Effect of atracurium, vecuronium, pancuronium and tubocurarine on renal sympathetic nerve activity in baroreceptor denervated dogs

I. YONEDA, H. GOTO, M. NISHIZAWA, G. K. UNRUH AND K. ARAKAWA

SUMMARY

The mechanism of arterial hypotension induced by non-depolarizing neuromuscular blocking agents may be multifactorial and differ between drugs. The purpose of this study was to evaluate the effect of high-dose atracurium and equivalent doses of other non-depolarizing neuromuscular blocking agents on haemodynamic state and sympathetic nervous activity. In studies on 24 mongrel dogs anaesthetized with alpha-chloralose, the left kidney was exposed retroperitoneally and renal sympathetic nerve activity was recorded continuously after bilateral sino-aortic denervation and cervical vagi section. The dogs were allocated to four groups: atracurium 1.5 mg kg⁻¹, tubocurarine 0.3 mg kg⁻¹, pancuronium 0.3 mg kg⁻¹ or vecuronium 0.3 mg kg⁻¹ was administered to six dogs in each group. Histamine 1 μg kg⁻¹ was given to two dogs in each group, 1 h before administration of neuromuscular blocking agents. We observed that atracurium and tubocurarine significantly decreased arterial pressure, heart rate and renal sympathetic nerve activity (P < 0.05), but pancuronium and vecuronium did not. Histamine-induced arterial hypotension but did not affect heart rate or renal sympathetic nerve activity. As both arterial and cardiopulmonary baroreflex pathways were inactivated in these animals, we conclude that atracurium decreased arterial pressure by suppressing efferent sympathetic nerve activity in a manner similar to that of tubocurarine. (Br. J. Anaesth. 1994; 72: 679-682)

KEY WORDS


We postulated that hypotension caused by atracurium might result, in part, from decreased efferent sympathetic activity, in a manner similar to that which occurs with tubocurarine-induced hypotension. To explore this possibility, we measured renal sympathetic nerve activity in dogs in which arterial and cardiopulmonary baroreceptors were denervated. We have also compared the haemodynamic and sympathetic nerve response to atracurium with those of other non-depolarizing neuromuscular blocking agents. Therefore, we examined also the effects of tubocurarine, pancuronium and vecuronium on sympathetic nerve activity.

MATERIALS AND METHODS

This study was approved by the Kansas University Institutional Animal Care and Use Committee and appropriate guidelines for the use of animals were observed.

Adult mongrel dogs of both sexes (18.4 to 24.5 kg), were anaesthetized with thiopentone 10 mg kg⁻¹ i.v. and alpha-chloralose 100 mg kg⁻¹ i.v. Anaesthesia was maintained with a continuous infusion of alpha-chloralose 20 mg kg⁻¹ h⁻¹ i.v. The trachea was intubated without neuromuscular block and the lungs ventilated with a Harvard animal ventilator (Millis, MA, U.S.A.), using oxygen in nitrogen (FiO₂ 0.4) at a tidal volume of 10–15 ml kg⁻¹ and a frequency of 15–20 b.p.m. A catheter was inserted into a femoral artery for measurement of arterial pressure via a pressure transducer (DTX Spectramed, Oxnard, CA, U.S.A.) for continuous recording. Mean arterial pressure (MAP) was obtained by electronic integration of the pulsatile pressure signal. Heart rate (HR) was calculated from lead II of the ECG using a cardiotachometer (1321 San-ei, Japan).

The cervical vagi were sectioned bilaterally through an upper median cervical incision to remove vagal afferent input. Bilateral sino-aortic denervation (SAD) was performed also by isolating and severing...
FIG. 1. Original tracing of the haemodynamic and nerve activity changes induced by bolus i.v. administration of the neuromuscular blocking agents tuberculosis (T) 0.3 mg kg⁻¹, atracurium (A) 1.5 mg kg⁻¹, vecuronium (V) 0.3 mg kg⁻¹ and pancuronium (P) 0.3 mg kg⁻¹, and histamine (H), 1.0 µg kg⁻¹. HR = heart rate; SAP = systemic arterial pressure; RSNA = actual and integrated (I) renal sympathetic nerve activity. Because of the initial high-speed recording, each RSNA (µV) trace does not reflect tall spikes (see text for explanation).

FIG. 2. Effects of histamine 1 µg kg⁻¹ on mean arterial pressure (MAP), heart rate (HR) and renal sympathetic nerve activity (RSNA) *P < 0.05 vs control (C).

carefully the carotid sinus and aortic nerves on both sides using a dissecting microscope. The aortic nerves were dissected free from the vago-sympathetic trunk between the ganglion nodosum and superior laryngeal nerve and then sectioned. The carotid sinus receptors on each side were isolated for denervation by stripping the arterial wall in the carotid sinus area, including the carotid sinus nerve between the internal and external carotid arteries. The glosso-

pharyngeal nerve and superior laryngeal nerves were also severed. The effectiveness of bilateral vagotomy and SAD were confirmed later by demonstrating failure of phenylephrine 2 µg kg⁻¹ to decrease and sodium nitroprusside 5 µg kg⁻¹ to increase HR and renal sympathetic nerve activity.

Measurement and recording of renal sympathetic nerve activity have been described previously [6]. Briefly, the left kidney was exposed and renal sympathetic nerves were isolated and placed on a bipolar silver electrode. Nerve impulses were amplified, rectified and integrated, and recorded continuously. To quantitate renal sympathetic nerve activity, the resting spontaneous nerve discharge before i.v. administration of agents is defined as 100% control value. All variables were measured continuously and recorded on a DAT tape PCM recorder (RD-100T TEAC, Montebello, CA, U.S.A.) and played back on a multichannel chart recorder (Ommicorder 8M14, San-ei, Japan).

Twenty-four dogs were allocated to four groups: atracurium, tuberculosis, pancuronium and vecuronium. After a stable haemodynamic state was established, baseline MAP, HR and renal sympathetic nerve activity were recorded. Then, vecuronium 0.3 mg kg⁻¹, pancuronium 0.3 mg kg⁻¹, atracurium 1.5 mg kg⁻¹ or tubocurarine 0.3 mg kg⁻¹ i.v. was administered randomly over 5 s (one drug to one animal). MAP, HR and renal sympathetic nerve activity were recorded continuously for 2 h after administration of the neuromuscular blocker. Two dogs in each group were given histamine 1 µg kg⁻¹ at least 1 h before the neuromuscular blockers were administered, and its effect on haemodynamic variables and sympathetic nerve activity observed.

All data are expressed as mean (SEM). Statistically significant differences were evaluated by analysis of variance (ANOVA) followed by Duncan's multiple range tests and P < 0.05 was considered significant.
RESULTS

Oxygenation and acid–base balance were maintained within normal limits before administration of neuromuscular blocking agents: mean $P_{aCO_2}$ 5.0 (sd 0.6) kPa, $P_{aO_2}$ 24.0 (0.7) kPa and pH 7.42 (0.06) and did not differ between groups. Figure 1 shows an original tracing of HR, systemic arterial pressure (SAP) and actual and integrated renal sympathetic nerve activity in each group. There were concomitant reductions in HR, SAP and renal sympathetic nerve activity after administration of tubocurarine and atracurium.

Histamine produced a significant reduction in MAP at 1 min after administration, without any change in HR or renal sympathetic nerve activity (fig. 2). MAP returned to baseline values at 5 min and HR and renal sympathetic nerve activity remained unchanged throughout the observation period. Figure 3 shows the time course of changes in MAP after administration of each neuromuscular blocking agent. Atracurium and tubocurarine produced significant hypotension at 1 and 5 min and both returned to baseline values at 30 min. Vecuronium and pancuronium did not affect MAP significantly. Atracurium produced significant bradycardia 1–30 min after administration. Tubocurarine also produced bradycardia at 1 and 5 min (fig. 4). Vecuronium and pancuronium produced no significant changes in HR. Atracurium depressed significantly renal sympathetic nerve activity at 1, 5 and 30 min compared with vecuronium and pancuronium. Tubocurarine depressed significantly renal sympathetic nerve activity at 1 and 5 min compared with both vecuronium and pancuronium (fig. 5).

DISCUSSION

To our knowledge, this is the first study to show that atracurium suppressed efferent sympathetic nerve activity, attributable to a reduction in arterial pressure. Among the intermediate-acting nondepolarizing neuromuscular blocking agents available currently, vecuronium and atracurium are believed to have the least cardiovascular side effects. Administration of either in large doses has been evaluated clinically for rapid sequence tracheal intubation [1]. However, large doses of atracurium may cause profound hypotension, an effect which is believed to be caused by release of histamine.

Several investigators have attempted to attenuate the side effects of atracurium by pretreatment with $H_1$ and $H_2$ antagonists. Scott and colleagues reported that pretreatment with cimetidine 4 mg kg$^{-1}$ and chlorpheniramine 0.1 mg kg$^{-1}$ abolished cardiovascular depression caused by rapid bolus injection of atracurium 0.6 mg kg$^{-1}$ in humans [2]. However, these drugs did not prevent hypotension when atracurium 0.8 mg kg$^{-1}$ was administered after the same pretreatment [3]. Hosking and co-workers suggested that the combined use of cimetidine
4 mg kg⁻¹ and diphenhydramine 1 mg kg⁻¹ could attenuate atracurium-induced hypotension in humans and rabbits [4, 5]. In humans, however, they observed that a slight decrease in mean arterial pressure still occurred [5]. Carter reported that bradycardia developed after atracurium in four patients, in spite of hypotension, suggesting that the sympathetic compensatory mechanism may be attenuated [7]. Hughes and Chappie investigated vagal and sympathetic responses to several non-depolarizing neuromuscular blockers in animals [8, 9]. They reported that vagal block with atracurium occurred only after doses 8–16 times greater than the full paralysing dose, while the effects of atracurium on sympathetic mechanisms were minimal [10]. In contrast, our study demonstrated that approximately three times the clinical dose of atracurium decreased renal sympathetic nerve activity, arterial pressure and heart rate. Atracurium, in common with tubocurarine, is known to release histamine; this occurs when it is administered at doses approximately three times the ED₉₀ [11]. Thus it was necessary to clarify the direct effect of histamine on the sympathetic nervous system. We found that exogenously administered histamine (1 μg kg⁻¹) decreased arterial pressure by the same magnitude as atracurium, but it did not have direct effects on efferent renal sympathetic nerve activity in baroreceptor denervated dogs. Therefore, histamine released after administration of atracurium must have contributed to arterial hypotension by a direct vasodilator action, but decreased sympathetic nerve activity produced by atracurium contributed also to arterial hypotension. However, we cannot comment on the extent to which hypotension can be attributed to the direct action of histamine on vascular beds or its depressant effect on sympathetic nerve activity.

Tubocurarine is known to block sympathetic ganglia, thereby reducing efferent sympathetic nerve activity and arterial pressure [8]. Savarese studied the autonomic safety margin for tubocurarine and metocurine in cats anaesthetized with pentobarbitone and alpha-chloralose [12]. Block of the sympathetic nervous system was assessed by the nictitating membrane responses to electrical stimulation of the cervical sympathetic trunk; it was not detectable until the cumulative dose of tubocurarine reached 0.4 mg kg⁻¹. In our study, however, tubocurarine 0.3 mg kg⁻¹ produced almost 60% reduction in renal sympathetic nerve activity. This difference may be ascribed to different methodologies, different modes of administration of tubocurarine or different species.

We administered bolus doses of atracurium and vecuronium at approximately three times their clinical doses. These doses have been used to facilitate rapid tracheal intubation. Accordingly, three times the clinical dose of pancuronium was used for comparison and we found that it did not increase heart rate in these vagally denervated animals. This is a similar situation to that where prior administration of atropine attenuates or eliminates the cardiovascular effects of pancuronium [13]. The dose of tubocurarine was selected to induce the same degree of hypotension as atracurium 1.5 mg. We found that three times the clinical dose of tubocurarine, administered to animals, caused irreversible hypotension in a pilot study. Based on the literature, we administered 21 times the ED₉₀ dose for vecuronium, 14 times the ED₉₀ for pancuronium, 15 times the ED₉₀ for atracurium and twice the ED₉₀ for tubocurarine in dogs [10, 14]. The dose of histamine was chosen to induce the same degree of hypotension as atracurium and tubocurarine.

REFERENCES