

Contribution of Prostacyclin to D-tubocurarine-Induced Hypotension in Humans

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In order to evaluate the role of prostacyclin in d-tubocurarine-induced hypotension in human, the authors examined the relationship of changes of arterial blood pressure and plasma 6-keto-PGF_{1α} level following iv administration of d-tubocurarine (dTc), with or without prior administration of aspirin and H₁ antagonist. The bolus injection of dTc 0.6 mg/kg caused a significant decrease in mean arterial pressure (MAP) that was associated with a significant increase in plasma 6-keto-PGF_{1α} ($P < 0.05$ in both). The maximum MAP decrease and plasma 6-keto-PGF_{1α} increase were noted at 2 min after dTc administration. Pretreatment with aspirin DL-lysine (25 mg/kg) or diphenhydramine (1 mg/kg) significantly attenuated the responses of MAP ($P < 0.05$ in both) and plasma 6-keto-PGF_{1α} level ($P < 0.01$ for aspirin group, $P < 0.05$ for diphenhydramine group). There was a significant correlation between the changes in plasma 6-keto-PGF_{1α} and those in MAP (Kendall tau (τ) = -0.504 , $P < 0.01$). These findings suggest that a bolus injection of dTc induces a release of prostacyclin through H₁ receptor, which is responsible for the dTc-induced transient decrease of blood pressure in humans. (Key words: Complications: hypotension. Hormones: prostacyclin. Neuromuscular relaxants, d-tubocurarine. Pharmacology, histamine: antagonists.)

IT HAS BEEN SUGGESTED that in humans, histamine release is the major factor in the dTc-induced hypotension.¹ Supporting this concept, our previous study demonstrated that the pretreatment with histamine H₁ but not H₂ antagonist significantly attenuated the transient hypotension following dTc administration in healthy surgical patients.² Inada *et al.* also reported a partial prevention by a mixture of H₁ and H₂ histamine antagonists of the dTc-induced hemodynamic changes in cardiac surgical patients with ischemic heart disease.³ It has been shown that histamine activates phospholipase A₂, the enzyme-releasing arachidonic acid from membrane phospholipids, and releases prostacyclin.⁴⁻⁶ Prostacyclin, with a half-life of about 3 min,⁷ is the most potent vasodilator of cyclooxygenase products of arachidonic acid,^{8,9} and is nonenzymatically converted to 6-keto-prostaglandin-(PG)F_{1α}.¹⁰ The release of prostacyclin from vascular endothelium, a major source

of prostacyclin, has been shown to be mediated *via* the H₁ receptor.^{4,5,11} The present study attempts to clarify the role of prostacyclin in dTc-induced hypotension and to evaluate the effects of aspirin and an histamine H₁ antagonist on prostacyclin release.

Methods

After institutional approval, 21 patients (ASA physical status 1 or 2), of either sex, age 20-50 yr, who were undergoing peripheral orthopedic, gynecologic, or mandibulofacial surgery, were studied. Informed consent was obtained from each patient. The patients had no history of allergy, hypertension, diabetes mellitus, and cardiopulmonary disease. They were randomly divided into three groups: control, aspirin (AP)-treated, and diphenhydramine (DH)-treated groups. All patients received oral diazepam 10 mg and im atropine sulfate 0.5 mg, 60 and 30 min before induction of anesthesia, respectively. In the AP-treated group, aspirin DL-lysine 25 mg/kg, (Venopirin[®], an iv preparation [900 mg/vial] of aspirin consisting of 497 mg aspirin and 403 mg DL-lysine, The Green Cross Corporation, Osaka, Japan) was given intravenously 30 min before induction of anesthesia. A radial artery was cannulated under local anesthesia for measurement of arterial pressure and blood sampling. After stabilization of blood pressure and heart rate, diphenhydramine 1 mg/kg was given to patients in the DH-treated group. One minute after the administration of diphenhydramine, anesthesia was induced with fentanyl (3 μg/kg), thiopental (6 mg/kg), and N₂O/O₂ (1:1), and ventilation was assisted using face mask to maintain end-tidal CO₂ at approximately 30 mmHg throughout the study. Five minutes after thiopental, dTc 0.6 mg/kg was given as a bolus. Arterial blood pressure and heart rate were continuously monitored, and blood samples for the measurement of 6-keto-PGF_{1α} were taken immediately before, 2, and 6 min after dTc administration. Blood gas analysis was done immediately before and 10 min after dTc administration.

In order to avoid artifactual release of prostaglandins, the blood samples for measuring 6-keto-PGF_{1α} were collected using a 10-ml disposable syringe containing 100 μl of 10⁻⁵ M indomethacin. The mixture was transferred to a 14-ml iced plastic shaking tube to which 200 μl of EDTA-2Na stock solution (7.5% W/V) was added to prevent coagulation. The samples were centrifuged at 300 rpm

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at 4° C for 10 min. After centrifugation, 4 ml of the aqueous phase was aspirated and frozen immediately in dry ice. The samples were stored at -80° C. The concentration of plasma 6-keto-PGF_{1α} was measured by the radioimmunoassay method after extraction by passage through "Sep-Pak" C₁₈ cartridges (Waters Associate).¹² The detection limit of this method was 10 pg/ml of 6-keto-PGF_{1α}. The inter- and intra-assay coefficients of variation were within 5%. The assay for each sample was done in triplicate. The recovery rate of 6-keto-PGF_{1α} to plasma was 71% and all results in this paper were corrected for recovery.

Data were expressed as the mean ± SE. However, no assumption was made regarding the distribution of the data, and all statistical tests used were for nonparametric data. For each of the categories of data (plasma 6-keto-PGF_{1α}, MAP, and HR), the variation within each group was analyzed by the Friedman statistic followed by the Wilcoxon signed rank test, and the variation between groups was analyzed by the Kruskal-Wallis one-way analysis of variance followed by the Mann-Whitney rank sum test. The correlation between the changes in 6-keto-PGF_{1α} and those in MAP was also analyzed nonparametrically using the Kendall's rank correlation coefficients. A value of *P* < 0.05 was considered statistically significant.

Results

There was no significant difference between the three groups in sex distribution, weight, and age. MAP just before induction of anesthesia in the control, AP-treated, and DH-treated groups were 110 ± 4.1 mmHg (n = 7), 105.5 ± 7.1 mmHg (n = 6), and 100.7 ± 3.3 mmHg (n = 7), respectively, which were not significantly different. The MAP, HR, and plasma concentration of 6-keto-PGF_{1α} following dTc administration are summarized in table 1. In control group, the administration of dTc (0.6 mg/kg)

caused a rapid and significant decrease in MAP, reaching the maximum decrease in 2 min, and thereafter, the MAP gradually returned toward the preadministration level. Phenylephrine 0.2 mg was administered in two patients of the control group, whose systolic blood pressure fell to 50 mmHg at 2 min after dTc administration. In the AP-treated and DH-treated group, MAP decreased to a lesser extent than that in control group. HR increased significantly in control and AP-treated groups following dTc administration. Plasma 6-keto-PGF_{1α} level increased significantly at 2 min after dTc administration (*P* < 0.01) and returned toward baseline level within 6 min. The increase in plasma 6-keto-PGF_{1α} level 2 min following dTc was significantly less in the AP- and DH-treated groups than in control group (*P* < 0.01 and *P* < 0.05, respectively). Plasma 6-keto-PGF_{1α} level in the AP-treated group tended to decline further from baseline even after dTc administration. The response of plasma 6-keto-PGF_{1α} concentrations of individual patients are shown in figure 1. The percent changes in MAP and those in plasma level of 6-keto-PGF_{1α} 2 min following dTc administration are shown in figure 2. Calculation of Kendall's rank correlation coefficients confirmed that significant relationship exists between the changes in 6-keto-PGF_{1α} and those in MAP at 2 min after dTc administration (*T* = -0.504, *P* < 0.01).

PaCO₂ and pH values immediately before and 10 min after administration of dTc did not differ significantly and these values were comparable between two groups. PaO₂ values before and after dTc were over 200 mmHg in both groups.

Discussion

Pharmacological studies with selective H₁ and H₂ receptor antagonists have shown that the histamine-induced hypotension consists of two components as follows.¹³⁻¹⁵

TABLE 1. Hemodynamic and Plasma 6-Keto-PGF_{1α} Responses to dTc Administration

		N	Minutes after dTc Administration			
			0	2	6	10
MAP (mmHg)	Control	7	105.3 ± 6.8	54.1 ± 6.4*‡	81.4 ± 8.6	91.4 ± 7.5
	AP-Treated	6	91.0 ± 8.5	81.5 ± 8.5†‡	87.5 ± 7.4	90.0 ± 6.9
	DH-Treated	7	88.1 ± 4.8	78.4 ± 4.0†‡	81.0 ± 3.2	84.7 ± 3.1
HR (bpm)	Control	7	77.9 ± 4.9	93.0 ± 6.5*‡	83.4 ± 7.6	78.7 ± 7.0
	AP-Treated	6	75.3 ± 4.6	86.7 ± 6.9*‡	78.3 ± 6.3	74.2 ± 6.2
	DH-Treated	7	84.7 ± 3.5	88.6 ± 4.4	82.4 ± 4.0	78.0 ± 3.2
6-keto-PGF _{1α} (pg/ml)	Control	7	121.4 ± 16.0	264.3 ± 25.2*‡	158.6 ± 17.4	—
	AP-Treated	6	149.0 ± 18.1	140.5 ± 18.0†§	123.3 ± 15.6	—
	DH-Treated	7	142.9 ± 7.8	170.6 ± 17.3†§	147.9 ± 15.5	—

MAP = mean arterial pressure. HR = heart rate. dTc = d-tubocurarine. DH = diphenhydramine. N = number of subjects studied.

* Compared to the value before dTc administration.

† Compared to control.

‡ *P* < 0.05.

§ *P* < 0.01.

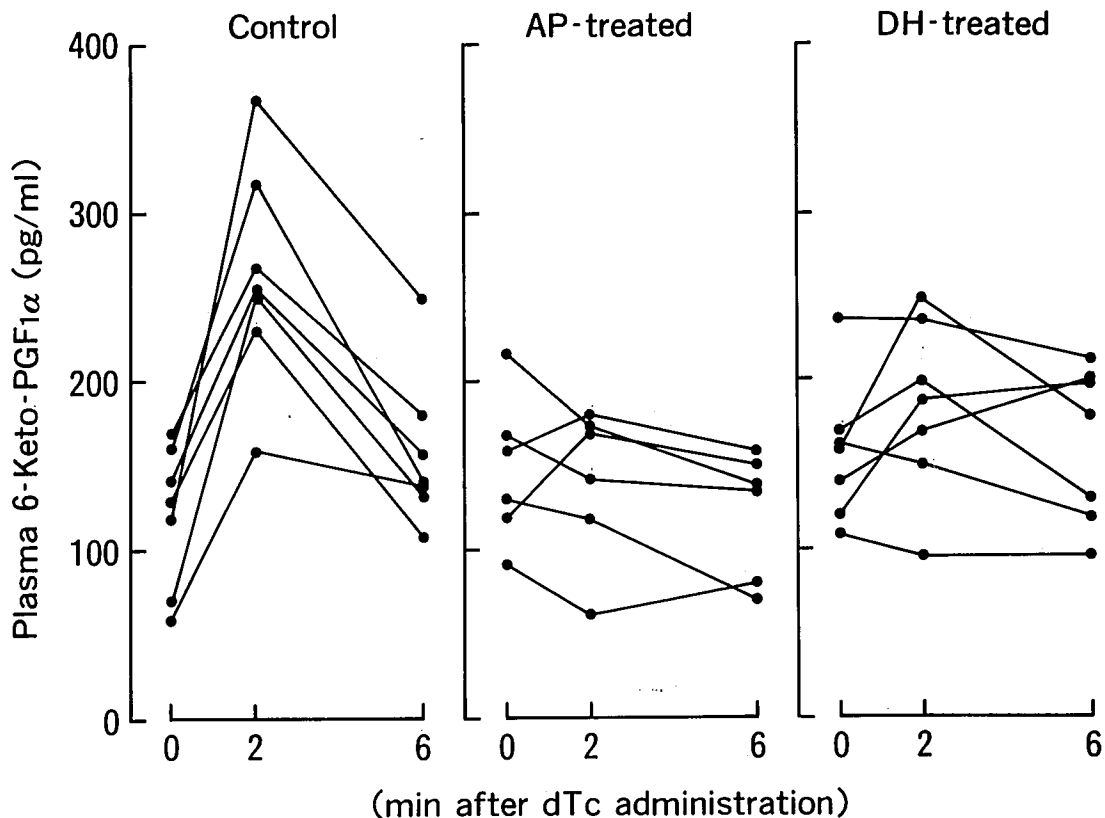


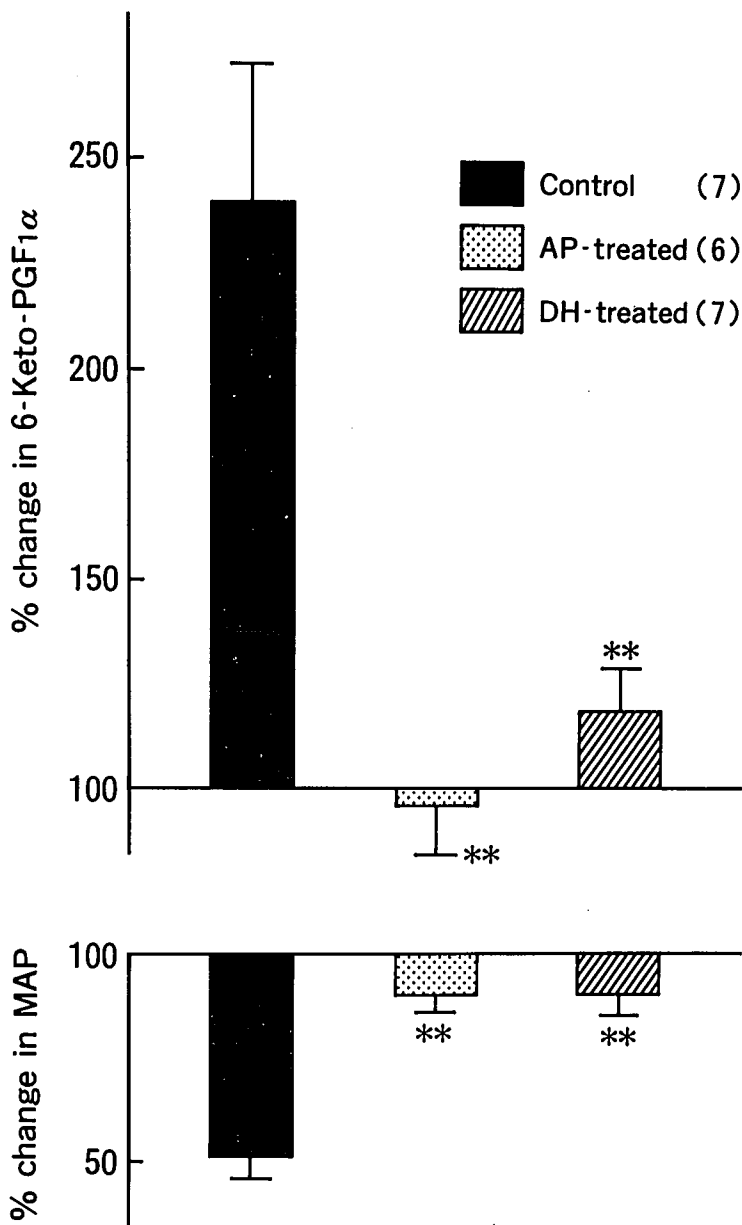
FIG. 1. Plasma 6-keto-PGF_{1α} concentrations before and after dTc administration in control (left), aspirin-treated (middle), and diphenhydramine-treated (right) patients.

A continuous infusion of histamine induces an immediate decrease followed by a sustained decrease in arterial pressure. An H₁ receptor antagonist significantly inhibits the initial decrease, leaving the later sustained phase unaffected. An H₂ antagonist, on the other hand, blocks the later sustained phase, leaving the initial phase unaffected. These indicate that the initial phase is mediated by H₁ receptor and the sustained phase by H₂ receptor.¹³⁻¹⁵ The initial phase occurs even following a small dose of histamine injection or infusion, while the later phase occurs only when histamine is supplied continuously.¹⁵ In the case of a morphine infusion, which causes a sustained elevation of plasma histamine and a sustained hypotension, both H₁ and H₂ receptors are involved, and thus pretreatment with both H₁ and H₂ antagonists is necessary to block the entire response.¹⁶ In contrast, the administration of dTc as a bolus injection, at doses of 0.6 mg/kg or less has been shown to induce a rapid but transient increase in plasma histamine.¹ Thus, as seen in our previous study,² the pretreatment with diphenhydramine, a H₁ antagonist, alone effectively attenuated the hypotensive response to dTc bolus injection, while pretreatment with cimetidine alone did not affect it; the results with diphenhydramine is consistent with those obtained in the

present study. It is suggested that H₁ receptors but not H₂ receptors are involved in the transient hypotension induced by dTc bolus injection.

It is well known that prostacyclin, when given intravenously, induces a transient hypotension associated with peripheral vasodilation in animals and humans.¹⁷⁻¹⁹ Measuring plasma 6-keto-PGF_{1α}, a stable product of prostacyclin, Seltzer *et al.*²⁰ has demonstrated an important role of prostacyclin in the hypotension induced by mesenteric traction during surgery. In the present study, the plasma concentration of 6-keto-PGF_{1α} before dTc administration ranged from approximately 100–200 pg/ml; these concentrations are consistent with the normal range reported by Machin *et al.*²¹ and are also comparable to those before mesenteric traction in the surgical patients anesthetized with isoflurane, fentanyl, and nitrous oxide.²⁰ The administration of dTc as a bolus injection induced a significant increase (2.3-fold) in 6-keto-PGF_{1α}, in association with a significant decrease in MAP. The time course of the change of MAP paralleled that of 6-keto-PGF_{1α} concentration. Pretreatment with aspirin, a well-known cyclooxygenase inhibitor, abolished the increase of plasma 6-keto-PGF_{1α} following dTc injection, and prevented decrease in blood pressure. Further, there was a significant

FIG. 2. Changes (%) in plasma 6-keto-PGF_{1α} concentration and in MAP 2 min following dTc administration in control (left), aspirin-treated (middle), and diphenhydramine-treated (right) patients. The values just before dTc administration were taken as 100%. Figures in parenthesis indicate the number of patients studied. ***P* < 0.01, significantly different from control.



correlation between the changes in 6-keto-PGF_{1α} and those in MAP. These suggest that prostacyclin is the vasodilating substance responsible for the hypotension induced by dTc injection.

Another important finding is that pretreatment with H₁ antagonist alone significantly attenuated the increase of plasma 6-keto-PGF_{1α}. Although we did not determine plasma histamine concentration, it has been shown that diphenhydramine does not attenuate histamine release induced by dTc.^{3,16} Histamine has recently been shown to release prostacyclin from vascular endothelium, and the release is mediated through H₁ receptors.^{4,5,11} All these data support the view that prostacyclin is a second

mediator in the dTc-induced hypotension and its release is caused by dTc-induced histamine release mediated through H₁ receptor located on the peripheral vascular endothelial cells; however, further study may be required to clarify a correlation between plasma histamine and prostacyclin concentrations.

Although pretreatment with aspirin or diphenhydramine abolished the elevation of 6-keto-PGF_{1α}, the MAP decreased slightly and to a similar extent at 2 min after dTc administration. Inada *et al.*³ have shown that pretreatment with H₁ and H₂ antagonists attenuate a decrease in systemic vascular resistance only partially in patients undergoing CABG surgery and treated with β blockers.

These suggest that other factors beside prostacyclin or histamine might be involved in the dTc-induced hypotension. Ganglionic blockade secondary to the administration of dTc has been demonstrated to occur in various species,^{22,23} however, it is virtually impossible to clarify how much the ganglionic blocking action of dTc contributes to the dTc-induced hypotension in normal anesthetized humans.

In conclusion, although histamine has long been recognized as the final chemical mediator responsible for the dTc-induced transient hypotension in humans, the present study revealed that prostacyclin is the final mediator and is released by histamine through H₁ receptors on vascular endothelium.

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