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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).

Anaesthesia protocol

Upon arrival in the operating room, standard monitoring (electrocardiography, non-invasive blood pressure, and pulse oximetry) and bispectral index (BIS™ XP version 3.0; Medtronic, Minneapolis, MN, USA) were established. In all patients, a peripheral i.v. catheter was placed for fluids and drug administration.

Total i.v. anaesthesia was performed in all patients with the Orchestra® Base Primea and DPS modules (Fresenius Kabi AG, Bad Homburg, Germany). Propofol was administered by target-controlled infusion with the Marsh model at an initial effect-site target of 4 μg ml^{-1}, and thereafter titrated to BIS 50–60. Remifentanil infusion was set at an initial rate of 0.3 μg kg^{-1} min^{-1} and titrated according to haemodynamic variables (heart rate and blood pressure). After loss of consciousness, a second peripheral venous catheter was placed in the contralateral arm for blood sampling. Dexmedetomidine administration was then started giving an initial bolus of 0.5 μg kg^{-1} over 10 min followed by a continuous infusion of 0.5 μg kg^{-1} h^{-1}. After induction, rocuronium 0.6 mg kg^{-1} was administered and the airway was intubated. Additional boluses of rocuronium were allowed during surgery according to the anaesthesiologist criteria. All drugs were dosed by lean body weight (LBW) measured by DXA.

All patients received a standardised analgesic regime (morphine 0.1 mg kg^{-1} LBW, parecoxib 40 mg, and acetaminophen 1 g) and anti-emetic prophylaxis (dexamethasone 4 mg and ondansetron 4 mg) during the intraoperative period. All infusions were stopped at the end of surgery. Tracheal extubation was performed in the operating room. Postoperative care took place in the post-anaesthesia care unit (PACU). Morphine bolus doses of 3 mg were used if patients had pain (verbal analogue scale >4).

Blood sampling and dexmedetomidine plasma concentration determination

Venous blood samples of 6 ml were drawn at 0, 5, 10, 20, 30, 45, and 60 min after the start of dexmedetomidine administration and thereafter every 30 min during anaesthesia maintenance. Once dexmedetomidine infusion was stopped at the end of surgery, samples were drawn at 0 (end of dexmedetomidine infusion), 5, 10, 20, 30, 60, 90, 120, 240, and 360 min, and the last sample was obtained between 720 and 1200 min. Blood samples were stored in K2 ethylenediaminetetraacetic acid tubes and transported to the laboratory within 2 h where they were centrifuged and serum stored at −80°C. Dexmedetomidine serum concentrations were measured by high-performance liquid chromatography coupled with tandem mass spectrometric (HPLC–MS/MS) detection using a modification of the method described by Li and colleagues.[21] Dexmedetomidine hydrochloride was used as the reference compound and tolazoline, purity 99% (Sigma-Aldrich, St Louis, MO, USA), as the internal standard (IS). Sample preparation was performed using liquid–liquid extraction. Plasma sample 0.5 ml plus IS solution 50 μl (10 μg ml^{-1} in methanol/water 90/10) was extracted with diethyl ether 3 ml and saturated Na_2CO_3 solution 50 μl. The mixture was vortexed for 3 min, and then centrifuged at 2900*g* for 10 min. The upper organic layer was transferred and evaporated to dryness with a gentle stream of nitrogen in a water bath at 37°C. The dry residue was dissolved in 150 μl of a solution containing formic acid 0.1% in methanol/water 50/50 and centrifuged at 15 000*g* for 10 min. Ten microlitres of the supernatant was injected into the HPLC–MS/MS system. Gradient HPLC separations were carried out by using an Intersil® ODS-3 column (3 μm particle size, 100 × 2.1 mm inner diameter; GL Sciences, Tokyo, Japan) and mobile phases consisting of formic acid 0.1% in methanol and formic acid 0.1% in water, with a flow rate of 0.2 ml min^{-1} at 30°C. Mass spectrometric detection was carried out with a QTRAP® 4500 (AB Sciex, Foster City, CA, USA) using turbospray ionisation in positive mode and multiple reaction monitoring. The precursor ion-fragment ion pairs detected were m/z 201→95 for dexmedetomidine and m/z 161→77 for the IS. Quantitation was based on peak area ratios of dexmedetomidine and the IS using Analyst 1.6.1 software (AB Sciex, Foster City, CA, USA) for data collection and analysis. The method calibration curve was linear over a concentration range of 10–5000 ng $litre^{-1}$. The lower limit of detection for dexmedetomidine was 4 ng $litre^{-1}$ and the lower limit of quantification was 10 ng $litre^{-1}$. Intra- and inter-day precision were assessed using three concentrations (80, 500, and 1000 ng $litre^{-1}$) and were found to be less than 15% for all concentrations. The average accuracy was between 91% and 105% for all three concentrations.

Liver function and liver perfusion assessment

All patients had a liver wedge biopsy performed during surgery. The specimen was divided and one portion was imbibed in a 2% solution of formaldehyde that was processed at the pathology department of our institution. The liver samples were evaluated by a pathologist to calculate the non-alcoholic fatty liver disease (NAFLD) activity score (NAS), which corresponds to anatomopathological features, such as steatosis, lobular inflammation, hepatocellular ballooning, and fibrosis. The NAS ranges from 0 to 8, and scores >2 are considered as consistent with NAFLD.[22]

Another portion of the liver biopsy was stored in RNAlater® solution (Thermo Fisher Scientific, Inc., Waltham, MA, USA). RNA from liver biopsies was isolated with SV Total RNA Isolation System (Promega Corporation, Madison, WI, USA) according to the manufacturer protocol. Two modifications were performed; the tissue homogenisation was performed using 600 μl of RNA lysis buffer and the extraction was realised with 200 μl of the tissue lysate.

The RNA samples were quantified in NanoDrop™ spectrophotometer (Thermo Fisher Scientific, Inc., Waltham, MA, USA) and analysed for integrity in TapeStation Instrument (Agilent Technologies, Santa Clara, CA, USA).

Retro transcription reaction was performed with ImProm-II™ Reverse Transcription System (Promega Corporation) using 1 μg of total RNA and 2.5 mM of $MgCl_2$, according to the manufacturer protocol. The quantitative polymerase chain reaction was performed using TaqMan® Universal PCR Master Mix (Applied Biosystems, Inc., Foster City, CA, USA) and TaqMan probes (Applied Biosystems, Inc. Foster City, CA, USA) for *UGT2B10* (ID #Hs02556282_s1), *UGT1A4* (ID #Hs01655285_s1), *YWHAZ* (ID #Hs03044281_g1), and *SRSF4* (ID #Hs00194538_m1) genes. Each reaction was realised in duplicate using 2 μl of a 10-fold dilution of cDNA at a 20 μl final reaction. The PCR cycle was 10 min hold at 95°C, followed by 40 cycles at 95°C for 15 s and 60°C for 1 min.

To assess blood flow, 2 h after surgery, all patients received a bolus dose of indocyanine green (ICG) 0.25 mg kg^{-1}, and we used the LiMON® monitor (PULSION Medical Systems SE, Feldkirchen, Germany), as specified by the manufacturer to measure the ICG plasma disappearance rate (PDR) (ICG–PDR) and the ICG retention ratio after 15 min (ICG-R15).[23]

Pharmacokinetic data analysis

A two-compartment distribution model with first-order elimination was used to describe the dexmedetomidine serum concentrations. Population-parameter estimates were obtained using non-linear mixed-effect models (NONMEM 7.3; ICON Development Solutions, Dublin, Ireland). The population-parameter variability was modelled as random-effect variables, each one with an assumed mean 0 and variance ω^2. The variability between subjects was modelled by exponentiating random effects.

The quality of fit was judged by NONMEM's objective function value (OFV), traditional measured *vs* predicted plots, and visual predictive checks (VPCs). Nested and non-nested models were selected based on the decrease in OFV. The introduction of a new variable into the model was considered an improvement if the OFV of the new model was diminished at least in 3.84 units, corresponding to an α-value of 0.05. Bootstrap methods provided a means to evaluate parameter uncertainty.[24] A total of 1000 bootstrap replications were used to estimate the parameter confidence intervals (CIs).

Covariate analysis

In the covariate analysis, we first searched for adequate size descriptors for volumes and clearances. Once a size scale model was obtained, we explored different covariates in dexmedetomidine metabolic clearance.

Size covariates

TBW, LBW measured by DXA, FM measured by DXA, and adjusted body weight (ABW) were used as size scalars for volumes and clearances. ABW was calculated as LBW plus a fraction F of FM (equation 1)

$$\mathrm{ABW} = \mathrm{LBW} + F \cdot \mathrm{FM} \tag{1}$$

where F is estimated as a model parameter. Linear and allometric relationships were tested in all size scale models.

Liver function and perfusion covariates

The tested covariates were (i) ICG–PDR and ICG-R15 as descriptors of hepatic blood flow, (ii) presence or absence of steatosis in the liver echography as a descriptor of liver steatosis, (iii) NAS score as a descriptor of NAFLD, and (iv) relative expression of hepatic cytochromes UGT1A4 and UGT2B10 and alanine aminotransferase (ALT) as descriptors of enzymatic capacity. Other covariates tested in clearance were FM measured by DXA and the presence or absence of metabolic syndrome.

Statistical analysis was performed in R (freely available language and environment for statistical computing and graphics). For correlations, Pearson or Spearman tests were performed as appropriate.

Results

General data

Forty patients were enrolled and all of them completed the study. The duration of anaesthesia was on average 97 min (range: 47–160 min). All patients were extubated after surgery and transferred to the PACU. The general study data are summarised in Table 1.

Table 1 Patient characteristics and general study data. Values in mean (range) or actual numbers

Male/female (*n*)	14/26
ASA (I/II)	6/34
Age (yr)	42.3 (23–59)
Weight (kg)	90 (47–126)
BMI (kg m^{-2})	34.2 (18–49)
Lean body weight (kg)	45.3 (30–80)
Fat mass (kg)	40.9 (12–70)

Pharmacokinetic analysis

A total of 637 dexmedetomidine serum assays were obtained. Time profiles of dexmedetomidine serum concentrations are shown in Figure 1. A two-compartment model described the data better than a one-compartment model, producing a major decrease in the OFV of −712.917 points ($P<0.00005$; four additional parameters). A three-compartment model produced only a minor improvement in model fit compared with the two-compartment model with a decrease in the OFV of only −7.985 ($P=0.09213$; four additional parameters). In addition, the volume of the third compartment was estimated with poor precision [V_3=66 litres (95% CI: 35–293 litres)]. The two-compartment model with first-order eliminations was selected as our base structural model. Diagnostic plots comparing the three structural models tested are shown in Supplementary Appendix S1. The addition of weight as a size scalar for volumes and clearances improved the fit (ΔOFV=−14.976) compared with the non-size scale model. The LBW scalar produced the best fit with a decrease in OFV of

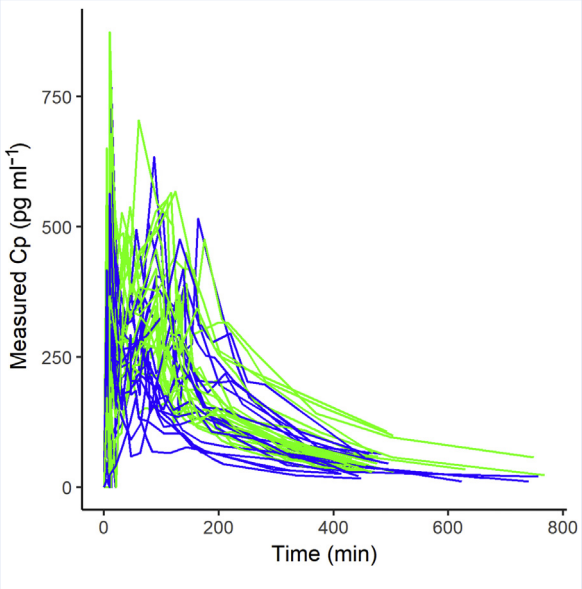

Fig 1. Serum dexmedetomidine concentration–time profile for each patient. Blue lines represent patients with BMI ≤35 kg m^{-2} and green lines are BMI >35 kg m^{-2}. No apparent differences in dexmedetomidine concentrations are observed between both BMI groups with the current dose scheme based on LBW. LBW, lean body weight. Cp, plasma concentration.

−33.222. The allometric LBW model was not better than the linear LBW model (ΔOFV=0.960). Supplementary Appendix S2 shows a summary of the size scale models tested. The use of ABW for volumes and clearances (two additional parameters) did not improve the model fit compared with the LBW linear model (ΔOFV=−0.308). The estimated FM fractions for volumes and clearances were 0.0508 and 0.0589, respectively, indicating that only LBW accounts for dexmedetomidine disposition. Based on the OFV, the final size scale model selected was the two-compartment linear LBW model. This model was used in the next step where clearance covariates were explored.

Clearance covariates

We found relatively moderate levels of liver damage in the population studied. Liver function and liver perfusion measurements used as covariates of dexmedetomidine clearance are summarised in Supplementary Appendix S3. Only liver perfusion measurements affected the dexmedetomidine clearance (ΔOFV>3.84). The relationship between *post hoc* estimated metabolic clearance and tested covariates is shown in Figure 2. The inclusion of FM as a covariate of clearance did not improve the model fit (ΔOFV=−0.379). The 95% confidence bounds of the θ estimate describing the effect of FM in clearance ranged from −0.003 to +0.01 litres min^{-1} in the log-likelihood profile analysis. This result confirms the adequacy of our model to discard a possible effect of this variable in clearance. Similarly, the 95% confidence bounds for this effect in an FFM scaled model ranged from −0.002 to +0.01 litres min^{-1}. It is our opinion that this last result ruled out the possibility that the negative effect of FM in clearance found in our previous study was caused by a mathematical compensation from a biased estimation of lean body mass. A significant improvement in model fit was observed only with ICG−PDR (ΔOFV=−4.523) and ICG-R15 (ΔOFV=−5.878). Inclusion of both ICG parameters was not justified (ΔOFV=0.069). The modelling steps are summarised in Supplementary Appendix S4. The relationship between liver covariates and BMI is shown in Figure 3.

Final model selected

The final model selected was a two-compartment model with volumes and clearances scaled linearly to LBW. The model includes the effect of ICG-R15 in clearance using an exponential relationship. The effect of ICG-R15 in dexmedetomidine plasma concentrations is represented in a typical patient in Supplementary Appendix S5. The estimated population PK parameters, their 95% CI, and inter-individual variability estimates are shown in Table 2. The VPC diagnostic plots are shown in Figure 4. Complementary diagnostic measured *vs* predicted plots are shown in Supplementary Appendix S6. Complementary likelihood profile plots are shown in Supplementary Appendix S7. Considering LBW measured by DXA and ICG-R15 measured by the LiMON® monitor are rarely available for clinicians, this previous model has more scientific than clinical applicability. Therefore, we also present a simpler model intended for clinical use scaled to FFM, which can be easily calculated from gender, TBW, and height, as shown in equation 2:

$$\mathrm{FFM} = \mathrm{WHS_{max}} \cdot \mathrm{HT}^2 \cdot \left[\frac{\mathrm{TBW}}{(\mathrm{WHS_{50}} \cdot \mathrm{HT}^2 + \mathrm{TBW})}\right] \quad (2)$$

where WHS_{max} is the maximum FFM for any given height (HT, metre), and WHS_{50} is the TBW value when FFM is half of WHS_{max}. For men, WHS_{max} is 42.92 kg m^{-2} and WHS_{50} is 30.93 kg m^{-2}, and for women WHS_{max} is 37.99 kg m^{-2} and WHS_{50} is 35.98 kg m^{-2}.

Parameter estimates for the FFM model are shown in Supplementary Appendix S8. The diagnostic plots of this last model are shown in Supplementary Appendix S9.

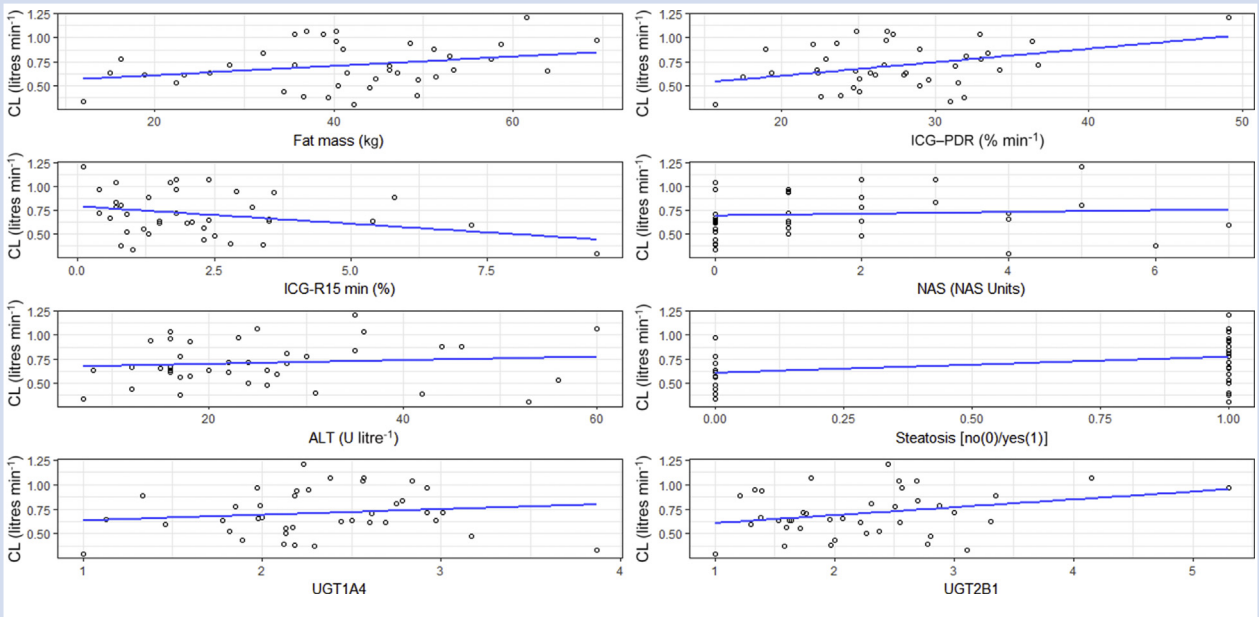

Fig 2. Scatter plot of *post hoc* clearances and hepatic variables tested.

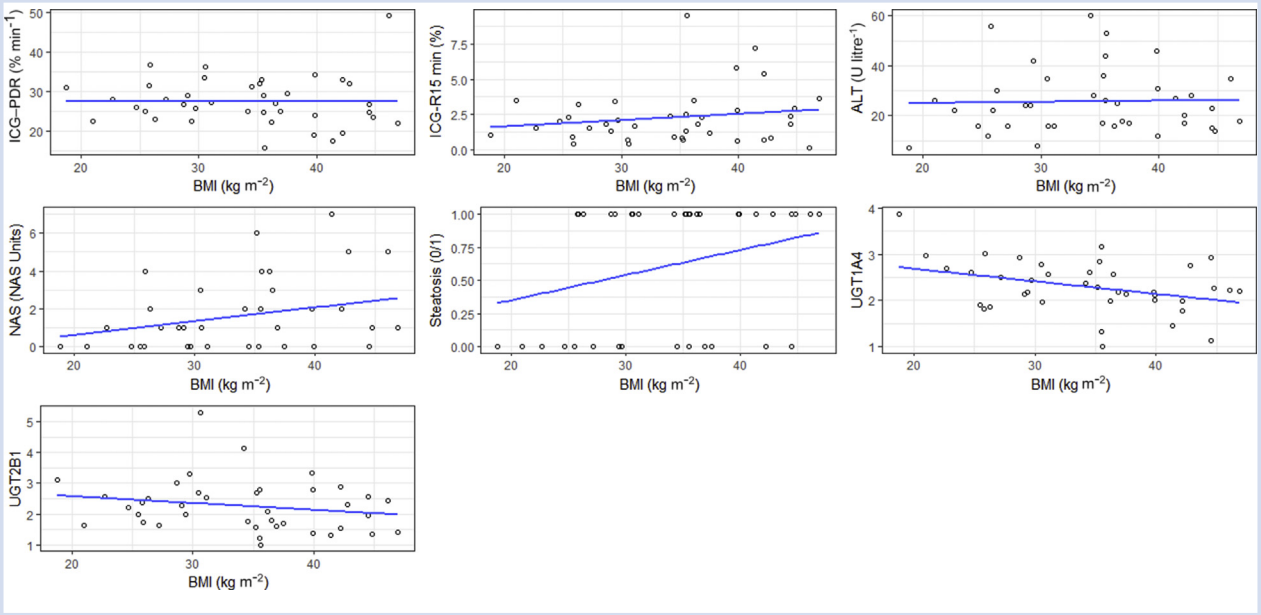

Fig 3. Scatter plot of hepatic variables *vs* BMI.

Discussion

We conducted a PK study in 40 patients of a wide range of body weights given dexmedetomidine based on LBW. We confirmed that LBW is an adequate descriptor to scale dexmedetomidine doses and that hepatic blood flow has a relevant effect in its clearance. Our results did not support, however, a deleterious effect of FM or liver disease in dexmedetomidine clearance in the population studied.

In the development of the current base population PK model, dexmedetomidine time profiles were adequately described by a two-compartment model. The typical mean volume of distribution of approximately 120 litres and elimination clearance of 0.7 litres min^{-1} estimated by the model are in accordance with previous studies.[10,16.25–28] In the modelling analysis, the lean body mass measured by DXA was found to be the best size scalar to describe the dexmedetomidine PK changes in obese patients. The current results agreed with our previous study in obese and normal-weight patients where FFM resulted better than other scalars to describe dexmedetomidine disposition.[10] Although both scalars are essentially the same, a minor difference is that the lean body mass measured with DXA does not consider mineral tissues.[29]

In our previous study in obese patients,[10] we found that FM, expressed as the difference between TBW and FFM, was associated with a negative effect in dexmedetomidine metabolic clearance, which suggested that obese patients have a decreased capacity to metabolise dexmedetomidine from liver disease or a decreased hepatic blood flow. Obesity is a risk factor for NAFLD.[19,30,31] NAFLD encompasses a range of liver disorders ranging from steatosis to progressive inflammation and fibrosis, which can lead to non-alcoholic steatohepatitis and cirrhosis.[22] To explore a potential effect of liver damage in dexmedetomidine clearance, we performed liver biopsies and measured serum ALT in all patients. The magnitude of histological damage was graded with the NAS.[22] Although we found

Table 2 Dexmedetomidine population pharmacokinetic parameter estimates of the lean body weight scaled model. Parameters are standardised to an LBW of 45 kg. Bootstrap estimate is the median value of the 1000 bootstrap repetitions; 95% CI is the 95% confidence interval of the parameter estimated by bootstrap analysis. CV is between-subject variability expressed as an apparent coefficient of variation. V_1 is central volume of distribution, V_2 is small peripheral volume of distribution, V_3 is large peripheral volume of distribution, Cl is elimination clearance, Q_2 is rapid distribution clearance, and Q_3 is slow distribution clearance. LBW, lean body weight; PK, pharmacokinetic

Pharmacokinetic parameters	Estimate of structural parameter	Bootstrap estimate	95% CI	CV (%)
V_1 (litres)=θ_1 LBW/45	θ_1=35.1	34.7	24–45	59.7
V_2 (litres)=θ_2 LBW/45	θ_2=82.9	83.7	68–101	36.2
Cl (litres min^{-1})=θ_3 ICG-R15CL LBW/45	θ_3=0.77	0.77	0.66–0.87	25.7
Q_2 (litres min^{-1})=θ_4 LBW/45	θ_4=2.3	2.6	1.7–6.1	59.9
ICG-R15CL=exp(θ_5 ICG-R15)	θ_5=−0.056	−0.053	−0.087 to 0.009	—
Proportional residual error (%)	0.222	—	—	—

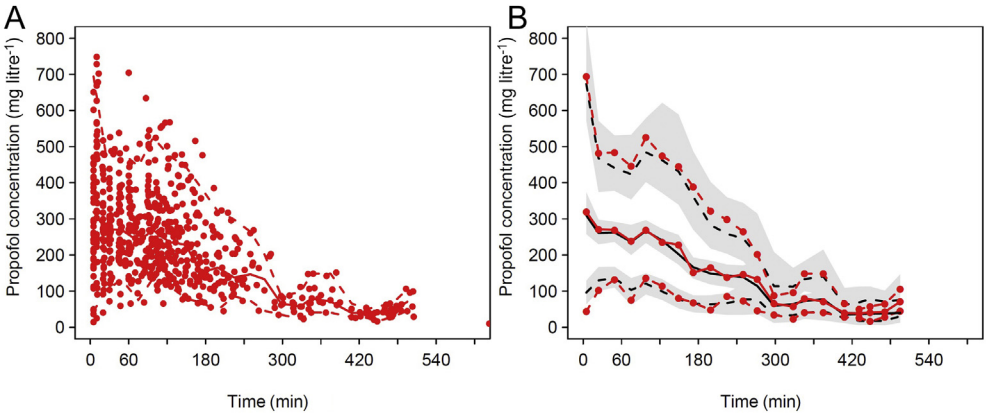

Fig 4. Visual predictive check plots of dexmedetomidine pharmacokinetic data. (a) The observed plasma concentrations are represented by red circles; (b) the solid and dashed red lines represent the median and the 5% and 95% percentiles of the observed data, respectively. The solid and dashed black lines are the model predicted median and 5–95% percentiles, respectively. The semi-transparent grey field represents the simulation-based 95% confidence interval for the predicted median and the 95% confidence intervals for the corresponding model predicted percentiles, which reflect an uncertainty range.

a mild tendency towards higher NAS scores in patients with higher BMI (R=0.28; P=0.08), only two patients had NAS >5, suggesting steatohepatitis.[32] In addition, only six patients had mildly elevated ALT levels, and we did not find any apparent association between ALT and BMI (R=0.03; P=0.86). It is not surprising, therefore, that, because of the only moderate levels of liver damage observed in the population studied, none of these variables affected the dexmedetomidine clearance in the current modelling analysis. Metabolic syndrome, as a clinical condition associated with cardiovascular disease, reflects a generalised damage caused by metabolic diseases related to obesity, such as high blood pressure, high cholesterol, and hyperglycaemia or insulin resistance.[33,34] Metabolic syndrome is related to NAFLD, which is associated with major liver fibrosis.[35] Our study population had a high prevalence of metabolic syndrome (60%), and all the patients that presented NAFLD had metabolic syndrome. We did not find evidence in the literature or in our results of a relevant role of this generalised organ damage in dexmedetomidine clearance.

Liver blood flow is an important determinant of metabolic clearance in highly hepatic extracted drugs, such as dexmedetomidine.[16] The PDR of ICG and ICG retention rate at 15 min (ICG-R15) were used as alternative estimates of liver blood flow.[36–38] A previous study characterising ICG–PDR in healthy patients reported mean (range) values of 23.1% min^{-1} (9.7–43.2% min^{-1}),[38] which are in close agreement with currently observed values of 27.5% min^{-1} (15.1–49.1% min^{-1}). Although our modelling analysis showed an effect of liver blood flow, estimated with both ICG–PDR and ICG-R15, in dexmedetomidine clearance, we did not observe an association between these indices and BMI (R=−0.03; P=0.86 and R=0.18; P=0.25, respectively), suggesting that neither obesity nor NAFLD affects total liver blood flow in the population studied. Previous studies assessing portal vein haemodynamic changes in NAFLD by Doppler have shown an inverse correlation between the severity of liver steatosis and portal vein flow, which is explained by an increase in the resistance of the portal vein flow from liver infiltration.[17,18] A compensatory increase in hepatic artery blood flow, which results in relatively normal values of total liver blood flow in these patients, as shown in our results, has been reported in patients with NAFLD.[39] As ICG–PDR and ICG-R15 account for the global liver blood flow, the specific role of hepatic artery and portal vein cannot be determined.

Liver damage can alter the function and expression of drug-metabolising enzymes.[40] We have measured the gene expression of hepatic cytochromes UGT1A4 and UGT2B10 in our population, and observed a negative correlation between mRNA of UGT1A4 and BMI (R=−0.39; P=0.014). We did not find, however, a decrease in dexmedetomidine clearance associated with this variable in the obese. In agreement, previous studies have found that, although hepatic UGT mRNA levels are reduced in the inflamed liver,[41] the glucuronidation of drugs is not affected by NAFLD.[42]

Physiological changes associated with general anaesthesia and surgery in conjunction with potential PK interactions with propofol and remifentanil most probably affected the PK profile of dexmedetomidine during the study period.[43–45] This limitation should be considered when extrapolating our results to a different clinical scenario.

In conclusion, with the current dose schemes based on LBW, we did not find a negative effect of FM in dexmedetomidine clearance. Other hepatic factors, including histopathological damage and differential expression of enzymes, did not affect the dexmedetomidine clearance in the population studied. Our results confirm the adequacy of LBW as a dose scalar for dexmedetomidine in obese patients, and show that hepatic blood flow plays a relevant role in dexmedetomidine elimination. Previous findings suggesting a negative effect of FM in dexmedetomidine clearance are most probably explained by a relative overdose of obese patients caused by dosing schemes based on TBW.

Authors' contributions

Study design: S.P., L.I.C., N.Q., C.R.
Patient recruitment: A.R., S.P., N.Q., V.C., J.C.
Data collection: A.R., S.P., N.Q., V.C., J.C., A.M.O., M.I.

Data analysis: A.R., L.I.C., B.J.A., S.S., F.A., J.T., D.C., M.I.
Writing of the first draft of the paper: A.R., S.P., L.I.C., B.J.A., M.I.

Declaration of interest

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.01.040.

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