

**Original Article**

## ***Do Different Heparin Brands Influence Activated Clotting Times?***

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### **ABSTRACT**

A change in brand suppliers of heparin at our institution resulted in a number of anecdotal reports of possible differences in potency. Both products are marketed as heparin sodium extracted from porcine intestinal mucosa. Heparin Leo® is 1000 international units (British Pharmacopeia) per ml. while Hepalean® is 10000 United States Pharmacopeia (U.S.P) units per ml.

Perfusion records were retrospectively reviewed for one month periods when Heparin Leo® (n=52) or Hepalean® (n=61) were used to provide anticoagulation therapy for cardiopulmonary bypass.

Heparin Leo® was found to be less clinically potent than Hepalean®. While increasing the initial loading dose of Heparin Leo® by 5% (378 vs 395 units/kg<sup>-1</sup>), the initial post load activated clotting time (ACT) was 17% lower (556 vs 666 seconds). Heparin units required per kilogram per minute of cardiopulmonary bypass were 23% higher for Heparin Leo®. Additionally 8 of 52 Heparin Leo® patients did not achieve an initial post load ACT of greater than 400 secs while this occurred in 2 of 61 patients treated with Hepalean®. These results were statistically significant.

British Pharmacopeia and United States Pharmacopeia heparin reference standards differences are insufficient to explain the discrepancies observed in this study.

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## INTRODUCTION

Heparin is extensively utilized to attain anticoagulation during cardiopulmonary bypass. Prior to July 1996, our hospital was supplied with Hepalean®<sup>a</sup>. Because of contractual obligations to a group purchase plan we were obligated to change suppliers and subsequently received Heparin Leo®<sup>b</sup>. Within several weeks of the product change, numerous anecdotal reports were received from both perfusionists and cardiac anesthesiologists suggesting that Heparin Leo® was not the same potency as Hepalean®. Both Heparin Leo® and Hepalean® are marketed as heparin sodium extracted from porcine intestinal mucosa. Heparin Leo® is provided as 1000 International Units (I.U.) per millimeter as defined by the British Pharmacopeia (BP) (1) while Hepalean® is 1000 U.S.P. units as defined by the United States Pharmacopeia (2,3). We therefore sought to document our experience with a change from Hepalean® to Heparin Leo®.

## MATERIALS AND METHODS

We retrospectively reviewed the perfusion records for open heart surgery patients operated on for the time periods October 1995 and October 1996. October 1995 represented exclusive Hepalean® utilization while in October 1996 only Heparin Leo® was used. There are five cardiac surgeons on staff at our institution.

Surgical procedures included; coronary artery bypass grafting, valvular replacement and ascending aortic aneurysm repair. Patients who received concomitant aprotinin therapy or who were treated with profound hypothermia and/or circulatory arrest were excluded from this review. All patients received epsilon amino caproic acid. This is routinely administered after induction of anesthesia as a 4 g loading dose over twenty minutes followed by an infusion of 1 g/hr for the duration of the surgical procedure. After determination of baseline ACT and on the surgeon's request a loading dose of heparin is administered via a central venous route. Samples for ACT determination are withdrawn from the patient's arterial line, except during cardiopulmonary bypass when samples are taken from the arterial sample port of the oxygenator. A post load ACT is taken approximately five

minutes after heparin administration. Subsequent ACT determinations are taken at least at 15-20 minute intervals; after further heparin administration and as required. Heparin bolusing during cardiopulmonary bypass (CPB) is left to the discretion of the perfusionist-in-charge. Guidelines for additional heparin include maintaining an ACT greater than 500 secs, a rapidly falling ACT as well as anticipated case duration. Heparin therapy was monitored utilizing an activated clotting time. Actual determinations of ACT were performed using high range 0.2 molar buffered Kaolin reagent<sup>c</sup>. All ACTs were averaged using dual chamber determinations. The Hemotec ACT instrument is temperature calibrated, using a distilled water filled cartridge in the actuator to 37±.5°C and functionally tested with a Hemotec® control (stabilized sheep red blood cells and plasma).

Five thousand units of heparin were also routinely added to the cardiopulmonary bypass prime. The requirement for supplemental heparin during cardiopulmonary bypass was determined by ACT measurements of less than 500 secs. If this occurred a bolus of 5000 units of heparin was administered.

Cardiopulmonary bypass was accomplished by a non occlusive roller pump<sup>d</sup>. Pulsatile flow, hollow fiber membrane oxygenators<sup>e</sup> and a 25µm arterial line filter were utilized on all cases. CPB flows are routinely maintained between 1.9 and 2.5 l/min/m<sup>2</sup> body surface area. A 4:1 blood cardioplegia ratio is routine as is arterial blood gas management by alpha stat.

- a Heparin sodium injection USP, Organon, Teknika
- b Heparin sodium injection BP, Leo Laboratories
- c Hemotec® Medtronic, Inc., Englewood, CO 80112
- d Cobe® Perfusion Systems, Arvada, CO 80004
- e Capiiox SX®, Terumo Medical Corp., Somerset, NJ, or Affinity®, Avacor Cardiovascular, Inc., Plymouth, MN 55443

**Table 1: Hepalean® – Heparin Leo® comparison**

	HEPALEAN® n = 61	HEPARIN LEO® n = 52	% CHANGE	P VALUE (t - test)
Loading Dose [units/kg]	378 (±57)	395 (±24)	↑ 5%	P < 0.05
Control ACT [seconds]	156 (±17)	149 (±18)		NS
Post Load ACT* [seconds]	666 (±172)	556 (±141)	↓ 17%	P < 0.0001
Total Heparin administered [units/kg]	512 (±78)	678 (±233)	↑ 32%	P < 0.0001
Heparin Utilization Index** [units/kg/min]	4.8 (±2.0)	5.9 (±2.6)	↑ 23%	P < 0.01
Cardiopulmonary bypass time [minutes]	124 (±47)	136 (±70)		NS
Patient Weight [kilograms]	79 (±16)	83 (±12)		NS
CABG	50	40		
Combined	2	5		
Valve Replacement	7	5		
Other	2	2		

Data given as mean(standard deviation); \*ACT = activated clotting time; \*\* Total heparin administered per kilogram per minute of cardiopulmonary bypass duration; NS = not significant; CABG - coronary artery bypass grafting; Combined = CABG plus valve replacement; Valve replacement = aortic, mitral or both; Other = root replacement, ascending aortic aneurysm repair

Parameters recorded included body weight, heparin loading dose, ACT recorded after the initial loading dose of heparin, total heparin utilized for the case and finally cardiopulmonary bypass time. Data analysis was by students' t-test and Fisher's Exact test.

## RESULTS

Data summary and calculated indices are shown in Table 1. The loading dose of heparin was increased by 5% and the initial post-load ACT was reduced by 17% for Heparin Leo®. Total heparin (on a per kilogram basis) was increased by 32%, while the heparin utilization index (units heparin/kg/min of cardiopulmonary bypass duration) increased by 23% for Heparin Leo®. There was no significant difference in either body weight, control ACT or cardiopulmonary bypass time between the two groups.

Table 2 summarizes the number of patients in each group where the ACT was less than 400 seconds after the initial heparin load. Eight of 52 patients who received Heparin Leo® did not attain an initial ACT of 400 seconds while two of 61 patients who received Hepalean® also had an ACT of less than 400 seconds.

## DISCUSSION

Previously published standards (1,2,3) have not demonstrated any chemical differences between Heparin Leo® or Hepalean®. Both are referred to as heparin sodium injection preparations and are comparable on the basis of molecular weight distribution, ratio of anti-Xa: anti-IIa activity or protamine neutralization requirements. Reference standards to assign potency are, however, not equivalent. The potency of Heparin Leo® is assigned by International Units as per the British Pharmacopoeia (BP) (2). Hepalean® potency is expressed in USP units according to assay methods and a reference standard of the United States Pharmacopoeia (USP) (3).

USP and BP reference standards have been compared previously (1) utilizing other assays of anticoagulant activity such as activated partial thromboplastin time, thrombin inhibition and factor -Xa inhibition. On a per unit basis, USP heparin is approximately 7% more potent than BP heparin. The reported difference in potencies(1) is insufficient to explain a 23 percent increase in the heparin utilization index for Heparin Leo® as reported in this study.

Of greater concern were the increased number of patients who failed to reach a threshold ACT (400 seconds) with the initial Heparin Leo® bolus. The 5% augmented heparin bolus, likely reflective of our institution's previous experience with BP assayed heparin, was insufficient to prevent the above from occurring. Recognizing that a threshold ACT of 400 seconds to demonstrate anticoagulation as safe for cardiopulmonary bypass,

**Table 2: Heparin Bolus and Anticoagulation**

	HEPALEAN®	HEPARIN LEO®
Initial ACT >400	59	44
Initial ACT <400 seconds	2	8*
Loading Heparin Dose (units•Kg <sup>-1</sup> )	378 (±57)	395** (±24)

ACT = Activated clotting time; \* P < 0.05 Fisher's Exact test; \*\* P < 0.05 Student's t-test. Data given as mean(standard deviation).

is arbitrary, it nonetheless can result in a significant intraoperative delay.

This study is not the first to suggest a clinically significant difference between heparin sodium brands. Hamilton et al (4) reported their concerns at the 1993 annual meeting of the Canadian Society of Clinical Perfusion. Unlike this study they reported a three month experience using Heparin Leo® (300 units/kg) for CPB. Gross thrombi were reported in 35% of the CPB circuits post event. Their minimum required ACT prebypass was 400 sec.

Although we are not aware of any other significant practice changes between the two time periods sampled, this retrospective study does not document patient gender, integrated patient temperatures, pre-, peri-, and postoperative coagulopathies, or preoperative heparin administration. Other authors report a significant number of patients who develop heparin antibodies especially with prolonged exposure (5).

Many other surgical disciplines routinely administer heparin on an empiric basis prior to vascular occlusion (carotid endarterectomy, abdominal aortic surgery, peripheral vascular anastomosis etc). ACT or other indices of heparin effect are not routinely monitored. Our data would suggest this practice should be revisited when using Heparin Leo®. The use of increased total Heparin Leo® as opposed to Hepalean® may also affect the ratio of anti-Xa to anti-IIa activity. The implications of Hepalean®-Heparin Leo® differences on protamine reversal are not addressed by this study.

In summary we observed a significant increase in the amount of heparin required for anticoagulation during cardiopulmonary bypass which cannot be explained by the pharmacological description of activity. Clinical effectiveness and documented potency must both be considered during a cost benefit analysis of any pharmacologic agent. The limitations of a retrospective analysis are recognized. A prospective double blinded clinical trial comparing Heparin Leo® and Hepalean® is warranted.

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