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Clinical Investigation

CLINICAL INVESTIGATION

Comparative effects of dexmedetomidine, propofol, sevoflurane, and S-ketamine on regional cerebral glucose metabolism in humans: a positron emission tomography study

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Abstract

Introduction: The highly selective α_2-agonist dexmedetomidine has become a popular sedative for neurointensive care patients. However, earlier studies have raised concern that dexmedetomidine might reduce cerebral blood flow without a concomitant decrease in metabolism. Here, we compared the effects of dexmedetomidine on the regional cerebral metabolic rate of glucose (CMR_{glu}) with three commonly used anaesthetic drugs at equi-sedative doses.
Methods: One hundred and sixty healthy male subjects were randomised to EC_{50} for verbal command of dexmedetomidine (1.5 ng ml^{-1}; n=40), propofol (1.7 μg ml^{-1}; n=40), sevoflurane (0.9% end-tidal; n=40) or S-ketamine (0.75 μg ml^{-1}; n=20) or placebo (n=20). Anaesthetics were administered using target-controlled infusion or vapouriser with end-tidal monitoring. ^{18}F-labelled fluorodeoxyglucose was administered 20 min after commencement of anaesthetic

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administration, and high-resolution positron emission tomography with arterial blood activity samples was used to quantify absolute CMR_{glu} for whole brain and 15 brain regions.

Results: At the time of [F^{18}]fluorodeoxyglucose injection, 55% of dexmedetomidine, 45% of propofol, 85% of sevoflurane, 45% of S-ketamine, and 0% of placebo subjects were unresponsive. Whole brain CMR_{glu} was 63%, 71%, 71%, and 96% of placebo in the dexmedetomidine, propofol, sevoflurane, and S-ketamine groups, respectively ($P<0.001$ between the groups). The lowest CMR_{glu} was observed in nearly all brain regions with dexmedetomidine ($P<0.05$ compared with all other groups). With S-ketamine, CMR_{glu} did not differ from placebo.

Conclusions: At equi-sedative doses in humans, potency in reducing CMR_{glu} was dexmedetomidine>propofol>ketamine=placebo. These findings alleviate concerns for dexmedetomidine-induced vasoconstriction and cerebral ischaemia.

Clinical trial registration: NCT02624401.

Keywords: cerebral blood flow; cerebral metabolism; positron emission tomography; sedation; target-controlled infusion

Editor's key points

- The effects of dexmedetomidine, propofol, S-ketamine, and sevoflurane on the regional cerebral metabolic rate of glucose (CMR_{glu}) were compared at equi-sedative doses.
- All but S-ketamine reduced cerebral metabolic rate relative to placebo with relative potencies of dexmedetomidine>propofol>ketamine=placebo.
- Sevoflurane decreased metabolism equally to propofol but the dose was not quite equipotent.
- These findings alleviate concerns for harmful effects of dexmedetomidine on the ratio of cerebral blood flow and metabolism.

Different anaesthetics produce characteristic effects on cerebral blood flow (CBF) and metabolism. While sevoflurane decreases cerebral metabolism more than CBF,[1–4] propofol induces a proportional decrease in both measures.[1–3,5–11] For this reason, propofol has been deemed particularly suitable for neurosurgical and neurointensive care patients. S-ketamine has been demonstrated to increase glucose metabolism in certain regions of the brain and to induce a global increase in CBF.[12–14] Although dexmedetomidine has become a popular sedative for neurointensive care patients, its effects on cerebral glucose metabolism have not been properly characterised in humans.

Dexmedetomidine is an α_2-adrenoceptor agonist with unique properties; it induces sufficient sedation while allowing patient arousal and awakening without changing infusion rate. This is a valuable feature, especially in intensive care patients, who need frequent assessment of their neurological state. In addition, dexmedetomidine has mild analgesic properties and minimal respiratory effects. Furthermore, experimental studies have suggested neuroprotective properties of dexmedetomidine,[15] but this has not been established in humans.[16] In early animal studies, dexmedetomidine was found to reduce CBF with no effect on the cerebral metabolic rate of oxygen.[17,18] This raised concern that the decreased blood flow might be inadequate for the cerebral metabolic needs. Studies in humans have, however, suggested that dexmedetomidine proportionally decreases CBF and oxygen metabolism.[19,20] Nevertheless, uncertainty remains on this issue.

We compared the effects of dexmedetomidine, propofol, sevoflurane, S-ketamine, and placebo on the regional cerebral metabolic rate of glucose (CMR_{glu}) with high-resolution positron emission tomography (PET) imaging. Our aim was to establish the relative potencies of these four anaesthetics with different mechanisms of action, all given at equi-sedative doses.

Methods

Trial design and participants

We conducted an open-label, randomised, controlled, parallel group, phase IV clinical drug trial at the Turku PET Centre, University of Turku, Finland. The study (ClinicalTrials.gov Identifier NCT02624401) was approved by the Ethics Committee of the Hospital District of Southwest Finland and the Finnish Medicines Agency Fimea (EudraCT 2015-004982-10).

Inclusion criteria were male sex, age 18–30 yr, normal hearing, right handedness, good sleep quality, ASA physical status class 1, fluency in the Finnish language and normal results in a thorough physical examination and laboratory tests including drug screening. Use of any medication or alcohol was prohibited for 48 h and caffeine products for 10–12 h before the study session. All subjects fasted from the previous midnight. Written informed consent was obtained from all subjects according to the Declaration of Helsinki.

The goal was to have 160 ($n=40$ in each group, except $n=20$ in the S-ketamine and placebo groups) subjects with complete data, and because of 20 premature withdrawals or dropouts (see Results), 180 subjects were recruited. Subjects were randomised with balanced permuted block sizes of 16 to receive either dexmedetomidine (Dexdor 100 μg ml^{-1}; Orion Pharma, Espoo, Finland), propofol (Propolipid 10 mg ml^{-1}; Fresenius Kabi, Uppsala, Sweden), sevoflurane (Sevorane 100%; Abbvie, Espoo, Finland), S-ketamine (Ketanest-S 25 mg ml^{-1}; Pfizer, Helsinki, Finland) or saline placebo. The person (H.S.) responsible for randomisation did not recruit the subjects to ensure random allocation of the treatments. Baseline characteristics of the subjects are shown in Table 1.

Anaesthetic protocol and monitoring

A radial artery was cannulated for all blood samplings and two forearm venous catheters were placed for administration of anaesthetics and Ringer's acetate (at a standard rate of ~100 ml h^{-1}), and ^{18}F-labelled fluorodeoxyglucose ([^{18}F]FDG). Subjects breathed room air.