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Dexmedetomidine metabolic clearance is not affected by fat mass in obese patients

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Abstract

Background: Obesity has been associated with reduced dexmedetomidine clearance, suggesting impaired hepatic function or reduced hepatic blood flow. The aim of this study was to clarify the effect of obesity in dexmedetomidine metabolic clearance.

Methods: Forty patients, ASA I–III, 18–60 yr old, weighing 47–126 kg, scheduled for abdominal laparoscopic surgery, were enrolled. Anaesthetic agents (propofol, remifentanil, and dexmedetomidine) were dosed based on lean body weight measured by dual X-ray absorptiometry. Serial venous samples were drawn during and after dexmedetomidine infusion. A pharmacokinetic analysis was undertaken using non-linear mixed-effect models. In the modelling approach, the total body weight, lean body weight, and adjusted body weight were first tested as size descriptors for volumes and clearances. Hepatic blood flow, liver histopathology, liver enzymes, and gene expression of metabolic enzymes (UGT2B10 and UGT1A4) were tested as covariates of dexmedetomidine metabolic clearance. A decrease in NONMEM objective function value (ΔOFV) of 3.84 points, for an added parameter, was considered significant at the 0.05 level.

Results: A total of 637 dexmedetomidine serum samples were obtained. A two-compartmental model scaled to measured lean weight adequately described the dexmedetomidine pharmacokinetics. Liver blood flow was a covariate for dexmedetomidine clearance (ΔOFV=−5.878). Other factors, including fat mass, histopathological damage, and

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differential expression of enzymes, did not affect the dexmedetomidine clearance in the population studied (ΔOFV<3.84).
Conclusions: We did not find a negative influence of obesity in dexmedetomidine clearance when doses were adjusted to lean body weight. Liver blood flow showed a significant effect on dexmedetomidine clearance.
Clinical trial registration: NCT02557867.

Keywords: anaesthetics i.v.; dexmedetomidine; obesity; pharmacokinetics

Editor's key points

- Dexmedetomidine is a highly selective α2-agonist used for procedural and intensive care sedation.
- Weight-based bolus and infusion regimens are usually recommended for this drug.
- When used in obese patients, they result in higher plasma concentrations than in lean patients.
- The current study showed that lean body mass is an appropriate dosing scalar for size in obese patients.

Obesity is reaching epidemic proportions in Western countries. This represents a challenge for clinicians, as many of these individuals require a plethora of different therapeutic interventions for a variety of diseases.[1] Thus, there is a growing need for dosing guidance in obese patients.[2–4]

Dexmedetomidine is a highly selective α2-adrenergic agonist with sedative[5–7] and analgesic[6–8] properties, but minimal respiratory effects. Dexmedetomidine is used as a sedative in the intensive care unit, the operating room, and occasionally in other locations. The opioid-sparing effect and the absence of respiratory effects make dexmedetomidine an attractive adjuvant drug for anaesthesia in obese patients who are at an increased risk for postoperative respiratory complications.[9]

In a previous study, we assessed the pharmacokinetic (PK) profile of dexmedetomidine in obese patients.[10] Our main results showed that commonly used infusion schemes, based on infusion of mass units of drug per kilogram of total body weight (TBW), were not appropriate for the obese, as they resulted in higher plasma concentrations than those observed in lean subjects. In the PK modelling analysis, we found that only lean tissues, expressed as fat-free mass (FFM), accounted for size-dependent changes in dexmedetomidine volume of distribution. In addition, we also found that, for any lean body mass, the total clearance decreased with increasing fat mass (FM)—an intriguing result, which might suggest liver disease or a decrease in hepatic blood flow in the obese population.

Dexmedetomidine is extensively metabolised in the liver by the uridine diphosphate glucuronosyltransferases (UGT2B10 and UGT1A4)[11] and, in a minor proportion, by the cytochrome P450 (CYP2A6) system.[12–15] It has a relatively high hepatic extraction ratio of 0.7, and therefore, its metabolism is dependent on liver blood flow.[16] Recent studies have shown an inverse correlation between the severity of liver steatosis and hepatic blood flow.[17,18] Moretto and colleagues[19] showed that 87% of patients undergoing bariatric surgery had an abnormal liver biopsy, mostly caused by steatosis (83%), but also steatohepatitis (2.6%) and cirrhosis (1.3%). The authors found that the degree of liver damage was related to higher BMI scores.

We hypothesise that the negative influence of fat excess on dexmedetomidine clearance, reported in our previous study, might be explained by either (i) a decrease in hepatic blood flow caused by fatty infiltration, (ii) a reduction in liver blood flow caused by an excessive drug dosing and sympathetic blockade in obese patients, (iii) a decreased liver enzymatic capacity to metabolise dexmedetomidine in obese patients, or (iv) a mathematical compensation from a biased estimation of lean body mass in our previous study.

The aim of this study was to clarify the effect of obesity in dexmedetomidine metabolic clearance using a comprehensive covariate modelling approach.

Methods

Study design and ethics approval

This study was designed as an interventional, prospective, non-randomised, single-centre trial. It was conducted in a tertiary care university hospital between August 2015 and July 2016. It was approved by the Institutional Review Board of the School of Medicine of Pontificia Universidad Católica de Chile (Project Number 14-253) and registered at ClinicalTrials.gov (NCT02557867).

Patients and preoperative evaluation

Patients scheduled for laparoscopic non-oncological abdominal surgery were invited to participate. Informed consent was obtained from all patients upon entering the study. The eligibility criteria were age between 18 and 60 yr, both genders, and ASA Class I–III. The exclusion criteria were known allergy to study drugs, uncontrolled hypertension, heart block greater than first degree, chronic hepatic and kidney diseases, patients taking any drug acting in the central nervous system within 24 h before surgery, patients taking drugs that induce overexpression of liver CYP complex enzymes, known addiction to illicit drugs, pregnancy, and oncological disease.

All patients underwent abdominal ultrasonography, to assess for signs of hepatic steatosis, and preoperative laboratory assessment on the day of surgery, which included liver function tests, lipid profile, glucose, and insulin. Height and weight were recorded on the day of surgery. The presence of metabolic syndrome was assessed according to the International Diabetes Federation consensus.[20]

Body composition was determined in all patients before surgery by dual X-ray absorptiometry (DXA) with a GE Lunar DPX® (GE Medical Systems, Madison, WI, USA) and GE enCORE® software version 12.10 (GE Medical Systems, Madison, WI, USA) in the Radiology Service of our hospital (Hospital Clínico UC Christus).