Atropine-induced heart rate changes: a comparison between midazolam-fentanyl-propofol-N_2O and midazolam-fentanyl-thiopentone-enflurane-N_2O anaesthesia

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Atropine-induced heart rate (HR) changes were studied in 19 patients (ASA physical status I) during anaesthesia maintained predominantly with propofol-N_2O or thiopentone-enflurane-N_2O. Ten patients (Group A) received midazolam (0.07 mg · kg^{-1}), fentanyl (1 μg · kg^{-1}), propofol (2 mg · kg^{-1}) and succinylcholine (1 mg · kg^{-1}). Following tracheal intubation, anaesthesia was maintained with propofol (6 mg · kg^{-1} · hr^{-1}), N_2O (67 per cent) and O_2 (33 per cent). In nine patients (Group B) thiopentone (4 mg · kg^{-1}) was substituted for propofol and anaesthesia maintained with N_2O (67 per cent) O_2 (33 per cent), and enflurane (0.5 per cent inspired concentration). The study was non-randomised because Group B patients were only included if HR before administration of atropine < 90 beats · min^{-1}. IPPV was performed in all patients using a Manley ventilator (minute vol. 85 ml · kg^{-1}; tidal vol. 7 ml · kg^{-1}). Ten minutes after tracheal intubation, incremental doses of atropine (equivalent cumulative doses: 1.8, 3.6, 7.2, 14.4, 28.8 μg · kg^{-1}) were administered at two-minute intervals and HR responses calculated during the last 45 sec of each intervening period. No differences were observed between the groups following 1.8 and 3.6 μg · kg^{-1} atropine, but propofol-N_2O anaesthesia was associated with reduced responses ($P < 0.01$) following 7.2, 14.4 and 28.8 μg · kg^{-1} atropine. These results suggest that there is a predominance of parasympathetic influences during propofol-N_2O anaesthesia compared with thiopentone-enflurane-N_2O anaesthesia.

Les changements de la fréquence cardiaque induits par l'atropine ont éte étudiés chez 19 patients (Classe ASA I) durant l'anesthésie maintenu surtout avec du propofol-N_2O ou thiopentone-enflurane-N_2O. Dix patients (Groupe A) ont reçu du midazolam (0.07 mg · kg^{-1}), fentanyl (1 μg · kg^{-1}), propofol (2 mg · kg^{-1}) et succinylcholine (1 mg · kg^{-1}). Après l'intubation, l'anesthésie a été maintenue avec du propofol (6 mg · kg^{-1} · hr^{-1}), N_2O (67 pour cent), O_2 (33 pour cent). Chez neuf patients (Groupe B) du thiopentone (4 mg · kg^{-1}) a été substitué pour du propofol et l'anesthésie fut maintenue avec du N_2O (67 pour cent), O_2 (33 pour cent) et enflurane (0,5 pour cent fraction inspirée). Cette étude n'était pas randomisée car les patients du groupe B ont été inclus seulement si la fréquence cardiaque avant l'administration de l'atropine était <90 batt · min^{-1}. La ventilation fut assurée par un ventilateur Manley chez tous les patients (vol. minute 85 ml · kg^{-1}; volume courant 7 ml · kg^{-1}). Dix minutes après l'intubation, des doses croissantes d'atropine (doses cumulatives: 1,8, 3,6, 7,2, 14,4, 28,8 μg · kg^{-1}) ont été administrées à deux minutes d'intervalle et les réponses de la fréquence cardiaque furent calculées durant les dernières 45 secondes après chaque période d'intervention. Aucune différence fut observée entre les groupes après 1,8 et 3,6 μg · kg^{-1} d'atropine mais l'anesthésie au propofol-N_2O était associée avec une réponse réduite ($P < 0.01$) aprés 7,2, 14,4 et 28,8 μg · kg^{-1} d'atropine. Ces résultats suggèrent qu'il y a une prédominance de l'influence du système parasympathique lors de l'anesthésie au propofol-N_2O comparativement à l'anesthésie au thiopentone-enflurane-N_2O.

Key words

ANAESTHETIC TECHNIQUES: inhalation, intravenous;
ANAESTHETICS, INTRAVENOUS: propofol, thiopentone;
PARASYMPATHETIC NERVOUS SYSTEM: atropine;
HEART: pulse rate.

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Propofol either alone or in combination with N_2O-O_2 produces a decrease in blood pressure accompanied by minimal change in heart rate.[1–3] Studies on baroreceptor reflex control mechanisms indicate that propofol differs from most other anaesthetic agents in that it appears to produce marked resetting of the reflex set point without depressing baroreflex sensitivity, and it has been suggested that this is the result of enhanced parasympathetic control of heart rate.[4]

The present study examined this proposition by comparing dose–response relationships for atropine-induced heart rate changes during anaesthesia maintained predominantly with propofol-N_2O and thiopentone-enflurane-N_2O.

Method

Following local ethical committee approval and informed consent, 20 patients (ASA physical status 1) aged 20–40 yr scheduled for extracorporeal shockwave lithotripsy (ESWL) were randomly allocated to two groups. All patients were unpremedicated.

Patients in group A received midazolam (0.07 mg·kg^{-1}), fentanyl (1 μg·kg^{-1}) and propofol (2 mg·kg^{-1}). Following succinylcholine (1 mg·kg^{-1}) and topical application of lidocaine (4 ml of four per cent solution) to the larynx, tracheal intubation was performed. Anaesthesia was maintained by infusion of propofol (6 mg·kg^{-1}·hr^{-1}) and an inspired gas mixture of N_2O (67 per cent) and O_2 (33 per cent). Induction of anaesthesia and tracheal intubation in Group B were performed in the same manner as in Group A with the exception that thiopentone (4 mg·kg^{-1}) was substituted for propofol. Anaesthesia was then maintained with N_2O (67 per cent), O_2 (33 per cent) and enflurane (0.5 per cent inspired concentration). The lungs of all patients were ventilated with a Manley ventilator using minute and tidal volumes of 85 ml·kg^{-1} and 7 ml·kg^{-1} respectively. Midazolam and fentanyl were administered at induction of anaesthesia in both groups of patients to facilitate mechanical ventilation via a tracheal tube during the observation period since we wished to avoid the use of non-depolarizing muscle relaxants, many of which have intrinsic effects on the cardiovascular system.[5] Blood pressure was monitored with a Dinamap automatic blood pressure recorder. All patients received approximately 7 ml·kg^{-1} Ringer's lactate solution IV in the period between induction of anaesthesia and administration of the first dose of atropine.

Ten minutes following intubation, continuous ECG recording was commenced using a strip chart recorder and the following incremental doses of atropine were administered to all patients: 1.8, 1.8, 3.6, 7.2, 14.4 μg·kg^{-1} (equivalent cumulative doses: 1.8, 3.6, 7.2, 14.4, 28.8 μg·kg^{-1}). These doses were selected to facilitate the plotting of log–dose response relationships and result in a total atropine dose of 2.0 mg in a 70 kg individual. Each dose was made up to 2 ml with normal saline and administered over five seconds at two-minute intervals. Heart rate responses were calculated from the ECG recordings during the last 45 sec of each observation period between doses. All patients received a muscle relaxant after completion of the study which lasted ten minutes and thereafter underwent ESWL as scheduled.

TABLE I Mean (SD) ages, weights, male/female distribution, baseline heart rates (HR) and blood pressure (BP) for the two groups.

	Propofol *n = 10*	*Thiopentone-enflurane* *n = 9**
Age (yr)	33.2 (6.3)	32.4 (8.0)
Weight (kg)	64.7 (11.8)	73.5 (15.3)
Male/female	5/5	5/4
HR (beats·min^{-1})†	72.4 (12.5)	73.6 (9.4)
Systolic BP† (mmHg)	96.9 (9.1)	99.2 (8.3)
Diastolic BP† (mmHg)	62.7 (7.9)	63.4 (6.9)

*Selected sample with baseline heart rates <90 beats·min^{-1}.
†Immediately before administration of atropine.

Although this study had initially been designed as a randomised comparison, three patients in the thiopentone-enflurane-N_2O group (Group B) had heart rates greater than 90 beats·min^{-1} before the scheduled administration of atropine, and were considered ineligible for the study. Two additional patients were therefore studied in order to supplement the number of patients in Group B. No patient reacted to the presence of the tracheal tube or exhibited any signs of light anaesthesia during the study period.

Demographic data and the changes in heart rate following each dose of atropine were analysed using unpaired Student's t test.

Results

Patient details for the two groups are shown in Table I. Both groups were comparable with regard to age, weight, sex distribution, baseline blood pressure and heart rate. The changes in heart rate (beats·min^{-1} from control value) following each cumulative atropine dosage are shown in Table II and the log–dose response relationships in the Figure.

Although there was no difference in the responses following the first and second doses of atropine, significant differences ($P < 0.01$) were observed following the third, fourth and fifth doses.

Three patients in Group B developed arrhythmias during the study. These arrhythmias were junctional in two cases and atrial in the other, of short duration, and ended spontaneously. No patients in the propofol group developed arrhythmias.

TABLE II Mean (SD) heart rate changes following cumulative atropine doses

Cumulative atropine dose $\mu g \cdot kg^{-1}$	*Propofol* $n = 10$	*Thiopentone-enflurane* $n = 9$
1.8	−2.5 (1.6)	−3.3 (1.4)
3.6	−5.2 (2.9)	−4.0 (2.5)
7.2	−1.4 (6.1)	8.0 (6.6)*
14.4	10.8 (7.7)	21.6 (4.9)*
28.8	18.6 (5.7)	27.8 (7.1)*

*$P < 0.01$.

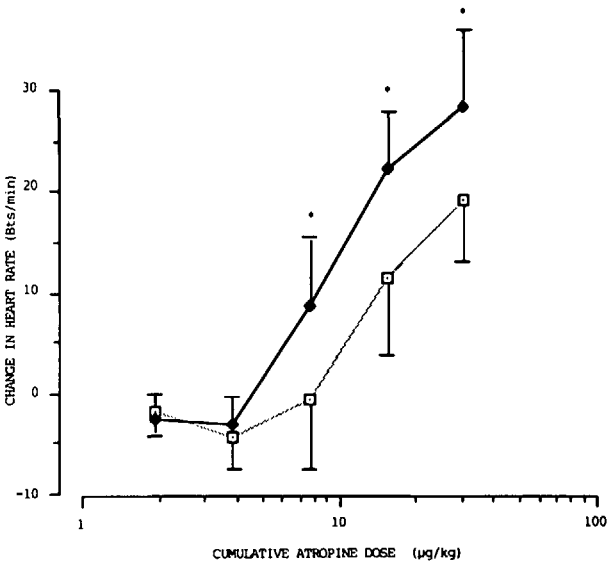

FIGURE Log–dose response relationships for the two groups. Values shown are mean ± SD. ◆ Thio-enflurane, ⊡ Propofol, *$P < 0.01$.

Discussion

It has been documented that whilst propofol decreases arterial pressure with minimal changes in heart rate,[1–3] enflurane anaesthesia results in hypotension with a slight increase in heart rate.[6] The haemodynamic changes occurring with propofol have been ascribed to a reduction in systemic vascular resistance, coupled with marked resetting of the baroreflex set point without actual depression of baroreflex sensitivity – the latter being thought to indicate enhancement of parasympathetic control of heart rate.[4]

The baseline heart rates of the two groups of patients initially recruited into the study confirm that heart rate during thiopentone-enflurane-N_2O anaesthesia may be increased relative to propofol-N_2O anaesthesia since three patients in Group B exhibited baseline heart rates >90 beats $\cdot$ min^{-1}. As we considered it undesirable to subject these patients to the administration of atropine, they were excluded from further investigation and two subsequent patients with baseline heart rates <90 beats $\cdot$ min^{-1} were studied. This resulted in a total of nine subjects in Group B with a mean baseline heart rate comparable to the ten patients in Group A. Although the exclusion of patients with baseline heart rates >90 beats $\cdot$ min^{-1} meant that randomisation was lost, we believe that the results comparing the responses in subjects starting from similar heart rates provide a useful indication of the balance between parasympathetic and sympathetic control of the heart rate during the two anaesthetic regimens.

Since depth of anaesthesia may affect the degree of vagal tone, and thus heart rate response to atropine, the comparability of the depth of anaesthesia achieved by the two regimens has to be considered. Both groups of patients were un-premedicated and received similar doses of midazolam and fentanyl before induction of anaesthesia with standard doses of thiopentone or propofol. The maintenance dose of enflurane (0.5 per cent inspired) and maintenance infusion rate of propofol (6 mg $\cdot$ kg^{-1} $\cdot$ hr^{-1}) were approximately similar to the quoted MAC value for enflurane in N_2O (0.57 per cent)[7] and the minimal infusion rate (ED_{95}) for propofol when used to supplement N_2O-O_2 anaesthesia after opiate premedication,[8] respectively. Although we cannot be certain that depth of anaesthesia was similar in both groups, it was our expectation that the regimen used would provide comparable conditions comprising (a) adequate hypnosis and tolerance of IPPV without neuromuscular blockade during the observation period and (b) adequate hypnosis and analgesia for ESWL extending up to 2000 shock-wave applications when supplemented with muscle relaxation. Although the small dose of fentanyl administered at induction might influence the response to atropine because of its intrinsic vagotonic activity,[9] such an effect would be present in both groups and it is therefore valid to regard any differences demonstrated as primarily reflecting the effects propofol in Group A and thiopentone-enflurane in group B.

The dose–response relationships demonstrated in this study clearly indicate that the chronotropic effect of atropine is significantly reduced during propofol-N_2O anaesthesia compared with thiopentone-enflurane-N_2O anaesthesia. This reinforces the findings of Yamaguchi *et al.*[10] that heart rate responses to atropine differ during anaesthesia with different anaesthetic agents and techniques. Although these differences are likely to be the manifestation of alterations in the balance between sympathetic and parasympathetic influences on the heart, the manner in which such imbalances might affect the response to atropine is debatable. Thus, Yamaguchi *et al.*[10] and Mirakhur[11] have assumed that a greater chronotropic response to atropine is indicative of increased

pre-existing vagal tone. These authors do not specify the reasons, but it is presumably based on the assumption that increased vagal tone will result in a slower resting heart rate or concomitantly increased sympathetic activity, and that removal of the vagal "brake" will result in a greater absolute rise in heart rate. Such a sequence of events is, however, dependent on the achievement of total vagal blockade by a maximal or supra-maximal dose of atropine. Administration of submaximal doses would not necessarily produce the above effect and because atropine is a competitive muscarinic antagonist,[12] submaximal doses would be expected to produce a decreased chronotropic response in the presence of increased vagal tone. Thus the direction of the heart rate response to atropine depends on whether a submaximal or maximal dose is administered. As the dose–response relationships in the Figure clearly show an increasing response in the dose range studied, we infer that the doses administered were submaximal, and that the decreased chronotropic response exhibited by Group B suggests that propofol-N_2O anaesthesia is associated with a predominance of vagal influences compared with thiopentone-enflurane-N_2O anaesthesia.

Attention must therefore be paid to the possibility that bradycardias may occur during propofol anaesthesia, particularly when it is used in patients who have not received anticholinergic premedication, and in conjunction with either opioids, e.g., fentanyl, with vagotonic properties[9] or neuro-muscular blocking agents, e.g., vecuronium, which are devoid of vagolytic properties.[5] Our results also indicate that if corrective treatment of bradycardia with atropine is required, the response to therapy during propofol anaesthesia will be attenuated when compared with thiopentone-enflurane anaesthesia.

References

1 *Claeys MA, Gepts E, Camu F.* Haemodynamic changes during anaesthesia induced and maintained with propofol. Br J Anaesth 1988; 60: 3–9.

2 *Sear JW, Shaw I, Wolf A, Kay NH.* Infusions of propofol to supplement nitrous oxide-oxygen for the maintenance of anaesthesia. Anaesthesia 1988; 43 (Suppl): 18–22.

3 *Prys-Roberts C, Davies JR, Calverley RK, Goodman NW.* Haemodynamic effects of infusions of diisopropyl phenol (ICI 35868) during nitrous oxide anaesthesia in man. Br J Anaesth 1983; 55: 105–11.

4 *Cullen PM, Turtle M, Prys-Roberts C, Way WL, Dye J.* Effect of propofol anaesthesia on baroreflex activity in humans. Anesth Analg 1987; 66: 1115–20.

5 *Hunter JM.* Adverse effects of neuromuscular blocking drugs. Br J Anaesth 1987; 59: 46–60.

6 *Adams AP.* Enflurane in clinical practice. Br J Anaesth 1981; 53: 27S-41S.

7 *Jones RM.* Inhalational and intravenous anaesthetic agents. *In*: Anaesthesia. Nimmo WS, Smith G (Eds.). Oxford: Blackwell Scientific Publications. 1989: 34–59.

8 *Spelina KR, Coates DP, Monk CR, Prys-Roberts C, Norley I, Turtle MJ.* Dose requirements of propofol by infusion during nitrous oxide anaesthesia in man. Br J Anaesth 1986; 58: 1080–4.

9 *Reitan JA, Stengert KB, Wymore ML, Martucci RW.* Central vagal control of fentanyl induced bradycardia during halothane anaesthesia. Anesth Analg 1978; 57: 31–6.

10 *Yamaguchi H, Dohi S, Sato S, Naito H.* Heart rate response to atropine in humans anaesthetized with five different techniques. Can J Anaesth 1988; 35: 451–6.

11 *Mirakhur RK.* Anticholinergic drugs and anaesthesia. Can J Anaesth 1988; 35: 443–7.

12 *Burks TF.* The autonomic nervous system in relation to anaesthesia. *In*: General Anaesthesia, 5th ed. Nunn JF, Utting JE, Burnell R Brown Jr (Eds.). Oxford: Butterworths, 1989: 259–82.