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Effects of Trimethaphan on Arterial Blood Histamine and Systemic Hemodynamics in Humans

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Because of lack of direct evidence of histamine release by trimethaphan, the authors determined serum histamine levels and hemodynamic responses to trimethaphan administration in 19 consecutive patients. Group 1 patients (n = 7) received a single intravenous injection of trimethaphan, 0.5 mg·kg^{-1}, while awake and again during stable halothane–nitrous oxide anesthesia. Group 2 patients (n = 6) were pretreated with intravenous H_1 (chlorpheniramine, 0.1 mg·kg^{-1}) and H_2 (cimetidine, 4 mg·kg^{-1}) receptor antagonists administered 15 min before trimethaphan, 0.5 mg·kg^{-1}, in the awake and anesthetized states. In Group 3 (n = 6), the effects of infusion of trimethaphan, 3 mg·min^{-1} for 15 min, were studied during halothane–nitrous oxide anesthesia. In Group 1, bolus doses of trimethaphan were associated with maximal increases in serum histamine from 0.56 ± 0.14 to 2.56 ± 0.35 ng·ml^{-1} ($P < 0.01$) and from 0.60 ± 0.11 to 2.58 ± 0.33 ng·ml^{-1} ($P < 0.01$) 2 min after drug administration in the awake and anesthetized states, respectively; there were also clinical manifestations of histamine release. Mean arterial pressure decreased maximally after 5 min in the awake (from 92.0 ± 3.4 to 69.9 ± 2.2 mmHg; $P < 0.01$) and anesthetized (from 82.6 ± 3.7 to 57.3 ± 2.5 mmHg; $P < 0.01$) states, and was associated with increases in cardiac output and heart rate; stroke volume increased in the awake state only. Pretreatment with H_1 and H_2 receptor antagonists did not modify the hemodynamic response to trimethaphan, despite increases in serum histamine levels comparable to Group 1. In contrast to Group 1, although trimethaphan infusion caused a significant ($P < 0.05$) increase in serum histamine concentration from 0.72 ± 0.1 to 1.1 ± 0.1 ng·ml^{-1}, the hypotension achieved was not associated with significant alterations in heart rate or cardiac output. In all patients, trimethaphan-induced hypotension was associated with a significant decrease in systemic vascular resistance, an effect that probably was related to the ganglionic blocking, direct vasodilating and alpha-adrenergic blocking action of trimethaphan. The authors conclude that histamine release by trimethaphan does not play an important role in the hemodynamic effects of the drug in humans. (Key words: Anesthesia: orthopedic. Anesthetic techniques: hypotension. Blood pressure: drug effects, trimethaphan. Histamine: chlorpheniramine; cimetidine; histamine release. Pharmacology: trimethaphan; chlorpheniramine; cimetidine.)

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TRIMETHAPHAN is a drug commonly used for the induction and maintenance of controlled hypotension during general anesthesia. Its hypotensive action has been attributed to autonomic ganglionic blockade,[1] a direct effect on vascular smooth muscle,[2–4] alpha-adrenergic blockade,[4] and histamine release.[5] Evidence for trimethaphan-induced histamine release in humans has been inferred largely from animal studies;[5] direct evidence is lacking. The present study therefore was undertaken to determine the effects of trimethaphan on arterial blood histamine levels and hemodynamics in humans.

Methods

Studies were performed in 19 consecutive patients scheduled for total hip replacement (11 patients) or resection of bone tumor with allograft bone replacement (eight patients) under general anesthesia and controlled arterial hypotension to decrease intraoperative blood loss. Informed consent regarding the nature of the study, which had been approved by the Subcommittee on Human Studies, was obtained from each patient. The patients gave no history of drug allergy. Their ages ranged from 22 to 61 yr (mean 44 yr), and their mean (±SE) weight was 73 ± 8 kg. Their physical status was ASA Class I or II. None had a history or clinical evidence of cardiovascular, pulmonary, or metabolic disease. All received 10 mg oral diazepam 1 h before induction of anesthesia. Peripheral venous, arterial, and right atrial catheters were inserted under local anesthesia.

A standard technique of anesthesia was employed for all patients. Thiopental sodium, 5 mg·kg^{-1}, was used for induction of anesthesia, followed by succinylcholine, 1 mg·kg^{-1}, to facilitate endotracheal intubation. Anesthesia was maintained with halothane, 1% inspired concentration, in nitrous oxide and oxygen, 3:2 l·min^{-1}, using a semiclosed system with a carbon dioxide absorber. Metocurine, 0.2 mg·kg^{-1}, was given after completion of measurements, at which time hypotension was induced and maintained with trimethaphan, 0.1% solution. Mean arterial pressure was reduced to 55 mmHg. Ventilation was controlled mechanically to maintain Pa_{CO_2} at normocapnia. Lactated Ringer's solution was infused at 7 ml·kg^{-1}·h^{-1}. Albumin and packed erythrocytes were administered to replace measured blood loss, determined

by weighing sponges and measuring the volume of blood in suction bottles.

The patients were divided into three groups. In Group 1, which comprised seven consecutive patients, the hemodynamic effects and serum histamine levels were determined before, and 2, 5, and 10 min after the administration of a bolus injection (over 30 s) of trimethaphan (5% solution), 0.5 $mg \cdot kg^{-1}$ in the awake state and during anesthesia. Group 2 patients (n = 6) were pretreated with an H_1 (chlorpheniramine, 0.1 $mg \cdot kg^{-1}$) and an H_2 (cimetidine, 4 $mg \cdot kg^{-1}$) receptor antagonist, administered intravenously 15 min before a bolus injection of trimethaphan, 0.5 $mg \cdot kg^{-1}$. Hemodynamic measurements and arterial blood sampling for determination of histamine followed the same time sequence as in Group 1. In Group 3, the effects of an infusion of trimethaphan (0.1% solution in 5% dextrose in water) 3 $mg \cdot min^{-1}$ were determined in another six consecutive patients. Measurements were made before, and 5 and 15 min after the infusion was begun during stable anesthesia, and at the termination of hypotension. Intravascular pressures were measured with Statham® transducers and recorded continuously, together with leads II and V5, on a multichannel recorder. Mean arterial (MAP) and mean right atrial (MRAP) pressures were obtained by electronic integration. The baseline for the transducers was taken at the level of the right atrium. All measurements were made with the patients in the horizontal position. Heart rate was calculated from the ECG tracing. Cardiac output (CO) was determined by the dye-dilution technique, with injection of 5 mg indocyanine green into the right atrium and the withdrawal of blood from the radial artery catheter through the cardiodensitometer (Lexington Instruments). Stroke volume was derived from cardiac output divided by heart rate. Systemic vascular resistance (SVR) was calculated from the following formula:

$$SVR = \frac{(MAP - MRAP)}{CO} \times 80 \text{ dyn} \cdot s \cdot cm^{-5}$$

Arterial blood samples, obtained simultaneously with the hemodynamic measurements, were drawn into chilled 12-ml plastic syringes. The blood then was transferred into chilled polypropylene tubes (Falcon® 2063), which then were centrifuged at 900 *g* for 20 min in a refrigerated centrifuge to separate the serum, which was stored at −70° C until assayed for histamine. Histamine levels in serum were measured by a specific double-isotope radioenzymatic method[6] sensitive to 100 pg per assay. All samples were coded and analyzed in triplicate on two separate occasions; the values presented are the average of six determinations. The intraassay and interassay coefficient of variation in our laboratory is under 10%.

Statistical evaluation of each variable used the analysis of variance, taking into account the repeated measurements over time. The significance of comparisons between a mean value before administration of trimethaphan and mean values at subsequent times was assessed by applying Dunnett's test. With this allowance for multiplicity, a $P < 0.05$ was considered significant. Values are presented as mean ± SE.

Results

The groups were comparable with respect to age, weight, and physical status. Baseline serum histamine values ranged from 0.56 ± 0.14 to 0.81 ± 0.14 $ng \cdot ml^{-1}$ in our patients. These values are within the normal range for our laboratory and that reported by others.[6,7] In Group 1, bolus doses of trimethaphan were associated with peak increases in arterial blood histamine 2 min after drug administration in the awake (from 0.56 ± 0.14 to 2.56 ± 0.35 $ng \cdot ml^{-1}$; $P < 0.01$) and anesthetized states (from 0.60 ± 0.11 to 2.58 ± 0.13 $ng \cdot ml^{-1}$; $P < 0.01$) (table 1). Thereafter, serum histamine declined gradually and approached baseline values after 10 min. Mean arterial pressure decreased maximally after 5 min by 23.7 (±2.2) and 30.1 (±3.3)% in the awake and anesthetized states, respectively (table 1). This was associated with a significant decrease in systemic vascular resistance ($P < 0.01$) both during anesthesia (43.5 ± 3.3%) and in the awake (44.1 ± 2.5%) state. Two, 5, and 10 min after injection of trimethaphan, cardiac output and heart rate increased significantly; stroke volume showed a small increase in the awake state only. There were no significant differences in the hypotensive effect of trimethaphan between the awake and anesthetized state. Mean arterial pressure returned toward control values after 14 and 24 min in the awake and anesthetized states, respectively. There were no rebound hemodynamic events such as those reported with nitroprusside withdrawal.[8]

Administration of trimethaphan in patients pretreated with both histamine antagonists elicited a significant increase in serum histamine concentration after 2 min in the awake state (from 0.81 ± 0.14 to 3.25 ± 0.25 $ng \cdot ml^{-1}$; $P < 0.01$) and during anesthesia (from 0.76 ± 0.17 to 2.96 ± 0.29 $ng \cdot ml^{-1}$; $P < 0.01$). When this group was compared with Group 1, the decrements in mean arterial pressure and systemic vascular resistance and the increments in cardiac output and heart rate were not significantly different. This implies that trimethaphan-induced histamine release was not responsible for the observed hemodynamic events (tables 1 and 2).

Infusion of 3 $mg \cdot min^{-1}$ of trimethaphan was associated with a small significant increase (69 ± 28%) in serum histamine level at 15 min; serum histamine at termination of hypotension was not significantly different from baseline (table 3). Mean arterial blood pressure decreased by 15 ± 2% after 5 min and ranged from 52

TABLE 1. Hemodynamic Data and Serum Histamine Concentration before and after a Single Injection of Trimethaphan, 0.5 mg·kg^{-1}, in Seven Patients in the Awake and Anesthetized States (Group 1)

	Before Injection	After Injection (min) 2	5	10
Mean arterial pressure (mmHg)				
Awake	92.0 ± 3.4	78.0 ± 4.3*	69.9 ± 2.2*	78.7 ± 2.4*
Anesthesia	82.6 ± 3.7	66.0 ± 3.7*	57.3 ± 2.5*	68.9 ± 4.7*
Heart rate (beats·min^{-1})				
Awake	66.7 ± 1.9	83.6 ± 3.6*	84.1 ± 3.2*	84.1 ± 3.2*
Anesthesia	65.3 ± 2.2	78.9 ± 3.5*	77.9 ± 4.0*	77.1 ± 4.3*
Cardiac output (l·min^{-1})				
Awake	4.7 ± 0.1	6.4 ± 0.2*	6.5 ± 0.2*	6.1 ± 0.2*
Anesthesia	4.0 ± 0.2	5.0 ± 0.4*	4.9 ± 0.4*	4.7 ± 0.5*
Stroke volume (ml·beat^{-1})				
Awake	70.8 ± 1.3	77.1 ± 2.0†	77.5 ± 2.5†	72.5 ± 2.1
Anesthesia	61.2 ± 3.0	62.9 ± 3.9	62.5 ± 2.9	60.6 ± 3.7
Systemic vascular resistance (dyn·s·cm^{-5})				
Awake	1,440.7 ± 76.5	910.2 ± 70.0*	797.4 ± 31.2*	972.6 ± 59.1*
Anesthesia	1,460.4 ± 99.0	937.7 ± 85.2*	817.1 ± 54.7*	1,097.3 ± 146.4*
Mean right atrial pressure (mmHg)				
Awake	7.6 ± 0.8	5.9 ± 0.7*	5.4 ± 0.9*	5.7 ± 0.9*
Anesthesia	11.1 ± 1.8	9.9 ± 1.5†	8.4 ± 1.3*	8.4 ± 1.2*
Serum histamine (ng·ml^{-1})				
Awake	0.56 ± 0.14	2.56 ± 0.35*	2.06 ± 0.22*	0.80 ± 0.12
Anesthesia	0.60 ± 0.11	2.58 ± 0.33*	1.98 ± 0.20*	0.78 ± 0.10

Values are mean ± SE.
* $P < 0.01$ *versus* before trimethaphan.
† $P < 0.05$ *versus* before trimethaphan.

to 60 mmHg after 15 min, at which time the infusion rate was adjusted to maintain mean blood pressure at about 55 mmHg. Hypotension was associated with significant decreases in systemic vascular resistance (table 3). Cardiac output, heart rate, and stroke volume were not altered significantly at 5 and 15 min after the

TABLE 2. Hemodynamic Data and Serum Histamine Concentration before and after a Single Injection of Trimethaphan, 0.5 mg·kg^{-1}, in Six Patients Pretreated with Intravenous Chlorpheniramine, 0.1 mg·kg^{-1}, and Cimetidine, 4 mg·kg^{-1}, 15 Minutes before Trimethaphan Administration (Group 2)

	Before Injection	After Injection (min) 2	5	10
Mean arterial pressure (mmHg)				
Awake	96.3 ± 4.5	84.2 ± 5.3*	74.3 ± 3.1*	86.2 ± 4.1*
Anesthesia	86.2 ± 4.1	71.7 ± 3.2*	60.2 ± 3.2*	70.2 ± 3.6*
Heart rate (beats·min^{-1})				
Awake	74.2 ± 2.9	88.3 ± 3.9*	89.7 ± 3.9*	78.0 ± 3.7
Anesthesia	70.2 ± 3.1	80.2 ± 3.1*	81.3 ± 4.1*	77.0 ± 3.3
Cardiac output (l·min^{-1})				
Awake	5.2 ± 0.4	6.4 ± 0.4*	6.6 ± 0.4*	6.0 ± 0.3*
Anesthesia	4.1 ± 0.3	5.1 ± 0.3*	5.3 ± 0.3*	5.0 ± 0.3*
Stroke volume (ml·beat^{-1})				
Awake	69.9 ± 3.5	72.6 ± 3.5	73.7 ± 3.3	77.0 ± 2.6†
Anesthesia	58.2 ± 3.2	63.9 ± 4.3	65.6 ± 3.8	65.0 ± 3.2
Systemic vascular resistance (dyn·s·cm^{-5})				
Awake	1,395.2 ± 147.3	997.8 ± 113.2*	842.1 ± 69.6*	1,098.8 ± 117.2*
Anesthesia	1,511.9 ± 134.7	1,006.8 ± 97.4*	815.7 ± 98.6*	1,039.6 ± 124.2*
Mean right atrial pressure (mmHg)				
Awake	8.2 ± 1.0	6.3 ± 0.8*	6.0 ± 0.8*	5.7 ± 0.6*
Anesthesia	10.5 ± 1.3	8.8 ± 0.9†	7.5 ± 1.1*	7.0 ± 1.0*
Serum histamine (ng·ml^{-1})				
Awake	0.81 ± 0.14	3.25 ± 0.25*	2.13 ± 0.27*	1.07 ± 0.12
Anesthesia	0.76 ± 0.17	2.96 ± 0.29*	2.42 ± 0.23*	1.51 ± 0.14†

Values are mean ± SE.
* $P < 0.01$ *versus* before trimethaphan.
† $P < 0.05$ *versus* before trimethaphan.

TABLE 3. Hemodynamic Data and Serum Histamine Concentrations before, during, and at Termination of Trimethaphan Infusion in Six Patients during Halothane–Nitrous Oxide Anesthesia (Group 3)

Variable	Before Infusion	Minutes during Infusion		Termination of Infusion
		5	15	
Mean arterial pressure (mmHg)	85.0 ± 2.2	72.0 ± 2.7†	56.5 ± 1.2†	57.0 ± 1.06†
Heart rate (beats · min^{-1})	73.7 ± 2.3	76.3 ± 3.3	78.3 ± 2.7	72.8 ± 2.1
Cardiac output (l · min^{-1})	4.35 ± 0.2	4.5 ± 0.16	4.36 ± 0.17	3.8 ± 0.11*
Stroke volume (ml · $beat^{-1}$)	59.2 ± 2.7	59.4 ± 2.8	56.0 ± 2.4	52.3 ± 1.9*
Systemic vascular resistance (dyn · s · cm^{-5})	1,425.1 ± 88.1	1,143.3 ± 63.4†	911.8 ± 49.7†	1,056.2 ± 50.3†
Mean right atrial pressure (mmHg)	8.5 ± 0.8	8.2 ± 0.9	7.2 ± 0.8*	7.2 ± 0.7*
Serum histamine (ng · ml^{-1})	0.72 ± 0.10	0.9 ± 0.11	1.1 ± 0.11†	0.83 ± 0.13

Values are mean ± SE.
* $P < 0.05$ *versus* before trimethaphan.
† $P < 0.01$ *versus* before trimethaphan.

infusion was begun. Mean right atrial pressure decreased. Upon termination of the infusion, mean arterial blood pressure returned to baseline values between 15 and 36 min (mean 22 min), with no rebound. The mean duration of infusion was 236 ± 26 min, and the total dose of trimethaphan was 376 ± 45 mg.

Together with the elevation in serum histamine levels, there also were subjective manifestations of histamine release in Group 1. These included a burning sensation in the injected vein; a generalized sensation of heat; a variable degree of flushing of the face, neck, and upper chest; dizziness; and headache. However, these subjective manifestations did not occur in pretreated patients (Group 2).

Discussion

The present studies demonstrate that 1) trimethaphan-induced histamine release in humans is related to the rate of drug administration; 2) the state of consciousness of the patient (awake *vs.* anesthetized) does not influence the hypotensive response to trimethaphan; and 3) histamine does not play an important role in the hemodynamic responses to trimethaphan. The baseline values of serum histamine were all within the normal range (0.1–1.1 ng · ml^{-1}), suggesting that psychologic stress, catheter insertion, and sample handling did not influence our results.[6] Furthermore, serum histamine values before and after bolus doses of trimethaphan during anesthesia were not significantly different from those obtained in the awake state; this indicates that the anesthetic drugs used did not change baseline serum histamine values or interfere with histamine liberation by trimethaphan.

The doses of trimethaphan employed in the present study have clinical relevance. A dose of 0.1 to 0.3 mg · kg^{-1} has been recommended for the treatment of hypertensive crisis and pulmonary edema.[9] For deliberately induced hypotension, trimethaphan may be administered by the intermittent intravenous technique, in which an initial dose of 50 mg (5% solution) is followed by doses of 10–30 mg at 10–15-min intervals to maintain the desired level of hypotension.[10] However, the drug usually is given by the continuous intravenous infusion of a 0.1% solution at an initial rate of 3–4 mg · min^{-1}.[10] Stronger solutions are used in children or neurosurgical procedures.[10]

Peak increases in serum histamine levels occurred 2 min after trimethaphan administration in the awake state and during anesthesia in both pretreated and unpretreated patients (tables 1 and 2). Subjective symptoms of histamine release were reported by unpretreated patients only. Infusion of trimethaphan at 3 mg · min^{-1} was associated with a 69 (±28)% increase in serum histamine after 15 min. Release of histamine is probably due to a direct pharmacologic effect of trimethaphan on mast cells or basophils or both.[11,12] Judged from the serum histamine levels, the magnitude of liberated histamine depended primarily on the concentration of drug achieved at receptor sites in these cells. Mitchell *et al.*[5] reported that injection of trimethaphan (dose not specified) in dogs liberated large amounts of histamine (no levels given) that killed the animals. Randall *et al.*[1] indicated that histamine release was a species characteristic unique to dogs among laboratory animals. Intradermal testing with trimethaphan elicited typical histamine wheal and flare in humans, guinea pigs, and dogs.[5]

A bolus injection of trimethaphan produced a decrease in systemic arterial pressure that was maximal after 5 min in both the awake and anesthetized states in pretreated and unpretreated patients. Trimethaphan produced similar decreases in mean arterial pressure in the awake and anesthetized state in Groups 1 and 2 patients. The rapid decrease in blood pressure was associated with an increase in cardiac output and heart rate; stroke volume showed a small significant change in the awake state only. In contrast, the slow induction of hypotension with infusion of trimethaphan was not associated with significant alterations in heart rate or cardiac output, as reported by others.[13,14] The difference in reflex response to hypotension might be related to the rate of reduction of arterial blood pressure.

The lowering of systemic blood pressure with intravenous injection (bolus or infusion) of trimethaphan in the awake state or during nitrous oxide–halothane anesthesia was related principally to a sharp reduction in systemic vascular resistance. This has been attributed to ganglionic blockade, direct vasodilation, alpha-adrenergic blockade, and histamine release. All our patients had pupillary dilation, a sign of ganglionic blockade. Trimethaphan has been shown to block transmission in both sympathetic and parasympathetic ganglia of dogs.[1] McCubbin and Page[15] demonstrated that hypotension elicited by small doses of trimethaphan was not affected by prior treatment with hexamethonium, suggesting that ganglionic blockade was not the principal cause of the hypotensive effect of trimethaphan. The direct vasodilating property of trimethaphan was documented by *in vivo* and *in vitro* studies. In anesthetized dogs, the potent vasodilating effect of trimethaphan was evidenced by dilation of the femoral vessels.[2] The drug relaxed canine mesenteric artery and saphenous vein strips to a similar extent.[3] In helically cut strips of dog cerebral, mesenteric, and femoral arteries contracted with prostaglandin F2α, trimethaphan caused a dose-related relaxation that was not influenced by atropine, propranolol, diphenhydramine, cimetidine, aminophylline, or indomethacin.[4]

Does histamine play a role in the effects of trimethaphan? The present results do not support an important role for histamine in the hemodynamic effects of trimethaphan. First, the peak increase in serum histamine concentration was observed after 2 min, whereas peak hemodynamic changes occurred after 5 min and continued until the 10-min observation period, at which time histamine levels had declined toward baseline values. Second, pretreatment with H_1 and H_2 receptor antagonists did not attenuate or prevent the hemodynamic effects of trimethaphan, despite a comparable increase in serum histamine levels in Groups 1 and 2. Finally, the degree of hypotension obtained with infusion of trimethaphan was comparable to that following bolus injection of the drug, despite a significantly lower serum histamine concentration (tables 1, 2, and 3). Randall *et al.*,[1] in 1949, suggested that histamine release contributed little to the overall vasodepressor response to trimethaphan, since the hypotensive response to trimethaphan was not altered by diphenhydramine, an H_1 antagonist (H_2 receptors were not yet known). However, histamine release was responsible for the subjective manifestations experienced by our awake patients (Group 1) and for the flush observed during anesthesia; the intensity and time course of these manifestations corresponded to the alterations in serum histamine concentrations. Furthermore, these manifestations were prevented by use of histamine receptor antagonists.

In conclusion, we have demonstrated that trimethaphan liberates histamine in humans, at a magnitude related to the rate of drug administration. Also, the hypotensive effect of trimethaphan depends on the rate of drug administration, is not modified by general anesthesia, and is not related to histamine release.

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