CLINICAL CIRCULATION II — CARDIOPULMONARY BYPASS

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DO SKIN TESTS CORRELATE WITH ANTIBODIES TO PROTAMINE?

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Life-threatening reactions to protamine constitute rare events, even among patients at theoretically greater risk due to protamine antibody presence.[1-3] Pre-screening for serum antibodies may be neither cost effective nor predictive of clinical outcome. Might skin testing prove more realistic?

With IRB approval, 32 patients for cardiac surgery gave informed consent to receive volar forearm skin testing[4] prior to induction of anesthesia with sufentanil-oxygen. Preservative-free saline 0.9% (S, negative control), d-tubocurarine 100 µg/mL (C, positive control), protamine 1 µg/mL (P)[4] and protamine 10 µg/mL (10P) were each injected intradermally as 0.02 mL via 27ga. needle. Coded syringes permitted double-blinded placement and measurement to eliminate operator bias. Measurements of skin induration diameter (1mm precision) occurred 10 and 30 min after injection but prior to anesthesia. Serum withdrawn prior to skin tests and frozen at -60°C underwent batch testing via ELISA for anti-protamine IgE, IgE_2, and IgG (AlerCHECK, Portland, ME). The false positive rate is 6% for IgE_2, and not quantitated for IgE or IgG. Fisher's exact test compared skin tests results with antibody presence.

Of the 32 patients, 9 were diabetic, 2 took NPH insulin, 3 had undergone vasectomy in the distant past. Heparin dose (≥300 U/kg) ranged from 16-40 K units, neutralized by protamine, 250-500 mg by slow iv infusion. Shipment error prevented antibody analysis of 4 samples. Since responses to curare and saline at 10 mins (**Table 1**) disclosed that an 8mm induration diameter criterion provided best sensitivity, specificity, and predictive value, a response ≥8mm at 10 min or 30 min defined a (+) response to P or 10P. "Positive" antibodies required titres at 1:10 or higher dilution. **Table 2** displays the skin test and antibody results. All patients displayed IgG at high titres (1:1600+). **Table 3** correlates antibody titres with skin tests. No patient experienced adverse sequelae of protamine infusion after bypass.

TABLE 1

	10mm	9mm	8mm	7mm
(+) C [sens]	22%	66%	78%	84%
(-) S [spec]	100%	100%	91%	81%
Pred.Val [+,-]	100,57%	100,74%	86,81%	75,82%

TABLE 2 Frequency of + results of skin tests and antibodies

Category	+P	+10P	+IgE	$+IgE_2$	+ IgG
Overall	4/32 (25%)	10/32	13/28 (46%)	15/28	28/28
Diabetics	1/ 9	3/ 9	6/ 8	5/ 8	8/ 8
NPH pts	0/ 2	1/ 2	1/ 2	1/ 2	2/ 2
Vasectomy	0/ 3	1/ 3	1/ 3	1/ 3	3/ 3

TABLE 3 Frequency of + skin tests and + antibodies

Skin Tests ↓; Antibodies →	+IgE	-IgE	$+IgE_2$	$-IgE_2$
Positive P	2	1	2	1
Negative P	11	14	13	12
Positive 10P	2	4	2	4
Negative 10P	11	11	13	9

P>.05 (NS) FOR ALL 4 COMPARISONS BY FISHER'S EXACT TEST.

This study utilized a ≥8mm standard for + skin test since the usual 10mm one was insensitive. Despite no adverse response, 25% of patients had + skin tests and ≥46% had antibodies. Skin tests are known for poor specificity. Antibody presence despite absence of clinical sequelae agrees with previous work. Since no patient had a clinical reaction, this small series cannot address sensitivity. Skin tests do not correlate with antibodies to protamine.

REFERENCES
1. Ann Allergy 61:277, 1988 2. N Engl J Med 320:886, 1989
3. J Thorac Cardiovasc Surg 98:200, 1989
4. Anaesth Intensive Care 12:115, 1984

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TITLE: CALCULATING THE PROTAMINE - HEPARINE REVERSAL RATIO

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Introduction: There is no consensus as to the dosage of protamine required to reverse a given dose of heparin. The amounts advised may vary widely e.g.

A. 1 mg protamine per mg heparin activity remaining (as calculated from the dose-response curve - Bull[1]).
B. 1 mg protamine per mg of heparin administered initially (e.g. 4 mg per kg protamine for patients receiving 4 mg per kg heparin which is the present practice in our institution)

We investigated the hypothesis that doses of protamine smaller than the above recommendations could be used following cardiac bypass surgery to successfully reverse the heparin activity as measured by activated clotting time (ACT). Institutional approval was obtained.

Method: A group of 20 patients scheduled for cardiopulmonary bypass surgery were investigated with their informed consent. A baseline ACT was measured before anticoagulation with heparin (4 mg/kg). An intra-operative ACT >480 sec was ensured and maintained by further doses of heparin. At the end of cardiopulmonary bypass protamine 2 mg/kg ("half-dose") was administered. The ACT was measured after 5 minutes and a further dose of protamine ("full-dose") 2 mg/kg was then administered. The heparin activity before and after half-dose protamine reversal was calculated according to the method described by Bull. The dose of protamine (2 mg/kg) was expressed as a ratio of the change in heparin activity (the latter also expressed as mg/kg). All ACT measurements were done in duplicate.

Results: The average age (± standard deviation) of the 20 patients was 40.6 ± 15.1 years with a range of 15 - 71 years. The average pre-operative ACT was 158.4 ± 21.7 sec with a range of 130 - 199 sec. Following heparin administration the ACT increased to 602 ± 153.1 seconds. After the first dose of protamine ("half-dose") of 2 mg/kg the average ACT of 159.95 ± 29.1 (range 121 - 250) was not statistically (NS) significantly different from the starting value. A further dose of 2 mg/kg of protamine ("full-dose") decreased (NS) the ACT only minimally to an average of 150.25 ± 18.1 (range 128 - 206) seconds. The heparin activity before and after half-dose protamine reversal was 3.78 ± 1.15 mg/kg (range 2.34 - 6.19) and -0.04 ± 0.29 (range -0.37 ± to 1.16). This change in heparin activity was caused by an average dose of 2.09 ± 0.36 mg/kg protamine i.e. 1 mg of heparin activity was reversed by 0.598 ± 0.15 mg of protamine.

Discussion: The methodology allowed us to calculate an in vivo protamine-heparin reversal ratio. In other words, this enabled a new method of calculation of the protamine requirement to reverse heparin activity (as expressed by the Bull dose-response method). The average protamine requirement for reversal of 1 mg/kg heparin activity was 0.598 mg/kg after "half-dose" protamine. No advantage as measured by ACT was gained by administration of a further dose of protamine.

Conclusion: The dosage of protamine required to reverse heparin is less than commonly used. Larger dosages of protamine cause no further significant change of ACT. Further studies are indicated to determine effective heparin reversal (vis-a-vis normalised ACT) as measured by post operative blood loss following such smaller dosages of protamine.

Reference: J Thorac Cardiovasc Surg. 1975; 69: 685-689.