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Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 2: Auditory and somatosensory evoked responses

C. Thornton[1], M. A. Lucas[2], D. E. F. Newton[1], C. J. Doré[1] and R. M. Jones[2]

[1]Academic Department of Anaesthetics, Imperial College School of Medicine at St Mary's, Northwick Park Hospital, Harrow, London HA1 3UJ, UK. [2]Academic Department of Anaesthetics, Imperial College School of Medicine at St Mary's Paddington, London W2 1NY, UK

The anaesthetic-sparing activity of dexmedetomidine during isoflurane anaesthesia was examined, using the end-point of lack of response to tetanic nerve stimulation. Nine subjects were given two doses of dexmedetomidine (target plasma concentrations of 0.3 ng ml^{-1} and 0.6 ng ml^{-1}, respectively) and saline on separate occasions. We measured auditory (AER) and somatosensory (SER) evoked responses at end-tidal isoflurane concentrations of 0.2–1.4%. Pa and P25–N35 amplitudes increased as isoflurane concentration was reduced ($P<0.001$). Dexmedetomidine had no significant effect on this relationship. In contrast, P15–N20 (SER) amplitude increased ($P<0.001$) as isoflurane concentration was reduced. The dose of dexmedetomidine had a significant interaction with this trend ($P<0.002$). Decreasing the concentration of isoflurane at the high dose of dexmedetomidine had less impact on P15–N20 amplitude than decreasing isoflurane at the low dose or with saline. The mechanism by which dexmedetomidine spares isoflurane is discussed in the light of these evoked response changes.

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Anaesthetic sparing of an inhalation agent such as isoflurane may be mediated by different mechanisms if sparing is achieved by adding another inhalation agent compared with adding nitrous oxide or an opioid. For a particular end-point, such as prevention of movement to surgical incision, the amount of isoflurane spared may be the same in both instances, but adding an inhalation agent to achieve this effect is equivalent to adding more isoflurane, whereas adding nitrous oxide or opioids may reduce the requirement for isoflurane by attenuating the effect of the noxious stimulus.

Before applying the noxious stimulus, patients receiving additional inhalation agent should exhibit a greater degree of hypnosis compared with those given nitrous oxide or opioid. Those receiving nitrous oxide or opioid would have greater analgesia. We hypothesized that evoked responses can be used to distinguish hypnosis from analgesia and thus this would enable us to categorize the anaesthetic-sparing activity of compounds such as dexmedetomidine.

We have shown clearly that the inhalation agents enflurane,[1] halothane,[1] isoflurane,[2] sevoflurane[3] and desflurane[4] depressed early cortical auditory evoked response (AER) amplitudes of Pa and Nb. This depressant effect was reversed to some extent by noxious stimuli of intubation[5] and incision,[6] such that more inhalation agent was required to return the AER to its pre-stimulus level. Alternatively, the arousal effect on the AER by noxious stimuli can be attenuated by opioids.[7] The AER can show the balance, observed in clinical practice, between the amount of general anaesthetic required and the noxious stimulus applied.

In spite of several studies involving opioids and nitrous oxide, we are uncertain to what extent these drugs affect the early cortical AER waves. Their effects are much less marked than those of inhalation agents. In patients before surgery, nitrous oxide produced significantly less depression of Pa and Nb amplitude than an equivalent concentration of isoflurane.[8] However, nitrous oxide had a greater depressant effect on the amplitute of the somatosenory evoked response (SER) wave P15–N20. In another study, the opioid remifentanil prevented an AER to intubation at a dose range where P15–N20 amplitude showed a graded attenuation.[9] These findings led us to speculate that the amplitude of the P15–N20 SER wave reflects the analgesic component of anaesthesia whereas the amplitudes of the early cortical AER waves Pa and Nb and of the SER waves P25–N35 and N35–P45, which show similar changes, reflect the hypnotic component.

To test our hypothesis, we studied the anaesthetic-sparing activity of two doses of dexmedetomidine and saline using a crossover design in healthy male volunteers anaesthetized

with isoflurane. The end-tidal isoflurane concentration required to prevent movement to tetanic stimulation was noted and changes in the auditory and somatosensory evoked responses with saline–dexmedetomedine and isoflurane combinations were examined.

Subjects and methods

The study was approved by the Local Ethics Committee. More details on drug administration and analysis are given in our accompanying paper on pharmacodynamic and pharmacokinetic interactions.[10] In brief, two doses of dexmedetomidine (target plasma concentrations of 0.3 ng ml^{-1} and 0.6 ng ml^{-1}, respectively) and saline were administered as infusions starting 2 h before induction of anaesthesia. Nine subjects, whose details are described in our accompanying paper[10], were allocated randomly to receive each of the treatments on three occasions, at least 2 weeks apart. Anaesthesia was induced with isoflurane, which was subsequently decreased in steps of 0.2% (end-tidal), held for 15 min. Evoked responses to auditory clicks (AER) and to median nerve electrical stimulation (SER) were recorded before the start of infusion of dexmedetomidine or saline and 2 h later, just before induction with isoflurane. However, only SER data, corresponding to these times, were analysed as on too many occasions subjects were insufficiently relaxed to obtain good quality AER recordings. Both AER and SER, corresponding to the end of each isoflurane concentration period, were analysed. A tetanic stimulus, typically a train of 40 mA, 200-μs pulses at 50 Hz, was then applied to the ulnar nerve for 10 s and whether the subject moved or not was noted. The highest end-tidal isoflurane concentration, at which the subject moved to tetanic stimulation, was noted.

Evoked response recordings

The auditory stimulus was a rarefaction click delivered to both ears simultaneously via purpose-made close-fitting ear pieces. It was presented at 75 dB above the average hearing threshold for adults, at a rate of 6 s^{-1}. The somatosensory stimulus used to stimulate the median nerve at the wrist was a 150-μs electrical pulse produced by a modified Duostim nerve stimulator fitted with an optically isolated trigger from the evoked responses apparatus. It was presented at a rate of 2.2 s^{-1} and an intensity just above the motor threshold, adjusted while the subject was still conscious.

The EEG was recorded using adhesive Ag–AgCl electrodes on the forehead and the left mastoid for the AER, and Ag–AgCl cup electrodes attached with collodion glue at F_z and C3′ (20 mm back from the C3 on the 10–20 system) for the SER. The EEG signals were analogue filtered with a bandwidth of 0.5–400 Hz, sampled at 1 kHz and digitally filtered with high-pass filters of 25 Hz and 10 Hz for the AER and SER signals, respectively. The signals were averaged with respect to the auditory and somatosensory stimuli and the resulting averaged evoked responses displayed on a computer screen. The raw EEG signals were stored on hard disc and subsequently re-analysed. Evoked responses were obtained over 2.6 min at the end of each isoflurane concentration period.

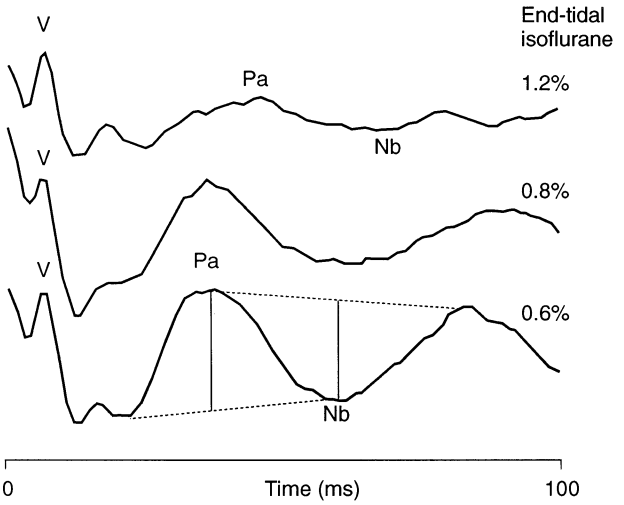

Fig 1 Changes in the early cortical auditory evoked response waveform with end-tidal isoflurane concentration. The methods of measurement of Pa and Nb amplitudes are indicated.

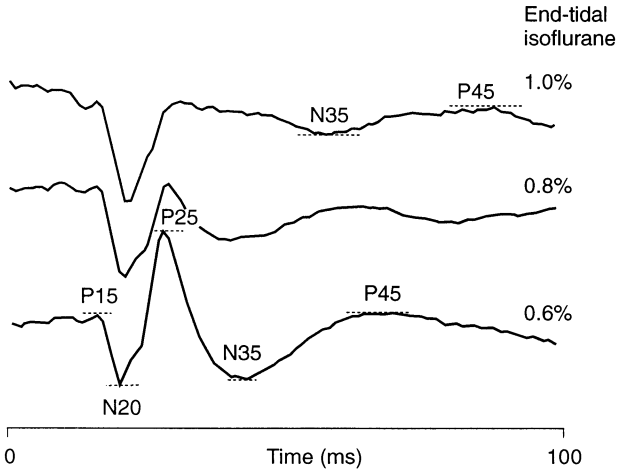

Fig 2 Changes in the somatosensory evoked response waveform with end-tidal isoflurane concentration. The methods of measurement of P15–N20, N20–P35 and P35–N45 amplitudes are indicated.

Before measuring the waveforms, additional digital filtering was applied. A high-pass filter of 25 Hz and three-point smoothing were applied to the AER waveform and a high-pass filter of 20 Hz to the SER waveform to reduce variability caused by noise. The amplitudes of the early cortical AER waves Pa and Nb were measured (μV) as the vertical distance from a peak to a line joining two adjacent troughs, or vice versa (Fig. 1). The amplitudes of the SER waves P15–N20, N20–P25, P25–N35 and N35–P45 were measured as the vertical distance (μV) between successive waves (Fig. 2). We concentrated on the amplitudes as opposed to the latencies of the evoked responses because

although the latencies of the AER waves Pa and Nb are important in sedation or light anaesthesia, they become unreliable at deeper levels of anaesthesia. SER latencies change with anaesthesia but not in a way that appears informative.

Statistical analysis

Where necessary, AER and SER variables were log transformed to normalize the data. For the transformed variables, geometric means are presented in the tables. Analyses of variance were carried out to compare evoked response amplitudes. There were two clearly defined primary goals to the statistical analyses.

Analysis one was carried out to compare the evoked response amplitudes at the end-tidal concentration at which movement after ulnar nerve tetanic stimulation occurred, for the placebo (saline infusion), low-dose and high-dose dexmedetomidine groups. For this analysis, each of the nine subjects contributed three datum points (one for placebo, one for the low-dose and one for the high-dose dexmedetomidine). The end-tidal isoflurane concentration at which 50% of subjects moved in response to ulnar nerve tetanic stimulation was estimated from a logistic regression.

Analysis two was carried out to examine the relationships between evoked response variables and end-tidal isoflurane concentration and how these were modified by dexmedetomidine (i.e. the nature of the dexmedetomidine–isoflurane interaction). Although the AER and SER were recorded at each isoflurane concentration for placebo, low-dose and high-dose dexmedetomidine, not all data were included in the analysis. The test procedure was such that an initial isoflurane concentration was chosen and isoflurane was reduced in steps of 0.2% until the subject moved with ulnar nerve tetanic stimulation. However, on five of the 27 test occasions, the subject moved to ulnar nerve stimulation during the first isoflurane concentration so it was increased further until no movement to tetany occurred. These initial isoflurane periods where the concentration was increasing were omitted from analysis. Of the remaining data, there were no observations for the placebo at 0.2%, only one at 0.4% and no observations at 1.4% and 1.6% for the high-dose dexmedetomidine group, so the analysis was restricted to isoflurane concentrations of 0.6%, 0.8%, 1.0% and 1.2% (n=24, 27, 27, 26, respectively). Analysis of variance was performed with the factors: subject, isoflurane concentration, dexmedetomidine dose, dexmedetomidine dose–isoflurane concentration interaction, occasion and carry over. Isoflurane concentration was modelled by a single linear trend with one degree of freedom.

In addition to these primary statistical goals, the effects on SER amplitude of the first 2 h of low- and high-dose dexmedetomidine infusions were compared with placebo. Analysis of variance was performed with the factors: subject, time (before or 2 h after the start of infusion), dose of dexmedetomidine, dexmedetomidine–time interaction, occasion and carry over.

Results

Analysis one

Mean end-tidal isoflurane concentration at which 50% of subjects moved to ulnar nerve tetanic stimulation was 1.05% during placebo treatment compared with 0.72% with low-dose dexmedetomidine infusion and 0.52% with the high dose. The evoked response amplitudes which indicate level of hypnosis–arousal are Pa, Nb of the AER and P25–N35, N35–P45 of the SER. At isoflurane concentrations at which subjects moved to ulnar nerve stimulation, mean amplitudes of these variables were highest with high-dose dexmedetomidine, intermediate with the low dose and lowest with placebo (Table 1). These linear trends with dexmedetomidine treatment were significant (P=0.006, 0.02, 0.005 and 0.02, respectively).

Analysis two

Changes in AER and SER waveforms with isoflurane concentration are shown in Figures 1 and 2. The amplitudes of Pa and Nb of the AER and P25–N35 of the SER showed significant linear increases as isoflurane concentration was reduced (P <0.001, 0.009 and <0.001, respectively). There were no significant differences between the three treatments on these relationships (i.e. no significant dexmedetomidine treatment–isoflurane concentration interaction). To illustrate this, Pa amplitude is plotted against end-tidal isoflurane concentration in Figure 3 for the two doses of dexmedetomidine and placebo. Mean values of these variables are given in Tables 2 and 3.

The amplitute of the subcortical SER wave P15–N20 decreased as isoflurane concentration was reduced (Fig. 2) and this linear trend was significant (P<0.001). P15–N20 amplitude is plotted against isoflurane concentration in Figure 4 and mean values are given in Table 3. Dexmedetomidine showed a significant interaction with this trend (P= 0.01), and the slopes (but not the intercepts on the y axis) were significantly different. Decreasing isoflurane concentration with the high dose of dexmedetomidine had less impact on P15–N20 than decreasing isoflurane concentration with the low dose of dexmedetomidine or with placebo.

Before isoflurane anaesthesia, there were significant interactions between dexmedetomidine dose (high, low or placebo) and changes in SER amplitude from before the start of infusion to 2 h after administration when steady blood concentrations had been achieved (time). These results are given in Table 4. P15–N20 and N20–P25 amplitude decreased after the high- and low-dose dexmedetomidine infusions and increased with placebo (the dexmedetomidine treatment–time interactions were significant, P<0.03 and 0.005, respectively). In contrast, P25–N35 amplitude increased after the high and low dexmedetomidine infusions and placebo (P=0.2, no significant interaction).

Table 1 Mean (95% confidence intervals) Pa, Nb, P25–N35 and N35–P45 amplitudes on movement to ulnar nerve tetanic stimulation in the placebo, low-dose dexmedetomidine and high-dose dexmedetomidine groups ($n=27$; nine subjects; three datum points per subject). Values for Pa and Nb amplitude are geometric mean (confidence intervals)

Treatment	Pa amplitude (μV)	Nb amplitude (μV)	P25–N35 amplitude (μV)	N35–P45 amplitude (μV)
Placebo	0.19 (0.14–0.26)	0.20 (0.14–0.27)	1.11 (0.84–1.39)	0.68 (0.44–0.92)
Low-dose	0.35 (0.25–0.49)	0.31 (0.22–0.44)	1.28 (1.00–1.56)	0.65 (0.41–0.89)
High-dose	0.41 (0.30–0.57)	0.38 (0.27–0.53)	2.20 (1.93–2.48)	1.20 (0.96–1.44)
P value for linear trend	0.006	0.02	0.005	0.02

Table 2 Geometric mean (95% confidence intervals) Pa and Nb amplitude at 0.6%, 0.8%, 1.0% and 1.2% end-tidal isoflurane concentrations with placebo, low-dose and high-dose dexmedetomidine

Isoflurane concn (%)	Pa amplitude (μV)			Nb amplitude (μV)		
	Placebo	Low-dose	High-dose	Placebo	Low-dose	High-dose
0.6	0.36 (0.21–0.61)	0.31 (0.18–0.53)	0.29 (0.17–0.50)	0.23 (0.15–0.36)	0.25 (0.16–0.40)	0.31 (0.20–0.50)
0.8	0.26 (0.15–0.45)	0.26 (0.15–0.44)	0.26 (0.15–0.46)	0.25 (0.16–0.39)	0.25 (0.16–0.39)	0.33(0.21–0.52)
1.0	0.19 (0.11–0.32)	0.16 (0.09–0.28)	0.17 (0.10–0.29)	0.17 (0.11–0.27)	0.20 (0.13–0.32)	0.21 (0.13–0.32)
1.2	0.24 (0.14–0.41)	0.20 (0.11–0.34)	0.16 (0.09–0.27)	0.23 (0.14–0.36)	0.21 (0.13–0.33)	0.16 (0.10–0.25)

Table 3 Mean (95% confidence intervals) P15–N20 and P25–N35 amplitude at 0.6%, 0.8%, 1.0% and 1.2% end-tidal isoflurane concentrations with placebo, low-dose and high-dose dexmedetomidine

Isoflurane concn (%)	P15–N20 amplitude (μV)			P25–N35 amplitude (μV)		
	Placebo	Low-dose	High-dose	Placebo	Low-dose	High-dose
0.6	1.25 (0.28–2.22)	1.67 (0.70–2.64)	2.15 (1.18–3.12)	1.89 (1.17–2.61)	1.44 (0.72–2.16)	1.88 (1.16–2.60)
0.8	1.36 (0.39–2.34)	1.75 (0.78–2.72)	2.39 (1.41–3.36)	1.29 (0.57–2.01)	0.92 (0.20–1.64)	1.24 (0.52–1.96)
1.0	1.72 (0.75–2.70)	1.97 (0.99–2.94)	2.47 (1.50–3.44)	0.86 (0.14–1.58)	0.85 (0.13–1.57)	1.11 (0.38–1.83)
1.2	2.05 (1.07–3.02)	2.17 (1.19–3.14)	2.49 (1.51–3.46)	0.82 (0.10–1.54)	0.67 (-0.05–1.39)	1.38 (0.65–2.10)

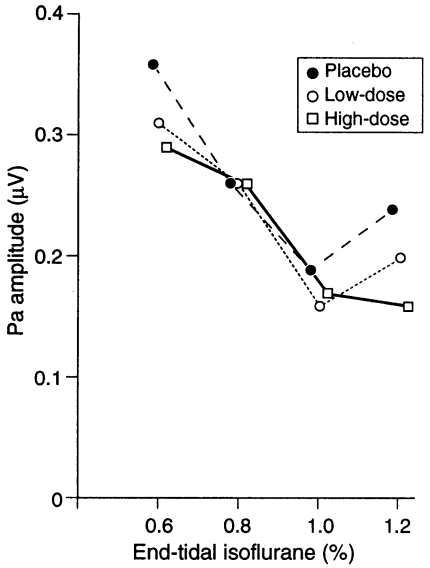

Fig 3 Pa amplitude (mean) for placebo, low-dose dexmedetomidine and high-dose dexmedetomidine at four end-tidal isoflurane concentrations (95% confidence intervals are given in Table 2).

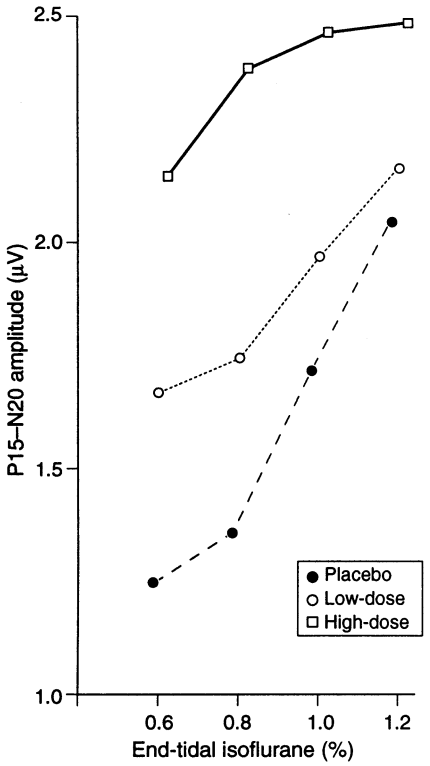

Fig 4 P15–N20 amplitude (mean) for placebo, low-dose dexmedetomidine and high-dose dexmedetomidine at four end-tidal isoflurane concentrations (95% confidence intervals are given in Table 3).

Discussion

Analysis two showed that isoflurane depressed the amplitudes of the cortical waves Pa, Nb and P25–N35 at high concentrations which returned towards awake values as isoflurane concentration was reduced. This is what we

Table 4 Mean (95% confidence intervals) P15–N20, N20–P25 and P25–N35 amplitudes before the start of infusion of dexmedetomidine and 2 h after the start of infusion

	P15–N20 amplitude (μV)		N20–P25 amplitude (μV)		P25–N35 amplitude (μV)	
	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	1.61 (0.58–2.64)	2.08 (1.05–3.11)	3.45 (1.87–5.03)	3.95 (2.37–5.54)	0.91 (0.44–1.88)	1.45 (0.71–3.00)
Low-dose	2.13 (1.10–3.16)	1.71 (0.68–2.74)	3.89 (2.31–5.47)	3.48 (1.90–5.07)	2.22 (1.08–4.57)	2.99 (1.45–6.16)
High-dose	2.54 (1.51–3.57)	2.21 (1.18–3.25)	3.76 (2.18–5.34)	2.29 (0.71–3.88)	2.46 (1.19–5.07)	2.89 (1.40 to5.96)
P value for dexmedetomidine treatment×time interaction	0.03		0.005		0.2	

would expect from previous work. The relationships were linear and dexmedetomidine had no effect on this relationship so that at any particular concentration of isoflurane (over this range), amplitudes would be similar irrespective of the dose of dexmedetomidine. This is illustrated in Figure 3 where plots of Pa amplitude against isoflurane concentration are superimposable. Also, before isoflurane anaesthesia was started, dexmedetomidine had a similar effect as placebo on P25–N35 amplitude. This lack of effect on these cortical evoked responses (both AER and SER) supports suggestions from animal studies that the sedative properties of dexmedetomidine result from indirect cortical depression caused by reduced activity from subcortical areas.[11]

The findings from *analysis one* follow those of *analysis two* because if subjects moved after ulnar nerve stimulation at a lower concentration of isoflurane with the higher dose of dexmedetomidine compared with placebo, then Pa amplitude would be greater with the higher dose of dexmedetomidine compared with placebo. We believe that Pa amplitude reflects the balance between hypnosis and cortical arousal so that when subjects moved to nerve stimulation they would have been lighter, at least in terms of hypnosis, with the high dose of dexmedetomidine than with placebo. The view that movement to noxious stimulation and hypnosis should be considered as separate components of the anaesthetic state is gaining ground. Rampil, Mason and Singh[12] showed that the measure of anaesthetic potency 'MAC', based on prevention of movement to surgical incision,[13] was not affected by decerebration in rats, suggesting that such movement is a spinal reflex. We[14] and others[15] have failed to predict movement to incision by monitoring cortical signals (electroencephalogram and AER). Our results suggest that the isoflurane-sparing activity of dexmedetomidine does not fall into the 'inhalation agent' category. If this were the case, Pa amplitude would not be expected to be different at isoflurane concentrations at which subjects moved. An anaesthetic-sparing activity of dexmedetomidine mediated by a similar mechanism to nitrous oxide and opioids has to be considered. Pa amplitude data would fit this hypothesis. Does the effect of dexmedetomidine on P15–N20 amplitude support this?

Analysis two showed that in contrast with the effect of isoflurane on cortical wave amplitudes of Pa, Nb and P25–N35, high concentrations of isoflurane enhanced P15–N20 amplitude which then decreased linearly as isoflurane concentration was reduced. Other general anaesthetics, such as etomidate,[16] sevoflurane[17] and desflurane,[18] produce similar increases on this section of the SER waveform which is thought to be generated subcortically.[19] The relationship between P15–N20 amplitude and isoflurane concentration was affected significantly by dexmedetomidine: the slope was less steep with high-dose dexmedetomidine compared with placebo. The reduction in slope suggests that dexmedetomidine counteracts enhancement of P15–N20 amplitude by isoflurane. In support of this, infusion of dexmedetomidine before isoflurane anaesthesia had started depressed P15–N20 amplitude more than placebo. Dexmedetomidine may be acting in a similar way to opioids or nitrous oxide. We have shown previously dose-related depression of P15–N20 amplitude by opioids.[9] McPherson and colleagues[20] showed that P1–N1 amplitude of the SER (the one we term P15–N20) was attenuated by 50% nitrous oxide in oxygen. This effect was not seen to the same degree with other inhalation agents. We demonstrated a greater depressant effect on P15–N20 amplitude with nitrous oxide than an equivalent concentration of isoflurane.[8] Recent animal studies suggest that the analgesic properties of nitrous oxide may be mediated via alpha-2 adrenoceptors.[21] A high density of $alpha_2$ adrenoceptors can be found in the locus coeruleus. This is a small neuronal nucleus located bilaterally in the upper brainstem. The locus coeruleus has several efferent connections which include projections via the subthalamic nucleus to the thalamus and cortex. It is likely that the P15–N20 complex originates in the pontine thalamic region of the brain[8]. This could be the mechanism by which $alpha_2$ adrenoceptor agonists such as dexmedetomidine have an effect on P15–N20 amplitude.

An alternative interpretation that should be considered is based on our studies with sevoflurane[17] and desflurane.[18] P15–N20 amplitude showed a quadratic relationship with anaesthetic concentration (initial increase, plateau at approximately 1–1.3 MAC and 0.83 MAC, respectively, followed by a decrease). Assuming that isoflurane behaves in a similar manner to sevoflurane and desflurane, high-dose dexmedetomidine may cause the slope to be less steep

because it has added to the effect of isoflurane and the dose–response curve has reached a plateau. With low-dose dexmedetomidine and placebo, P15–N20 amplitude may be on the steeper (lower isoflurane concentration) part of the dose–response curve. Dexmedetomidine would therefore be acting in a similar way to isoflurane.

In summary, changes in AER and SER suggest a different anaesthetic mechanism for dexmedetomidine than that of inhalation agents such as isoflurane, at least for effects on the cortex. Further investigations are required to interpret whether the changes in the subcortical wave P15–N20 amplitude with dexmedetomidine lend support to anaesthetic-potentiating activity similar to nitrous oxide or opioids or an activity similar to isoflurane when it acts on subcortical structures.

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