British Journal of Anaesthesia **95 (6)**: 773–5 (2005)
doi:10.1093/bja/aei263 Advance Access publication October 21, 2005

BJA

Case Report

Central apnoea after balanced general anaesthesia that included dexmedetomidine

A. M.-H. Ho*, S. Chen and M. K. Karmakar

Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR, PRC

**Corresponding author. E-mail: hoamh@hotmail.com*

Dexmedetomidine is an α_2-adrenoreceptor agonist that, in spite of its potent sedative, amnesic, and analgesic properties, has minimal respiratory depressant effect. Even at doses adequate for general anaesthesia, it does not cause central apnoea. Thus, it has been claimed that 'combining α_2-agonists with opiate narcotics or non-steroidal anti-inflammatory drugs can enhance the analgesic efficacy without increasing the respiratory depressant effect of the latter' and 'the combination of α_2-adrenoceptor agonists with opioids does not lead to further ventilatory depression'. We present a case of central apnoea after general anaesthesia that included opioids and dexmedetomidine, and remind the readers that in susceptible patients, dexmedetomidine may cause life-threatening respiratory depression through potentiation of co-administered central nervous system depressants.

Br J Anaesth 2005; **95**: 773–5

Keywords: agonists, α_2-adrenergic; complications, apnoea; complications, respiratory failure; opiates; premedication, dexmedetomidine

Accepted for publication: September 12, 2005

Dexmedetomidine (Precedex; Abbott Laboratories, Abbott Park, IL, USA) has potent sympatholytic, analgesic, and sedative properties,[1–12] mediated through α_2-adrenoceptors in the central and peripheral nervous systems, in autonomic ganglia at pre- and post-synaptic sites, and at the locus coeruleus.[8 11] One of the most important advantages of dexmedetomidine is the lack of significant respiratory depression.[1–8 12] As such, it has been used for sedation in the intensive care unit and for weaning from respiratory support.[7 9] It reduces the MAC of potent inhalational anaesthetics[1] and is morphine-sparing.[7 9 10] Even at doses high enough to be used as a sole general anaesthetic agent, dexmedetomidine did not cause any significant respiratory depression.[6] We report the case of a patient who suffered central apnoea in the post-anaesthetic care unit after a general anaesthetic that included opioids and dexmedetomidine.

Case report

A 69-yr-old, 64-kg, 153-cm Chinese woman was scheduled to undergo vaginal hysterectomy, repair of cystocoele and enterocoele, MaCall's culdoplasty, perineoplasty, and vaginal taping. Comorbidity included controlled hypertension (treated with nifedipine and enalapril) but no cardiorespiratory, neurological, or neuromuscular disease. There was no history of regular sedative, psychotropic or recreational drug, or analgesic use. Her preoperative ECG and blood tests were all normal. She received no preoperative sedation.

After placement of routine monitors (bispectral index monitor not included) and preoxygenation of the lungs, general anaesthesia was induced with fentanyl 100 μg, propofol 120 mg, and rocuronium 35 mg, and the patient's trachea was intubated. Maintenance was with N_2O and isoflurance 0–1%. Ten minutes after induction of anaesthesia, shortly before the first surgical stimulation, morphine 7.5 mg, the only dose for the case, was given as a bolus. Fifty-five minutes after induction the isoflurane was switched off, and dexmedetomidine was started as per a previously published and apparently effective protocol[10]: 60 μg was given over 30 min, followed by an infusion of 0.5 μg kg^{-1} h^{-1}. Surgery was completed sooner than expected. Intraoperative blood loss was 200 ml. Just before transport to the post-anaesthetic care unit, the patient's end-tidal isoflurane, N_2O, and CO_2 were 0%, 3%, and 48–50 mm Hg, respectively. She was breathing spontaneously with a tidal volume of 380–420 ml and ventilatory frequency of

10 min^{-1}, had normal vital signs, and had only reacted transiently and mildly to the tracheal tube. Muscle relaxation had been fully reversed (two strong twitches on train-of-four stimulation to ulnar nerve before reversal with standard doses of atropine and neostigmine). She was not responsive when her name was called. The patient left theatre 40 min after commencement of dexmedetomidine. Five minutes later she started to cough on the tracheal tube and attempted to open her eyes when her name was called. The tracheal tube was removed and an O_2 facemask was applied. Within 1 min of extubation, she stopped breathing and her Sp_{O_2} quickly deteriorated. There was no respiratory effort detectable. She did not respond to verbal stimulation. She was immediately hand-mask-bag-ventilated and her Sp_{O_2} came from a low of 81% quickly back to 99%. During the apnoeic episode, the dexmedetomidine infusion was discontinued. She started to breath on her own again about 5 min later and opened her eyes to verbal stimulation another 5 min later. She made an uneventful recovery.

Discussion

Dexmedetomidine, a highly selective α_2-agonist, induces analgesia, sympatholysis, and sedation that partially mimics natural sleep.[3–5] Evidence suggests that, unlike most other powerful sedatives and analgesics, it has minimal respiratory depressing properties.

In dogs[1] and rabbits,[2] dexmedetomidine caused moderate dose-dependent respiratory depression but a paradoxic increase in ventilation at high doses.

In controlled settings, dexmedetomidine 0.25, 0.5, and 1 $\mu g\ kg^{-1}$ infused over 2 min in healthy volunteers (age 18–45 yr) resulted in a mild and dose-dependent reduction in ventilation.[3] However, at 2 $\mu g\ kg^{-1}$, ventilation paradoxically was less depressed.[3] In healthy men (age 21–40 yr) given stepwise target infusion plasma dexmedetomidine concentrations of 0.6, 1.2, 1.8, and 2.4 ng ml^{-1}, the ventilatory frequency increased in a dose-dependent manner, which more than compensated for the slight reductions in tidal volume.[4] The Sp_{O_2} and blood pH did not change.[4] In non-medicated men (age 20–27 yr) given target infusions of 0.5–8.0 ng ml^{-1}, Pa_{CO_2} increased by 3–4 mm Hg at the higher concentrations.[5]

Clinical experience is consistent with the respiratory-sparing sedative effect of the drug. Ramsay and Luterman[6] described the use of i.v. dexmedetomidine as the sole anaesthetic agent. They gave 1 $\mu g\ kg^{-1}$ plus an infusion of 10 $\mu g\ kg^{-1}\ h^{-1}$ plus topical airway anaesthesia to a 66-yr-old woman with subglottic stenosis for laser treatment. The patient required chin support. On room air, the Sp_{O_2} was 94–98%, and Pa_{CO_2} was 43 mm Hg. A 65-yr-old man with emphysema underwent resection of facial lesions with full-thickness skin grafting receiving only dexmedetomidine 1 $\mu g\ kg^{-1}$ loading plus an infusion of less than 5 $\mu g\ kg^{-1}\ h^{-1}$, presumably with local anaesthetic-coverage. On room air, his Sp_{O_2} was greater than 90% throughout. A 50-yr-old man underwent rigid and fibre-optic bronchoscopy, laryngoscopy, bronchopulmonary lavage, and revision of a tracheal prosthesis, receiving only dexmedetomidine 1 $\mu g\ kg^{-1}$ plus an infusion of less than 5 $\mu g\ kg^{-1}\ h^{-1}$. On room air, his Sp_{O_2} was greater than/equal to 92%.

In the ICU setting, dexmedetomidine 1 $\mu g\ kg^{-1}$ given over 10 min plus an infusion of 0.2–0.7 $\mu g\ kg^{-1}\ h^{-1}$, compared with placebo, in post-surgical patients resulted in, respectively, a 80% and a more than 50% reduction in midazolam and morphine requirement, with no difference in the level of sedation, Pa_{CO_2}, and blood pH.[7]

Triltsch and colleagues[9] gave dexmedetomidine (1 $\mu g\ kg^{-1}$ over 10 min plus 0.1–0.7 $\mu g\ kg^{-1}\ h^{-1}$) or placebo to post-surgical patients on admission to the ICU. Dexmedetomidine-treated patients required 57 and 27% of the propofol requirements during mechanical ventilation and weaning, respectively, and 41% of the morphine to achieve the same bispectral indices as controlled patients. Time to extubation did not differ between the groups, both of which had three cases of respiratory failure out of 15 patients.

After major abdominal surgery, dexmedetomidine 1 $\mu g\ kg^{-1}$ loading over 10 min plus 0.4 $\mu g\ kg^{-1}\ h^{-1}$ infusion resulted in 66% reduction in morphine consumption in the PACU with no significant change in the RR and Sp_{O_2}.[10]

In summary, in young healthy volunteers, dexmedetomidine, even at high doses, induces sedation with minimal respiratory effect during quiet, unchallenged breathing, and variable but somewhat blunted ventilatory responses to hypercarbia and hypoxia. Likewise, clinical evidence also points to the α_2-agonist as a potent sedative and analgesic without significant central respiratory depression, even at very high doses, albeit occasionally causing obstructive apnoea. This unique combination of effects is also a characteristic of clonidine, another α_2-agonist.[12] It has thus been claimed that 'combining α_2-agonists with opiate narcotics or non-steroidal anti-inflammatory drugs can enhance the analgesic efficacy without increasing the respiratory depressant effect of the latter',[8] and 'the combination of α_2 adrenoceptor agonists with opioids does not lead to further ventilatory depression'.[12] Our case challenges this notion.

This case of central apnoea sounds a cautionary note that dexmedetomidine, notwithstanding its unique and favourable respiratory effect profile, is ultimately a potent sedative and analgesic. Sedation and normal sleep lead to variable degrees of analgesia, muscle hypotonia, and amnesia due to changing aminergic-cholinergic balance in the pons,[13–15] explaining in part why sleep- and hypnosis-inducing agents are opioid-sparing. In sleep and sedation and as one ages, the hypercapnic ventilatory response is reduced.[15] Agents that induce sleep or sedation, such as barbiturates, benzodiazepines, and α_2-adrenergic agonists, thus may all potentiate the ventilatory depressive effect of opiates, especially in the elderly. Moreover, ventilatory drive is modulated in part by the intensity on the brainstem of nociceptive inputs,

which are depressed by hypnotics and analgesics.[13–15] This mutually enhancing respiratory depressant effect between opioids and sedating agents is well known to anaesthetists—a heavily sedated patient can go from minimal respiratory depression to apnoea with just a small dose of narcotic.

Based on the above arguments, we speculate that the main cause of our patient's apnoea was likely the combined effects of dexmedetomidine, morphine, and fentanyl. Contributory factors included the patient's age, the low level of post-surgical and post-extubation noxious stimulation, the lack of a history of habitual sedative use, and possibly her ethnicity. Her arterial CO_2 and serum glucose and electrolytes, although not measured, probably had no bearing on her central apnoea. She was not paralysed, dehydrated, septic, and had, in all likelihood, not suffered from seizure or an intracranial event.

Compared with patients receiving morphine alone, patients given dexmedetomidine require 50–66% less morphine.[7 9 10] Using this degree of morphine sparing capability as a rough guide, it would be akin to having given this elderly Chinese opiate-naïve lady rather large doses of opioids, some 19 mg of morphine and some 250 μg of fentanyl at 90 and 100 min, respectively, before the respiratory arrest.

In conclusion, although by itself, dexmedetomidine, even at high doses, possesses only minimal central respiratory depressant properties, it may, through its potent sedative and analgesic actions, greatly potentiate the respiratory depressant properties of co-administered sedatives and analgesics, especially in patients who are more susceptible.

References

1 Nguyen D, Abdul-Rasool I, Ward D, *et al*. Ventilatory effects of dexmedetomidine, atipamezole, and isoflurane in dogs. *Anesthesiology* 1992; **76**: 573–9

2 Nishida T, Nishimura M, Kagawa K, *et al*. The effects of dexmedetomidine on the ventilatory response to hypercapnia in rabbits. *Intens Care Med* 2002; **28**: 969–75

3 Belleville JP, Ward DS, Bloor BC, Maze M. Effects of intravenous dexmedetomidine in humans. *Anesthesiology* 1992; **77**: 1125–33

4 Hsu Y-W, Cortinez LI, Robertson KM, *et al*. Dexmedetomidine pharmacodynamics: Part I. Crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. *Anesthesiology* 2004; **101**: 1066–76

5 Ebert TJ, Hall JE, Barney JA, *et al*. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology* 2000; **93**: 382–94

6 Ramsay MA, Luterman DL. Dexmedetomidine as a total intravenous anesthetic agent. *Anesthesiology* 2004; **101**: 787–90

7 Venn RM, Hell J, Grounds RM. Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care* 2000; **4**: 302–8

8 Ebert T, Maze M. Dexmedetomidine: another arrow for the clinician's quiver. *Anesthesiology* 2004; **101**: 568–70

9 Triltsch AE, Welte M, von Homeyer P, *et al*. Bispectral index-guided sedation with dexmedetomidine in intensive care: a prospective, randomized, double blind, placebo-controlled phase II study. *Crit Care Med* 2002; **30**: 1007–14

10 Arain SR, Ruehlow RM, Uhrich TD, Ebert TJ. The efficacy of dexmedetomidine versus morphine for postoperative analgesia after major inpatient surgery. *Anesth Analg* 2004; **98**: 153–8

11 Maze M, Bonnet F. Analgesics. Receptor ligands—α_2 adrenergic receptor agonists. In: Evers AS, Maze M, eds. *Anesthetic Pharmacology: Physiologic Principles and Clinical Practice*. Philadelphia: Churchill Livingstone, 2004; 473–89

12 Khan ZP, Ferguson CN, Jones RM. Alpha-2 and imidazoline receptor agonists. Their pharmacology and therapeutic role. *Anaesthesia* 1999; **54**: 146–65

13 Hobson JA. Consciousness: lessons for anesthesia from sleep research. In: Yaksh TL, Maze M, Lynch III C, Biebuyck JF, Zapol WM, Saidman LJ, eds. *Anesthesia Biologic Foundations*. Philadelphia: Lippincott-Raven, 1998; 423–31

14 Lydic R, Baghdoyan HA. Cholinergic contributions to the control of consciousness. In: Yaksh TL, Maze M, Lynch III C, Biebuyck JF, Zapol WM, Saidman LJ, eds. *Anesthesia Biologic Foundations*. Philadelphia: Lippincott-Raven, 1998; 433–50

15 Tabatabai M, Behnia R, Pretto E. Neurochemical regulation of respiration. In: Collins VJ, ed. *Physiologic and Pharmacologic Bases of Anesthesia*. Baltimore: Williams & Wilkins, 1996; 47–63