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Preliminary UK experience of dexmedetomidine, a novel agent for postoperative sedation in the intensive care unit

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Summary

Dexmedetomidine, a highly selective and potent α_2-adrenergic agonist, has a potentially useful role as a sedative agent in patients requiring intensive care. As part of a larger European multicentre trial, a total of 119 postoperative cardiac and general surgical patients requiring ventilation and sedation in an intensive care unit were enrolled in four centres in the United Kingdom. One hundred and five patients were randomly allocated to receive either dexmedetomidine or placebo with rescue sedation and analgesia provided by midazolam and morphine, respectively. Compared with the control group, intubated patients receiving dexmedetomidine required 80% less midazolam [mean 4.9 (5.8) $\mu g.kg^{-1}.h^{-1}$ vs. 23.7 (27.5) $\mu g.kg^{-1}.h^{-1}$, $p < 0.0001$], and 50% less morphine [11.2 (13.4) $\mu g.kg^{-1}.h^{-1}$ vs. 21.5 (19.4) $\mu g.kg^{-1}.h^{-1}$, $p = 0.0006$]. Cardiovascular effects and adverse events could be predicted from the known properties of alpha-2 agonists. In conclusion, dexmedetomidine is a useful agent for the provision of postoperative analgesia and sedation.

Keywords *Dexmedetomidine*; sedation. *Intensive care*; postoperative.

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Intubated, mechanically ventilated patients on the intensive care unit (ICU) require sedation and analgesia in order to tolerate the tracheal tube, artificial ventilation and other intensive care procedures such as bronchial suctioning, physiotherapy and catheter placement. Sedation may improve outcome by reducing the stress response and its sequelae to these interventions [1]. However, sedation regimens also have potentially adverse effects which may increase morbidity and prolong the clinical course [2].

Consequently, sedation techniques are changing and new drugs, working at different sites in the central nervous system to traditional agents, have been developed. Dexmedetomidine is a new, highly selective and potent α_2-adrenoreceptor agonist under investigation as a sedative agent in intensive care patients. As well as offering sedation and anxiolysis, α_2 agonists have analgesic qualities and reduce the stress response to surgery and intensive care procedures [3]. Importantly, at therapeutic doses, dexmedetomidine does not cause any significant respiratory depression [4]. This paper reports the initial experience of this agent for postoperative sedation in four ICUs in the United Kingdom (UK).

Methods

Patients admitted postoperatively to general or cardiothoracic intensive care units at four teaching hospitals in the UK were enrolled into the study. Patients were aged 18 years or over and were expected to require a minimum of 6 h postoperative sedation and ventilation. Exclusion criteria were patients with serious central nervous system trauma or undergoing neurosurgery, a requirement for neuromuscular blocking agents, epidural or spinal anaesthesia, any contraindications or allergy to any of the trial drugs, gross obesity (over 50% above ideal body weight), admission for a drug overdose, prior enrolment in a trial

with any experimental drug in the last 30 days, uncontrolled diabetes and excessive bleeding which would be likely to require re-operation. Ethics committee approval was gained at each participating hospital and informed consent was obtained pre-operatively from each patient.

Anaesthetic technique prior to entry into the ICU was left to the individual anaesthetist, the only constraint being that benzodiazepines were not used as sole anaesthetic agent. If remifentanil was used for intra-operative analgesia, morphine was given prior to leaving the operating theatre.

The first four patients at each centre could be enrolled into an open label study to gain familiarity with dexmedetomidine. Data from these patients were included in the safety analysis. Subsequent patients were then entered into a randomised, double-blind, placebo-controlled trial on entry into the ICU. They received either placebo or dexmedetomidine, with midazolam and morphine used as clinically indicated for rescue sedation and analgesia, respectively.

Both dexmedetomidine and placebo solutions were labelled 'study drug' and coded for later analysis. Dexmedetomidine was supplied in 2-ml ampoules at a concentration of 100 $\mu g.ml^{-1}$, and diluted with normal saline to a concentration of 4 $\mu g.ml^{-1}$. Placebo solution (normal saline) was supplied and prepared in a similar fashion. Patients were randomly allocated on entry into the ICU to receive either dexmedetomidine or placebo, which was commenced within 1 h of arrival on the unit. The patients received a loading dose of 1 $\mu g.kg^{-1}$ over 10 min followed by a maintenance infusion rate of 0.2–0.7 $\mu g.kg^{-1}.h^{-1}$ into a peripheral or central vein. The sedation level of the patient was measured using the Ramsay Sedation Score [5] (Appendix A) and patients were maintained at a Ramsay sedation score greater than 2 whilst intubated. The infusion rate could be increased if this was not achieved or reduced if Ramsay sedation score 6 was reached. The protocol stipulated a maximum infusion rate of 0.7 $\mu g.kg^{-1}.h^{-1}$; bolus injections were not permitted. The patients were intubated and ventilated with oxygen-enriched air to attain acceptable arterial blood gases for a minimum of 6 h. They were extubated when clinically indicated. Following extubation, the infusion was continued for a further 6 h and adjusted to achieve a Ramsay sedation score of more than 1. Sedation with the trial drug could be continued up to a total maximum duration of infusion of 24 h. If patients still required sedation and ventilation after 24 h, they were switched to the usual regimen used on each individual ICU.

If adequate sedation was not achieved at the maximum study drug infusion rate, 0.02 $mg.kg^{-1}$ midazolam boluses could be given intravenously. If more than three such boluses were required within 1 h, a midazolam infusion could be commenced (range 0.01–0.2 $mg.kg^{-1}.h^{-1}$). Morphine could be administered for pain relief in 2-mg intravenous boluses as required, but not by continuous infusion. After extubation, paracetamol and morphine could be used as analgesic agents.

Ramsay sedation scores were recorded hourly and prior to every infusion rate change, or prior to administration of midazolam. A further assessment was made at 10 min following each change. Total doses of midazolam, morphine and the study drug administered were recorded.

Heart rate, arterial blood pressure, central venous blood pressure, respiratory rate and oxygen saturation were monitored continuously and recorded hourly for the duration of the study period and then at three-hourly intervals for 24 h after the infusion had ended. Temperature and arterial blood gases were recorded at regular intervals and a 12-lead electrocardiogram taken before and after the study infusion.

Results are presented as mean (standard deviation (SD)). Analysis of variance for repeated measures was performed on haemodynamic parameters, with compensation for multiple *post hoc* comparisons using the Bonferroni correction. Intergroup statistical analyses were performed using the Mann–Whitney *U*-test. Statistical significance was considered at $p < 0.05$.

Results

Of the 119 patients recruited into the UK study, 14 patients entered the open-labelled study to receive dexmedetomidine and 105 patients were recruited into the double-blind randomised study. Seven of these 105 patients received less than 4 h study drug infusion as three returned to the operating theatre because of bleeding, two had bradycardia with hypotension, one had residual neuromuscular blockade and the other was withdrawn from the study at the surgeon's request because of operative complications. Details from these seven patients, plus those from the 14 patients entered into the open labelled study, were used only in the safety analysis. None of the patients in the open-labelled study were withdrawn because of complications.

Of the 98 patients with complete data, 47 received dexmedetomidine (35 male, 12 female), and 51 received placebo (38 male, 13 female). Eighty-one patients (83%) underwent cardiac surgery requiring cardiopulmonary bypass, 39 of whom received dexmedetomidine. The remaining 17 patients underwent general, orthopaedic, head & neck, oncological or vascular surgery, of whom eight received dexmedetomidine. No differences were found between the groups with respect to age, sex, weight, height, operation time and intra-operative analgesia doses (Table 1).

Table 1 Patient, anaesthetic and operative characteristics in the two groups (mean (SD)).

	Dexmedetomidine ($n=47$)	Placebo ($n=51$)
Age; years	63.3 (13.7)	64.2 (12.3)
Weight; kg	76.3 (16.4)	75.9 (13.7)
Male: Female	2.9: 1	2.9: 1
Duration of intubation; h	11.4 (4.9)	10.8 (5.8)
Duration of study drug infusion; h	18.2 (4.6)	16.1 (4.4)
Operation time; h	4.1 (1.1)	4.1(1.3)
Intra-operative analgesia in morphine equivalents; mg	16.8 (13.4)	17.8 (10.0)
Type of surgery	39 cardiac/8 general	42 cardiac/9 general

Table 2 Midazolam requirements for the first 6 h of study and whilst intubated, followed by morphine requirements for the first 6 h, whilst intubated, whilst extubated and during observation period (mean (SD)).

	Dexmedetomidine ($n=47$)	Placebo ($n=51$)	p-value
Midazolam			
0–6 h ($\mu g.kg^{-1}$)	4.3 (5.8)	$18.5\ (24.6)\times10^{-3}$	<0.0001
whilst intubated ($\mu g.kg^{-1}.h^{-1}$)	4.9 (5.8)	$23.7\ (27.5)\times10^{-3}$	<0.0001
Morphine			
0–6 h ($\mu g.kg^{-1}$)	9.1 (9.6)	$15.3\ (17.4)\times10^{-3}$	0.0135
whilst intubated ($\mu g.kg^{-1}.h^{-1}$)	11.2 (13.4)	$21.5\ (19.4)\times10^{-3}$	0.0006
whilst extubated ($\mu g.kg^{-1}.h^{-1}$)	4.8 (11.0)	$5.8\ (5.5)\times10^{-3}$	0.027
observation period ($\mu g.kg^{-1}.h^{-1}$)	5.6 (10.6)	$9.7\ (17.7)\times10^{-3}$	ns

There were no overall differences in the distribution of Ramsay sedation scores between the dexmedetomidine and placebo groups while intubated. However, intubated patients receiving dexmedetomidine required significantly less midazolam than those receiving placebo [4.9 (5.9) vs. 23.7 (27.5) $\mu g.kg^{-1}.h^{-1}$, $p=0.0001$]. The requirement for morphine was reduced by half in the dexmedetomidine group while intubated [11.2 (13.4) vs. 21.5 (19.4) $\mu g.kg^{-1}.h^{-1}$, $p=0.0006$], and by 17% after extubation [4.8 (11.0) vs. 5.8 (5.5) $\mu g.kg^{-1}.h^{-1}$, $p=0.0270$] (Table 2).

Those patients ($n=9$) on the higher infusion rates of dexmedetomidine (0.56–0.7 $\mu g.kg^{-1}.h^{-1}$) whilst intubated as compared with those ($n=4$) on the lowest infusion rates (0.1–0.25 $\mu g.kg^{-1}.h^{-1}$) required more midazolam (9.3 (1.7) vs. 0.58 (0.58) $\mu g.kg^{-1}.h^{-1}$) and morphine (11.1 (3.2) vs. 4.3 (2.2) $\mu g.kg^{-1}.h^{-1}$) (Fig. 1).

Six of the patients receiving placebo and 17 receiving dexmedetomidine required no midazolam while intubated. In addition, two on placebo and six receiving dexmedetomidine required no analgesia. All were cardiac surgical patients with no significant differences in their intra-operative analgesia, age or pathology. In general surgical patients, the placebo group required six times as much midazolam in the first 6 h compared with the dexmedetomidine group ($p=0.02$). Overall, morphine requirements in general surgical patients were twice those of cardiac surgical patients, irrespective of the method of sedation.

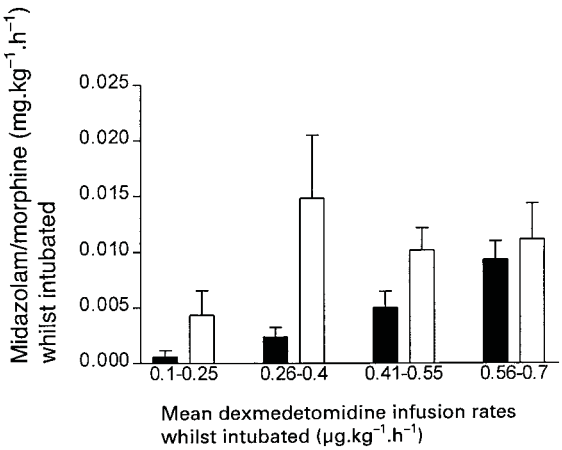

Figure 1 Requirements for rescue sedation and analgesia at differing dexmedetomidine infusion rates. (■) Midazolam; (□) morphine.

There were no significant differences in the duration of intubation (11.4 (4.9) h vs. 10.8 (5.8) h), nor the duration of weaning (3.4 (3.2) h vs. 3.1 (3.0) h) between the dexmedetomidine and placebo groups, respectively. The mean duration of infusion in the dexmedetomidine group was 18.2 h (range 0.17–29 h). The mean infusion rate of dexmedetomidine during intubation was 0.345 (0.15) $\mu g.kg^{-1}.h^{-1}$ and, after extubation, 0.146 (0.08) $\mu g.kg^{-1}.h^{-1}$ ($n = 43$ as four patients remained intubated for > 24 h).

There were no significant differences in respiratory rates nor arterial oxygen saturations between the dexmedetomidine and placebo groups. Insufficient arterial blood gas samples were collected to provide evaluable data on oxygen and carbon dioxide tensions. In the general surgical subgroup, those receiving dexmedetomidine had lower, albeit nonsignificant, respiratory rates (14 (4.7) vs. 21 (7.2) $breath.min^{-1}$, $p = 0.08$) at 2 h after extubation, with 2% higher pulse oximetry readings (98.1 (0.8) vs. 96 (1.9), $p = 0.0136$). No differences were seen between the cardiac patient subgroups.

During the first hour of study drug infusion, systolic and diastolic arterial blood pressures, and heart rates were significantly lower in patients receiving dexmedetomidine. Thereafter, these differences in blood pressure diminished but those patients receiving dexmedetomidine continued to have significantly lower heart rates at around 75 $beat.min^{-1}$. This was well demonstrated for the period 4 h before and after extubation (75 (5.6) vs. 91 (6.5) $beat.min^{-1}$, < 0.0001] (Fig. 2). Over this same period, the mean systolic and diastolic arterial pressures in the dexmedetomidine group were consistently slightly lower than placebo by 6 mmHg and 5 mmHg, respectively (both $p = 0.05$), with a reduction in the variability of the systolic pressures ($p = 0.05$). No significant differences were seen in central venous pressures. General surgical patients showed more pronounced cardiovascular differences with a 9-mmHg reduction in diastolic arterial pressure in the dexmedetomidine group (57 (7) vs. 66 (8) mmHg, $p = 0.03$) and significant tachycardia in the placebo group (78 (6) vs. 101 (9) $beat.min^{-1}$, $p = 0.02$) in the period around extubation (Fig. 3).

Safety was examined in all 119 patients recruited, 66 of whom received dexmedetomidine. There were four deaths (three in the placebo group, one in the dexmedetomidine group) but none of these deaths was considered attributable to the study drug. Ten patients who received dexmedetomidine and nine receiving placebo had clinically significant ECG changes – all these patients had undergone cardiac surgery (Table 3).

Eighteen of the 66 patients receiving dexmedetomidine experienced significant hypotension (mean arterial pressure < 60 mmHg or > 30% fall from preinfusion values)

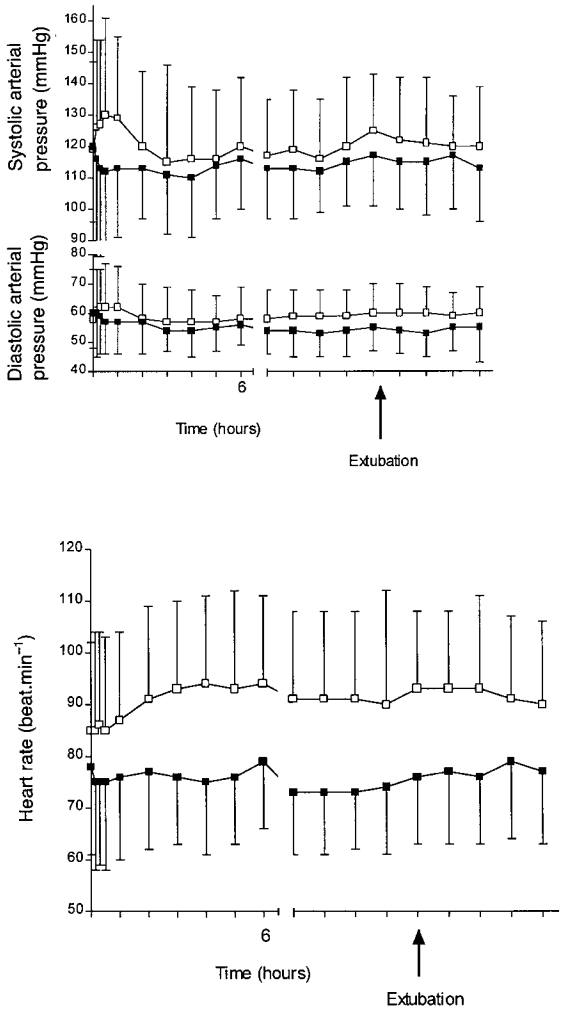

Figure 2 Cardiovascular profiles of all patients ($n = 98$) for 0–6 h and extubation ± 4 h. Mean (SD) arterial pressures and heart rates for the two groups. (■) Dexmedetomidine; (□) placebo.

or bradycardia (< 50 $beat.min^{-1}$). In 11 patients, this occurred during the loading dose period. This resulted in a temporary interruption of the infusion in three patients and withdrawal from the study in a further three. There was no difference in the use of vasoactive drugs between groups (Table 4).

Loading dose hypertension was reported as an adverse event in six patients receiving dexmedetomidine and five patients on placebo. In the dexmedetomidine group, this was a transient event (less than 10 min) but hypertension was sustained in the placebo group (between 10 min and 4 h).

Table 3 Adverse events excluding hypotension and/or bradycardia.

Event	Dexmedetomidine ($n = 66$)	Placebo ($n = 53$)
Death	1	3
Loading dose hypertension	6	5
Atrial fibrillation/tachyarrythmias	8	5
Postoperative bleeding	6	6
Stroke	0	3
Angina	1	1
Myocardial infarction	0	2
Nausea and vomiting	16	5
Flashing lights	2	0
ECG changes	10	9

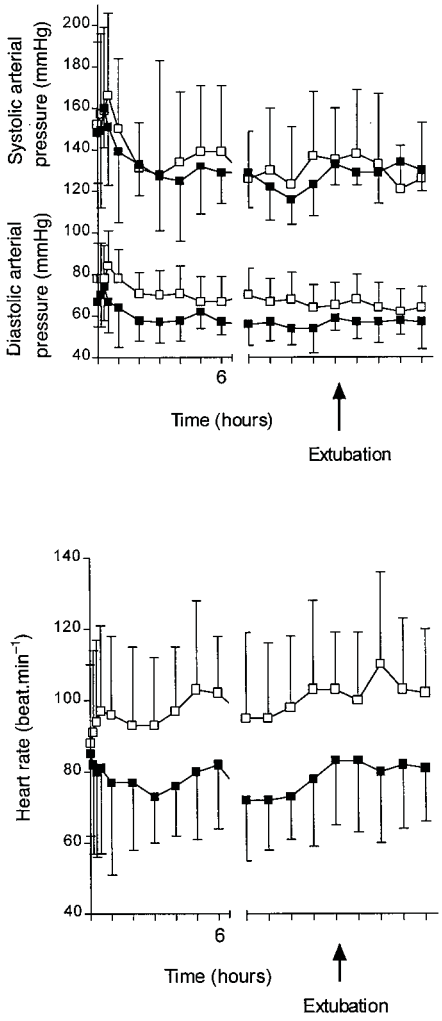

Figure 3 General surgical patients' cardiovascular profile ($n = 17$) for 0–6 h and extubation ± 4 h. Mean (SD) arterial pressures and heart rates for the two groups. (■) Dexmedetomidine; (□) placebo.

Discussion

Dexmedetomidine is the dextro-stereoisomer and active ingredient of medetomidine, an agent used for many years in veterinary anaesthesia. It is a highly selective α_2 agonist with an affinity eight times that of clonidine for the adrenoceptor ($\alpha_2 : \alpha_1$ ratio 1600 : 1) [3]. α_2 adrenoceptors can be found in the central nervous system, peripheral nerves and autonomic ganglia at presynaptic and postsynaptic sites. Stimulation of presynaptic α_2 receptors located in sympathetic nerve endings inhibits the release of noradrenaline. Activation of postsynaptic receptors by α_2 agonists in the CNS leads to inhibition of sympathetic activity, decreases in blood pressure and heart rate, and sedation, while binding of agonists to α_2 adrenoceptors in the spinal cord produces analgesia [3]. Peripheral α_2 receptors in blood vessels mediate vascular smooth muscle contraction and a rapid injection of a potent α_2 agonist can result in transient hypertension [6]. Dexmedetomidine is rapidly and extensively distributed to tissues with a distribution half-life of 5 min and elimination half-life of 2–3 h. It is extensively metabolised by phase one and phase two reactions in the liver and both urinary and faecal excretion are involved in elimination of dexmedetomidine and its metabolites (Personal communication. Abbott Laboratories, Abbott Park, IL, USA). Although dexmedetomidine inhibits cytochrome P450 metabolism in the laboratory, clinically relevant drug interactions at the plasma concentrations found in humans are not expected [7]. Unlike etomidate, dexmedetomidine has negligible effects on adrenal steroidogenesis in dogs [8].

The principal end-points of the study were to see if there were any differences in midazolam and morphine requirements between postoperative patients receiving dexmedetomidine and placebo. This was clearly demonstrated by an 80% reduction in midazolam and a 50% reduction in morphine requirements. While intubated, 36% of patients on dexmedetomidine and 11% on placebo required no midazolam. The placebo-controlled nature of the protocol ultimately meant that the initial method of sedation differed between patients receiving dexmedetomidine and placebo. The dexmedetomidine group received a loading dose followed by an infusion of the sedative agent, whereas the placebo group received a loading dose followed by an infusion of placebo and so initially remained sedated under the influence of their intra-operative anaesthesia. On waking, they received midazolam boluses, sometimes followed by an infusion. Consequently, this made interpretation of the results difficult, especially during the first hour of the study, due to the less fluent

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