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## Activated Clotting Times and Cardiopulmonary Bypass II: The Accuracy of Activated Coagulation Time Protamine Dose Calculations

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**Michael A. Newsome, B.S.; Leon J. Camerlengo, B.S.; and James P. Dearing, B.S., C.C.P.**

From the Extracorporeal Circulation Technology Program  
and the  
Division of Cardiothoracic Surgery  
Medical University of South Carolina  
Charleston, South Carolina

### Introduction

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Protamine has been demonstrated to neutralize heparin effectively both in vivo and in vitro.<sup>1,2</sup> In 1976 Guffin et al. demonstrated increases in the prothrombin time and partial thromboplastin time with increases in protamine dose. Guffin also demonstrated increased chest tube drainage after surgery with increasing protamine overdoses.<sup>3</sup> These effects were attributed to the fact that protamine is an antithromboplastin. Recently, protamine has been found to demonstrate this effect through inhibition of clotting factors IX and activated X.<sup>4,5</sup> It has additionally been shown to cause platelet aggregation as well as a striking factor VIII deficiency.<sup>6</sup>

Systemic effects of protamine include arterial hypotension, brady-cardia, decreased cardiac output, decreased total vascular resistance, increased resistance and decreased blood flow in the superior mesenteric artery.<sup>7</sup>

With the side effects of protamine in mind, the importance of estimating the proper protamine dose for heparin neutralization after cardiopulmonary bypass (CPB) should become obvious. One method employed for estimating the protamine dose is protamine titration, a quantitative assay for heparin. Another method employed is the measurement of the Activated Clotting

Time (ACT)<sup>9</sup> as described by Bull et al.<sup>10</sup> This study was performed to validate the use of ACT dose response curve (ACT/DRC) in predicting protamine doses.

### Methods

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Forty adult patients undergoing routine CPB for periods of one to three hours were utilized in this study. The patient population is described in Table I. Each patient was perfused with the Travenol modular pump and a Travenol Membrane Oxygenator.\* A Pall arterial line filter\*\* was incorporated. The pump was primed with two thousand ml. of Ringers Lactate, five hundred ml. of six percent Hydroxyethyl Starch (Volex)\*\*\* and 1,500 units of beef lung heparin.\*\*\*\*

For each patient, a heparin DRC was constructed in a manner similar to that as described by Bull.<sup>10</sup> A baseline ACT was drawn prior to any major surgical trauma and recorded. The patient's heparin loading

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\* Travenol Laboratories, Deerfield, Illinois

\*\*Pall Biomedical Products Corp., Glen Cove, New York

\*\*\* McGaw Laboratories, Atlanta, Georgia

\*\*\*\* Upjohn Laboratories, Kalamazoo, Michigan

TABLE I  
Patient Population

# Cases	Operation	Mean Pump Time
21	CABG	2 hr. 44 min.
5	MVR	2 hr. 22 min.
6	AVR	2 hr. 2 min.
1	VSD closure	2 hr. 7 min.
3	ASD closure	57 min.
3	AVR/MVR	2 hr. 32 min.
1	Mitral Valvulotomy	55 min.

dose was determined by body weight (300 units per kilogram). Five minutes after heparin administration, a second ACT was determined and these two points were used to construct the DRC. Anticoagulation was managed with this response curve and the ACT value kept between 3.5 to 4.5 times the base line ACT. A modified Hattersley<sup>9</sup> technique for ACT determination was used, tilting the tube every ten seconds instead of five seconds.

The patients were randomly assigned to Group I (ACT) or Group II (protamine titration). At approximately ten minutes prior to termination of CPB, both an ACT and five tube protamine titration<sup>8</sup> were performed to estimate the residual heparin concentration. After termination of CPB, protamine was administered on a mg. to mg. basis, the actual dose being randomly selected from either of the two dose calculations. Twenty minutes after the protamine administration, an ACT, protamine titration, Lee White Time, thrombin time, prothrombin time, partial thromboplastin time, fibrinogen concentration and platelet count were measured. At the time of chest tube re-

TABLE II  
Heparin and Protamine Dosages

	Group	
	I	II
Protamine Administered* (mg/kg)	2.34 ± 0.53	1.84 ± 0.76
Initial Heparin Administered (mg/kg)	3:00 ± 0.00	3.00 ± 0.00
Additional Heparin Administered (mg/kg)	0.71 ± 0.63	0.56 ± 0.63
ACT/DRC Predicted Protamine Dose (mg/ kg)	2.34 ± 0.53	2.48 ± 0.91
Protamine Titration Predicted Protamine Dose (mg/kg)	2.14 ± 0.56	1.84 ± 0.76

\* Comparing Groups I and II (p < .05)

moval, total post operative blood loss was recorded. All statistical comparisons of the two groups were made by the student's t-test.

## Results

Table II is a summary of the heparin and protamine doses estimated and administered to the two groups. Although the heparin doses for the two groups were not significantly different, the protamine doses administered were significantly different (p < .05). When the ACT/DRC was used to predict protamine doses, 10% more protamine was given to Group I than would have been given had the protamine titration method been used. Thirty-five percent more protamine would have been given to Group II using the ACT/DRC method rather than the protamine titration.

The average protamine/heparin ratios for the two groups differed by 21%. (Group I .63/1 and Group II .52/1).

Table III summarizes the post-pump studies and compares results between groups. There were no statistically significant differences between groups in coagulation parameters, platelet count, fibrinogen concentration or post operative bleeding. Furthermore, both protamine titration and thrombin time indicate that all heparin was neutralized.

## Discussion

Although the simplicity of the ACT/DRC makes it an attractive means for estimating heparin concentration, its limitations must be recognized. Since the ACT may be affected by factors other than heparin concentration, the linear relationship assumed between the heparin concentration and the ACT may not be constant. Hemodilution, coagulation factor depletion<sup>11</sup> and hypothermia<sup>12</sup> have all been shown to prolong the ACT and thus might lead to over estimation of the protamine dose. In those cases where a non-heparin induced prolongation of the ACT is suspected, protamine titration should be used to determine the protamine requirement.

The ACT/DRC and protamine titration methods for protamine dose estimation were not compared to any of the standard protocols that require a 1:1 or greater protamine:heparin dose.<sup>3,13,14</sup> The investigators felt that it was morally indefensible to administer such large protamine doses in light of the significant prolongation of prothrombin time and partial thrombo-

TABLE III  
Postoperative Results

	Group		Significance*
	I	II	
Prothrombin Time (sec)	15.2 ± 1.56	15.3 ± 1.32	NS
Partial Thromboplastin Time (sec)	34 ± 16	33 ± 7	NS
Thrombin Time (sec)	25.3 ± 22.3	24 ± 26.4	NS
Protamine Titration (mg/ml)	.005	.005	NS
Fibrinogen (mg/dl)	160 ± 36	157 ± 44	NS
Platelets (thousand/mm <sup>3</sup> )	133 ± 45	107 ± 43	NS
ACT (sec)	101 ± 8.5	105 ± 13	NS
Lee-White Time (min)	5.8 ± 1.38	6.27 ± 1.48	NS
Total Chest Tube Drainage (ml)	339 ± 250	395 ± 180	NS

\* Comparing groups I and II

plastin time, decreased platelet count, and increased post operative bleeding reported when a 1:1 protocol was used.<sup>3</sup>

### Conclusion

The data collected show that for routine CPB cases of one to three hours, the ACT/DRC is effective for calculating a protamine dose. Although it yields a slight over estimation, the overdose has no clinical significance.

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