The effects of dexmedetomidine on the ventilatory response to hypercapnia in rabbits

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Abstract  Objective: Dexmedetomidine is a highly selective \(\alpha_2\)-adrenergic agonist that can reduce anesthetic requirements. This study, to assess its effect on respiration, examined the effects of various doses of dexmedetomidine (1, 10, 30 and 50 µg/kg) on the respiratory response to carbon dioxide (CO\(_2\)) breathing in rabbits. 

Design: Randomized prospective study.

Setting: Animal laboratory at a university school of medicine.

Intervention: From 28 animals, four groups of seven were randomly assigned to receive different doses of dexmedetomidine (groups D1, D10, D30 and D50). Under inhalation of sevoflurane, each animal was tracheostomized and intubated with a 4 mm internal diameter (i.d.) endotracheal tube.

Measurements and results: After end-tidal sevoflurane concentration had decreased below 0.03% and during quiet breathing (QB); respiratory rate (RR), tidal volume (VT) and inspiratory time (TI) were measured, from which minute ventilation (MV) and mean inspiratory flow (VT/TI) were calculated. After these measurements had been completed, each animal breathed the balloon gas (5% CO\(_2\) and 95% O\(_2\)) until the end-tidal CO\(_2\) (ETCO\(_2\)) reached 10%. The respiratory measurements were repeated during the latter period. After the collection of these data, dexmedetomidine was infused intravenously and the same measurements were repeated 15 and 45 min after dexmedetomidine infusion. The slopes of the ventilatory response to hypercapnia in D50 was significantly higher compared with D30 animals. In the range 1–30 µg/kg, during both QB and at 10% ETCO\(_2\), MV was decreased in a dose-dependent manner. Dexmedetomidine depressed both VT and RR during QB and at 10% ETCO\(_2\). 

Conclusion: Dexmedetomidine depressed resting ventilation and the respiratory response to CO\(_2\), but it did not induce profound hypoxemia or hypercapnia in rabbits.

Keywords  Dexmedetomidine · Respiratory depression · Respiratory response to carbon dioxide

Introduction

\(\alpha_2\)-adrenergic agonists have been used primarily as antihypertensive drugs and have been reported to reduce the requirement for anesthetics and narcotics or both. This action is thought to be due to their sympatholytic, analgesic and sedative effect [1, 2, 3, 4]. Lower doses of anesthetic agents mean more rapid emergence from anesthesia and less narcotic-related respiratory depression. It is therefore important to evaluate fully any side effects that \(\alpha_2\)-agonists may have on the cardiovascular and respiratory systems when they are used during the perioperative period.

While it is known that \(\alpha_2\)-agonists induce hypotension and bradycardia [1, 5], their effect on respiratory depression remains unknown [5, 6, 7, 8, 9, 10, 11].
though clonidine was initially considered to induce minimal respiratory depression, recent reports associate it with clinically significant respiratory depression [12]. This suggests that, in clinical practice, α2-agonists may have adverse effects on respiration. Recently, clinicians have started using dexmedetomidine, a highly selective α2-agonist, for sedation in intensive care units. Although it is believed to have minimal effects on respiration, it is essential to evaluate this critically.

The aim of this study was to examine if dexmedetomidine affects respiration, utilizing the hypercapnic response of rabbits.

# Materials and Methods

The study was approved by the institutional review board at the Osaka University Medical School and all animals were handled in accordance with National Institutes of Health guidelines.

Preparations

After an ear vein was cannulated, each rabbit (New Zealand white rabbit) was set in the prone position and anesthetized via a mask with a 2–3% admixture of sevoflurane and oxygen at 2 l/min. Once the corneal reflex was depressed, the animals were placed supine and local anesthesia (2 ml 1% lidocaine) was infiltrated around the mid-neck. A tracheostomy was performed and a 4 mm internal diameter (i.d.) endotracheal tube (Blue line tracheostomy tube, Portex, Kent, UK) was inserted into the trachea. The internal carotid artery was subsequently cannulated with a 20gaue catheter (Angiocath 20, Becton Dickinson Vascular Access, Sandy, Utah) to monitor arterial pressure (Custom Product, Abbott Ireland, Sligo, Ireland) and to aspirate blood for respiratory gas measurements. Body temperature was monitored either per rectum or nose (Mon-a-therm/Model 6500, Mallinckrodt Medical, St. Louis, Mo.) and, using an electric blanket, temperature was maintained in the range of 39.1–42.0°C.

After the operative procedure had been completed, each rabbit was left in its cage for 5–15 h until the end-tidal sevoflurane concentration decreased to less than 0.03%. The concentration was monitored with an infrared gas analyzer (CAPNOMAC ULTIMA ULT-SV-31-04, Datex Instrumentarium, Helsinki, Finland).

Measurements and experimental protocol

Twenty-eight animals (2751±215 g) were randomly assigned to four groups according to the dose of dexmedetomidine administered. In each group seven animals received either 1, 10, 30 or 50 µg/kg of dexmedetomidine (groups D1, D10, D30 and D50). Measurements were recorded during quiet breathing (QB) and CO2 breathing. Rabbits stood unseated and breathed through a tracheostomy tube via a heat-moisture exchanger (Pneumo moist PMH+IN, TKB International, Costa Mesa, Calif.) and a pneumotachograph (Hans Rudolph, Kansas City, Mo.), which was connected to a differential pressure transducer (TP-602T, ±5cmH2 O, Nihon Kohden, Tokyo, Japan) to measure flow. Using a software application (Windaq Playback, Dataq Instruments, Akron, Ohio), arterial blood pressure (mBP) and pulse rate (PR) were measured from an arterial line, were measured and stored in a computer system. The arteri -valves were sampled from the data during QB, and at ETCO2 of 6, 7, 8, 9 and 10% before, and 15 and 45 min after, dexmedetomidine. Baseline data were sampled twice before administration of dexmedetomidine. At each level of ETCO2, respiratory rate (RR), minute ventilation (MV) and mean inspiratory flow were analyzed as follows: RR = 60/(mean of respiratory cycle of 5 breaths) (breaths/min), MV = V̇f/T I (ml/sec) where T I is inspiratory time. The slope of the hypercapnic ventilatory response 15 min after dosing was calculated using the linear portion of the hypercapnic response curves. RR was too high to analyze on a breath-by-breath basis. To calculate the CO2 response slope, MV at 6, 7, 8, 9 and 10% ETCO2 was plotted against ETCO2. Mean blood pressure (mBP) and pulse rate (PR) were measured from arterial pressure waveforms during QB as an average of ten pulse waveforms. The data are shown as means ± SD except in Fig. 3, where standard error (SE) is used for clarity. The data with regard to slope were analyzed using one-way analysis of variance (ANOVA). All other data were tested using two-way ANOVA with repeated measurements, and post hoc analysis was performed with Tukey’s test. Probability values of less than 0.05 were considered significant.

Results

Data from the second baseline sampling period were analyzed for only one animal in each group because of a problem with disconnection of the measuring devices caused by movements of the animals. Arterial blood could not be sampled in two instances from the group D1, once from D10 and once from D30.

There was no significant difference in MV during QB and at 10% ETCO2 among the groups. MV tended to decrease dose-dependently in the range of 1–30 µg/kg both during QB and at 10% ETCO2 (Table 1). MV significantly decreased 15 and 45 min after dosing compared with baseline both during QB and at 10% ETCO2, when all dose groups were combined (Fig. 1). Hypercapnic ventilatory response 15 min after dosing is shown in Fig. 2. The slope in D50 was significantly higher than that in D30.