

ORIGINAL ARTICLES

## DEXMEDETOMIDINE ATTENUATES SYMPATHOADRENAL RESPONSES TO TRACHEAL INTUBATION AND REDUCES THE NEED FOR THIOPENTONE AND PEROPERATIVE FENTANYL

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### SUMMARY

The effects of the new, highly selective  $\alpha_2$ -adrenergic agonist, dexmedetomidine, were studied in a randomized, placebo-controlled, double-blind trial in 24 ASA I patients. Dexmedetomidine  $0.6 \mu\text{g kg}^{-1}$  or saline was given i.v. 10 min before induction of anaesthesia. The required dose of thiopentone was significantly ( $P < 0.001$ ) smaller in the dexmedetomidine group (mean  $4.4$  (SD  $0.9$ )  $\text{mg kg}^{-1}$ ) than in the control group ( $6.9$  ( $1.6$ )  $\text{mg kg}^{-1}$ ), and the drug attenuated the cardiovascular responses to laryngoscopy and tracheal intubation. The concentration of noradrenaline in mixed venous plasma was smaller in the dexmedetomidine group during all phases of induction ( $P < 0.01$ ). During surgery, fentanyl was required in a dose of  $0.5$  ( $0.6$ )  $\text{mg kg}^{-1}$  and  $2.8$  ( $2.6$ )  $\text{mg kg}^{-1}$  in the dexmedetomidine and control groups, respectively ( $P < 0.001$ ). During 2 h postoperative follow-up, oxycodone  $0.06$  ( $0.06$ )  $\text{mg kg}^{-1}$  and  $0.16$  ( $0.1$ )  $\text{mg kg}^{-1}$  ( $P < 0.05$ ) was given to the two groups respectively.

### KEY WORDS

Anaesthesia, general: opioid requirement. Intubation, tracheal: sympathoadrenal response. Sympathetic nervous system, pharmacology:  $\alpha_2$ -adrenergic agonist, dexmedetomidine.

Clonidine has been investigated extensively as an adjunct to anaesthesia. It causes sedation and potentiates the effects of general anaesthetic agents and opioids, and provides improved haemodynamic, metabolic and hormonal stability by attenuating the sympathoadrenal activation elicited by anaesthesia, tracheal intubation and surgery [1-6].

Dexmedetomidine is a new, highly selective and potent  $\alpha_2$ -adrenoceptor agonist [7-10]. It is a pure  $\alpha_2$ -adrenoceptor agonist in some pharmacological models in which clonidine has shown only partial agonistic activity [9]. Animal experiments have indicated that it has prominent anaesthetic effects [10-12]. Studies in human volunteers have demonstrated clonidine-like sedative, sympatholytic and cardiovascular effects [13-15].

In recent studies in patients, dexmedetomidine

has been shown to have clinically significant effects on anaesthetic requirements and on the sympathoadrenal and haemodynamic responses induced by anaesthesia and surgery [16-19]. In addition, in common with previous observations on clonidine, dexmedetomidine appears to have an analgesic effect in healthy volunteers [20, 21] and surgical patients [22].

The aim of the present study was to investigate in healthy patients the safety and efficacy of dexmedetomidine as a preanaesthetic agent and its effects on the cardiovascular and sympathoadrenal responses to laryngoscopy and intubation and on opioid requirements during and after surgery.

### PATIENTS AND METHODS

We investigated 24 (ASA I) patients undergoing elective surgery (table I). The study was approved by the Ethics Committee of the Hospital and written informed consent was obtained from all patients. Patients taking any medication, with childbearing potential or with a known allergy were excluded.

The patients were premedicated with oral diazepam  $0.2 \text{ mg kg}^{-1}$  60-90 min before induction of

TABLE I. Patient characteristics and type of surgery, (mean (range or SD)). DEX = Dexmedetomidine

	Control group	DEX group
Sex (M/F)	5/7	6/6
Age (yr)	37 (19-47)	40 (28-52)
Weight (kg)	72.6 (8.4)	71.9 (9.8)
Height (cm)	171 (6)	174 (12)
Surgery		
Laparotomy	3	1
Breast surgery	4	5
Anal surgery	2	3
Various	3	3

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anaesthesia. At the same time, the skin over the basilic vein in the antecubital fossa and the site for cannulation of the radial artery were covered with local anaesthetic cream (prilocaine–lignocaine cream, EMLA). A venous cannula was inserted on the dorsum of the hand. The radial artery was cannulated for continuous measurement of arterial pressure. A 70-cm catheter was inserted via the basilic vein on the contralateral arm. The position of the catheter tip in the right ventricle of the heart was verified by the pressure wave form. The ECG (aVR-lead) was displayed on an oscilloscope and recorded continuously on paper.

The QT intervals were retrospectively measured manually from the onset of the QRS complex to the end of the T-wave. The mean QT interval of four successive beats was calculated. A heart rate dependent correction (QT<sub>corr</sub>) was made according to the formula:

$$QT_{corr} = \frac{QT}{\sqrt{R-R'}}$$

where the R–R' interval is expressed in seconds [23].

When the monitoring equipment had been attached, the patient was allowed to rest for 20 min. Cardiovascular recordings were then made and the first blood samples obtained.

The patients were allocated randomly to receive in a double-blind manner either dexmedetomidine ( $n = 12$ ) or saline ( $n = 12$ ). The contents of a coded 10-ml syringe containing either dexmedetomidine  $0.6 \mu\text{g kg}^{-1}$  in saline or the same volume of saline only were then injected over 1 min via the peripheral cannula, preceded by glycopyrronium  $5 \mu\text{g kg}^{-1}$  i.v. The interval between glycopyrronium and the trial drug was 3 min. After the trial drug was given, the grades of sedation and alertness were recorded for 10 min. Then a dose of thiopentone sufficient to abolish the eyelash reflex was injected ( $5 \text{ mg s}^{-1}$ ) into the i.v. cannula attached to a fast running infusion of Ringer's lactate, followed by vecuronium  $0.1 \text{ mg kg}^{-1}$  to provide neuromuscular block. The lungs were ventilated with 50% nitrous oxide in oxygen for 3 min. Laryngoscopy lasting 10 s was performed with a Macintosh laryngoscope and the trachea was then intubated. Ventilation with 50% nitrous oxide in oxygen continued for 5 min after tracheal intubation. The end-tidal carbon dioxide concentration was maintained at 5% (Datex, Normocap).

During surgery, anaesthesia was maintained with isoflurane and 70% nitrous oxide in oxygen. The inspiratory concentration of isoflurane was adjusted in steps of 0.2% when needed as judged by lachrymation or an increase in heart rate or arterial pressure exceeding 30% of preanaesthetic values or a reduction in arterial pressure of 20% of the earlier value. Fentanyl in increments of  $1.5 \mu\text{g kg}^{-1}$  was given immediately when 1% inspiratory isoflurane was needed. The isoflurane concentration was decreased 1 min after administration of fentanyl. The mean inspiratory concentration was calculated as the sum of the products of inspiratory concentrations and times divided by total anaesthesia time. Neuromuscular block was achieved with a vecuronium

infusion ( $0.1 \text{ mg kg}^{-1} \text{ h}^{-1}$ ) and controlled using a nerve stimulator.

Residual neuromuscular block was antagonized with neostigmine 2 mg preceded by glycopyrronium 0.4 mg i.v.

The interval from discontinuation of inhalation of nitrous oxide at the end of surgery to the time when the patient opened the eyes on command was recorded as the recovery time. All patients were observed in the recovery room for 2 h after surgery. Every 10 min the patient was asked about feelings of sleepiness and well-being. Oxycodone  $0.07 \text{ mg kg}^{-1}$  was given i.v. when the patient complained of pain. All patients were interviewed on the first day after operation.

Blood samples for catecholamine measurements were obtained from the right ventricle of the heart simultaneously with recording of ECG, heart rate and arterial pressure at the following times: 1 min before administration of the drug; 10 min after administration of the drug; 3 min after administration of vecuronium; after 10 s of laryngoscopy; 10 s after tracheal intubation; 5 min after tracheal intubation. The samples were collected into pre-chilled polypropylene tubes containing EDTA and placed immediately in ice. They were centrifuged at  $0^\circ\text{C}$  within 30 min and the plasma stored in polypropylene tubes at  $-70^\circ\text{C}$  until analysis. Plasma concentrations of catecholamines and the catecholamine metabolites 3,4-dihydroxyphenylglycol (DHPG) and 3,4-dihydroxyphenyl-acetic acid (DOPAC) were measured using HPLC with electrochemical detection [24]. The method in its present form has intra-assay coefficients of variation of approximately 2% for noradrenaline, 4% for DHPG, 10% for adrenaline and 15% for DOPAC in the physiological range of concentrations.

#### Statistical methods

Statistical evaluation was performed using analysis of variance (ANOVA) for repeated measurements with one between factor (drug) and one within factor (time). When a statistically significant drug  $\times$  time interaction was found, the analysis was continued by calculating contrasts for each time point *vs* baseline. Data were analysed with Student's *t* test, Mann-Whitney *U* test or chi-square test, as appropriate.  $P < 0.05$  was considered statistically significant. Statistical analysis was performed using BMDP (BMDP Statistical Software Inc., CA, U.S.A.) statistical programs. The results are presented as means and SD.

#### RESULTS

The two groups were comparable in patient characteristics (table I). Dexmedetomidine was well tolerated and no drug related adverse events were observed. About 5 min after receiving the trial drug, patients were drowsy but arousable.

#### Anaesthetic requirements

The mean sleep dose of thiopentone was significantly greater in the control group than in the dexmedetomidine group (table II). The mean in-

TABLE II. Anaesthesia characteristics (mean (SD)). DEX = Dexmedetomidine

	Control group	DEX group	P
Thiopentone (mg kg <sup>-1</sup> )	6.92 (1.6)	4.44 (0.9)	< 0.001
Fentanyl (µg kg <sup>-1</sup> )	2.8 (2.6)	0.55 (0.6)	< 0.001
Isoflurane (mean insp. concn) (%)	0.52 (0.18)	0.42 (0.2)	ns
Duration of anaesthesia (min)	112 (61)	109 (80)	ns
Duration of surgery (min)	67 (61)	68 (76)	ns
Recovery time (min)	7.8 (2.8)	9.1 (3.6)	ns
Oxycodone (mg kg <sup>-1</sup> /2 h)	0.16 (0.1)	0.06 (0.06)	< 0.05

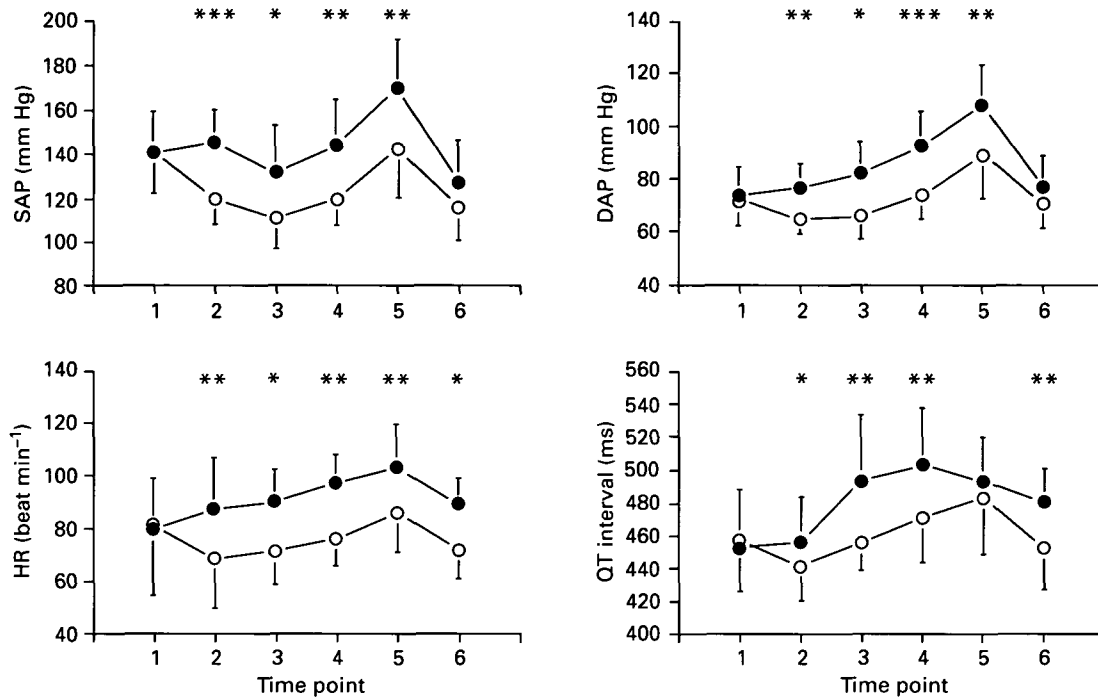


FIG. 1. Cardiovascular responses during induction of anaesthesia and tracheal intubation in the control (●) and dexmedetomidine (○) groups. HR = Heart rate; SAP = systolic arterial pressure; DAP = diastolic arterial pressure. Time points: 1 = Before test drug; 2 = 10 min after test drug; 3 = 3 min after vecuronium; 4 = after 10 s of laryngoscopy; 5 = 10 s after tracheal intubation; 6 = 5 min after tracheal intubation. Statistically significant drug × time interaction (ANOVA) in SAP ( $P < 0.01$ ), DAP ( $P < 0.01$ ) and heart rate ( $P < 0.01$ ). Significant differences for each time point compared with baseline (Student's  $t$  test): \* $P < 0.05$ , \*\* $P < 0.01$ ; \*\*\* $P < 0.001$  (see text for details).

spiratory concentrations of isoflurane were comparable between the groups. However, the control group required more fentanyl (table II).

#### Cardiovascular responses

Dexmedetomidine induced slight decreases in arterial pressure and heart rate, but also attenuated the increases induced by laryngoscopy and intubation, revealed by significant drug × time interactions in ANOVA (fig. 1). Maximal average increases (*vs* baseline) were 1% and 21% in systolic, 23% and 46% in diastolic arterial pressure and 6% and 29% in heart rate in the dexmedetomidine and saline groups, respectively. Dexmedetomidine also attenuated the QT interval increase induced by induction of anaesthesia and tracheal intubation (fig. 1). Maximal average increases in QT intervals were 6% and 11% in the two groups.

During surgery, arterial pressure and heart rate remained slightly less in the dexmedetomidine group compared with the control group; the difference in heart rate was not statistically significant (table III).

TABLE III. Systolic (SAP) and diastolic (DAP) arterial pressures and heart rate (HR) during surgery (mean (SD)). DEX = Dexmedetomidine

	Control group	DEX group	P
SAP (mm Hg)			
Max.	139.7 (19.9)	119.6 (13.5)	< 0.01
Min.	96.8 (6.8)	89.5 (9.1)	< 0.05
DAP (mm Hg)			
Max.	84.8 (11.4)	75.8 (8.8)	< 0.05
Min.	57.5 (5.9)	54.5 (5.8)	ns
HR (beat min <sup>-1</sup> )			
Max.	92.2 (10.2)	84.5 (12.6)	ns
Min.	63.3 (6.2)	60.5 (8.8)	ns

In the recovery room, haemodynamic variables did not differ between groups. No extra anticholinergic drugs were required.

#### Catecholamine responses

The concentration of noradrenaline in mixed venous plasma decreased after dexmedetomidine and

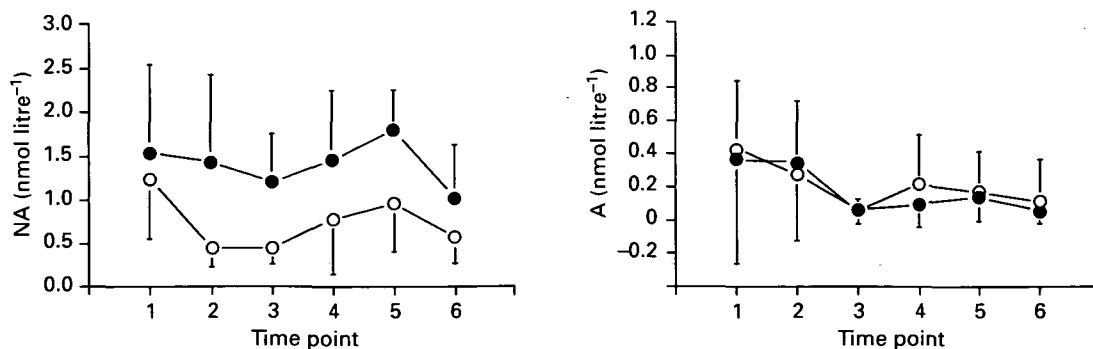


FIG. 2 Concentrations of noradrenaline (NA) and adrenaline (A) in mixed venous plasma during induction of anaesthesia in the control (●) and dexmedetomidine (○) groups. ANOVA revealed a statistically significant drug effect for plasma NA ( $P < 0.01$ ), but the drug  $\times$  time interaction was not significant. Adrenaline concentrations decreased in both groups ( $P < 0.01$  for time factor). Baseline data compared by Student's  $t$  test.

remained significantly reduced throughout the collection period (fig. 2). Adrenaline concentrations in plasma decreased during induction of anaesthesia and there were no statistically significant differences between the groups (fig. 2). Plasma concentrations of DHPG increased slightly (18%) in the control group, but remained stable (about 7 nmol litre<sup>-1</sup>) in the dexmedetomidine group (ANOVA  $P < 0.01$  for interaction). Plasma concentrations of DOPAC did not show statistically significant time or drug-related changes.

#### Recovery and analgesic requirements

The duration of recovery was similar in both groups (table II). In the recovery room there was no difference between the groups in the patients' opinions of their drowsiness. The need for oxycodone during the first 2 h after operation was greater in the control group than in the dexmedetomidine group (table II). During this follow-up, three patients in the dexmedetomidine group and two patients in the control group experienced nausea. In the recovery room, dry mouth was reported by 11 and 10 patients, respectively. Transient headache occurred in one dexmedetomidine patient in the recovery room and in one control patient on the ward. None of the patients had any explicit recall of awareness or complained of any discomfort when interviewed after operation.

#### DISCUSSION

Tracheal intubation is associated with increases in arterial pressure, heart rate and plasma catecholamine concentrations [25–27]. In the present study, pretreatment with dexmedetomidine 0.6  $\mu\text{g kg}^{-1}$  attenuated, but did not totally obtund, the cardiovascular and catecholamine responses to tracheal intubation after induction of anaesthesia.

Intubation-induced increases in arterial pressures and heart rate observed in the control group in the present study were similar to those reported in earlier studies on patients not receiving an opioid as part of the anaesthetic medication [25, 28–31].

In our control group, the QT interval was prolonged significantly during induction of anaesthesia, confirming earlier reports in healthy patients. Prolongation of the QT interval reflects the increase

in plasma noradrenaline [31, 32] and is a predictor of cardiac arrhythmia [33].

Catecholamines, especially noradrenaline, are taken up selectively by the lungs [34, 35]. We sampled, therefore, venous blood from the right ventricle of the heart for measurement of catecholamines. Thus even slight increases in plasma concentration of noradrenaline could be detected, as found by Derbyshire and co-workers [25], who observed greater concentrations of catecholamines in central venous than in arterial or peripheral venous blood. Nevertheless, the mean intubation-induced increases in plasma concentrations of noradrenaline and adrenaline were modest in our control group, which suggests a relatively low intensity of stress associated with the present anaesthetic technique.

It has been suggested that the deaminated catecholamine metabolite DHPG derives mainly from intraneuronal release-independent noradrenaline metabolism and does not accurately reflect release of noradrenaline from sympathetic nerve endings [24]. This explains why the marked changes in noradrenaline concentration were not reflected in equally great changes in DHPG.

The dose of thiopentone needed for induction was reduced significantly in the patients receiving dexmedetomidine, as found also by Aantaa and co-workers [16–18], demonstrating the anaesthesia-potentiating effects of the drug. In our study, isoflurane was used as the main anaesthetic agent. No difference was observed between the groups in isoflurane requirements. This was caused partly by the study design: a need for an inspiratory concentration of 1% isoflurane resulted in administration of fentanyl. The total amount of fentanyl required was greater in the control than in the dexmedetomidine group. The significantly smaller doses of oxycodone needed by the dexmedetomidine patients in the recovery room suggests analgesic efficacy. Analgesic properties have been demonstrated earlier in a study with dexmedetomidine as the sole analgesic after surgery [22] and in experimental ischaemic pain in healthy volunteers [21]. Reduction in fentanyl requirements has been reported also for clonidine [2].

Previous clinical studies with dexmedetomidine have reported mainly on patients undergoing minor surgery under thiopentone–nitrous oxide anaes-

thetia [16–18]. Aho and co-workers [19] reported that dexmedetomidine is well tolerated during major surgery (abdominal hysterectomy). The present results corroborate their findings. No adverse cardiovascular effects from the drug were seen in the present study. Bradycardia, a possible consequence of administration of the  $\alpha_2$ -agonist, was counteracted by the use of glycopyrronium.

Nakagava and co-workers [36] have suggested that spinal noradrenergic systems are involved together with serotonin in the modulation of ascending nociceptive stimulation, possibly through an  $\alpha_2$ -adrenergic mechanism. The  $\alpha_2$ -agonists would, thus, offer a new, interesting possibility for suppression of pain. It is not clear if the reduced opioid requirements after administration of the  $\alpha_2$ -adrenergic agonists in our study reflect potentiation of opioid-induced analgesia or other mechanisms.

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