

Dexmedetomidine inhibits gastric emptying and oro-caecal transit in healthy volunteers

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Editor's key points

- Dexmedetomidine is widely used for sedation, but its effects on gastric emptying and gastrointestinal transport are unclear.
- In a study of 12 healthy volunteers, i.v. infusion of dexmedetomidine significantly delayed gastric emptying and gastrointestinal transit.
- Further studies with lower doses in critically ill patients are necessary to determine the clinical relevance of these findings.

Background. Dexmedetomidine is a potent and selective α_2 -adrenoceptor agonist used for perioperative and intensive care sedation with certain beneficial qualities. However, based on preclinical observations, it might inhibit gastric emptying and gastrointestinal transit, which could result in unwanted effects in intensive care patients. This study evaluated the effects of dexmedetomidine on gastric emptying and oro-caecal transit time in healthy volunteers.

Methods. Twelve healthy male subjects were given $1 \mu\text{g kg}^{-1}$ of dexmedetomidine i.v. over 20 min followed by a continuous i.v. infusion of $0.7 \mu\text{g kg}^{-1} \text{ h}^{-1}$ for 190 min. For comparison, subjects were also given 0.10 mg kg^{-1} of morphine hydrochloride i.v. over 20 min and a placebo infusion in a randomized order. Gastric emptying was assessed with the paracetamol absorption test and oro-caecal transit time with the hydrogen breath test.

Results. The time to maximum paracetamol concentration in plasma was significantly longer, maximum paracetamol concentration was significantly lower, the area under the plasma paracetamol concentration–time curve was significantly smaller, and oro-caecal transit time was significantly longer during dexmedetomidine infusion compared with morphine or placebo infusion.

Conclusions. Dexmedetomidine markedly inhibits gastric emptying and gastrointestinal transit in healthy volunteers.

Keywords: dexmedetomidine; gastric emptying; gastrointestinal transit

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Dexmedetomidine is a potent and selective α_2 -adrenoceptor agonist used for perioperative and intensive care sedation. Compared with other drugs currently used for intensive care sedation, it has certain beneficial qualities such as lack of respiratory depression,¹ improved haemodynamic stability,² reduced stress responses to noxious stimuli,³ alleviation of pain,³ reduced incidence of delirium compared with benzodiazepines,^{4,5} and possibly shorter length of stay in the intensive care unit (ICU).⁶

There are reports suggesting that dexmedetomidine inhibits gastric emptying and gastrointestinal transit in rats,^{7,8} an unwanted effect if it occurs in intensive care patients. Only one study has assessed the gastrointestinal effects of dexmedetomidine infusion in humans, and the low dose of dexmedetomidine used did not significantly inhibit gastric emptying.⁹ Other previous studies on the gastrointestinal effects of α_2 -adrenoceptor agonists have yielded

contradictory results. Clonidine did not inhibit gastric emptying in humans,^{10,11} but dexmedetomidine and clonidine inhibited gastric emptying in rats to some extent,^{7,8} whereas dexmedetomidine had no effect on gastric emptying in mice.¹² The results on gastrointestinal transit seem to be more consistent: both clonidine and dexmedetomidine inhibited gastrointestinal transit in most studies, both in humans and in rodents.^{7,8,12–14}

As the gastrointestinal effects of high-dose infusions of dexmedetomidine in humans were unknown, we designed this study using clinically relevant doses of dexmedetomidine to assess its effects on gastric emptying and oro-caecal transit in healthy volunteers. We chose a dosage of dexmedetomidine equal to the maximum suggested dose for sedation of ICU patients. A three-way cross-over study design was used to compare dexmedetomidine infusions with placebo (presumably no effect) and morphine (presumably a

significant effect). Absorption of paracetamol was used as a measure of gastric emptying, and the hydrogen breath test was used to determine oro-caecal transit time.

Methods

Study subjects

The study (EudraCT number 2009-018170-66/ClinicalTrials.gov identifier NCT01084473) was conducted according to the revised Declaration of Helsinki of the World Medical Association and ICH guidelines for good clinical trial practice. The study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland and the Finnish Medicines Agency. The study underwent limited monitoring by a qualified representative of Turku Clinical Research Centre.

Healthy, unmedicated males older than 18 yr and weighing more than 60 kg were eligible for the study. Subject candidates with drug allergy, alcohol or drug abuse, significant psychological problems, positive urine drug screen, a 'yes' answer to any of the questions of a modified Finnish version of the Abuse Questionnaire,¹⁵ a special diet or lifestyle, a BMI >30 kg m⁻² or clinically significant abnormal findings in physical examination, ECG, or routine laboratory screening were not considered eligible for the study. Smoking was prohibited during and within 4 weeks before the study.

Subjects had to avoid drugs known to cause enzyme induction or inhibition for 30 days, any medications and some natural products (including grapefruit products) for at least 14 days, and alcohol and caffeine-containing products for at least 24 h. Ibuprofen was allowed for occasional headache or other conditions.

On the day before each study session, subjects were not allowed to eat foods rich in fibre or long-chain carbohydrates (such as rye bread, porridge, other full grain products, pasta, vegetables, fruits, berries). Eating and physical exercise were not allowed for 12 h, water intake for 4 h, and sleeping for 1 h before session start. On study days, subjects had to fast until an increase in exhaled hydrogen was detected or at least 4 h after lactulose administration.

A venous catheter was inserted into a large forearm vein for study drug administration and another into an antecubital vein in the opposite extremity for blood sampling. ECG, non-invasive arterial pressure, and arteriolar oxygen saturation (SpO₂) were monitored for safety purposes.

Study treatments

A three-period cross-over design with balanced randomization was used. The wash-out period between consecutive administrations was at least 7 days. Subjects were given three different treatments in a randomized order:

- (i) Dexmedetomidine: 1 µg kg⁻¹ dexmedetomidine (dexmedetomidine 100 µg ml⁻¹, Precedex[®], Abbott Laboratories, North Chicago, IL, USA) infused over 20 min, followed by a continuous infusion of 0.7 µg kg⁻¹ h⁻¹ for 190 min.

- (ii) Morphine: 0.10 mg kg⁻¹ morphine (morphine hydrochloride 2 mg ml⁻¹, Morphin[®], Nycomed Austria GmbH, Linz, Austria) infused over 20 min, followed by a placebo (saline) infusion for 190 min.
- (iii) Placebo: 0.9% saline infused in the same manner as the active drugs.

After running the infusions for 30 min, the subjects were given paracetamol 1 g per os (Panadol Forte[®], GlaxoSmithKline Consumer Healthcare A/S, Copenhagen, Denmark) with 100 ml of tap water (25°C), and 10 g of lactulose (Laktulos Merck NM[®] 667 mg ml⁻¹, Merck NM AB, Stockholm, Sweden) with 50 ml of tap water.

Assessment of gastric emptying

Venous blood samples were collected immediately before administration of paracetamol (baseline) and thereafter at 10, 20, 30, 40, 50, 60, 70, 80 min and 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, and 4 h. Plasma paracetamol concentrations were measured using reversed-phase high-performance liquid chromatography.¹⁶ The lower limit of plasma paracetamol quantification was 0.1 mg litre⁻¹. Gastric emptying was assessed by the rate of paracetamol absorption using the time to peak plasma concentration, the peak plasma concentration, and the area under the plasma concentration-time curve.

Assessment of oro-caecal transit time

Hydrogen is produced and exhaled when lactulose, an unabsorbable disaccharide, is fermented by colonic bacteria. The time between ingestion of lactulose and an increase in exhaled hydrogen represents the oro-caecal transit time.^{17 18} The hydrogen concentration in exhaled air was measured with a hand-held device (Gastro⁺ Gastrolzyer[®], Bedfont Scientific Ltd, Rochester, Kent, UK) immediately before administration of lactulose (baseline) and thereafter at 15 min intervals, and the time between lactulose intake and the first occurrence of a sustained increase in exhaled hydrogen concentration (i.e. an increase of >10 ppm above baseline in at least three consecutive measurements) was taken as a measure of the oro-caecal transit time.

Pharmacokinetic analysis of paracetamol

The peak plasma paracetamol concentrations (C_{max}) and the corresponding time points (T_{max}) were measured. Areas under the paracetamol plasma concentration-time curves from 0 to 90 min were estimated using the trapezoidal rule (AUC_{0-90 min}). We used the linear trapezoidal rule when successive concentration values were increasing and the logarithmic trapezoidal rule when successive concentration values were decreasing after the observed peak concentration. Data were analysed using the WinNonlin pharmacokinetic program (version 4.1; Pharsight, Mountain View, CA, USA).

Statistical analysis

On the basis of previous studies,⁹ we calculated that 10 subjects would be required to demonstrate a 30% difference in

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