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Systemic Vascular Responses to Atracurium during Enflurane–Nitrous-Oxide Anesthesia in Humans

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Systemic circulatory responses to atracurium (0.2 and 0.4 mg/kg) were studied in 15 healthy (ASA I or II) adult patients during enflurane (1.0 to 1.25% inspired) and nitrous oxide (70% inspired) anesthesia. All patients were premedicated with intramuscular morphine (10–15 mg) and glycopyrrolate (0.2 mg). Compared with control measurements during enflurane–nitrous oxide anesthesia, heart rate, cardiac and stroke index, central venous pressure, and systemic mean arterial pressure remained unchanged at 2, 5, and 10 min after administration of both doses of atracurium. Systemic vascular resistance was minimally decreased (7% compared to control) ($0.01 < P < 0.05$) at 10 min following both doses of atracurium. No patient demonstrated a decrease in systemic mean arterial pressure greater than 6 mmHg. The authors conclude that atracurium in doses which produce adequate skeletal muscle relaxation during steady-state enflurane anesthesia produces no clinically significant alteration in hemodynamic variables. (Key words: Anesthetics, volatile: enflurane. Neuromuscular relaxants: atracurium.)

ATRACURIUM is a nondepolarizing, neuromuscular relaxing drug with intermediate duration of action, lack of cumulative effect with repeated doses, possible lack of dependence on normal hepatic and renal function for metabolism and excretion, and minimal cardiovascular hemodynamic changes.[1] This lack of change of systemic vascular responses to atracurium has been studied mainly in animals and in the presence of background anesthesia (nitrous oxide, intravenous drugs) which produces minimal alterations in baseline cardiovascular hemodynamic variables. Data obtained from patients during background anesthesia (nitrous oxide, potent inhalation anesthetic drugs) that significantly alters baseline cardiovascular hemodynamic variables is needed to confirm the safety or hazard of atracurium. Therefore, we studied the systemic vascular effects of atracurium in 15 healthy, adult patients during relative constant levels of enflurane–nitrous-oxide anesthesia.

Methods

Fifteen healthy, (ASA I or II) adult patients were studied following anesthetic induction and prior to surgical stimulation. All patients gave their informed consent to participate in this study and the study protocol was approved by appropriate institutional review committees. No patient was receiving medication known to affect neuromuscular or cardiovascular function. Preanesthetic medication was with morphine (10–15 mg) and glycopyrrolate (0.2 mg) intramuscularly 60 to 90 min before induction of anesthesia. Induction of anesthesia was with thiopental (4–6 mg/kg) immediately followed by the inhalation of nitrous oxide (70% inspired) and enflurane (1.0 to 1.25% inspired). Intubation of the trachea was accomplished without muscle relaxants.

Peripheral intravenous cannulae were placed for fluid and drug infusion. A radial arterial cannula was inserted for measurement of arterial blood pressure, blood-gas sampling, and cardiac output (CO) determination. A central venous catheter was inserted through the right internal jugular vein for recording mean right atrial pressure ($\overline{RAP}$) and for injecting indocyanine dye for determination of CO by the dye-dilution technique. Heart rate (HR) was calculated from the electrocardiogram. Systemic vascular resistance (SVR) as $dyn \cdot s \cdot cm^{-5}$ was calculated as follows: $SVR = MAP - RAP \times 80 \div CO$. Cardiac index (CI) was calculated by dividing CO by body surface area, and stroke index (SI) was determined by dividing CI by HR.

Control measurements were obtained after patients breathed enflurane and nitrous oxide for 30 min and achieved a stable heart rate and systemic arterial pressure. Following control measurements, seven patients (27 ± 2 years, 83 ± 5 kg, mean ± SEM) received atracurium (0.2 mg/kg) and eight patients (32 ± 6 years, 75 ± 3 kg) received atracurium (0.4 mg/kg) in random fashion as an intravenous bolus injection. All measurements were repeated at 2, 5, and 10 min following atracurium administration. Arterial blood-gas tensions and *p*H were determined two minutes following atracurium administration. Prior to anesthetic induction, each patient received lactated Ringer's solution ($1.5\ ml \cdot kg^{-1} \cdot h^{-1}$) to replace any fluid deficit incurred through fasting the night before surgery. Ventilation was controlled during the entire study period. All measurements were made at end-expiration. Data within each dose group were analyzed by two-way analysis of variance without interaction and Dunnet's test. Data (age, weight, arterial blood gases) between dose groups were analyzed using unpaired Student's *t* test. $P < 0.05$ was considered statistically significant.

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TABLE 1. Hemodynamic Changes Following Administration of Atracurium (0.2 mg/kg) to Healthy Adult Patients (Mean ± SEM)

	Time after injection (min)			
	Control	2	5	10
Heart rate (beats/min)	70 ± 4	71 ± 4	72 ± 3	70 ± 3
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	2.74 ± 0.13	2.68 ± 0.12	2.73 ± 0.14	2.84 ± 0.14
Stroke index ($ml \cdot min^{-1} \cdot m^{-2}$)	39.5 ± 2.3	37.8 ± 2.0	38.4 ± 2.0	40.7 ± 2.4
Systemic arterial pressures (mmHg)				
Systolic	84 ± 2	84 ± 2	83 ± 2	83 ± 2
Diastolic	54 ± 2	53 ± 1	53 ± 2	52 ± 2
Mean	63 ± 1	63 ± 1	62 ± 1	62 ± 2
Mean right atrial pressure (mmHg)	7.6 ± 0.9	7.1 ± 0.9	7.0 ± 0.9	7.1 ± 1.0
Systemic vascular resistance ($dyn \cdot s \cdot cm^{-5}$)	822 ± 61	836 ± 63	810 ± 61	763 ± 54*

* Significant ($0.01 < P < 0.05$) difference between control and value obtained following atracurium administration.

Results

Data are summarized in tables 1 and 2. Compared with control measurements, the administration of atracurium (0.2 or 0.4 mg/kg) resulted in no statistically significant change in heart rate, cardiac and stroke index, mean right atrial pressure, and systemic mean arterial pressure at 2, 5, or 10 min following drug administration ($P > 0.05$). Systolic arterial pressure was decreased minimally at 2, 5, and 10 min compared with control measurements following atracurium (0.4 mg/kg) ($0.01 < P < 0.05$). Likewise, SVR was decreased minimally at 10 min compared with control measurements following both doses of atracurium ($0.01 < P < 0.05$). However, no significant difference was demonstrated between the SVR values at 10 min following atracurium administration in either drug dose group, suggesting the SVR changes are not dose-related but rather an anesthetic effect. No patient demonstrated a decrease in systemic mean or systolic arterial pressure greater than 6 mmHg. The mean Pa_{CO_2} and *p*H values for both groups were within normal limits. Furthermore, no statistically significant difference existed between the two atracurium dose groups comparing arterial blood-gas tensions and *p*H values. Likewise, patient age and weight were not significantly different between the two dose groups.

Discussion

The effect of atracurium on the systemic circulation in humans has not been studied extensively. During halothane (1% inspired) and oxygen anesthesia, Payne and Hughes[2] observed insignificant changes in heart rate and systemic mean arterial pressure following atracurium (0.2 to 0.6 mg/kg) administration to nine patients. In other clinical trials, supramaximal doses (0.5 to 0.6 mg/kg) of atracurium have caused hypotension and skin flushing in several patients.[3] Our study of 15 healthy, adult patients determined the systemic circulatory responses to doses of atracurium previously determined to produce adequate skeletal muscle relaxation (ED_{95} approximately equals 0.2 mg/kg) and adequate intubating conditions (twice ED_{95} approximately equals 0.4 mg/kg) in the absence of volatile anesthetic drugs.[2,3] At these doses, atracurium produced no clinically significant alterations in either measured or calculated hemodynamic variables. These results are similar to those determined following metocurine administration during halothane or enflurane anesthesia in that HR, MAP, CI, RAP, and SVR did not demonstrate any significant change.[4,5] However, metocurine (0.2 mg/kg) produced decreases in MAP greater than 20 mmHg in four of 20 patients.[4] In our study, no patient demonstrated a decrease in MAP greater than 6 mmHg

TABLE 2. Hemodynamic Changes Following Administration of Atracurium (0.4 mg/kg) to Healthy Adult Patients (Mean ± SEM)

	Time after injection (min)			
	Control	2	5	10
Heart rate (beats/min)	72 ± 5	74 ± 4	73 ± 4	72 ± 4
Cardiac index ($l \cdot min^{-1} \cdot m^{-2}$)	3.10 ± 0.16	3.26 ± 0.23	2.99 ± 0.15	3.18 ± 0.18
Stroke index ($ml \cdot min^{-1} \cdot m^{-2}$)	43.3 ± 2.8	43.7 ± 3.7	41.4 ± 2.5	45.0 ± 4.3
System arterial pressures (mmHg)				
Systolic	85 ± 6	83 ± 5*	83 ± 6*	83 ± 6*
Diastolic	52 ± 3	52 ± 3	51 ± 3	51 ± 3
Mean	62 ± 4	61 ± 4	61 ± 4	61 ± 4
Mean right atrial pressure (mmHg)	8.0 ± 1.2	8.2 ± 1.2	8.0 ± 1.3	8.2 ± 1.3
Systemic vascular resistance ($dyn \cdot s \cdot cm^{-5}$)	740 ± 58	700 ± 56	744 ± 47	687 ± 49*

* Significant ($0.01 < P < 0.05$) difference between control and value obtained following atracurium administration.

following doses of atracurium producing similar degrees of skeletal muscle relaxation. In this regard, atracurium is less likely to produce undesirable systemic circulatory changes compared to metocurine.

The systemic vascular responses to atracurium have been studied in animals. When administered to cats, atracurium (0.125 to 1.0 mg/kg) produced insignificant decreases in MAP while heart rate remained unchanged. However, significant hypotension (greater than 30% decrease) and slight bradycardia were observed after 4 mg/kg, a dose 20 times the estimated ED_{95} for muscle relaxation in the cat. These systemic circulatory responses were felt to be related to histamine release since these responses could be attenuated by H_1- and H_2-receptor antagonists. Similar results have been obtained in other animals (monkeys and dogs).[1]

Our results also contrast previous findings obtained during *d*-tubocurarine and pancuronium administration. Stoelting[6] observed the MAP during halothane–nitrous-oxide anesthesia to decrease 25 mmHg following *d*-tubocurarine (0.4 mg/kg) while HR increased slightly. These changes were maximal at 3 min and returned to near control values by 10 to 20 min. These changes were attributed to histamine release and sympathetic ganglionic block. A comparable dose of pancuronium (0.08 mg/kg) increased MAP and HR approximately 10 mmHg and 10 beats/min, respectively. Although the MAP returned to near control values by 10 to 20 min, the HR remained elevated throughout the study period. CO also was elevated as a result of the increased HR. These changes were speculated to result from a vagolytic and/or sympathomimetic effect of pancuronium. In our study, comparable doses of atracurium (0.2 mg/kg) did not change HR, MAP, CI, or RAP. This indicates that atracurium, at clinically effective doses, produces minimal alterations in autonomic nervous system activity. Indeed, significant autonomic effects in animals were observed only at doses of atracurium eight to ten times the dose required to produce full muscle relaxation.[1]

Surgical stimulation, blood volume, anesthetic depth, and background anesthesia may alter hemodynamic responses to muscle relaxants. In our study, surgical stimulation was absent. Blood volume was judged to be normal since the patients were healthy and had normal hematocrits. Furthermore, fluid deficits incurred through fasting the night before surgery were replaced with lactated Ringer's solution. End-tidal enflurane concentration was not measured in this study. However, we would predict that anesthetic depth was similar for all patients since the inspired concentration and duration of enflurane administration before atracurium administration were similar for all patients. Background anesthesia may influence the circulatory responses to muscle relaxants. Indeed, Savarese *et al.*[7] observed no significant decreases in MAP in 11 patients (0%) following metocurine (0.2 mg/kg) during nitrous-oxide–morphine–thiopental anesthesia, while Stoelting[4] observed significant decreases in MAP in four of 20 patients (20%) during halothane–nitrous-oxide anesthesia following the same dose of metocurine. Study groups for both investigators were similar except for background anesthesia. Our study was conducted in the presence of enflurane–nitrous-oxide anesthesia which suggests stable cardiovascular responses are predictable following atracurium administration, even in the presence of potent inhalation anesthetic drugs.

The clinical significance of stable circulatory responses with atracurium are obvious. For example, patients with severe systemic illnesses (*e.g.*, sepsis, anemia, dehydration) or limited cardiac reserve depend on maintaining normal cardiovascular hemodynamics in order to minimize the likelihood of developing tissue hypoxia or myocardial ischemia.' Our results were obtained in healthy patients. Patients with severe systemic illnesses or limited cardiac reserve may respond differently to atracurium. Nevertheless, our results indicate atracurium given in clinically effective doses results in minimal cardiovascular hemodynamic changes in healthy patients.

In summary, the systemic vascular responses to atracurium during controlled ventilation in healthy adult patients during enflurane–nitrous-oxide anesthesia revealed no clinically significant change in any measured or calculated hemodynamic variable. This stable circulatory hemodynamic pattern of atracurium may provide a desirable choice for patients with severe systemic illness or limited cardiac reserve.

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