prevent this.

References

1. Selmi AL, Mendes GM, Figueiredo JP et al. (2004) Comparison of medetomidine-ketamine and dexmedetomidine-ketamine anesthesia in golden-headed lion tamarins. Can Vet J 45, 481-485.
2. Kuusela E, Raekallio M, Anttila M et al. (2000) Clinical effects and pharmacokinetics of medetomidine and its enantiomers in dogs. J Vet Pharmacol Therap 23, 15-20.
3. Savola JM, Virtanen R (1991) Central α_2-adrenoreceptors are highly stereoselective for dexmedetomidine, the dextro enantiomer of medetomidine. J Pharm 195, 193-199.
4. Flecknell PA (2009) Laboratory Animal Anaesthesia, 3rd ed. Academic Press, London, UK.

Acknowledgements

Animals were kindly supplied by Charles River.