TRIMETHAPHAN-INDUCED HYPOTENSION: EFFECT ON RENAL FUNCTION

RAHIM BEHNIA, ADRIAN MARTIN, ESMAIL KOUSHANPOUR AND EDWARD A. BRUNNER

ABSTRACT

This study was designed to evaluate the effects of trimethaphan-induced hypotension on renal function in healthy young patients undergoing maxillofacial surgery. Anaesthesia was induced with thiopentone and was maintained with halothane 1.5–2.0 per cent in oxygen. Each patient served as his own control, and data were analyzed using the paired *t*-test. Trimethaphan was infused at a rate of $45\text{--}52\ \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ for an average hypotensive period of 53 ± 4 (mean $\pm$ SEM) minutes to reduce the mean arterial pressure (MAP) to 49 ± 2 torr. Endogenous creatinine clearance, urinary PO_2 , sodium reabsorption rate (TNa), and serum and urine osmolalities were determined before, during and after arterial hypotension with trimethaphan. Urine flow averaged 2.9 ± 1 ml/min during the period of hypotension. Endogenous creatinine clearance and TNa were significantly decreased ($p < 0.05$) in the hypotensive period. These values returned to normal levels within one hour upon discontinuation of trimethaphan and restoration of blood pressure. We found no statistical difference in urine PO_2 , and serum and urine osmolalities during control, hypotensive and recovery periods. These results suggest that medullary renal tissue oxygenation, an index of tissue viability, may have remained adequate despite a significant reduction in endogenous creatinine clearance during the hypotensive period. Furthermore, it appears that the effect of trimethaphan-induced hypotension on renal function is similar to the sodium nitroprusside-induced hypotension in man which we have reported previously.

KEY WORDS: KIDNEY, function, induced hypotension; HYPOTENSION, induced, trimethaphan, sodium nitroprusside; ANAESTHETICS, volatile, halothane.

INTRODUCTION

DELIBERATE ARTERIAL hypotension induced by halothane, sodium nitroprusside (SNP), trimethaphan (TMP) and other ganglionic blockers during anaesthesia provides improved operating conditions, reduced blood loss, and a bloodless surgical field.¹ However, there is considerable controversy concerning the use of induced hypotension for surgical procedures and its possible undesirable effects on vital organs.^{2,3} The present study focuses on the effects of induced

hypotension on the kidney, an organ particularly sensitive to ischaemia and possible damage during hypotension.

Previous studies concerning the effect of TMP-induced hypotension on kidney function have produced inconclusive and conflicting results. Consequently, the present study was designed to evaluate the renal effects of trimethaphan-induced hypotension in young patients undergoing elective maxillofacial operations. Specifically, we measured endogenous creatinine clearance and urine PO_2 during the entire course of the study, as well as the rate of spontaneous recovery of renal function following discontinuation of TMP.

METHODS

Fifteen consenting young patients with no known cardiopulmonary or renal diseases undergoing elective maxillofacial operations requiring induced hypotension were selected for this study. The experimental protocol was in accord with the ethical standards of the Committee on

Rahim Behnia, M.D., Assistant Professor of Clinical Anaesthesia; Adrian Martin, M.B., Associate in Clinical Anaesthesia; Esmail Koushanpour, Ph.D., Associate Professor of Physiology and Anaesthesia; Edward A. Brunner, M.D., Ph.D., Professor and Chairman, Department of Anaesthesia. Departments of Anaesthesia and Physiology, Northwestern University Medical School, 303 E. Chicago Avenue, Chicago, Illinois, 60611.

Correspondence and reprint requests to: Dr. Rahim Behnia, Department of Anaesthesia, Northwestern University Medical School, 303 East Chicago Avenue, Chicago, Illinois, 60611.

Human Experimentation and was approved by the Institutional Review Board of Northwestern University.

Each patient, serving as his own control, underwent the following procedures before induction of anaesthesia. Two peripheral veins were cannulated and five per cent dextrose in lactated Ringer's solution was infused at the rate of $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$. A third catheter was placed in the radial artery to measure arterial pressure with a Bentley pressure transducer adjusted to reflect systemic arterial pressure at the level of the surgical field. Mean arterial pressure (MAP) was displayed as the digital readout on a Tektronix dual-channel model 414 monitor. The radial artery catheter was also used for periodic sampling of arterial blood for measurement of gas tensions, as well as blood samples for chemical determinations of serum creatinine, osmolality and electrolytes. During the course of the study, patients were kept in the supine position and body temperatures were maintained at $36 \pm 1^\circ \text{C}$ with an automatic warming blanket.

Anaesthesia without premedication was induced with thiopentone, halothane and oxygen and a naso-tracheal intubation was done with the aid of succinylcholine. Anaesthesia was maintained with halothane 1.5–2.0 per cent in oxygen using a semi-closed circle carbon dioxide absorption system and ventilation was controlled with a volume-cycled ventilator. Arterial PCO_2 was maintained at $4.9 \pm 0.3 \text{ kPa}$ ($37 \pm 2 \text{ torr}$) (mean $\pm$ S.E.M.) during the control period, $4.5 \pm 0.13 \text{ kPa}$ ($34 \pm 1 \text{ torr}$) during the hypotension period and $5.4 \pm 0.13 \text{ kPa}$ ($41 \pm 1 \text{ torr}$) during the recovery period.

After induction of anaesthesia and as described previously,⁴ a 16 gauge polyethylene catheter equipped with a three-way stopcock was inserted into the urinary bladder through an indwelling Foley catheter for subsequent anaerobic collection of urine. Before the collection of urine the Foley catheter was clamped distal to the polyethylene catheter. Gentle aspiration of the bladder using a glass syringe attached to the polyethylene catheter was used to keep the bladder empty of urine and to remove trapped air. Bladder contents were removed every 20 minutes for measurement of urine volume and determinations of creatinine, osmolality and electrolytes. Urine samples for pH, PCO_2 and PO_2 determination were also taken anaerobically at each sampling period and analyzed immediately. The blood samples were drawn in the middle of urine collection periods, as required

by clearance calculations. During control and recovery periods, two consecutive 20-minute urine and blood samples were obtained and the mean of the calculated clearance values was used as the value for these periods. In the case of hypotension periods, depending on the length of the hypotension period required by the surgical procedure, two or three 20-minute urine and blood samples were obtained for creatinine analysis and the mean of the calculated clearance values was used as the value for that period.

One hour before collection of blood and urine samples, anaesthetic concentration was adjusted to maintain arterial blood pressure within preoperative limits. During this period, the average MAP was $78 \pm 2 \text{ torr}$. Hypotension, as needed for surgery, was induced by infusion of trimethaphan 1 mg/ml in 5 per cent dextrose in water through a minidrip administration set and a Dial-a-Flow (Sorenson Research Co.) at a rate of $45\text{--}52 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for over an average hypotension period of $53 \pm 4 \text{ minutes}$, to reduce the MAP to $49 \pm 2 \text{ torr}$. Blood and urine samples were taken anaerobically at the end of the hypotensive period as described previously. Mean arterial pressure returned to $84 \pm 8 \text{ torr}$ following discontinuation of trimethaphan infusion while continuing halothane-oxygen anaesthesia. Blood and urine samples in the recovery period were obtained after blood pressure was stabilized at normotensive levels for at least one hour.

Steady-state endogenous creatinine clearance was calculated from blood and urine values obtained during the control, hypotensive and recovery periods using the Jaffe technique.⁵ Blood and urine samples for gas analysis were iced and immediately analyzed for pH, PCO_2 , PO_2 and HCO_3^- by standard techniques. The data were analyzed for statistical significance using the paired t-test.⁶ A value of $p < 0.05$ was considered statistically significant.

RESULTS

Table I presents values for serum creatinine, endogenous creatinine clearance, sodium reabsorption rate ($\dot{T}\text{Na}$), and serum and urine osmolalities before, during and after trimethaphan-induced hypotension. There was no significant difference in serum creatinine levels before ($0.72 \pm 0.04 \text{ mg per cent}$) during ($0.69 \pm 0.05 \text{ mg per cent}$) or after ($0.68 \pm 0.06 \text{ mg per cent}$) induced hypotension. However, endogenous creatinine clearance was significantly lower during hypotension ($72 \pm 9 \text{ ml/min}$) than under

TABLE I
RENAL FUNCTION BEFORE, DURING AND AFTER HYPOTENSION INDUCED BY TRIMETHAPHAN

Experimental Period	Serum Creatinine (mg%)	Creatinine Clearance (ml/min)	$\dot{V}_{Na}$ (mmol/min)	Serum Osmolality (mOsm/kg H ₂ O)	Urine Osmolality (mOsm/kg H ₂ O)
Control	0.72 ± 0.04	157 ± 14	21.00 ± 2.01	296 ± 5	440 ± 28
Hypotension	0.69 ± 0.05	72 ± 9*	9.52 ± 1.22*	297 ± 4	451 ± 19
Recovery	0.68 ± 0.06	157 ± 14	20.92 ± 1.99	289 ± 3	501 ± 36

Data are mean ± SEM.

*Significant at $p < 0.05$ level.

normotensive condition (157 ± 14 ml/min), and during recovery (157 ± 14 ml/min) from hypotension. Clearance values for control and recovery periods did not differ statistically. There was a significant decrease in $\dot{V}_{Na}$ during hypotension (9.52 ± 1.22), as compared to control (21.00 ± 2.01) and recovery (20.92 ± 1.99) periods. Serum sodium concentration, not shown here, remained unchanged during the course of the study. The changes in $\dot{V}_{Na}$ paralleled corresponding changes in endogenous creatinine clearances. There was no significant difference in serum osmolality before (296 ± 5), during (297 ± 4) or after (289 ± 3) induced hypotension. Although urine osmolality was slightly higher during the recovery period (501 ± 36), we found no significant difference in urine osmolality before (440 ± 28), during (451 ± 19) or after induced hypotension. Urine outputs were 4.60 ± 0.4 ml·min⁻¹ during control, 2.9 ± 1 ml·min⁻¹ during hypotension, and 4.5 ± 1.3 ml·min⁻¹ during the recovery periods in these patients. The high urine outputs, particularly during the hypotensive period, may reflect the large volume of fluid received by these patients. Three patients had less than 1 ml·min⁻¹ urine output during the hypotensive period. These patients were excluded from this study because at least 1 ml·min⁻¹ urine flow is required for an accurate clearance calculation.

Table II compares arterial blood and urine gases for the three experimental periods. We found no statistical difference in urine P_{O_2} during control (10.4 ± 0.4 kPa; 78 ± 3 torr), hypotensive (10.6 ± 0.5 kPa; 80 ± 4 torr), or recovery (10.5 ± 0.5 kPa; 79 ± 4 torr) periods. It can be seen that urine P_{CO_2} values during control (7.2 ± 0.4 kPa; 54 ± 3 torr), hypotension (7.3 ± 0.5 kPa; 55 ± 4 torr), and recovery (8.6 ± 0.5 kPa; 65 ± 4 torr) periods were higher than the corresponding arterial P_{CO_2} values throughout the periods of study. This finding confirms the anaerobic sampling of urine and the

minimum possibility of gas diffusion through the bladder wall.

DISCUSSION AND CONCLUSIONS

The purpose of this study was to examine the effects of trimethaphan-induced hypotension on renal haemodynamics and medullary tissue oxygenation. We found that an approximately 37 per cent reduction in the mean arterial blood pressure resulted in a marked depression of the endogenous creatinine clearance, which is a measure of the glomerular filtration rate (GFR), as well as a decrease in the sodium reabsorption rate secondary to induced hypotension. These indices of renal function, however, returned to normal levels upon discontinuation of trimethaphan infusion and restoration of the blood pressure to normal. In addition, bladder urine P_{O_2} , a possible index of medullary tissue oxygen tension, remained unchanged during the three experimental periods.

Endogenous creatinine clearance has been widely used in clinical practice as a relatively accurate and reliable measure of glomerular filtration rate.⁷ Although the presence of non-specific chromogens in plasma may cause some variation in measurements, creatinine clearance was employed because of both ease of measurement and accepted accuracy for practical medical purposes.⁸ Unlike urea clearance, endogenous creatinine clearance is minimally influenced by urine flow, and serum creatinine concentration is independent of daily dietary protein intake.⁹ In this study, the attainment of a steady state and the accuracy of sampling assured maximum validity of the clearance measurement.

Our findings are in agreement with those of Moyer and associates¹⁰ which have shown that trimethaphan-induced hypotension caused decreased GFR and sodium excretion, but increased renal vascular resistance. However, we

TABLE II
ARTERIAL AND URINARY pH, PCO₂ AND PO₂ BEFORE, DURING AND AFTER HYPOTENSION INDUCED BY TRIMETHAPHAN

Sample	Control			Hypotension			Recovery		
	pH	PCO ₂ kPa (torr)	PO ₂ kPa (torr)	pH	PCO ₂ kPa (torr)	PO ₂ kPa (torr)	pH	PCO ₂ kPa (torr)	PO ₂ kPa (torr)
Arterial	7.42 ± 0.02	4.9 ± 0.3 (37 ± 2)	62.1 ± 1.9 (467 ± 14)	7.46 ± 0.01	4.4 ± 0.1 (33 ± 1)	56.2 ± 3.2 (423 ± 24)	7.37 ± 0.01	5.4 ± 0.1 (41 ± 1)	51.6 ± 3.8 (388 ± 29)
Urine	5.48 ± 0.50	7.2 ± 0.4 (54 ± 3)	10.4 ± 0.4 (78 ± 3)	5.56 ± 0.3	7.3 ± 0.5 (55 ± 4)	10.6 ± 0.5 (80 ± 4)	5.88 ± 0.2	8.6 ± 0.5 (65 ± 4)	10.5 ± 0.5 (79 ± 4)

Data are mean ± SEM.

examined the rate of spontaneous recovery of depressed renal function, while they used norepinephrine infusion to evaluate the recovery of renal function. Thompson and co-workers¹¹ observed no impairment of renal function on the first, second, seventh, and eighth postoperative days, following halothane and sodium nitroprusside-induced hypotension. However, they did not use a urinary catheter in their subjects and the renal function and its immediate recovery was not evaluated during the course of the operation. Hugosson and Hogstrom¹² evaluated postoperative creatinine clearance in 96 patients following deep halothane and trimethaphan-induced hypotension and found no change in creatinine clearance. However, six patients who had abnormal kidney function during the preoperative period also showed abnormal creatinine clearance during the postoperative period. Again, renal function during the operation and the immediate rate of recovery from depressed function, if any, were not evaluated by these investigators.

Our finding from a previous study with sodium nitroprusside-induced hypotension and this present study with trimethaphan-induced hypotension demonstrate phasic changes in kidney function and spontaneous recovery within one hour after restoration of blood pressure. It appears that hypotension induced with the two drugs has similar effects on kidney function in man. These findings contrast with those reported by Wang and associates.¹³ This difference can be attributed to the fact that they used an electromagnetic blood flow measuring technique to compare the effects of trimethaphan-induced and sodium nitroprusside-induced hypotension on renal blood flow in dogs. Although the hypotensive period in their study was only 5–15 minutes, and their technique measured only transient changes in renal blood flow and not the actual renal function, they concluded that renal function is better preserved with sodium nitroprusside than with trimethaphan. This discrepancy could also be attributed to a greater amount of histamine release during trimethaphan-induced hypotension in dogs than that in man.

The observed reduction in the endogenous creatinine clearance during the trimethaphan-induced hypotension is a reflection of reduced cortical blood flow, secondary to the haemodynamic effects of hypotension. The observed decrease in T_{Na} during hypotension might be secondary to a reduced filtered load of sodium. It has been shown that the urinary oxygen tension,

when urine flow is adequate, is closely related to the medullary blood flow, medullary tissue oxygen tension, sodium reabsorptive capacity, and renal oxygen consumption.^{14–18} Since there is a direct relationship between T_{Na} and renal oxygen consumption,¹⁹ and the fact that renal blood flow and hence renal oxygen supply are reduced during trimethaphan-induced hypotension,^{9,10,13} the depressed T_{Na} could be accompanied by a reduced oxygen demand.

In conclusion, although trimethaphan-induced hypotension results in a transient depression of renal function, we found no evidence of detrimental effects on renal function. Our findings also suggest that despite hypotension, renal tissue oxygenation and viability were essentially unaffected by the trimethaphan-induced hypotension in man. Furthermore, it appears that the effect of trimethaphan-induced hypotension on renal function is similar to the sodium nitroprusside-induced hypotension in man which we have reported previously.

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RÉSUMÉ

Cette étude a été entreprise dans le but d'évaluer le retentissement de l'hypotension produite par le trimetaphan (TMP) sur la fonction rénale de jeunes adultes en bon état subissant une intervention maxillo-faciale. L'anesthésie a été induite au thiopentone et maintenue à l'halothane 1.5-2.0 pour cent dans l'oxygène. Chaque patient était son propre contrôle et les données ont été analysées avec le test de Student. Le TMP a été perfusé à la vitesse de $45-52 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ pour une durée moyenne d'hypotension de 53 ± 4 (moyenne $\pm$ SEM) minutes de façon à abaisser la pression artérielle moyenne à 49 ± 2 torr. La clairance de la créatinine endogène, la PO_2 urinaire, la vitesse de réabsorption au sodium (TNa) et l'osmolalité urinaire et sérique ont été déterminées avant, pendant et après l'hypotension au TMP. Le débit urinaire était en moyenne de $2.9 \pm 1 \text{ ml/min}$ pendant la période d'hypotension. La clairance de la créatinine endogène et la TNa se sont abaissées de façon significative ($P < 0.05$) pendant la période hypotensive. Il n'y a eu de différence significative dans la PO_2 urinaire et les osmolalités sérique et urinaire pendant la période de contrôle, d'hypotension et de recouvrement. Ces résultats suggèrent que l'index de viabilité du tissu rénal qu'est l'oxygénation médullaire pourrait être adéquat malgré une baisse significative de la clairance de la créatinine endogène pendant la période hypotensive. De plus, il semble que le retentissement de l'hypotension produite par le TMP sur la fonction rénale est identique à celle produite chez l'homme par le nitroprussiate de soude.