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# *Preservation of Platelet Function During Trimethaphan Infusion*

*Roberta Hines, M.D.**

**The effect of trimethaphan (Arfonad) infusion on platelet function was prospectively evaluated in 38 (n = 38) patients (28 patients receiving trimethaphan, ten control patients) undergoing elective cardiac surgery. Any patient with a positive history for the ingestion of medication known to interfere with platelet function was excluded from the study. Following induction of anesthesia with fentanyl (and prior to cardiopulmonary bypass) 28 patients (n = 28) received trimethaphan as clinically indicated to maintain a mean blood pressure of 80 mmHg. The infusion rate and total dose of trimethaphan delivered was recorded for each patient. The evaluation of platelet function was performed *via* adenosine diphosphate (ADP) and epinephrine-induced platelet aggregation tests. The administration of trimethaphan failed to result in any detrimental effect on platelet function as assessed *via* these aggregation studies. Template bleeding times were also performed on all study patients. Bleeding time measurements performed in patients following trimethaphan administration were unchanged from baseline values. Platelet aggregation studies and bleeding time performed in control group following the administration of fentanyl (30 μg/kg) plus enflurane (inspired concentration 0.5–1%) did not reveal any deviation from baseline values. These results are in contrast to a previous study that demonstrated a negative effect upon platelet function following sodium nitroprusside administration (at clinically acceptable doses). These data demonstrate that trimethaphan provides control of arterial pressure with preservation of platelet function. (Key words: Anesthesia: cardiac. Coagulation: platelet aggregation; bleeding time. Pharmacology: trimethaphan.)**

THE PRESERVATION of platelet function and normal hemostatic parameters is an important consideration in the selection of pharmacologic therapy designed to control arterial pressure and vascular resistance during cardiac surgery. Traditionally, nitrates (*i.e.*, sodium nitroprusside and nitroglycerin) have been the primary pharmacologic agents chosen to accomplish these goals. However, sodium nitroprusside (SNP) and nitroglycerin (NTG), in clinically relevant dosages, have been shown to significantly alter hemostatic mechanisms and inhibit platelet function.[1–3] As a result of alteration in platelet function and the abnormalities in coagulation factors occurring following cardiopulmonary bypass (CPB), cardiac surgical patients may be at an increased risk for developing abnormalities in platelet function and increases in bleeding time. This combination of platelet dysfunction (following nitrate administration) and the hematologic derangements with CPB may limit the perioperative use of these agents.

Trimethaphan provides an alternative to the use of nitrates for the control of perioperative hypertension. In addition, because trimethaphan is a ganglionic blocker and does not generate the formation of nitric oxide, which has been postulated to account for the platelet inhibitory effects of SNP, it provides an excellent alternative for the management of perioperative hypertension.[4] Despite the lack of biochemical similarities between trimethaphan and the nitrates and therefore a reduced chance of platelet dysfunction, the ganglion blockade provided by trimethaphan may result in diminished vascular tone. This decreased vascular tone has been one of the mechanisms proposed for the prolongation of bleeding time seen with nitrate containing agents.[5]

To date, however, no prospective study has evaluated the effect of ganglionic blockade on platelet function and bleeding time *in vivo*. Consequently, a controlled prospective study was designed to evaluate the effects of trimethaphan on platelet function and bleeding time measurements in patients undergoing elective cardiac surgery.

## Methods

Following patient consent, this study was undertaken with a protocol approved by the Human Investigation Committee. Thirty-eight (n = 38) adult patients with a mean age of 66 ± 3.8 yr scheduled to undergo elective coronary artery bypass surgery were included. Patients were interviewed on the evening prior to surgery and any patient having ingested medications known to interfere with platelet function was excluded from the study. In addition, prothrombin time, partial thromboplastin time, and standardized template bleeding (Simplate-II, General Diagnostics) times were determined upon admission to the hospital. All patients included in this protocol had normal hemostatic indices preoperatively.

Patients received intramuscular morphine (0.15 mg/kg) and scopolamine (0.4 mg) 90 min prior to arrival in the operating room. No peripheral iv catheters were inserted in the left upper extremity so that fluid administration would not interfere with the results of the template bleeding test which was always performed on the patients left forearm.[6]

Induction of anesthesia was performed using fentanyl (30 μg/kg), and pancuronium (0.1 mg/kg) was used for muscle relaxation. Following tracheal intubation, mechanical ventilation was maintained using 100% $O_2$.

Prior to skin incision (and following induction), a baseline bleeding time and platelet aggregation studies were

* Assistant Professor.

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Address reprint requests to Dr. Hines: Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, P. O. Box 3333, New Haven, Connecticut 06510.

performed. Bleeding times were measured using a Simplate-II system. A solution of trimethaphan was prepared as a 1 mg/ml concentrative using 5% dextrose in water. Trimethaphan was infused when clinically indicated following induction to maintain a mean arterial pressure = 80 mmHg (infusion rate of 1–4 mg/min). In addition to baseline determinations, blood samples for determination of platelet aggregation and bleeding times were obtained 30, 60, and 90 min following the institution of trimethaphan therapy. The infusion rate and total amount of trimethaphan delivered were recorded at each of these study intervals. Platelet aggregation studies and bleeding time were also performed in a group of control patients (n = 10) anesthetized with fentanyl but receiving no trimethaphan. In the control group of patients, blood pressure control (MAP = 80 mm) was achieved using inhalational anesthesia (enflurane). No patient received any halothane or isoflurane during the study period.[7–9] These two study groups were matched (trimethaphan *vs.* control) for demographic characteristics (age, sex, and operative procedure, etc).

The methods for preparation of samples for platelet aggregation are as previously described in detail.[1] To obtain platelet-rich plasma, a 15 ml sample of blood was anticoagulated with sodium citrate and centrifuged for 20 min at room temperature. All equipment used to handle the blood or platelet-rich plasma was plastic except for the aggregometer tubes that were untreated glass. All aggregation studies were performed on aliquots of platelet rich plasma in which the platelet concentration was equal to or greater than 300,000/mm$^3$. Aggregation studies were performed by exposure of the platelet-rich plasma to epinephrine (5 $\mu$M) or adenosine diphosphate (ADP 2 $\mu$M). Measurement of aggregation was performed using a Chrono-log® aggregometer, model #540. Maximal aggregation was read as the percentage increase in light transmission observed at 5 min from the strip chart recorder following addition of the aggregation agent (*e.g.*, ADP or epinephrine). The rate of aggregation and the extent of aggregation of the primary wave (height of maximum platelet aggregation) was calculated for each determination.[10] All samples obtained for measurement of platelet function were drawn prior to heparinization and the institution of cardiopulmonary bypass. No parenteral infusions known to alter platelet function were administered at any time during the study period.

Data are expressed as the mean ± SD. Statistical analysis was performed using one-way analysis of variance and correlation coefficient with $P < 0.05$ considered significant.

## Results

Platelet counts obtained from all patients (n = 38) at baseline ranged from 146,000–180,000/mm$^3$, (mean 163,580 ± 16,000/mm$^3$). All measurements of platelet aggregation performed during the pretrimethaphan infusion period (baseline) were found to be in the clinically acceptable range for normal platelet function with a mean of 76% ± 1.2 ADP aggregation. Following trimethaphan infusion, no significant difference in patient's platelet counts was observed at any of the sampling intervals (table 1). In addition, preservation of both primary and secondary waves of platelet aggregation was observed at all sampling intervals (30, 60, and 90 min). Neither the total dose of trimethaphan delivered (mg) nor the rate of infusion (mg/min) was significantly correlated with any decrease in the level of platelet aggregation as measured *via* ADP platelet aggregation studies (r = 0.28, r = 0.21, respectively).

Platelet function as assessed by epinephrine-induced aggregation, parallel data obtained with ADP. The addition of epinephrine (5 mM) to platelet-rich plasma yields maximum aggregation. Similarly, a normal biphasic aggregation signature is seen when epinephrine is added to platelets that have been exposed to trimethaphan (fig. 1).

Data obtained from bleeding time measurements in the study population are seen in table 1. The mean value for baseline bleeding time values was 4.2 ± 0.8 min (SD) (normal range 4–8 min). The administration of trimethaphan resulted in no significant increase in bleeding time at any of the study intervals. In the control group of patients anesthetized with fentanyl and enflurane but receiving no trimethaphan, platelet aggregation and template bleeding time determinations also remained unchanged from baseline values (table 2).

TABLE 1. Trimethaphan Infusion Rate and Template Bleeding Time in Study Patients

| Trimethaphan Infusion Rate (mg/min) | % Aggregation (ADP) | % Aggregation (EPI) | Bleeding Time (min) | n |
|---|---|---|---|---|
| 0 | 76 ± 1 | 82 ± 0.6 | 4.2 ± 0.8 | 28 |
| 1 | 78 ± 0.8 | 79 ± 0.4 | 4 ± 0.4 | 8 |
| 2 | 83 ± 1.1 | 84 ± 0.5 | 4.6 ± 1.1 | 12 |
| 3 | 81 ± 0.9 | 77 ± 1.1 | 5.1 ± 0.6 | 6 |
| 4 | 77 ± 1.2 | 84 ± 1.3 | 4.9 ± 0.2 | 2 |

Mean ± SD; n = 28.

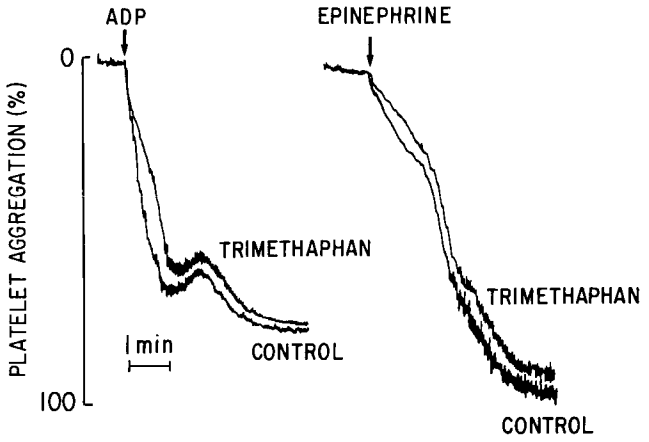


FIG. 1. Administration of trimethaphan did not result in any significant alteration of platelet function as assessed *via* ADP- and epinephrine-induced aggregation studies.

## Discussion

Trimethaphan is a vasodilator and ganglionic blocker that directly relaxes capacitance vessels and blocks autonomic nervous system reflexes. The sympathetic blockade produced by trimethaphan reflects occupation of receptors normally responsive to acetylcholine as well as stabilization of the postsynaptic membrane against the actions of acetylcholine liberated from nerve endings. As a result, trimethaphan is a potent vasodilator useful in the treatment of perioperative hypertension and low cardiac output syndromes. The therapeutic advantage of vasodilators for control of blood pressure and vascular resistance in the treatment of perioperative myocardial dysfunction is well described.[11–14] However, in the pharmacologic management of the cardiac surgical patient, it is crucial that any agent chosen to accomplish these goals does not adversely affect normal hemostatic mechanisms.

Previous studies have shown that sodium nitroprusside (SNP) inhibits platelet aggregation at clinical relevant doses.[15] Numerous mechanisms have been proposed to explain the mechanism of platelet inhibition seen following SNP administration. Early investigators thought these inhibitory effects might be secondary to the direct inhibition of actinomycin.[15,16] However, more recent studies have described a more complex and multifactorial etiology focus on the generation of endothelium-derived relaxing factor (EDRF).[17–22] Although this hypothesis represents one of the most widely investigated areas of nitrate-induced platelet inhibition it represents only a partial explanation of the entire process responsible for platelet dysfunction.[23] The effects of prolonged exposure to nitrates on EDRF needs to be further investigated to more precisely define and establish the central link in the EDRF hypothesis.

In an attempt to elucidate the effect of trimethaphan upon platelet function *in vitro,* this study uses the doses of trimethaphan most frequently employed in the perioperative management of cardiac surgical patients (1–4 mg/min). These data demonstrates that trimethaphan at clinically relevant doses does not alter platelet function as assessed *via* epinephrine- or ADP-induced aggregation studies. These assays provide the most sensitive modalities for evaluating platelet function *in vitro.* In patients receiving trimethaphan at 1–4 mg/kg (accepted therapeutic range) no significant deviation from baseline aggregation was observed. This is in direct contrast to the inhibitory effect seen on platelet function following sodium nitroprusside administration. Results of a recent study demonstrate that the infusion of SNP at clinically acceptable doses (SNP $\geq$ 3 mg $\cdot$ kg$^{-1}$ $\cdot$ min$^{-1}$) results in a dose-related decreases in platelet aggregation.[1] Platelet aggregation was determined in this study by exposing platelet-rich plasma from patients receiving SNP to either epinephrine (5 mM) or ADP (2 mM). The preparation of all samples (*i.e.,* for platelet aggregation) were handled in a way identical to methods described in this report.

In addition, prolongation of bleeding time measurements have also been reported with the use of nitroprusside and nitroglycerin.[5,23] The mechanism by which these agents produce a dose-related prolongation of bleeding time is thought to be due to vasodilation and a secondary increase in venous capacitance. However, the effect of trimethaphan on platelet aggregation and bleeding time has not been previously determined. Of note, bleeding time measurements performed during trimethaphan administration revealed no significant deviation from baseline values. This lack of alteration in bleeding time following trimethaphan's administration is in contrast to the previously described increase in bleeding time measure-

TABLE 2. Bleeding Time Determination and Platelet Aggregation in the Control Patient Population

| Time | % Aggregation (ADP) | % Aggregation (EPI) | Bleeding Time (min) | n |
|---|---|---|---|---|
| Baseline | 74 ± 0.6 | 82 ± 1.3 | 4.6 ± 0.5 | 10 |
| 30 min postinduction | 76 ± 0.2 | 79 ± 0.9 | 5.1 ± 0.3 | 10 |
| 60 min postinduction | 74 ± 0.3 | 81 ± 1.2 | 4.8 ± 0.8 | 10 |
| 90 min postinduction | 73 ± 0.2 | 80 ± 0.7 | 5.3 ± 0.6 | 10 |

Mean ± SD; n = 10.

ments following other vasodilator therapy.[5,24] The proposed mechanism responsible for changes occurring in bleeding time (secondary to vasodilation) focuses on an increase in venous capitance seen with these agents. This theory was initially proposed by Leier *et al.* when they were able to demonstrate that whenever NTG decreased limb vascular resistance and increased limb blood flow, bleeding time was increased.[25] Subsequent investigations noting a prolongation of bleeding time associated with NTG used this explanation of a prolonged bleeding time associated with vasodilation to "be compatible with the idea that larger aggregates would be required to plug a dilated vessel."[5] However, as trimethaphan (*via* ganglionic blockade) also increases venous capitance but did not prolong bleeding time, this suggests that an alternative mechanism must be responsible for the prolonged bleeding time seen with in SNP and TNG. Although prostacyclin has been suggested as a possible mediator in the abnormalities of bleeding time observed with TNG, further investigations are now needed to more specifically identify the precise mechanism.[26,27]

In summary, the combination of trimethaphan's ability to preserve platelet function and maintain normal hemostatic parameters (as assessed *via* the bleeding time measurements) suggests it as an attractive therapeutic alternative for the control of hypertension in the perioperative period.

## References

1. Hines R, Barash PG: Infusion of sodium nitroprusside induces platelet dysfunction *in vitro*. ANESTHESIOLOGY 70:611–615, 1989
2. Saxon A, Kattlove HE: Platelet inhibition by sodium nitroprusside, a smooth muscle inhibitor. Blood 47:957–961, 1976
3. Graybar G, Lobar D, Jones J: Comparison of nitroprusside and nitroglycerin in perioperative blood loss with open heart surgery. Crit Care Med 240–242, 1980
4. Feelisch M, Noack E: Nitric oxide (NO) formation from nitrovasodilators occurs independently of hemoglobin or non-heme iron. Eur J Pharmacol 142:465–469, 1987
5. Lichtenal P, Rossi E, Louis G, Rehnberg K, Wade L, Michaelis K, Fung HL, Patrignani P: Dose related prolongation of the bleeding time by intravenous nitroglycerin. Anesth Analg 64: 30–33, 1985
6. Mielke CH Jr, Kaneshiro MM, Maher JA, Weiner JM, Rappaport SI: The standardized normal IV bleeding time and its prolongation by aspirin. Blood 34:204–15, 1969
7. Fyman P, Triner H, Schranzlt, Hartung J, Cashely PA, Abrams LM, Keaney AE, Cottrell JE: Effect volatile anesthetics and nitrous oxide—Fentanyl anesthesia on bleeding time. Br J Anaesth 56:1197–1200, 1984
8. Stengert KB, Harrison J, Lazerson J: Isoflurance (Forane) induced platelet dysfunction. Anesth Analg 62:245–92, 1983
9. Stengert KB, Sellick CL, Lazerson L: Halothane induced platelet dysfunction. Anesth Analg 61:212–218, 1982
10. Born GVR: Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature 196:927–928, 1962
11. Snow N, Lucas A, Gray R: Effect of sodium nitroprusside on postoperative blood loss in the cardiac surgical patient. Crit Care Med 2:827–828, 1981
12. Leler CV, Bambach D, Thompson MJ, Cattaneo SM, Goldberg RJ, Unverferth DV: Central and regional hemodynamics effects of intravenous post isosorbide dinitrate, nitroglycerin and nitroprusside in patients with congestive heart failure. Am J Cardiol 48:115–123, 1981
13. Cohn JN, Franciosa JA: Vasodilator therapy of cardiac function. N Engl J Med 297:232–37, 1977
14. Mehta J, Iacona M, Feldman RL, Lepine CJ, Conti CR: Comparative hemodynamic effects of intravenous SNP and oral prazosin in refractory heart failure. Am J Cardiol 41:925–931, 1978
15. Schaffer AI, Alexander RW, Handin RI: Inhibition of platelet function by organic nitrate vasodilators. Blood 55:649–654, 1980
16. Cunningham M, Los Calzo J: Nitroprusside can induce clinically important platelet dysfunction only detectable in vitro by incubation with reduced thiol (abstract). Clin Res 33:337A, 1985
17. Furlong B, Henderson AH, Lewis MJ, Smith JA: Endothelium-derived relaxing factor inhibits in vitro platelets aggregation. Br J Pharmacol 90:687–692, 1987
18. Hawkins DJ, Meyrick BO, Murray JJ: Activation of guanylate cyclase and inhibition of platelet aggregation by endothelium-derived relaxing factor released from cultured cells. Biochim Biophys Acta 969:289–296, 1988
19. Furchgott RF, Zawadzki JV: The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 288:373–376, 1980
20. Azuma H, Ishikawa M, Sekizaki S: Endothelium-dependent inhibition of platelet aggregation. Br J Pharmacol 88:411–415, 1986
21. Fiscus RR, Rapoport RM, Murad F: Endothelium-dependent and nitrovasodilator-induced activation of cyclic GMP-dependent protein kinase in rat aorta. J Cyclic Nucleotide Protein Phosphor Res 9:415–425, 1983
22. Moncada S, Palmer RMJ, Higgs EA: The discovery of nitric oxide as the endogenous nitrovasodilator. Hypertension 12:365–372, 1988
23. Hines R, Barash PGB: Reply to Letter. ANESTHESIOLOGY 71: 805–806, 1989
24. Ring T, Knudsen F, Kristensen S, Larsen C: Nitroglycerin prolongs the bleeding time in healthy males. Thromb Res 29:553–559, 1983
25. Leier CV, Bambach D, Thompson MJ, Cattaneo SM, Goldberg RJ, Unverferth DV: Central and regional hemodynamic effects of intravenous isosorbide dinitrate, nitroglycerin, and nitroprusside in patients with congestive heart failure. Am J Cardiol 48:115–23, 1981
26. Steer ML, MacInatyre DE, Levine L, Salzman EW: Is prostacyclin a physiologically important circulating anti-platelet agent? Nature 283:194–195, 1980
27. FitzGerald GA, Pedersen AK, Patrono C: Analysis of prostacyclin and thromboxane biosynthesis in cardiovascular disease. Circulation 67:1174–1177, 1983