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Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care†

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Background. The pharmacokinetics of the alpha-2 adrenoceptor agonist dexmedetomidine were studied in 10 patients requiring postoperative sedation and mechanical ventilation in the intensive care unit (ICU), and compared with previous volunteer data.

Methods. On arrival in the ICU, sedation with dexmedetomidine was commenced with a loading dose of 2.5 $\mu g\ kg^{-1}\ h^{-1}$ over 10 min followed by a maintenance infusion of 0.7 $\mu g\ kg^{-1}\ h^{-1}$ into a central vein. Blood samples for measurement of plasma dexmedetomidine concentrations were taken during and after sedative infusions at predetermined intervals. Pharmacokinetic variables were estimated using non-compartmental methods. In addition, non-linear mixed effects modelling was used to obtain variable estimates not readily attainable from non-compartmental methods. Respiratory and haemodynamic data were recorded to enable correlation of any adverse events with the calculated pharmacokinetic profile.

Results. The harmonic mean distribution half-life of dexmedetomidine was 8.6 min and the harmonic mean terminal half-life was 3.14 h. Steady-state volume of distribution averaged 173 litres, clearance averaged 48.3 litres h^{-1}, and the mean residence time averaged 3.86 h.

Conclusions. Mean dexmedetomidine pharmacokinetic variables seen in postoperative, intensive care patients were similar to those previously found in volunteers, with the exception of the steady-state volume of distribution. A small loading dose provided effective sedation with no adverse events.

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The alpha-2 agonist, dexmedetomidine, is an effective sedative and analgesic agent for the postoperative patient requiring artificial ventilation in the intensive care unit (ICU).[1] Dexmedetomidine offers haemodynamic stability, particularly over the stressful extubation period,[1] has minimal effects on respiration,[2 3] and has only minor effects on cognitive function, allowing easy communication and cooperation between the patient and the medical and nursing staff.[1 4]

The pharmacokinetics of dexmedetomidine have been studied following intramuscular and computer-controlled i.v. infusions in human volunteers.[5 6] The pharmacokinetics of dexmedetomidine are not influenced by isoflurane anaesthesia,[7] and the influence of cardiac output on dexmedetomidine pharmacokinetics has been investigated.[8] However, all these studies have described the pharmacoki-

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netics of dexmedetomidine in healthy volunteers, and there are no published pharmacokinetic data on patients receiving dexmedetomidine infusions in the ICU.

We have therefore characterized the pharmacokinetic profile of dexmedetomidine in 10 patients requiring postoperative sedation and ventilation in the ICU, and examined potential side-effects, such as haemodynamic and respiratory changes.

Patients and methods

The local Research Ethics Committee approved the study, and written informed consent was obtained from all patients. Ten adult patients (over 18 years of age) admitted to the ICU following complex major abdominal or pelvic surgery, who were expected to require 6 h postoperative sedation and ventilation, were studied. Exclusion criteria were allergy to any of the trial drugs, pregnancy, and severe hepatic or renal disease.

The anaesthetic technique used prior to admission to ICU was chosen by the individual anaesthetist.

On arrival in the ICU, sedation with dexmedetomidine was commenced, and additional analgesia, if required, was provided by an alfentanil infusion. Dexmedetomidine was supplied in 2 ml ampoules at a concentration of 100 $\mu g\ ml^{-1}$, and diluted to 8 $\mu g\ ml^{-1}$ with normal saline. Patients received a loading dose of 2.5 $\mu g\ kg^{-1}\ h^{-1}$ for 10 min followed by a maintenance infusion rate of 0.7 $\mu g\ kg^{-1}\ h^{-1}$ into a central vein. If supplementary analgesia was required, alfentanil (1 mg ml^{-1}) was infused at 0.25–1 $\mu g\ kg^{-1}\ min^{-1}$. The level of sedation was measured and recorded hourly using the Ramsay sedation score[9] and bispectral index.[10] Atracurium boluses were allowed if required to provide muscle relaxation, and paracetamol could be used as an antipyretic. Otherwise, no other sedative or analgesic agents were used.

Patients were mechanically ventilated with oxygen-enriched air to attain satisfactory blood gases. Extubation was considered when there was no evidence of bleeding, and patients were alert, cardiovascularly stable, normothermic, with an arterial oxygen tension $\geqslant$10 kPa or an inspired oxygen concentration $\leqslant$40%, and positive end-expiratory pressure $\leqslant$5 cm H_2O. Extubation was undertaken when spontaneous respiration was established with pressure support $\leqslant$10 cm H_2O, tidal volumes >6 ml kg^{-1} and ventilatory frequency $\geqslant$10 bpm but $\leqslant$20 bpm.[11] Dexmedetomidine was discontinued before extubation. The extubation time was defined as the time from cessation of sedation infusion to extubation. Heart rate, arterial pressure, central venous pressure, and oxygen saturation were monitored continuously, and recorded every 10 min for the first 30 min and then hourly. Ventilatory frequency was recorded hourly and arterial blood gas analysis 2 hourly following extubation. Cardiovascular and respiratory adverse events were defined as a change in arterial pressure $\geqslant$40% from baseline, bradycardia <50 beats min^{-1}, tachyarrhythmia, and ventilatory frequency <8 bpm or >25 bpm following extubation.

Blood samples (5 ml) for measurement of plasma dexmedetomidine concentrations were taken at the start of the dexmedetomidine infusion (time=0 min) and at 5, 10, 20, 30, 45 and 60 min, and then at 2, 3.5, 6, 10, 14, 19 and 24 h if the patient was still receiving a dexmedetomidine infusion. A blood sample was taken immediately after discontinuation of dexmedetomidine, and again at 10, 25, 40, 60, 90 min and 2, 3, 4, 5, 6, 12 and 24 h. Blood samples were taken from the radial artery cannula, after first removing the dead space volume, and were collected into prechilled tubes containing no additives, and immediately centrifuged in the ICU.

Plasma was frozen and stored at –70°C until assayed at Oneida Research Services (Whitesboro, NY, USA). Internal standard (d-MPV-872 HCl; empirical formula $C_{12}H_{14}N_2HCl$; molecular weight 222.72) was added to aliquots of plasma, and samples were simultaneously extracted with hexanes under basic conditions and derivatized with pentafluorobenzoyl chloride in hexanes. After derivatization, the hexane layer was evaporated to dryness, reconstituted in toluene, vortexed, and samples injected into a gas chromatograph–mass spectrometer; ions monitored 394 m/z (derivative of dexmedetomidine) and 380 m/z (derivative of internal standard). Intra-assay coefficients of variation were 10.7% at 20 pg ml^{-1}, 8.4% at 600 pg ml^{-1}, and 8.7% at 1200 pg ml^{-1}. Interassay coefficients of variation were 10.9% at 20 pg ml^{-1}, 8.2% at 600 pg ml^{-1}, and 8.6% at 1200 pg ml^{-1}.The lower limit of quantitation was 10 pg ml^{-1}. The mean coefficient of correlation was 0.997 for calibration curves, with standards ranging from 10 to 1498 pg ml^{-1}.

Pharmacokinetic calculations

Pharmacokinetic variables of dexmedetomidine were estimated using non-compartmental methods. The variables estimated were: the maximum observed plasma concentration (C_{max}), time to C_{max} (peak time, T_{max}), the terminal half-life ($t_{1/2}$), the terminal phase elimination rate constant (β) the area under the plasma–concentration time curve (AUC), area under the first moment curve (AUMC), mean residence time (MRT), and the apparent steady-state volume of distribution (V_{ss}). In addition, non-linear mixed effects modelling was used to estimate variables not readily attainable using non-compartmental methods. Typical values of clearance and volume are represented by CL and V_1 respectively. Central estimate of clearance and volume are represented by CL_2 and V_2 respectively. Distribution half-life is represented by $t_{1/2\alpha}$.

Non-compartmental analyses

C_{max} and T_{max} were determined directly from the plasma concentration–time data. The value of the terminal phase elimination rate constant (β) was obtained from the slope of

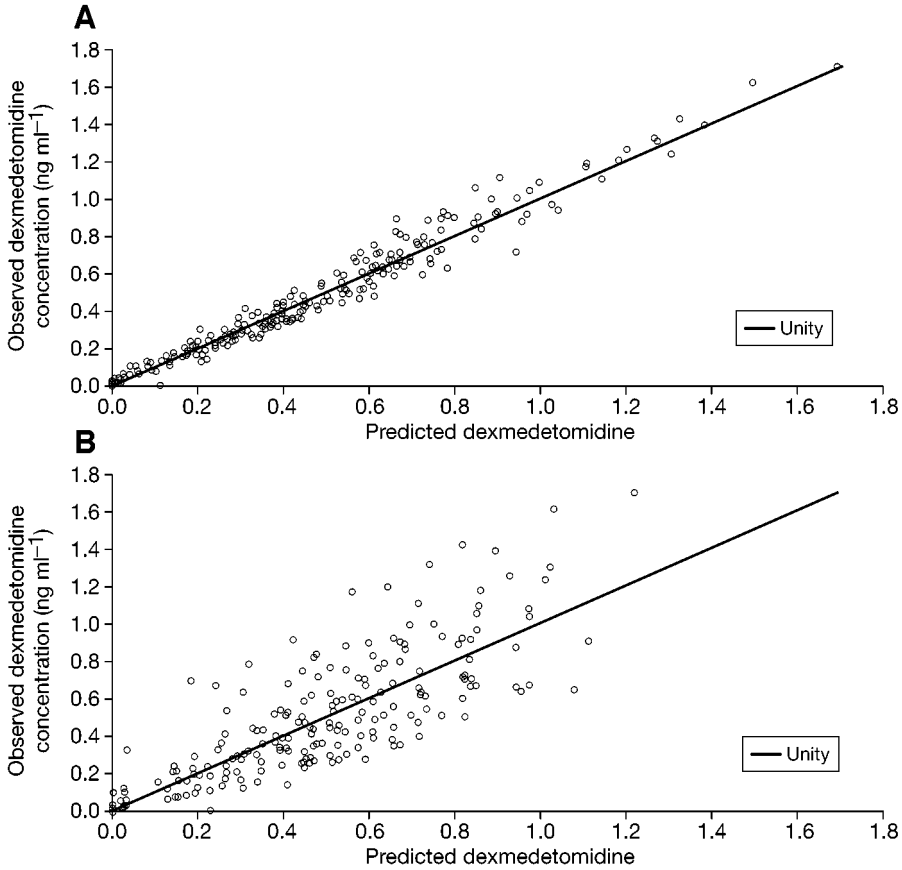

Fig 1 Observed dexmedetomidine plasma concentration (ng ml^{-1}) versus model-predicted concentrations for individual subjects (A) and for the population (B).

the least-squares linear regression of the logarithms of the plasma concentration–time data, from the terminal log-linear phase of the profile. The terminal log-linear phase was identified by visual inspection. The terminal elimination half-life ($t_{1/2}$) was calculated as $\ln(2)/\beta$.

The AUC from time 0 to the time of the last measurable concentration (AUC_t) was calculated by the linear trapezoidal rule. The AUC was extrapolated to infinity by dividing the last measurable plasma concentration (C_t) by β. Denoting the extrapolated portion of the AUC as AUC_{ext}, the AUC from time 0 to infinite time (AUC_∞) was calculated as:

$$AUC_\infty = AUC_t + AUC_{ext}$$

The area under the first moment of the plasma concentration–time curve from time 0 to the time of the last measurable concentration ($AUMC_t$) was calculated by the linear trapezoidal rule as applied to the concentration–time product *vs* time (first moment) data. The AUC was extrapolated to infinity using the following equation:

$$AUMC_{ext} = tC_t/\beta + C_t/\beta^2$$

$AUMC_\infty$ was calculated as:

$$AUMC_\infty = AUMC_t + AUMC_{ext}$$

Area under the drug administration rate curve (AUC_R) and first moment of the drug administration rate curve ($AUMC_R$) were computed as for the corresponding parameters of the concentration–time curve, substituting administration rate for concentration.

MRT can be computed as the ratio of the area under the first moment curve and the area under the curve (AUMC/AUC) when drug administration is instantaneous. When drug administration takes a measurable finite time, the mean administration or input time must be subtracted. Under conditions where drug administration is not constant, such as a loading dose followed by a maintenance dose, the mean input time is computed as $AUMC_R/AUC_R$.[12] Thus, the MRT, the average of the times that the administered drug molecules remained in the body, was computed as:

$$MRT = AUMC/AUC - AUMC_R/AUC_R$$

Clearance was calculated by dividing the administered dose by the AUC_∞. V_{ss} was calculated as the product of clearance and MRT.

Non-linear mixed effects modelling analyses

Non-linear mixed effects modelling was done using the program WinNonMix.[13] A two-compartment open model

Table 1 Individual patient, operative, and ICU sedation characteristics. M=male, F=female

Patient	Operation	Age (yr)	Operation duration (h)	APACHE II score	Duration of dexmedetomidine infusion in the ICU (h)	Median (range) depth of sedation during dexmedetomidine infusion		Extubation time (min)
						Bispectral index	Ramsay score	
1 M	Repair of abdominal aortic aneurysm	60	3	19	7	44 (34–70)	5 (4–6)	20
2 M	Repair of abdominal aortic aneurysm	54	5	19	14	58 (40–80)	5 (3–6)	20
3 F	Gastrectomy for sarcoma	71	6	8	16	55 (41–92)	4 (3–5)	15
4 F	Radical hysterectomy	66	5	12	6	44 (35–60)	4 (4–6)	10
5 F	Gastrectomy, splenectomy	69	8	12	14	46 (37–66)	5 (4–6)	45
6 M	Abdominoperineal resection	78	4	18	6	41 (32–61)	4 (4–6)	30
7 M	Repair of abdominal aortic aneurysm	80	4	14	6	63 (47–80)	4 (4)	45
8 M	Open reduction and fixation of pelvic fracture	35	7	3	6	51 (40–60)	4 (4–5)	30
9 M	Extended Whipple's procedure	69	12	14	14	65 (50–98)	4 (2–5)	10
10 M	Intra-abdominal resection of melanoma metastases	36	10	12	14	58 (40–75)	4 (4–6)	5
Median (interquartile range)		68 (57–70)	6 (5–8)	13 (12–16)	11(6–14)	53(45–58)	4 (4–5)	20 (13–27)

Table 2 Non-compartmental pharmacokinetic parameters. $t_{1/2}$, terminal elimination half-life (half-lives averaged harmonically); AUC, area under the curve; V_{ss}, volume of distribution at steady state; MRT, mean residence time; C_{max}, maximum observed plasma concentration

Patient	Weight (kg)	Duration of infusion (h)	$t_{1/2}$ (h)	AUC (ng h^{-1} ml^{-1})	V_{ss} (litres)	MRT (h)	Clearance (litres h^{-1})	C_{max} (ng ml^{-1})
1	80	7	2.62	10.41	109.7	2.75	39.95	1.26
2	80	14	3.38	11.77	282.3	4.11	68.68	0.91
3	60	16	2.52	12.06	152.4	2.66	57.22	0.89
4	100	6	3.80	18.84	175.0	7.33	23.88	1.71
5	50	14	3.90	13.84	137.9	3.78	36.48	0.99
6	70	6	2.77	7.87	101.9	2.55	40.02	1.11
7	80	6	3.54	9.55	212.2	5.63	37.70	1.04
8	80	6	2.70	4.98	180.2	2.49	72.33	0.71
9	70	14	4.60	16.00	195.5	4.42	44.19	1.09
10	70	14	2.75	11.32	180.7	2.89	62.44	1.49
Mean (SD)	74 (14)	10 (4)	3.14 (0.62)	11.66 (3.95)	172.8 (52.5)	3.86 (1.59)	48.29 (15.90)	1.12 (0.30)

(model 9) with clearance and volume parameterization was used. Deviation of individual pharmacokinetic parameters from the typical population value was modelled using the exponential model:

$$P_j = P_{TV} * e^{(\eta_{pj})}$$

where P_{TV} represents the typical value or central estimate of the parameter P, in this case clearance, V_1, CL_2, or V_2, pj represents the jth individual parameter value, η_{pj} characterizes the difference between the individual and the population central estimate, such that $P_{TV} * e^{(\eta_{pj})}$ gives P_j; η_{pj} is assumed to be normally distributed with a mean of 0 and a variance of ω_p. Interpatient variability was modelled with additive and proportional error as:

$$Y_{ij} = F_{ij} + F_{ij}*\varepsilon_{ij1} + \varepsilon_{ij2}$$

where Y_{ij} represents the jth individual ith observation, F_{ij} represents the predicted concentration for the jth individual at the ith observation, and ε_{ij1} and ε_{ij2} represent the proportional and additive intra-individual variability, respectively. ε were assumed to be normally distributed with a mean of 0 and a variance of σ^2. Within the program WinNonMix, this interpatient variability function was selected by designating 'a + |Yhat|^2' as the variance function. The modelling method was set to conditional first order.

Appropriateness of fit was assessed by achievement of convergence and inspection of observed *vs* predicted, weighted residual *vs* predicted, weighted residual *vs* time, and typical value as well as individual concentration *vs* time plots. Observed versus model-predicted individual and population dexmedetomidine concentrations are shown in Figure 1A and 1B, respectively.

Statistical analysis

Normally distributed data are shown as mean (SD) values. Medians and interquartile ranges (IQR) are quoted for skewed data.

Table 3 Pharmacokinetic parameters from modelling, and parameters computed from modelling. Typical value estimates were determined by non-linear mixed effects modelling. $t_{1/2}\alpha$ was taken as the mean of individual subject's parameter estimates. Standard error (SE) was obtained directly from mixed effects modelling, with the exception of SE for $t_{1/2}\alpha$, which was estimated from individual subject values. %CV represents the coefficient of variation for the standard deviation and is estimated from individual subject's parameter estimates. Typical values represented by CL, V_1; central estimate represented by CL_2, V_2

	Clearance (litres h^{-1})	Volume V_1 (litres)	Clearance CL_2 (litres h^{-1})	Volume V_2 (litres)	Distribution half-life $t_{1/2}\alpha$ (min)
Typical value estimate	49.2	44.1	135.3	104.5	8.64
SE	4.3	5.8	19.8	11	1.31
%CV	33	50	43	45	48

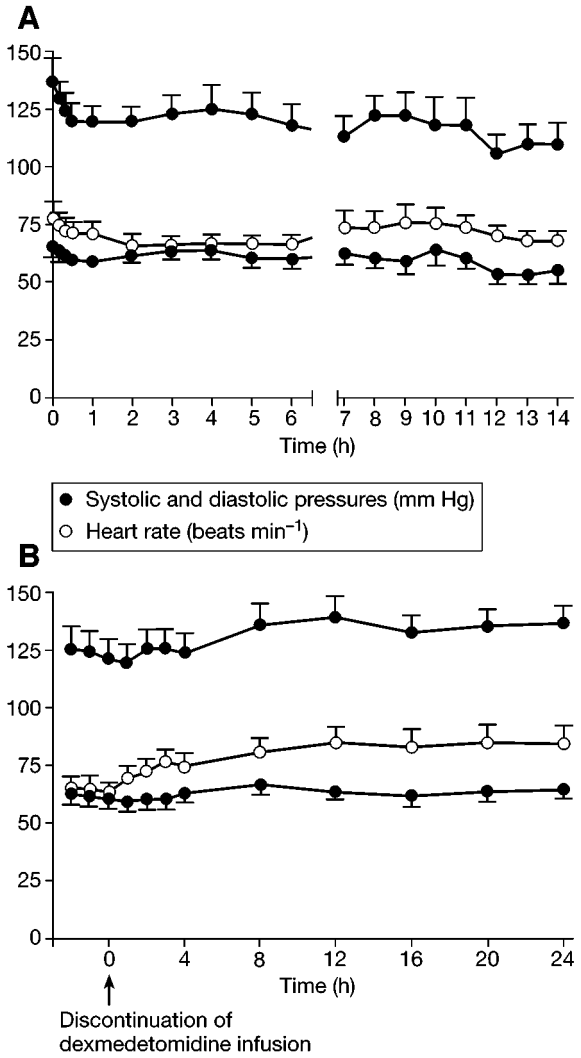

Fig 2 Haemodynamic variables for patients whilst intubated and sedated with dexmedetomidine (A), and following termination of dexmedetomidine infusion and extubation (B). Values are mean (SD). In A, data for the first 6 h are from 10 patients, and data for 7–14 h are from the five patients who received dexmedetomidine infusions for longer than 7 h.

Results

Individual and median patient, operative, and ICU sedation characteristics are shown in Table 1. Five patients required sedation with dexmedetomidine in the ICU for 6–7 h; the other five patients required sedation for at least 14 h. Initially, only peripheral venous access was available in patient 10. The loading infusion of dexmedetomidine was therefore administered peripherally in this patient before gaining central venous access for the maintenance infusion. No patient required atracurium during the study.

Pharmacokinetics

Peak dexmedetomidine concentrations averaged 1.12 ng ml^{-1}, with a range of 0.71–1.71 ng ml^{-1}. The harmonic mean distribution half-life was 8.6 min and the harmonic mean terminal half-life was 3.14 h. V_{ss} averaged 173 litres, MRT averaged 3.86 h and clearance averaged 48.3 litres h^{-1}. Estimates of pharmacokinetic parameters are shown in Tables 2 and 3.

Haemodynamics

There were no adverse cardiovascular events at any time during the study in any of the 10 patients. Changes in arterial pressure and heart rate during the infusion and following discontinuation of the infusion are shown in Figure 2A and 2B, respectively.

Respiratory measurements

There were no adverse respiratory events following extubation, despite persistence of sedative plasma levels of dexmedetomidine for several hours. Median (IQR) extubation time was 20 (12.5–27) min. Median Ramsay sedation scores and mean oxygen saturations, ventilatory frequenciess, Pa_{CO_2}, and arterial-inspired oxygen ratios (Pa_{O_2}/FI_{O_2}) are shown in Table 4.

Discussion

The aim of this study was to establish the pharmacokinetic profile of dexmedetomidine given by infusion to post-operative patients requiring sedation and mechanical ventilation in the ICU. Dexmedetomidine is eliminated almost exclusively by metabolism. Patients and healthy volunteers may differ physiologically because of differences in regional blood flow. However, following a 10 min dose

Table 4 Respiratory and depth of sedation for the first 4 h following extubation, in all patients. Values are mean (SD) or median (interquartile range)

	Time following extubation (h)				
	0	**1**	**2**	**3**	**4**
Ramsay score	3 (3–4)	4 (4)	4 (4)	4 (3–4)	3 (3–4)
Ventilatory frequency (bpm)	14 (3)	15 (4)	15 (2)	16 (3)	15 (3)
Oxygen saturation (%)	97 (3)	97 (2)	98 (3)	97 (2)	98 (3)
Pa_{O_2}/FI_{O_2} ratio	43.4 (7.3)		44.8 (11.6)		40.5 (6.3)
Pa_{CO_2} (kPa)	5.5 (0.5)		5.5 (0.6)		5.5 (0.4)

(2 μg kg^{-1} i.v.) of radiolabelled dexmedetomidine to humans, unchanged dexmedetomidine was not detected in the urine.[14] The hepatic extraction ratio of dexmedetomidine has been previously estimated at about 70%. Thus, changes in regional hepatic blood flow may have an effect on dexmedetomidine pharmacokinetics, but the effect is small. Previous research has shown that a 19% decrease in cardiac output resulted in an estimated 12% decrease in total body clearance.[8] Changes in renal blood flow would not be expected to affect dexmedetomidine pharmacokinetics. Additionally, the pharmacokinetics in subjects with normal renal function, and mild, moderate and severe renal impairment, as defined by creatinine clearance, did not differ. The product label (PL) for dexmedetomidine (Precedex™; dexmedetomidine hydrochloride injection) reports mean pharmacokinetic values in volunteers ranging from 35.3 to 46.3 litres h^{-1} for clearance, 1.78 to 2.50 h for $t_{1/2}$ and 88.7 to 102.4 litres for V_{ss}. Statistical comparison, based on two-sample *t*-test, examining these measurements yielded no statistically significant differences between the estimates obtained in the patients in the current study and at least one set of measurements in the PL, with the exception of V_{ss}. Clearance values in patients in the current study and those reported in some subjects (PL) are similar. For example, mean (SD) values of 46.3 (8.3) litres h^{-1} are reported for some subjects (PL) compared with 48.3 (15.9) litres h^{-1} in the current study. Likewise, $t_{1/2}$ values of 2.50 (0.61) h are reported for volunteers (PL), compared with 3.14 (0.62) h in this study. V_{ss} in the current study does appear to be greater, how much greater is uncertain. Mean V_{ss} values of 102.4 (20.3) litres have been reported for healthy subjects (PL), whereas in the current study estimates of 173 litres (non-compartmental) and 148.5 litres (sum of V_1 and V_2 from modelling) are obtained depending upon methodology. Additionally, in the current study, all patients had infusions into a central vein, with the exception of patient 10 who had the loading infusion only into a peripheral vein, whereas in the volunteer study (PL) dexmedetomidine was infused peripherally. Furthermore, samples for pharmacokinetic analyses were arterial in the current study, whereas samples from the reference subjects (PL) were venous. This may also cause volume estimates to differ.[15] In comparing volumes, it is important to note that persistence of the drug in the individual is a function of $t_{1/2}$, and plasma concentrations maintained during an infusion are a function of clearance. Following extensive surgery, the systemic inflammatory response generated may result in oedema. This alteration in fluid distribution may alter drug distribution, particularly for drugs with a small-to-moderate volume of distribution such as dexmedetomidine. The greater V_{ss} in these postoperative patients may be the result of increased oedema formation. Although alfentanil was administered concomitantly, previous research indicates that the clearance of dexmedetomidine in the presence of alfentanil is similar to that obtained for dexmedetomidine alone in other studies. Thus, an effect of alfentanil on dexmedetomidine in the current study is unlikely (data on file, Abbott Laboratories, Abbott Park, IL).

It is reassuring that despite $t_{1/2}$ values in the order of 3 h, patients could be extubated soon after termination of the dexmedetomidine infusion. Presumably this reflects the unique ability of dexmedetomidine to sedate with only mild functional and cognitive impairment,[4] and with minimal effects on respiration.[2 3] In this study, there also appeared to be little effect on clinically measured respiratory variables in patients following extubation. Thus, despite therapeutic sedative concentrations of dexmedetomidine up to at least the $t_{1/2}$ (3 h) following termination of the infusion, there were no clinically detectable adverse respiratory effects in our spontaneously breathing postoperative patients. The patients remained comfortably sedated (Ramsay sedation score 4) for several hours after termination of the dexmedetomidine infusion.

In an earlier study examining dexmedetomidine infusions in the ICU,[1] 18 of 66 patients experienced significant hypotension or bradycardia, and the majority of these events occurred during the loading period. The loading dose was subsequently reduced by over 50% for the present study, and sedation continued to be effective following the patients' arrival in the ICU. No adverse cardiovascular events were seen in any of the patients in this study at any time period. As would be expected of an alpha-2 adrenoceptor agonist, arterial pressure and heart rate gradually decreased from baseline following commencement of dexmedetomidine and then increased slowly again following termination of the infusion, with no evidence of any clinically important rebound cardiovascular events. Haemodynamics remained stable over the extubation period, as has been reported previously.[1]

In summary, the mean dexmedetomidine pharmacokinetic parameters seen in postoperative patients requiring sedation and mechanical ventilation in the ICU are similar to those found previously in volunteers, with the exception of V_{ss}. V_{ss} appears to be greater in postoperative patients, and this may be explained by differences in pathology or methodology when compared with volunteer studies. A reduction in the initial loading dose infusion of dexmedetomidine provides adequate sedation, with no cardiovascular adverse events. Extubation time following discontinuation of dexmedetomidine was rapid, and there appeared to be no harmful effects on respiration in spontaneously breathing patients in the ICU, despite therapeutic sedative dexmedetomidine plasma concentrations.

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