

## CLINICAL INVESTIGATIONS

## Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 1: Pharmacodynamic and pharmacokinetic interactions

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Dexmedetomidine is a highly selective  $\alpha_2$ -adrenoceptor agonist with anaesthetic-sparing effects. We have determined the pharmacodynamic and pharmacokinetic interactions between dexmedetomidine and isoflurane in volunteers. Nine male subjects were allocated randomly to receive isoflurane anaesthesia preceded by infusion of dexmedetomidine on three separate occasions, 2 weeks apart. Dexmedetomidine target plasma concentrations were 0.0 (placebo), 0.3 ng ml<sup>-1</sup> (low-dex) and 0.6 ng ml<sup>-1</sup> (high-dex). End-tidal isoflurane concentrations at which gross purposeful movement and response to verbal commands occurred were identified. In the recovery period, sedation scores and digit symbol substitution tests were recorded. Venous blood samples were obtained before, during and after anaesthesia at predetermined intervals for measurement of plasma concentrations of dexmedetomidine and calculation of standard pharmacokinetic indices (AUC, Cl, V<sup>ss</sup>, T<sub>1/2</sub><sup>α</sup>, T<sub>1/2</sub><sup>β</sup>). The end-tidal isoflurane concentration at which 50% of subjects first responded to the tetanic stimulus was 1.05% in the placebo group, 0.72% in the low-dex group and 0.52% in the high-dex group. We conclude that dexmedetomidine decreased isoflurane requirements in a dose-dependent manner and reduced heart rate, systolic and diastolic arterial pressures. Sedation and slight impairment of cognitive function persisted for several hours after anaesthesia and the end of infusion of dexmedetomidine. Isoflurane did not appear to influence the pharmacokinetics of dexmedetomidine.

*Br J Anaesth* 1999; **83**: 372–80

**Keywords:** anaesthetics volatile, isoflurane; interactions (drug); sympathetic nervous system, dexmedetomidine; pharmacokinetics, dexmedetomidine; pharmacodynamics

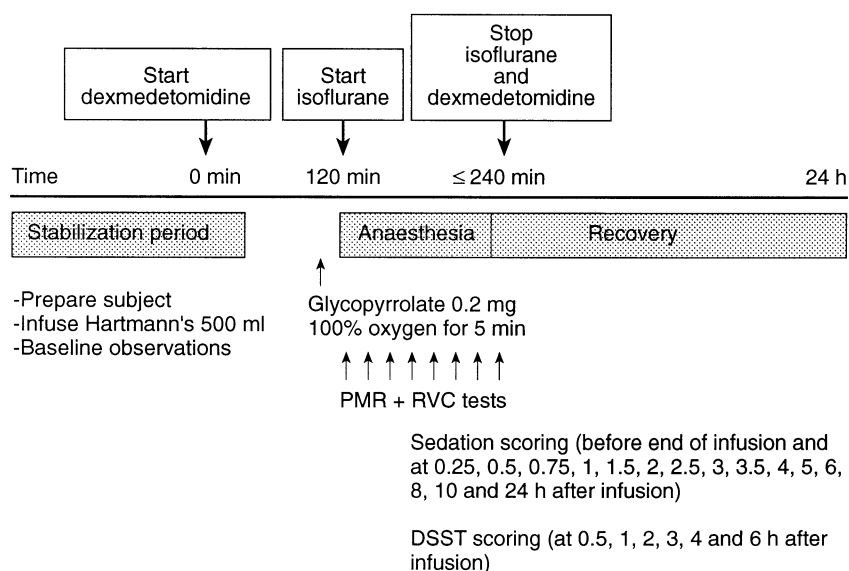
Accepted for publication: April 13, 1999

Clonidine is currently the only  $\alpha_2$ -adrenoceptor agonist available for anaesthetic or analgesic use, but it is only a partial agonist with an  $\alpha_1/\alpha_2$  ratio of 1:220. Dexmedetomidine is a highly selective and potent  $\alpha_2$ -adrenoceptor agonist, with an  $\alpha_1/\alpha_2$  ratio of 1:1620. It is a dextro-enantiomer and the pharmacologically active component of the racemate medetomidine.<sup>1,2</sup> Alpha<sub>2</sub> adrenoceptor agonists, such as xylazine, have been used widely in veterinary anaesthetic practice in Europe for more than 20 yr.<sup>3</sup> The renewed interest in this class of agents stems from the dose-related sedative,<sup>4</sup> anxiolytic,<sup>5</sup> anaesthetic<sup>6–10</sup> and analgesic<sup>11</sup> sparing effects, and ability to blunt the sympathetic response to surgery,<sup>12–14</sup> resulting in intraoperative haemodynamic stability.

A single i.v. dose of dexmedetomidine given before induction of anaesthesia diminished isoflurane requirements during abdominal hysterectomy.<sup>15</sup> In this study, we have investigated the pharmacokinetic and pharmacodynamic interactions of dexmedetomidine and isoflurane in human subjects, with particular reference to the dose-dependent effects of dexmedetomidine on isoflurane requirements.

### Subjects and methods

This was a phase I, single-centre, randomized, double-blind, crossover controlled study conducted in non-smoking, male ASA I volunteers. After obtaining approval from the Local Ethics Committee and written informed consent, we studied



**Fig 1** Linear flow chart of the study plan.

**Table 1** Three-stage infusion technique in the high-dex, low-dex and placebo groups. Placebo=0.9% saline; low-dex=dexmedetomidine target concentration  $0.3\text{ ng ml}^{-1}$ ; high-dex=dexmedetomidine target concentration  $0.6\text{ ng ml}^{-1}$

Stage	Infusion rate ( $\mu\text{g kg}^{-1}\text{ h}^{-1}$ )			Volume ( $\text{ml kg}^{-1}\text{ h}^{-1}$ )	Duration
	High-dex	Low-dex	Placebo		
1	2.85	1.43	0.00	0.476	20 min
2	1.35	0.68	0.00	0.226	40 min
3	0.42	0.21	0.00	0.070	<4 h

nine subjects. All were aged 22–32 yr and weighed 60–100 kg. Exclusion criteria were: those in whom inhalation induction was contraindicated; those with significant cardiovascular, respiratory, renal or hepatic disease, as determined by medical history, physical examination, a 12-lead electrocardiogram (ECG) and laboratory tests for haematology and serum chemistry; and those receiving any prescribed or over-the-counter medications in the 2 months preceding and during the planned study period, or with a history of cigarette smoking, drug or alcohol abuse. Serum chemistry and urinalysis included drug and alcohol screening tests.

After a 6-h fast and starting standard anaesthetic monitoring using a Capnomac 2 (Datex Capnomac; Instrumentarium, Finland), baseline measurements were recorded (baseline was defined as the mean of three arterial pressure (AP) and heart rate (HR) readings obtained at 10-min intervals during the stabilization period). Each subject received Hartmann's solution (Baxter Travenol) 500 ml i.v. over 30 min and this was maintained at  $1\text{ ml kg}^{-1}\text{ h}^{-1}$  until 3 h after anaesthesia (Fig. 1). Subjects were allocated randomly to receive two doses of dexmedetomidine and placebo (0.9% saline), 2 weeks apart. Target plasma concentrations of dexmedetomidine were  $0.3\text{ ng ml}^{-1}$  (low-dex group) and  $0.6\text{ ng ml}^{-1}$  (high-dex group). Dexmedetomidine was infused in three-stages and dosage was based on the weight of each subject (Table 1). Infusion rates for dexmedetomidine were designed to achieve steady-state

plasma concentrations of the target concentrations within 2 h and to maintain those concentrations.<sup>16</sup> Dexmedetomidine was infused for 120 min before and during administration of isoflurane and stopped at the end of anaesthesia.

Blood samples (5 ml) were obtained for measurement of plasma concentrations of dexmedetomidine at the start of infusion of dexmedetomidine (time=0 min) and at 20, 30, 45, 60, 75, 90 and 120 min. During anaesthesia, blood samples were collected at the end of each isoflurane 15-min equilibration period. Immediately after stopping isoflurane and dexmedetomidine, blood samples were obtained and again at 0.5, 1, 2, 3, 4, 6, 8, 10 and 24 h.

For measurement of plasma concentrations of dexmedetomidine, 5-ml venous blood samples were collected into pre-chilled lithium polypropylene tubes. After centrifugation, plasma was frozen and stored at  $-20^{\circ}\text{C}$  or below until assayed at Oneida Research Services ((ORS), Inc., Whitesboro, NY, USA). Plasma concentrations of dexmedetomidine were measured using a gas chromatographic–mass spectrometric (GC/MS) method with a lower limit of quantitation of  $0.01\text{ ng ml}^{-1}$ . The mean correlation coefficient for calibration curves with standards ranging from 10 to  $1498\text{ pg ml}^{-1}$  was 0.998

After a period of 120 min after starting infusion of the study drug, glycopyrrolate  $0.2\text{ mg}$  was administered i.v. (Fig. 1). After preoxygenation for 5 min, anaesthesia was induced with isoflurane in oxygen with the subject breathing

spontaneously through a facemask via a co-axial Bain circuit. The inspired isoflurane concentration was increased until loss of consciousness and a laryngeal mask airway was inserted. The subject was allowed to breathe an oxygen-air-isoflurane mixture spontaneously; the fractional inspired oxygen concentration was maintained at 0.3. Gas was sampled continuously from a probe attached to the laryngeal mask, and derived  $FE'_{CO_2}$  was maintained throughout the period of anaesthesia at or below 6.6 kPa by manually assisting ventilation, if necessary.

End-tidal isoflurane ( $FE'_{iso}$ ) concentration was maintained initially at 1.2% for an equilibration period of 15 min. A supramaximal tetanic stimulus of 50 Hz for 5 s was applied to the subject's left ulnar nerve at the wrist. If this resulted in purposeful movement,  $FE'_{iso}$  concentration was increased in 0.2% increments and equilibrated for 15 min, until the purposeful motor response was abolished.  $FE'_{iso}$  concentration was then decreased by 0.2% until a purposeful motor response re-appeared after tetanic ulnar nerve stimulation.

At this time,  $FE'_{iso}$  concentration was recorded, and a motor response to the verbal command 'squeeze my hand' was sought and recorded. If the subject did not respond to the verbal command, then further 0.2% reductions in  $FE'_{iso}$  concentration were performed until the subject either responded to verbal command or no longer tolerated the laryngeal mask airway. Administration of both isoflurane and infusion of the study drug were then discontinued.

During recovery, the incidence of nausea and vomiting, sedation scores and the presence or absence of shivering were noted. Shivering was recorded as present if there was tremor of the head, jaw and arms associated with piloerection and a subjective sensation of cold. Subjects were evaluated for sedation during the recovery period (1=awake; 2=asleep, easy to rouse; 3=asleep, difficult to rouse; and 4=asleep, unrousable). To evaluate differences between treatment groups, data were transformed and plotted as the percentage of subjects with a sedation score >1 (i.e. not awake) at each time after the end of infusion of the study drug. Cognitive impairment, as judged using the digit symbol substitution test (DSST), was also evaluated. This test examines the number and percentage of correct substitutions of symbols for numbers according to a key within 90 s, and has been used to measure satisfactory recovery from anaesthesia.<sup>17</sup> A decrease in systolic arterial pressure by more than 30% below baseline was recorded as a hypotensive episode and treated with an increase in the crystalloid infusion rate to 999 ml h<sup>-1</sup>; if this was ineffective, methoxamine 1 mg i.v. was also administered. A decrease in heart rate of greater than 20% below baseline was treated with atropine 0.1 mg i.v.

### Pharmacokinetic methods

#### Non-compartmental analysis

The pharmacokinetic variables of dexmedetomidine were estimated using non-compartmental methods with the observed sampling times. Maximum plasma concentration

( $C_{pmax}$ ) and time to reach  $C_{pmax}$  ( $tC_{pmax}$ ) were obtained directly from individual concentration vs time profiles. The area under the plasma concentration-time curve ( $AUC_{0-\infty}$ ) was calculated as the sum of  $AUC_{0-t}$ , the area up to the last measurable concentration computed using the linear trapezoid rule, and extrapolation to infinity, calculated as the quotient of the last measurable concentration ( $C_t$ ) and the elimination rate constant ( $\beta$ ). The elimination rate constant was calculated using the negative slope of the regression of the logarithmic plot of plasma dexmedetomidine concentrations vs time. Elimination half-life ( $T_{1/2}^{\beta}$ ) was obtained by dividing the natural logarithm of 2 by  $\beta$ . Systemic clearance ( $Cl$ ) was calculated by dividing the ratio of the total dose infused by  $AUC_{0-\infty}$ . Mean residence time (MRT) was computed as  $MRT = (AUMC/AUC) - MIT$ , where MIT is the mean input time for the three stages of the infusion. MIT is calculated as the ratio of  $AUMC_1$  divided by  $AUC_1$ , where  $AUMC_1$  and  $AUC_1$  are the area under the moment curve and area under the curve, respectively, of the input rate vs time plot. Steady-state volume of distribution ( $V^{ss}$ ) was calculated as  $V^{ss} = Cl \times MRT$ .

#### NONMEM analysis

The non-linear regression analysis program NONMEM was used to perform a pharmacokinetic analysis of dexmedetomidine plasma concentrations for all subjects. As no differences were found in the pharmacokinetic variables between the two dose groups, data from the low-dex and high-dex groups were combined for NONMEM analysis. One-, two- and three-compartment models were examined. A two-compartment model was accepted as it was found to fit the data better, as judged by the smaller objective function, and was less complex than the three-compartment model. NONMEM was used to estimate four values: (1) the population typical value of the pharmacokinetic parameter ( $\theta$ ), (2) precision of the typical value estimate, (3) inter-individual variability in the variable ( $\omega^2$ ) and (4) precision of the estimate of  $\omega^2$ . Inter-subject difference for each population pharmacokinetic estimate was modelled as an exponential error term. For example, clearance of dexmedetomidine was modelled as:  $Cl = \theta \times e^{\eta}$ , where  $\theta$  is the typical or central value for  $Cl$  in the population from which the study subjects were drawn and  $\eta$  is a random variable having a normal probability distribution with mean 0 and variance  $\omega^2$ .

#### Statistical methods

Plasma concentrations of dexmedetomidine for each sampling time were tabulated and analysed for each treatment group. For each treatment group, summary statistics were tabulated for each of the pharmacokinetic variables determined using non-compartmental and population analyses. In all tables, calculations were performed before rounding.

Analyses of variance (ANOVA) was performed on non-compartmental pharmacokinetic variables, including dose-

normalized  $C_{pmax}$ ,  $t_{Cpmax}$ , MRT,  $V^{ss}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $Cl$  and  $\beta$ . ANOVA was performed to assess the effect of isoflurane exposure, expressed as end-tidal isoflurane AUC and dexmedetomidine clearance. Logistic regression analyses were performed to estimate the probability of a positive motor response or response to verbal command in relation to end-tidal isoflurane concentration. A similar approach was used to analyse sedation score.

DSST scores were related to plasma concentrations of dexmedetomidine using the following inhibitory sigmoid model:

$$E = E_0 - (E_0 \times C^\gamma) / (EC_{50}^\gamma + C^\gamma)$$

where  $E$  = DSST score expressed as the number of correct responses;  $EC_{50}$  = plasma dexmedetomidine concentration producing 50% of  $E_0$ ;  $C$  = plasma dexmedetomidine concentration; and  $\gamma$  = Hill exponent (sigmoid factor) describing the shape of the effect vs concentration relationship. Because of the large variability in response, individual data from all subjects receiving the same treatment were pooled and fitted to the inhibitory Emax model, using the non-linear regression analysis program PCNONLIN (Version 4.0, SCI Software, Lexington, KY).

PROC GLM, MIXED, LOGISTIC and PROBIT of SAS (Version 6.1) were used for the above analyses. Analyses of variance were performed using Genstat 5 release 3 to test for effects of tetanic stimulation, isoflurane concentration and dexmedetomidine dose and placebo on heart rate, and systolic and diastolic arterial pressures. All tests of hypotheses were two-tailed. In all statistical analyses,  $P \leq 0.05$  was considered significant.

## Results

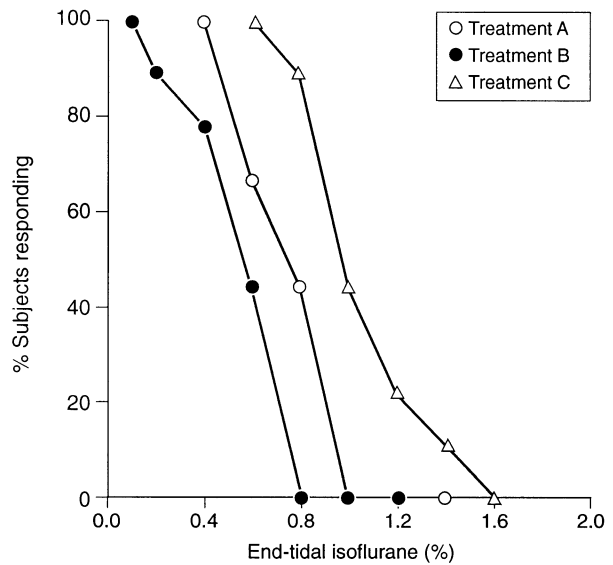
### Pharmacodynamics

#### MAC-reducing effect

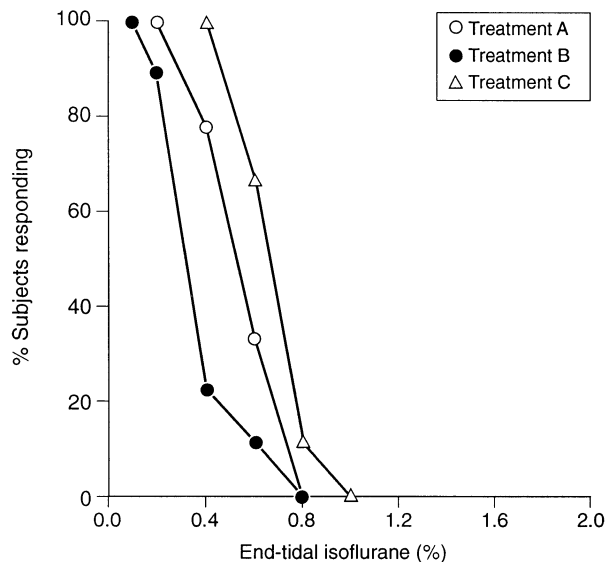
The percentage of subjects showing a motor response and a response to verbal commands at each end-tidal isoflurane concentration are illustrated in Figures 2 and 3, respectively. There was a left shift in the isoflurane response curves indicating that lower isoflurane concentrations were required to suppress both the motor response to tetanic stimulation and the response to verbal commands, as dexmedetomidine concentrations were increased. Table 2 shows estimates of  $EC_{50}$  values (i.e. isoflurane concentration required to elicit a response in 50% of subjects for each treatment group).

The  $EC_{50}$  of isoflurane to prevent a positive motor response was 0.72% in the low dexmedetomidine concentration group, 0.52% in the high dexmedetomidine concentration group and 1.05% in the placebo group ( $P < 0.0001$ ). Also, the  $EC_{50}$  value required to prevent a response to verbal commands was significantly lower ( $P < 0.001$ ) in the high dexmedetomidine concentration group (0.33%) than in the placebo group (0.61%).

At 2.5 h, approximately 40% of subjects who had received



**Fig 2** Percentage of subjects showing a motor response to tetanic stimulation at different end-tidal concentrations of isoflurane. Treatment A = dexmedetomidine target concentration 0.3 ng ml<sup>-1</sup>; treatment B = dexmedetomidine target concentration 0.6 ng ml<sup>-1</sup>; and treatment C = placebo.

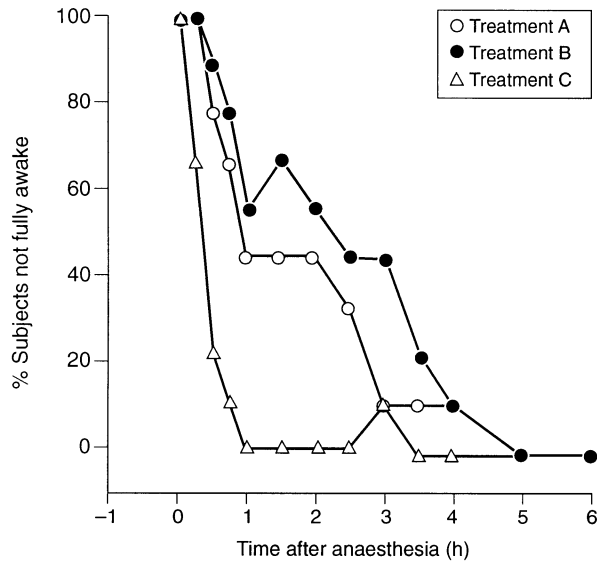


**Fig 3** Percentage of subjects responding to a verbal command at different end-tidal concentrations of isoflurane. Treatment A = dexmedetomidine target concentration 0.3 ng ml<sup>-1</sup>; treatment B = dexmedetomidine target concentration 0.6 ng ml<sup>-1</sup>; and treatment C = placebo.

dexmedetomidine were still not awake compared with 0% of the placebo group (Fig. 4). This was also apparent in the estimated times at which 50% of subjects still had some degree of sedation ( $T_{50}$ ). These were 0.36 (0.03–0.58) h, 1.62 (1.20–2.06) h and 2.22 (1.78–2.71) h for the placebo, low-dex and high-dex groups, respectively. Although the difference was not statistically significant between the two dexmedetomidine groups,  $T_{50}$  for the low-dex and high-dex groups was significantly longer ( $P < 0.0001$ ) compared with placebo.

**Table 2** Estimates of EC<sub>50</sub> and 95% confidence intervals (CI) for purposeful motor response and response to verbal commands. Treatment groups: placebo=0.9% saline; low-dex=dexmedetomidine target concentration 0.3 ng ml<sup>-1</sup>; high-dex=dexmedetomidine target concentration 0.6 ng ml<sup>-1</sup>. EC<sub>50</sub>=end-tidal isoflurane concentration at which 50% of subjects responded

Group	Purposeful motor response		Response to verbal command	
	EC <sub>50</sub> (%)	95% CI	EC <sub>50</sub> (%)	95% CI
Placebo	1.048	0.915–1.229	0.610	0.507–0.712
Low-dex	0.722	0.611–0.828	0.523	0.419–0.625
High-dex	0.520	0.402–0.632	0.327	0.240–0.413



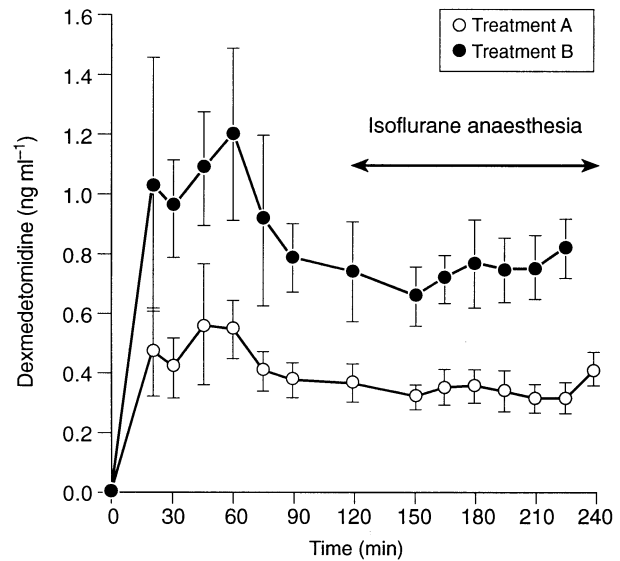
**Fig 4** Percentage of subjects not awake (sedation score >1) vs time after anaesthesia. Treatment A=dexmedetomidine target concentration 0.3 ng ml<sup>-1</sup>; treatment B=dexmedetomidine target concentration 0.6 ng ml<sup>-1</sup>; and treatment C=placebo.

DSST scores at baseline were similar between groups, with mean values of 54.8%, 55.0% and 55.3% for the placebo, low-dex and high-dex groups, respectively. DSST scores were lower than baseline after exposure to isoflurane and dexmedetomidine, with the lowest score recorded 0.5 h after anaesthesia in the high-dex group. DSST scores returned to baseline more rapidly in the placebo group compared with the dexmedetomidine groups. DSST scores in the placebo and low-dex groups were similar at 3 h, and scores in all three groups were similar at 4 h.

Differences in the pharmacodynamic–pharmacokinetic relationship between DSST scores and dexmedetomidine concentrations were apparent between the two doses of dexmedetomidine (Fig. 5). At any given plasma dexmedetomidine concentration, mean DSST score was higher for subjects in the high-dex group compared with the low-dex group, probably because of the contributing effect of the different final concentration of isoflurane. An inhibitory sigmoid Emax model was fitted to the data separately for the low-dex and high-dex groups (Table 3).

#### Haemodynamic variables

Before infusion of the study drug, mean values for HR, SAP and DAP were similar for the placebo, low-dex and



**Fig 5** Mean (SD) plasma dexmedetomidine concentrations vs time during infusion. Treatment A=dexmedetomidine target concentration 0.3 ng ml<sup>-1</sup>; and treatment B=dexmedetomidine target concentration 0.6 ng ml<sup>-1</sup>.

**Table 3** Inhibitory Emax model variable estimates (mean (SEM)) from PCNONLIN. Treatment groups: low-dex=dexmedetomidine target concentration 0.3 ng ml<sup>-1</sup>; high-dex=dexmedetomidine target concentration 0.6 ng ml<sup>-1</sup>. E<sub>0</sub>=baseline DSST score expressed as the number of correct responses; EC<sub>50</sub>= plasma dexmedetomidine concentration producing 50% of E<sub>0</sub>. σ=Hill exponent (sigmoid factor)

Variable	Low-dex	High-dex
E <sub>0</sub>	54.1 (1.1)	54.8 (3.5)
EC <sub>50</sub> (ng ml <sup>-1</sup> )	0.304 (0.01)	0.437 (0.36)
γ <sup>σ</sup>	4.68 (0.85)	3.65 (1.18)

high-dex groups (Table 4). However, 2 h after the start of infusion, just before anaesthesia, HR, SAP and DAP were significantly lower ( $P=0.002$ ,  $0.005$  and  $0.005$ , respectively) after dexmedetomidine compared with placebo infusions. The means for the placebo group were not significantly different from those before infusion. There was no significant differences between the effects of low and high doses of dexmedetomidine, which are combined in Table 4.

During anaesthesia, mean values for HR, SAP and DAP were significantly less ( $P=0.003$ ,  $<0.001$ ,  $0.009$ , respectively) after both low and high dexmedetomidine infusions compared with placebo. In addition, for SAP and

**Table 4** Mean (95% confidence intervals) HR, SAP and DAP before anaesthesia, showing the effect of dexmedetomidine infusions (low and high doses combined) compared with placebo

	HR (beat min <sup>-1</sup> )		SAP (mm Hg)		DAP (mm Hg)	
	Pre-infusion	2 h after start of infusion	Pre-infusion	2 h after start of infusion	Pre-infusion	2 h after start of infusion
Placebo	57.0 (52.5–61.5)	61.2 (56.7–65.7)	121.1 (116.6–125.7)	121.2 (116.7–125.8)	67.3 (63.6–71.1)	67.9 (64.1–71.6)
Dexmedetomidine	57.1 (53.9–60.3)	50.0 (46.8–53.1)	118.7 (115.5–121.9)	108.2 (104.9–111.4)	64.8 (62.2–67.5)	59.6 (53.9–59.2)
<i>P</i>	0.002	0.002	0.005	0.005	0.005	0.005

**Table 5** Mean DAP (95% confidence intervals) during anaesthesia showing the effect of tetanic stimulation at 0.6%  $FE'_{iso}$  compared with higher concentrations (0.8%, 1.0% and 1.2% end-tidal isoflurane concentrations combined) and modification of this effect by dexmedetomidine (low and high doses combined)

$FE'_{iso}$ concn	Placebo		Dexmedetomidine	
	Pre-tetanic	Post-tetanic	Pre-tetanic	Post-tetanic
0.6%	54.0 (48.6–59.4)	66.0 (60.6–71.4)	47.2 (44.4–49.9)	49.8 (47.0–52.5)
0.8%, 1.0%, 1.2%	50.3 (44.8–55.7)	52.6 (47.2–58.1)	44.7 (41.9–47.40)	46.0 (43.2–48.7)

**Table 6** Hypotensive events and interventions. Treatment groups: low-dex=dexmedetomidine target concentration 0.3 ng ml<sup>-1</sup>; high-dex=dexmedetomidine target concentration 0.6 ng ml<sup>-1</sup>. C=Crystalloid infusion rate increased to 999 ml h<sup>-1</sup>; C+M=crystalloid infusion rate increased to 999 ml h<sup>-1</sup> and methoxamine 1 mg given i.v.; A=atropine 0.1 mg i.v.; iso.=isoflurane

Subject	Low-dex		High-dex	
	End-tidal iso. (%)	Intervention	End-tidal iso. (%)	Intervention
1	0.4	C+M	0.4	C+M
4	1.2	C+M	–	–
4	1.4	C+M	–	–
7	1.2	C	1.2	C+M
7	–	–	1.4	A
8	1.2	C+M	0.8	C
8	–	–	1.0	C+M
8	–	–	1.2	C+M
9	–	–	1.0	C+M

DAP, there was a significant interaction ( $P=0.064$ , 0.003, respectively) between the effect of tetanic stimulation and isoflurane concentration (two-factor interaction). SAP and DAP increased after tetanic stimulation, but there was a greater increase when subjects received an  $FE'_{iso}$  concentration  $\leq 0.6\%$  than during the three higher recorded end-tidal concentrations of 0.8%, 1.0% and 1.2%. For DAP, this was modified further by dexmedetomidine, that is there was a significant three-factor interaction ( $P=0.005$ ) (Table 5). DAP increased significantly after tetanic stimulation in the placebo group compared with both of the dexmedetomidine groups (combined in Table 5), but this difference was only significant at an  $FE'_{iso}$  concentration of  $\leq 0.6\%$ .

There were 12 hypotensive events in five subjects requiring observer intervention (Table 6); 75% of these occurred in subjects with an end-tidal isoflurane concentration of at least 1%, and there was no significant difference in the incidence between the low-dex and high-dex groups. No subject in the placebo group had hypotension requiring treatment.

Before anaesthesia, there was no detectable effect of dexmedetomidine on ventilatory frequency. During anaesthesia, spontaneous ventilation was assisted manually in most subjects (placebo group, six of nine subjects; low-dex

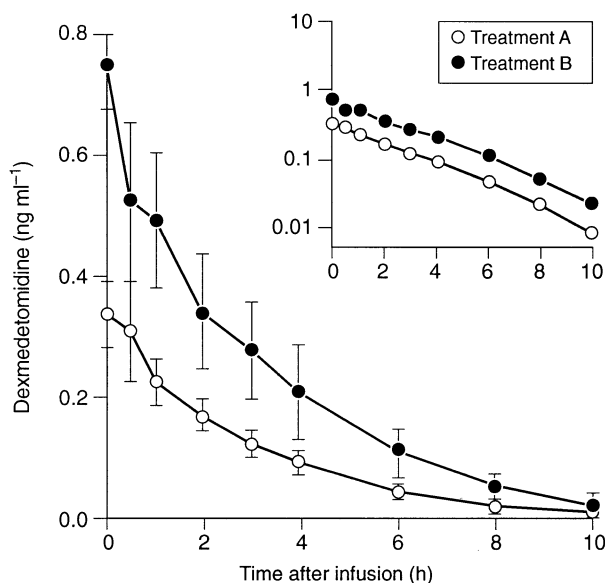
group, seven of nine; high-dex group, six of nine) to maintain end-tidal carbon dioxide tension less than 6.7 kPa.

There was no significant difference in the incidence of nausea or vomiting. No shivering was recorded in any patient.

### Pharmacokinetics

Mean plasma concentrations of dexmedetomidine vs time from 2 h before anaesthesia (when infusion of dexmedetomidine commenced), to the end of the period of anaesthesia (when infusion was discontinued), and 10 h into the subsequent recovery period are illustrated in Figures 5 and 6, respectively.

Immediately before isoflurane anaesthesia, observed mean plasma concentrations of dexmedetomidine were 0.37 ng ml<sup>-1</sup> and 0.75 ng ml<sup>-1</sup> in the low-dex and high-dex groups, respectively. There were no significant differences between groups for any of the pharmacokinetic variables, including dose-normalized  $C_{pmax}$ ,  $t_{Cpmax}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $AUC_{0-4}$ ,  $Cl$ ,  $MRT$ ,  $V^{ss}$  and  $\beta$ . There was no significant relationship between isoflurane exposure (based on end-tidal isoflurane AUC) and steady-state plasma dexmedetomidine concentration or clearance in either group (Table 7).  $Cl$  and  $V^{ss}$ , estimated using NONMEM, were



**Fig 6** Mean (SD) plasma dexmedetomidine concentrations after infusion vs time during recovery. Treatment A=dexmedetomidine target concentration 0.3 ng ml<sup>-1</sup>; and treatment B=dexmedetomidine target concentration 0.6 ng ml<sup>-1</sup>.

**Table 7** Dexmedetomidine pharmacokinetic variables (mean (SD)) obtained using non-compartmental analysis ( $n=9$ ). Treatment groups: low-dex=dexmedetomidine target concentration 0.3 ng ml<sup>-1</sup>; high-dex=dexmedetomidine target concentration 0.6 ng ml<sup>-1</sup>.  $C_{120}$ =Concentration measured at 120 min, before isoflurane anaesthesia;  $C^{ss}$ =apparent steady-state concentration calculated as the mean of concentrations measured between 120 min and the end of the infusion for each subject.  $T_{1/2}^{\beta}$  is reported as the harmonic mean (pseudo SD)

Variable	Low-dex	High-dex
$C_{120}$ (ng ml <sup>-1</sup> )	0.370 (0.064)	0.748 (0.166)
$C^{ss}$ (ng ml <sup>-1</sup> )	0.352 (0.046)	0.729 (0.106)
$AUC_{0-\infty}$ (ng h ml <sup>-1</sup> )	2.375 (0.277)	5.061 (0.864)
$T_{1/2}^{\beta}$ (h)	1.86 (0.39)	1.94 (0.14)
$Cl$ (litre h <sup>-1</sup> kg <sup>-1</sup> )	0.520 (0.062)	0.495 (0.094)
MRT (h)	2.82 (0.77)	2.73 (0.43)
$V^{ss}$ (litre kg <sup>-1</sup> )	1.47 (0.46)	1.33 (0.19)
$\beta$ (h <sup>-1</sup> )	0.372 (0.076)	0.356 (0.056)
Extraction ratio	0.67 (0.09)	0.64 (0.10)

similar to those obtained using non-compartmental analysis, with values for NONMEM of 0.529 litre h<sup>-1</sup> kg<sup>-1</sup> and 1.43 litre kg<sup>-1</sup>, respectively. The harmonic mean half-lives for the distribution ( $\alpha$ ) and elimination ( $\beta$ ) phases were 0.15 h and 2.25 h, respectively.

## Discussion

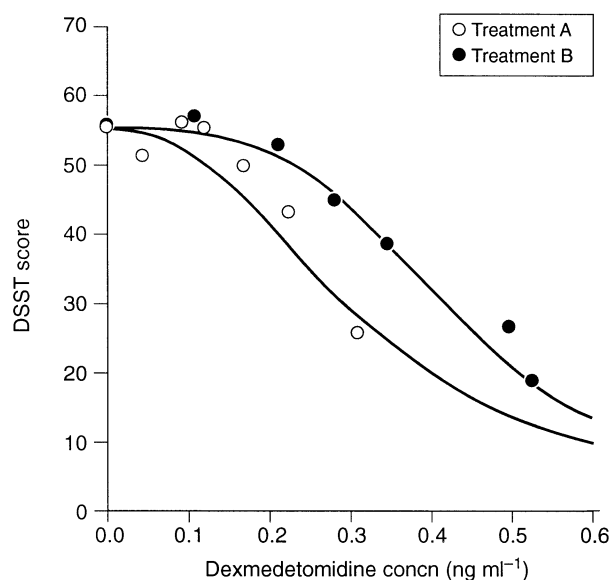
The locus coeruleus is a small neuronal nucleus located bilaterally in the upper brainstem and is the largest noradrenergic cell group. It is an important modulator of wakefulness and may be the major site of the hypnotic action of  $\alpha_2$ -adrenoceptor agonists, which cause a decrease in noradrenergic activity.<sup>18</sup> In this study, we determined the pharmacodynamic interaction of dexmedetomidine and isoflurane and the pharmacokinetics of the  $\alpha_2$ -adrenoceptor agonist during isoflurane anaesthesia. To reduce the influ-

ence of confounding factors, we chose to undertake the study in healthy volunteers.

Pharmacodynamically, the primary end-point was to determine the MAC-sparing effect of dexmedetomidine in a dose-related manner. Dexmedetomidine has been shown to reduce perioperative dose requirements for isoflurane,<sup>19</sup> but haemodynamic criteria were used to assess depth of anaesthesia which may be inappropriate because of the direct cardiovascular effects of dexmedetomidine. Using volunteers allowed us to carefully control isoflurane concentration but we were unable to use the standard noxious stimulus for defining MAC (response to skin incision) and we had to substitute a non-invasive stimulus. Our group and others have used response to supramaximal 50 Hz tetanic ulnar nerve stimulation.<sup>20 21</sup> This may not mimic the stimulus of skin incision precisely, but as the primary end-point was shift of the dose-response relationship, this is of less concern. We found that dexmedetomidine 0.35 ng ml<sup>-1</sup> decreased anaesthetic requirements for isoflurane by approximately 35% and 0.75 ng ml<sup>-1</sup> by approximately 50%. These results are broadly comparable with previous studies in patients, most recently by Aantaa and colleagues.<sup>22</sup> The authors correctly stated that their results should be treated with caution as thiopental and alfentanil were also administered. The  $EC_{50}$  for isoflurane in the placebo group (1.05) was similar to that found by Mather, Raftery and Prys-Roberts (1.0).<sup>23</sup> The difference may be a result of the use of temazepam as premedication in their study.<sup>23</sup>

Both isoflurane and dexmedetomidine contributed to the sedative effects in the recovery period. Although we did not specifically determine sedation scores just before induction of anaesthesia, it was clear that a proportion of subjects were sedated before receiving isoflurane, indicating that the active treatment was associated with some innate sedative effects. Logistic regression was used to evaluate the difference between treatment groups. After anaesthesia, there was no significant difference between the two dexmedetomidine groups in the time taken to regain full consciousness (sedation score 1). Calculated  $T_{50}$  for both dexmedetomidine groups was significantly longer compared with the placebo group. There was no difference between groups using a cut-off sedation score of >2 (i.e. asleep and either difficult to arouse or unrousable). The sedative actions of dexmedetomidine in humans<sup>24</sup> have proved beneficial when used as premedication before induction of anaesthesia.<sup>5</sup>

Cognitive state was measured using DSST scoring before the start of infusion and during recovery. The relationship between DSST scores and plasma concentrations of dexmedetomidine measured during recovery (Fig. 7) suggest that for any given plasma dexmedetomidine concentration, mean DSST score was greater for subjects in the high-dex group compared with the low-dex group. This is probably because of the lower final concentration of isoflurane administered in the high-dex group thus contributing less to the overall effect on DSST scores. We also found that at the same dexmedetomidine concentration soon after discontinuation



**Fig 7** Mean DSST scores vs mean dexmedetomidine concentrations. Treatment A=dexmedetomidine target concentration  $0.3 \text{ ng ml}^{-1}$ ; and treatment B=dexmedetomidine target concentration  $0.6 \text{ ng ml}^{-1}$ . The line represents the fit of the inhibitory Emax model to individual data.

of both dexmedetomidine and isoflurane, the decrease in DSST scores was greater in subjects in the high-dex group. This may also be explained by the greater contribution of isoflurane to the decrease in DSST scores in those subjects during the early period after the end of infusion.

There was no significant difference between the low and high doses of dexmedetomidine on haemodynamic variables. Our findings of a slight decrease in heart rate and arterial pressure at the end of the 2-h periods in the low-dex and high-dex groups, and during anaesthesia, are similar to those reported in other clinical studies.<sup>12,13</sup> Before anaesthesia, all subjects received anticholinergic medication to prevent the marked bradycardia reported to occur with dexmedetomidine.<sup>19</sup> Systolic and diastolic arterial pressures increased after tetanic stimulation in all cases, but was greater when the end-tidal isoflurane concentration was  $\leq 0.6\%$ . In addition, at an  $FE'_{\text{iso}}$  concentration of  $\leq 0.6\%$ , the placebo group showed a statistically greater increase in diastolic arterial pressure after tetanic stimulation than the dexmedetomidine groups. This was presumably a result of the increase in systemic vascular resistance mediated by sympathetic activation, this effect being blunted by higher concentrations of isoflurane. The central sympatholytic effect of dexmedetomidine can blunt the cardiovascular response to noxious stimuli during anaesthesia.<sup>13</sup>

Our observations regarding the respiratory effects of dexmedetomidine support those of other workers<sup>25</sup> who showed that infusion of dexmedetomidine in healthy volunteers produced a slight increase in  $Pa_{\text{CO}_2}$  and a decrease in minute ventilation, with little change in ventilatory frequency.

Measured plasma concentrations of dexmedetomidine confirmed that the target levels were achieved just before

anaesthesia, using our three-stage infusion technique (Table 1). Mean steady-state plasma concentrations of dexmedetomidine actually achieved for the duration of the period of anaesthesia (Fig. 7) were approximately 25% greater than target concentrations. As there were no differences in any of the pharmacokinetic variables between treatments, dexmedetomidine plasma concentrations measured in the low-dex and high-dex groups were combined, and a two-compartment model was fitted to the data using the non-linear regression model NONMEM. Inter-patient variability (i.e. difference between individual values and the population estimate) was small, related in part to the homogeneity of the population. Intra-patient variability was estimated as 29.0%. The plot of predicted vs observed dexmedetomidine concentrations using the NONMEM model showed the data to be well distributed around the unity line, supporting the validity of the NONMEM pharmacokinetic model. The quality of the fit was also confirmed by examining plots of weighted residuals vs predicted dexmedetomidine concentrations.

Our calculated pharmacokinetic variables (Table 7) support those of other workers.<sup>26,27</sup> The observed decrease in plasma concentration is influenced by all of these variables. However, our findings suggest that dexmedetomidine pharmacokinetics are linear and that it is an intermediate extraction ratio drug, at the two doses studied. Other workers suggest that the pharmacokinetics of dexmedetomidine are best described by a three-compartment model, with dexmedetomidine exhibiting a concentration-dependent non-linear profile.<sup>16</sup> Thus at high concentrations, the large volume of distribution of dexmedetomidine is likely to be reduced by predominating peripheral vasoconstriction, resulting from attenuation of its  $\alpha_2$ -effects.<sup>28</sup> The effect of isoflurane on dexmedetomidine pharmacokinetics was evaluated by examining the relationship between isoflurane exposure and dexmedetomidine clearance. We found no significant relationship between end-tidal isoflurane AUC and dexmedetomidine clearance for either low or high dexmedetomidine treatments. In addition, measured plasma dexmedetomidine concentrations during the steady-state period of anaesthesia were not altered by addition of isoflurane.

In summary, the highly selective  $\alpha_2$ -adrenoceptor agonist, dexmedetomidine, caused a dose-related decrease in the MAC of isoflurane. The mechanism of action of dexmedetomidine has been reported to be different from that of isoflurane.<sup>29</sup> Significant MAC-sparing effects occurred at plasma concentrations of  $0.35\text{--}0.75 \text{ ng ml}^{-1}$ . Isoflurane did not appear to affect the pharmacokinetics of dexmedetomidine.

## Acknowledgement

The study was performed at Guy's Drug Research Unit, London. We acknowledge support for this study from Abbott Laboratories.



## References

- 1 Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomidine as an  $\alpha_2$  adrenoceptor agonist. *Eur J Pharmacol* 1988; **150**: 9–14
- 2 Maze M, Tranquilli W. Alpha-2 adrenoceptor agonists: defining the role in clinical anesthesia. *Anesthesiology* 1991; **74**: 581–605
- 3 Tranquilli W, Maze M. Clinical pharmacology and use of  $\alpha_2$ -adrenergic agonists in veterinary anesthesia. *Anesth Pharmacol Rev* 1993; **1**: 229–309
- 4 Laurito CE, Baughman VL, Becker GL, Desilva TW, Carranza CJ. The effectiveness of oral clonidine as a sedative/anxiolytic and as a drug to blunt the hemodynamic response to laryngoscopy. *J Clin Anesth* 1991; **3**: 186–93
- 5 Scheinin H, Jaakola ML, Sjövall S, et al. Intramuscular dexmedetomidine as premedication for general anesthesia. *Anesthesiology* 1993; **78**: 1065–75
- 6 Segal IS, Vickery RG, Walton JK, Doze VA, Maze M. Dexmedetomidine diminishes halothane anesthetic requirements in rats through a postsynaptic alpha-2-adrenergic receptor. *Anesthesiology* 1988; **69**: 818–23
- 7 Savola MK, MacIver MB, Doze VA, Kendig JJ, Maze M. The alpha 2-adrenoceptor agonist dexmedetomidine increases the apparent potency of the volatile anesthetic isoflurane in rats in vivo and in hippocampal slice in vitro. *Brain Res* 1991; **548**: 23–8
- 8 Aantaa R, Kanto J, Scheinin M, Kallio A, Scheinin H. Dexmedetomidine, an  $\alpha_2$ -adrenoceptor agonist, reduces anesthetic requirements for patients undergoing gynecologic surgery. *Anesthesiology* 1990; **73**: 230–5
- 9 Jaakola ML, Ali-Melkkilä T, Kanto J, Kallio A, Scheinin H, Scheinin M. Dexmedetomidine reduces intraocular pressure, intubation responses and anaesthetic requirements in patients undergoing ophthalmic surgery. *Br J Anaesth* 1992; **68**: 570–5
- 10 Vickery RG. Anesthetic and hemodynamic effects of the stereoisomers medetomidine, an  $\alpha_2$ -adrenoceptor agonist, in halothane anesthetized dogs. *Anesth Analg* 1988; **67**: 611–15
- 11 Cigarni I, Kaba A, Bonnet F, et al. Epidural clonidine combined with bupivacaine mixture to provide analgesia during labor. *Reg Anesth* 1995; **75**: 113–20
- 12 Scheinin B, Lindgren L, Randell T, Scheinin H, Scheinin M. Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and perioperative opioids. *Br J Anaesth* 1992; **68**: 126–31
- 13 Aho M, Scheinin M, Lehtinen AM, Erkola O, Vuorinen J, Korttila K. Intramuscularly administered dexmedetomidine attenuates hemodynamic and stress hormone responses to gynecologic laparoscopy. *Anesth Analg* 1992; **75**: 932–9
- 14 Kulka PJ, Tryba M, Zenz M. Dose–response effects of intravenous clonidine on stress response during induction of anesthesia in coronary artery bypass graft patients. *Anesth Analg* 1995; **80**: 263–8
- 15 Aho M, Lehtinen AM, Erkola O, Kallio A, Korttila K. The effects of intravenously administered dexmedetomidine on perioperative hemodynamics and isoflurane requirements in patients undergoing abdominal hysterectomy. *Anesthesiology* 1991; **74**: 997–1002
- 16 Dyck JB, Maze M, Haack C, Vuorilehto L, Shafer SL. The pharmacokinetics and hemodynamic effects of intravenous and intramuscular dexmedetomidine hydrochloride in adult human volunteers. *Anesthesiology* 1993; **78**: 813–20
- 17 Smith RB, Krobroth PD, Vanderlugt JT, Phillips JP, Juhl RP. Pharmacokinetics and pharmacodynamics of alprazolam after oral administration. *Psychopharmacology* 1984; **84**: 452–6
- 18 Lidbrink P. The effect of lesion of ascending noradrenergic pathways on sleep and waking in the rat. *Brain Res* 1974; **74**: 19–40
- 19 Erkola O, Korttila K, Aho M, Haasio J, Aantaa R, Kallio A. Comparison of intramuscular dexmedetomidine and midazolam premedication for elective abdominal hysterectomy. *Anesth Analg* 1994; **79**: 646–53
- 20 Jones RM, Cashman JN, Eger EI II, Damask MC, Johnson BH. Kinetics and potency of desflurane (I-653) in volunteers. *Anesth Analg* 1990; **70**: 3–7
- 21 Zbinden AM, Maggiorini M, Petersen-Felix S, Lauber R, Thomson DA, Minder CE. Anesthetic depth defined using multiple noxious stimuli during isoflurane/oxygen anesthesia: I. Motor reactions. *Anesthesiology* 1994; **80**: 253–60
- 22 Aantaa R, Jaakola M-L, Kallio A, Kanto J. Reduction of the MAC of isoflurane by dexmedetomidine. *Anesthesiology* 1997; **86**: 1055–60
- 23 Mather C, Raftery S, Prys-Roberts C. Somatic movement and oesophageal motility during isoflurane anaesthesia. *Br J Anaesth* 1992; **69**: 40–4
- 24 Aantaa R. Assessment of the sedative effects of dexmedetomidine, an  $\alpha_2$ -adrenoceptor agonist, with analysis of saccadic eye movements. *Pharmacol Toxicol* 1991; **68**: 394–8
- 25 Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. I: Sedation, ventilation and metabolic rate. *Anesthesiology* 1992; **77**: 1125–33
- 26 Stanski DR, Shafer SL. Quantifying anesthetic drug interaction: Implications for drug dosing. *Anesthesiology* 1995; **83**: 1–5
- 27 Dyck JB, Shafer SL. Dexmedetomidine pharmacokinetics and pharmacodynamics. *Anaesth Pharmacol Rev* 1993; **1**: 238–45
- 28 Schwinn DA, Correa-Sales C, Page SO, Maze M. Functional effects of activation of alpha-1 adrenoceptors by dexmedetomidine: in vivo and in vitro studies. *J Pharmacol Exp Ther* 1991; **259**: 1147–52
- 29 Thornton C, Lucas MA, Newton DEF, Dore CJ, Jones RM. Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 2: Auditory and somatosensory evoked potentials. *Br J Anaesth* 1999; **83**: 381–6