The Cardiovascular Effects of Atracurium and it's Metabolite

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The administration of atracurium to humans has been reported to produce little cardiovascular effects in clinical doses. The cardiovascular effect, histamine-releasing and catecholamine releasing effects of intravenous injection of atracurium 0.6 and 1.2 $mg \cdot kg^{-1}$ were studied in man, and also the cardiovascular and catecholamine releasing effects of laudanosine which is a metabolite of atracurium by Hofmann degeneration, were studied in dogs. The increase in human plasma concentration of histamine, hypotension and tachycardia were found with the dose of atracurium 1.2 $mg \cdot kg^{-1}$. The intravenous administration of laudanosine 10 $\mu g \cdot kg^{-1}$ to dogs produced minimal epinephrine, norepinephrine releases and cardiovascular changes. (Key words: Cardiovascular effects, atracurium, Laudanosine, histamine and catecholamine release)

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Atracurium which is a new non-depolarizing neuromuscular blocking drug, has a short duration of action and minimal cardiovascular effects[1–3]. However, Basta[4] reported that atracurium causes a dose-dependent histamine-releasing and cardiovascular effects. The drug was designed to undergo rapid chemical inactivation by Hofmann elimination at physiological pH and temperature. The major metabolite of atracurium is laudanosine which has been demonstrated convulsant and cardiovascular depressant effects[5]. Nagashima, et al.[6] reported that laudanosine produces vagal block with slight tachycardia and catecholamine release from the right atria of guinea-pigs. The present studies were designed to investigate histamine-releasing potencies of atracurium and mechanism of the cardiovascular effects of atracurium and of it's metabolite laudanosine in human and in dogs.

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Methods

1. In clinical studies

22 surgical patients (age 48.3 ± 2.9 years) classified ASA status 1–2 were studied after obtained the informed consents. Anesthesia was induced with intravenous injection of thiopental (5 $mg \cdot kg^{-1}$) and patients were ventilated with N_2O 4 $\ell \cdot min^{-1}$ and O_2 2 $\ell \cdot min^{-1}$ via mask inhalation. Atracurium 0.6 or 1.2 $mg \cdot kg^{-1}$ was administered intravenously to the patients. Arterial blood samples were collected for measurement of plasma concentration of histamine in 12 patients and catecholamine (epinephrine and norepinephrine) in 10 patients prior to and at 1, 3, 5, 10 and 15 min following the administration of atracurium. All blood samples were centrifuged, and the plasma was stored at −40°C until analyzed. Serum concentrations of histamine were measured using

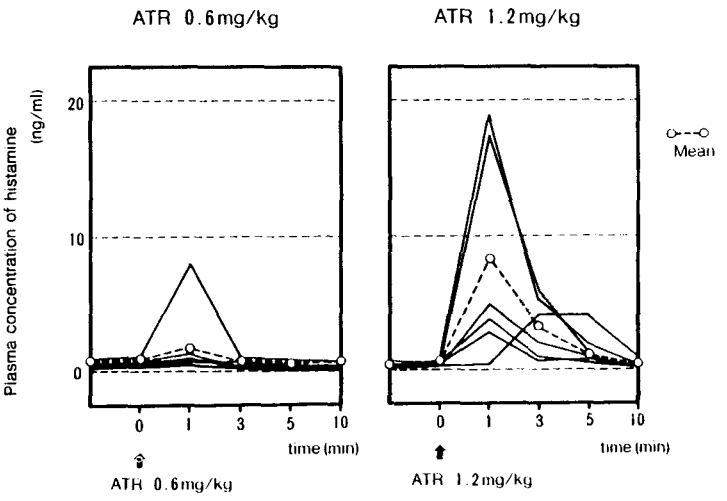

Fig. 1. Plasma histamine following administration of atracurium (ATR)

the modified single radioenzymatic assay described by Beaven[7] and the concentration of epinephrine and norepinephrine were measured using high performance liquid chromatography (HPLC). In addition, arterial blood pressure (BP), heart rate (HR) were monitored continuously and cutaneous signs were observed during the study. Sensitivity of assays for histamine is 0.1 ng·ml^{-1} in single enzymatic isotope procedure and 0.01 ng·ml^{-1} for catecholamine in HPLC.

2. In animal studies

6 dogs, weighing 10–13 kg, were studied. Anesthesia was induced with intravenous thiopental (5 mg·kg^{-1}) and the trachea was intubated. Anesthesia was maintained with 0.5% halothane ($F_{I_{O_2}} = 0.3$) and ventilation was controlled to maintained Pa_{CO_2} between 35 to 45 mmHg. Femoral artery catheterization was performed to measure BP and to provide access for blood sampling. Femoral vein was secured for administration of laudanosine and maintenance of fluid (lactaded Ringer 12 ml·kg^{-1}·hr^{-1}). Swan-Ganz cannule was inserted through right external jugular vein for measurement of pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP) and cardiac output (CO). Systemic vascular and pulmonary vascular resistances (SVR and PVR) were calculated. Laudanosine 10 μg·kg^{-1} was administered as an intravenous bolus. Blood samples were obtained prior to and at 1, 3, 5, 10 and 20 min following injection. Blood samples were centrifuged below 0°C and plasma was stored at −40°C until analyzed. Serum concentrations of epinephrine and norepinephrine were measured using HPLC.

Values within each group were compared to the control values using paired t test. For all statistical comarisons, differences were considered significant at a $P < 0.05$.

Results

1. In clinical studies

The plasma concentration of histamine increased in one of six patients 1 min after atracurium 0.6 mg·kg^{-1} injection, however, there was no change in other five patients. With dose of 1.2 mg·kg^{-1} atracurium, the plasma histamine level increased in all six at 1 to 5 min following the injection (fig. 1). HR, systolic and diastolic BP (SBP and DBP) were not changed in the dose of atracurium 0.6 mg·kg^{-1}, however, with dose of 1.2 mg·kg^{-1}, HR increased at 1 to 5 min, and SBP and DBP decreased significantly 1 min after the injection.

Although plasma concentration of histamine increased slightly from 0.362 ± 0.035 ng·ml^{-1} (mean ± SE) of control to 1.871 ± 1.185 ng·ml^{-1} 1 min after atracurium 0.6 mg·kg^{-1} injection, there was no significant difference due to wider variability in measured values of histamine. The plasma

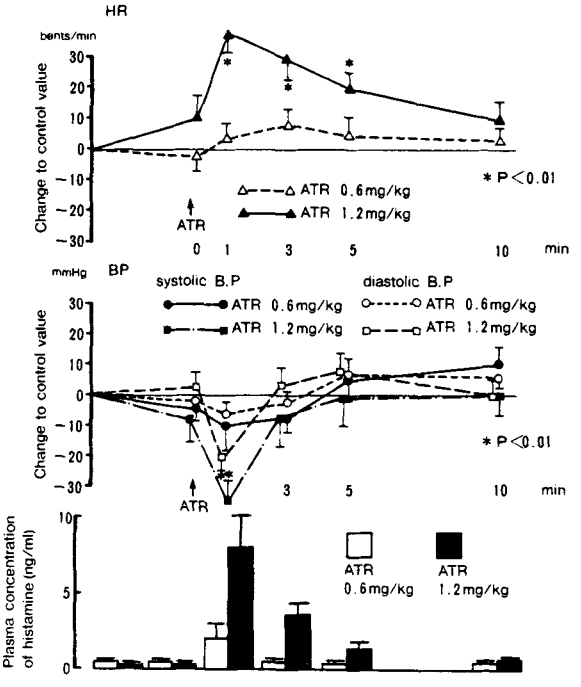

Fig. 2. Effects of atracurium on blood pressure, heart rate and plasma histamine concentration

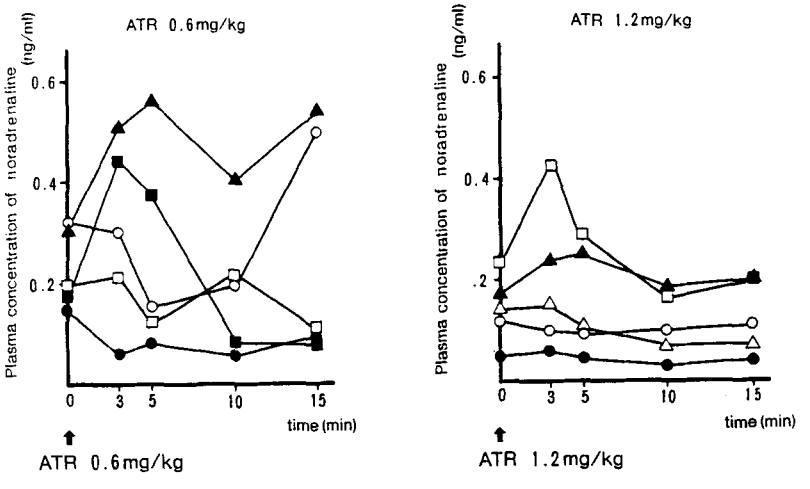

Fig. 3. Plasma noradrenaline following administration of atracurium (ATR)

histamine level increased from 0.303 ± 0.090 $ng \cdot ml^{-1}$ of control to 8.141 ± 2.990 $ng \cdot ml^{-1}$ 1 min after atracurium 1.2 $mg \cdot kg^{-1}$ injection (fig. 2). Skin rash over the chest was observed in two patients with the dose of 0.6 $mg \cdot kg^{-1}$ and in three patients with dose of 1.2 $mg \cdot kg^{-1}$.

Significant increase of epinephrine and norepinephrine was not demonstrated, however, in two of five cases in both groups, which were given atracurium 0.6 or 1.2 $mg \cdot kg^{-1}$, respectively, the concentration of norepinephrine increased.

2. In animal studies

The plasma concentration of epinephrine and norepinephrine increased in one of six dogs following intravenous administration of laudanosine 10 $\mu g \cdot kg^{-1}$ (fig. 4), but sta-

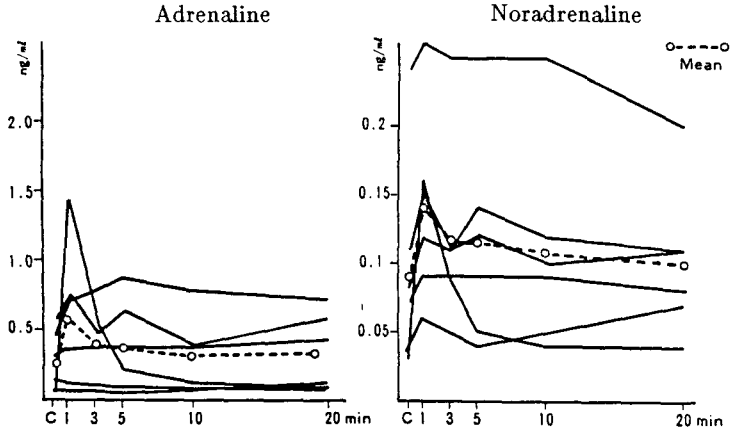

Fig. 4. Plasma level of adrenaline and noradrenaline following administration of laudanosine 10 $\mu g \cdot kg^{-1}$ in Dog

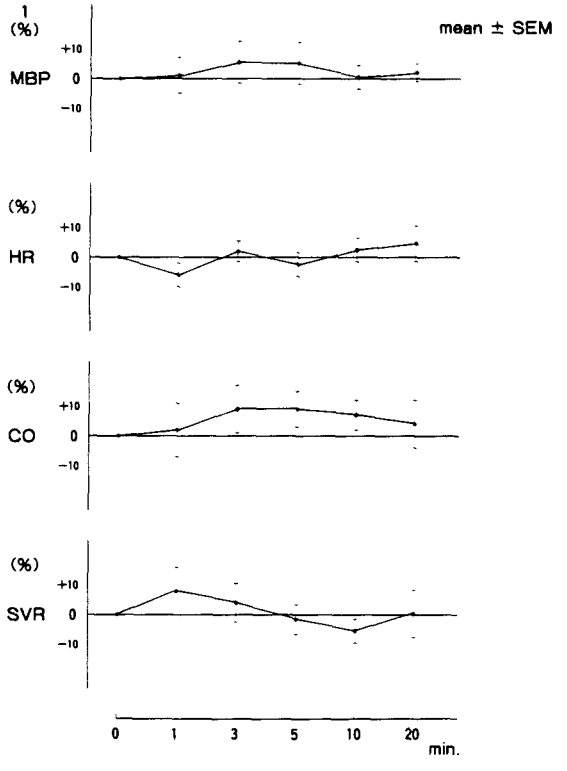

Fig. 5. Influence of laudanosine on mean arterial blood pressure, heart rate cardiac output and systemic vascular resistance. (Laudanosine 10 $\mu g \cdot kg^{-1}$ administered at 0 min, 1: change of percent)

tistically there was no significant difference from the control values. Mean BP (MBP), HR, CO, SVR, mean PAP (MPAP), PVR, PCWP and CVP were not changed following the laudanosine injection (fig. 5 and 6).

Discussion

One of major reasons for developing new neuromuscular blocking agents is that all currently used drugs have more or less cardiovascular effects, some of which may be related to the release of histamine or catecholamine[4,8]. Atracurium has been shown to have little cardiovascular effect in clinical doses. In our studies, no cardiovascular effect was demonstrated in the patients anesthetized with nitrous oxide and oxygen following the intravenous injection of 0.6 $mg \cdot kg^{-1}$ of atracurium. Coincidently, Payne and Huges[3] also demonstrated that there

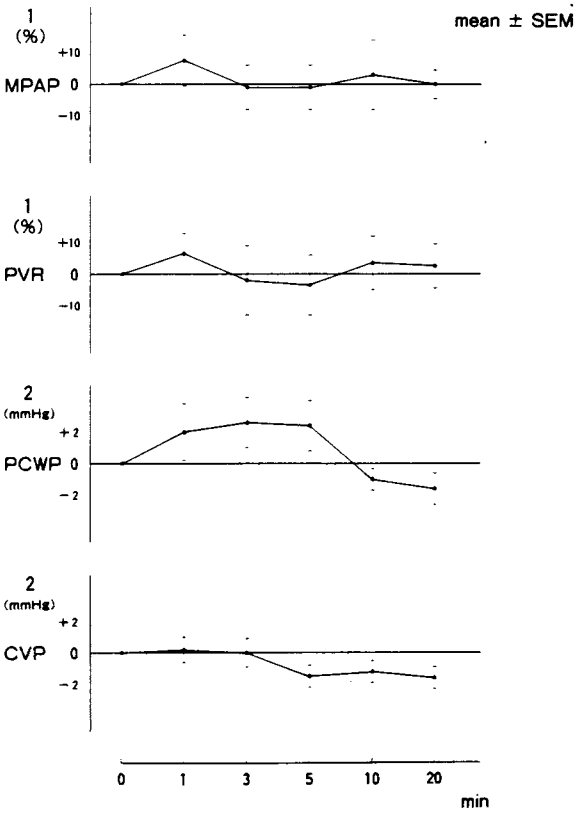

Fig. 6. Influence of laudanosine on mean pulmonary arterial pressure, pulmonary vascular resistance, pulmonary capillary wedge pressure and central venous pressure. (Laudanosine 10 $\mu g \cdot kg^{-1}$ administered at 0 min. 1: change of percent. 2: change of mmHg)

were no remarkable changes in BP and HR following the injection of 0.6 $mg \cdot kg^{-1}$ of atracurium. However, significant decreases in BP and increase in HR were found when 1.2 $mg \cdot kg^{-1}$ of atracurium was administered. BP returned to the control within 3 min and tachycardia lasted for 10 min. There was difference between recovery time of BP and that of HR.

It has been reported that normal plasma concentration of histamine ranged from 0.6 to 1.0 $ng \cdot ml^{-1}$.[2] In our data, the concentration of histamine was almost within normal range following atracurium 0.6 $mg \cdot kg^{-1}$ injection, but increased significantly 1 to 5 min after 1.2 $mg \cdot kg^{-1}$ injection. These findings indicate that hypotension and tachycardia induced by atracurium is quantitatively related to the level of plasma histamine. Hypotension and plasma histamine level were also correlated with the dose of administered atracurium. The hypotension recovered within 3 min in spite of a high plasma concentration of histamine. From these clinical findings it seems that vasoactive substances such as catecholamine were released during increased plasma concentration of histamine and these substances may mask the activity of released histamine. Nagashima et al.[6] reported that atracurium and it's metabolite, laudanosine enhanced the evoked release of ^{3}H-norepinephrine in the right atria of guinea pig. Oxotremorine, which acts as a potent muscarinic agonist, significantly depressed the evoked release of ^{3}H-norepinephrine, and gallamine, pancuronium and atracurium antagonized the action of oxotremorine.[9,10]

Plasma level of 1.9 to 5.1 $\mu g \cdot ml^{-1}$ (7 to 18 μM) of laudanosine was found in patients after either intravenous bolus injection 0.5 $mg \cdot kg^{-1}$ or continuous infusion of 0.8 $mg \cdot kg^{-1} \cdot min^{-1}$ atracurium[10]. These laudanosine concentration are in the same range as those which caused significant increase of evoked release of norepinephrine in in vitro

studies[9]. Therefore, we speculated that increased release of ^{3}H-norepinephrine in the atrium preparations of guinea-pig following exposure of atracurium might be caused by laudanosine. However, in our clinical studies no increase of plasma concentration of catecholamine was demonstrated following the intravenous injection of atracurium. Also in the animal studies, there were no change in the concentration of catecholamine and hemodynamics with 10 $\mu g \cdot kg^{-1}$ laudanosine.

We concluded that an increase in plasma histamine is dose-dependent with the administration of atracurium, and is significantly correlated with hypotension and tachycardia. Catecholamine release due to atracurium and laudanosine was not confirmed in this study.

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