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# The Hemochron® Response RxDx® Heparin and Protamine Dosing System

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**Abstract:** The use of dosing assays to calculate heparin and protamine dose requirements during cardiac surgery has been shown to significantly improve overall postoperative patient outcome. When patients are managed with an individualized dosing system, intraoperative and postoperative transfusion requirements and bleeding are reduced. The Hemochron® RxDx® system is widely used as a complement to traditional activated clotting time testing to optimize anticoagulation management. The system consists of the heparin response test, the protamine response test, and the protamine dose assay. All are modifications of the activated clotting time using either Celite® (Celite Corporation, Santa Barbara, CA) or kaolin as the activator. Dosing is calculated manually using earlier version Hemochron instruments (model 801) or automatically with the Hemochron 8000 or with the early versions of the Hemochron® Response and the personal digital assistant (PDA) RxDx calculator. Missing from available user options is an automated RxDx system for the Response. A study was conducted at four clinical sites to compare recently developed Response RxDx software, which eliminates the need for the PDA RxDx calculator, to the existing Hemochron 8000 RxDx and to the Response-PDA RxDx systems. Similar to the current system, the operator inputs the patient's height, weight, and gender, and the software automatically calculates the blood volume. Using the clotting times determined on the Response, bolus heparin and protamine doses and any additional heparin and protamine requirements are calculated automatically. Data were collected from 76 patients, of which, 64 patients were on pump, 11 patients were off pump, and 1 patient was converted from off to on pump. The Response estimated blood volume calculations showed a correlation coefficient of 0.989 when compared with available systems. A good correlation was also observed for the bolus heparin ($r = 0.925$) and protamine doses ($r = 0.900$) with equivalence confirmed by a paired student's *t* test. These data confirm that the Response RxDx system yields results that are identical ($P > 0.05$) to those obtained using the Hemochron 8000 RxDx or Response-PDA RxDx calculator. The Response RxDx also offers expanded user options related to blood volume limits, expanded clotting time ranges for presetting default values, and flexibility in test sequence. Case records can be printed or downloaded to a PC via the HRDM data management program. The Hemochron Response RxDx represents a complete anticoagulation management system for the cardiac surgical patient. **Keywords:** Hemochron Response RxDx, heparin, protamine, cardiac surgery. *JECT. 2004;36:258–262*

During cardiopulmonary bypass surgery (CPB), patients are anticoagulated with high doses of heparin on the order of 300–500 units per kilogram body weight. Heparin is a sulfated mucopolysaccharide that inhibits the action of thrombin on fibrinogen by potentiating antithrombin (1), thereby interfering with the blood clotting cascade and preventing blood clots within the patient's circulatory system and the extracorporeal circuit. Protamine, a heparin antagonist, is administered at the end of CPB to neutralize the effects of any circulating heparin remaining in the patient's system (2). It is critical to determine the appropriate dose of both heparin and protamine to give each individual patient to minimize the potential for adverse patient outcomes. The use of dosing assays to calculate patient-specific heparin and protamine requirements has been shown to significantly improve intraoperative and overall postoperative outcomes, including reduction of bleeding and transfusion requirements (3,4).

The Hemochron® RxDx® system (International Technidyne Corporation, Edison, NJ), which is widely used for anticoagulation management (5), uses *in vitro* dose re-

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sponse tests to determine the patient's heparin requirement using the heparin response test, protamine dose required to reverse the effects of heparin using the protamine response test, and verification of complete heparin neutralization using the protamine dose assay (PDA-O) (6).

Although the original RxDx program was a manual operation for earlier model Hemochron systems (eg, 801), automated calculations are available with the Hemochron 8000 or by using a personal digital assistant (PDA RxDx calculator). Recently, automated RxDx calculation software was developed for the Hemochron Response. Similar to current methods, the operator inputs the patient's height, weight, and gender; then, the system automatically calculates the blood volume. As the surgical case progresses, heparin and protamine dose calculations are made automatically based on clotting time test results. This is used for both initial and subsequent dosing of these pharmaceuticals.

This clinical study was conducted to examine the equivalence of Response RxDx calculations to those of the systems currently in clinical use: the Hemochron 8000 and the Response with the PDA RxDx calculator. The successful completion of this verification trial demonstrates the clinical value of the Response RxDx for management of the cardiac surgery patient.

## MATERIALS AND METHODS

Standard hospital procedures for dosing were followed at the respective study sites. Institutional review board approvals were obtained as required by each site. All anticoagulation monitoring assays were performed simultaneously with the native system in place at the respective study site (Table 1) as well as the new Response RxDx system using both Celite® and kaolin activated assays. Dosing calculations performed by the Response were recorded for informational purposes only. All dose administration judgments were based upon the Hemochron 8000 RxDx system or the Response–PDA RxDx calculator system. Patient selection criteria consisted of any patient undergoing cardiac surgery. Patients were excluded from the trial if clinical judgment indicated that alternative dosing protocols were to be used.

### Statistical Analyses

All correlation statistics were established using linear regression models, mean vs. difference bias analysis (7), and two-tailed, paired Student's *t* tests.

## RESULTS

Patients presented in the operating room for coronary artery bypass grafting and valve-replacement surgery (i.e., mitral, aortic). Both "on pump" and "off-pump" patients were enrolled. Patient demographics and procedures performed are presented in Table 2.

The regression statistics for the parameters evaluated in this study are shown in Table 3. Excellent correlation is seen for estimated blood volumes ($r = 0.989$; Figure 1) with no bias (average difference = 6 milliliters; Table 4). One patient's blood volume was greater than 10 L, beyond the calculations of the system. Blood volumes for five other patients were not recorded. In Figures 2 and 3, similar excellent correlation ($r = 0.925$ and 0.900) can also be seen for the bolus heparin and initial protamine doses, respectively and no bias (average difference = –1140 units heparin and 33 mg protamine). Bolus heparin doses were not recorded for two patients. Both systems calculated a bolus heparin dose of >100,000 units for one patient. Eight protamine doses were excluded as the 8000-system calculation was out of range (>500 mg). An additional five-protamine dose results were not reported.

Most (88%) of the comparisons conducted as part of this study involved the Response RxDx and Hemochron 8000 RxDx systems (Table 1). In these cases, all tests were performed in duplicate, one sample on the 8000 and the other with the Response. Each instrument uses the clotting time values obtained automatically to perform all necessary calculations. Thus, these comparisons represent a total system evaluation. The data obtained reflect both the similarity of the mathematical calculations, and the comparability of the clotting times obtained on these two Hemochron instruments.

Two-tailed, paired Student's *t* tests performed on all assays showed no statistical difference ($P > 0.05$) between the Response RxDx system and either the Hemochron 8000 or Response PDA systems.

PDA-O tests were performed on 68 of the 76 patients participating in the study. No additional protamine was recommended in 65 cases by the 8000 and in 64 cases by the Response (Table 3B). Although the limited data set precludes statistical analysis, those few doses recommended by each instrument system were comparable, none exceeding 50 mg of protamine.

Despite the excellent correlations observed, the possibility of a clinically significant bias existing between the

**Table 1.** Participating centers.

| Center | Lead Perfusionist for Trial | Current Method |
|---|---|---|
| San Ramon Regional Medical Center, San Ramon, CA | Sherry Armstrong | Response-PDA |
| St. Vincent's Hospital, New York, NY | Eric Wilson | Hemochron 8000 |
| St. Peter's Medical Center, Albany, NY | Dan Brown | Hemochron 8000 |
| Valley Regional and Brownsville Medical Centers, Brownsville, TX | J.J. Nelson, Trey Smith, Timi Tolley | Hemochron 8000 |

**Table 2.** Demographics—all sites combined.

| | | |
|---|---|---|
| No. of patients | 76; 50 male, 26 female | |
| Age range (years) | 29–83 | |
| Height range (m) | 1.1–1.9 | |
| Weight range (kg) | 43–161 | |
| On/off pump | 64 on pump | |
| | 11 off pump | |
| | 1 converted off to on | |
| No. procedures per patient | Procedures | # of Patients |
| (multiple grafts counted | 1 | 66 |
| as one procedure) | 2 | 8 |
| | 3 | 2 |
| Procedure | No. patients | |
| AVR | 12 | |
| CABG | 62 | |
| MVR | 8 | |
| TVR | 2 | |
| Other | 2 | |
| Not specified | 2 | |

CABG, coronary artery bypass graft; TVR, tricuspid valve replacement; MVR, mitral valve replacement/repair; other, aortic repairs; AVR, aortic valve replacement.

**Table 3A.** Correlation.

| Test | No. Sites | No. Samples | Correlation (r) | y = mx + b |
|---|---|---|---|---|
| Estimated blood volume | 4 | 70 | 0.989 | y = 0.99× + 76 |
| Bolus heparin dose | 4 | 73 | 0.925 | y = 1.02× + 630 |
| Protamine dose | 4 | 63 | 0.900 | y = 0.75× + 39.9 |

y, response.

**Table 3B.** Neutralization vertification.

| | 8000 & Palm | Response |
|---|---|---|
| N | 68 | 68 |
| No additional protamine | 65 | 64 |
| Protamine dose recommended | 32–50 mg | 22–33 mg |

systems was evaluated. An analysis of the difference between the paired data and the average absolute percent difference of each pair was performed (Table 4). The absolute average difference is determined by calculating the mean of the absolute value of the difference for each paired data point. This value averts the danger, inherent in the calculation of the average difference, of large deviations on either side of zero negating each other and falsely indicating minimal deviations for a population. The average absolute percent difference for the estimated blood volume, bolus heparin dose, and protamine dose was 2%, 10%, and 15%, respectively (data not shown). These data indicate that there is no systemic bias between the three systems examined.

## DISCUSSION

The Hemochron RxDx system has been shown to be a reliable method of heparin and protamine dose calcula-

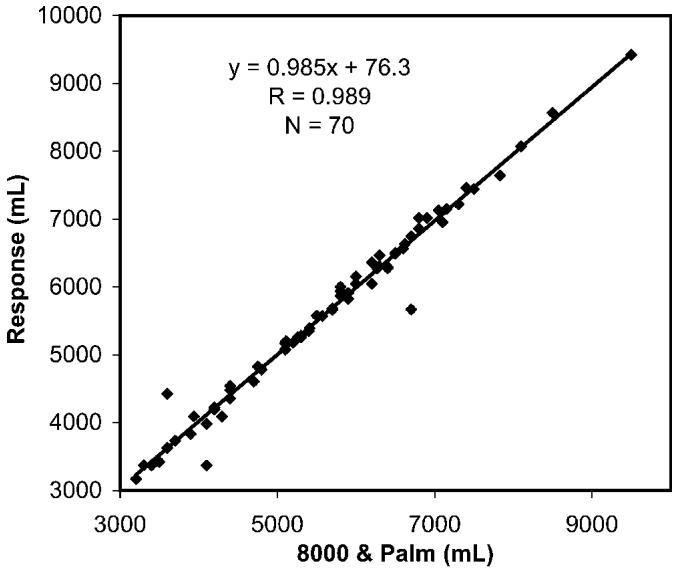


**Figure 1.** Correlation of the estimated blood volume between the Hemochron Response RxDx system and the combined data from the Hemochron 8000 and Response PDA RxDx systems. The combined data collected across six clinical sites showed excellent correlation. No statistical difference was seen among the sites. Of the 76 patients in the study, one patient's blood volume was excluded from the data set as the blood volume was >9999 mL.

**Table 4.** The average differences between paired data.

| | Average Difference | Average Absolute Difference |
|---|---|---|
| Estimated blood volume (mL) | 6 | 103 |
| Bolus heparin dose (u) | –1140 | 2600 |
| Protamine dose (mg) | 33 | 45 |

tions (3,4,8). Previous studies have shown that using the RxDx system reduces the dose of protamine, minimizing the risk of adverse reactions such as postoperative bleeding and reducing the need for intra and postoperative blood products (3,4,9). With the introduction of an automated RxDx system for the Hemochron Response, the system is now a complete, user-friendly system for patient-specific heparin and protamine dosing.

In drug dosing calculations, blood volume estimates play a critical role. The total blood volume calculated with the Hemochron Response was equivalent (r = 0.989) to the Hemochron 8000 and the Response PDA systems (Table 3, Figure 1) as expected, as all three systems use the same equation to calculate the estimated blood volume using each patient's gender, body weight and height (10). An insignificant absolute percent difference of 2.0 ± 3.2% was observed.

The bolus heparin dose required for each patient to achieve the target ACT was comparable in the three systems, which calculate heparin dosing through *in vitro* titration (11). In addition, the Hemochron Response RxDx system calculated additional units of heparin necessary to

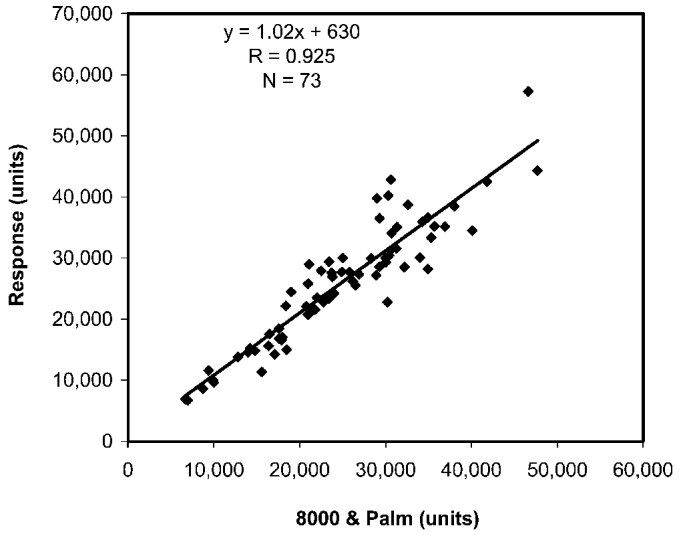


**Figure 2**. Correlation of the bolus heparin dose between the Hemochron Response RxDx system and the combined data from the Hemochron 8000 and Response PDA RxDx systems. The combined data collected across six clinical sites showed excellent correlation. No statistical difference was seen among the sites. Of the 76 patients in the study, one patient's bolus heparin dose was excluded from the data set as the blood volume was >100,000 units.

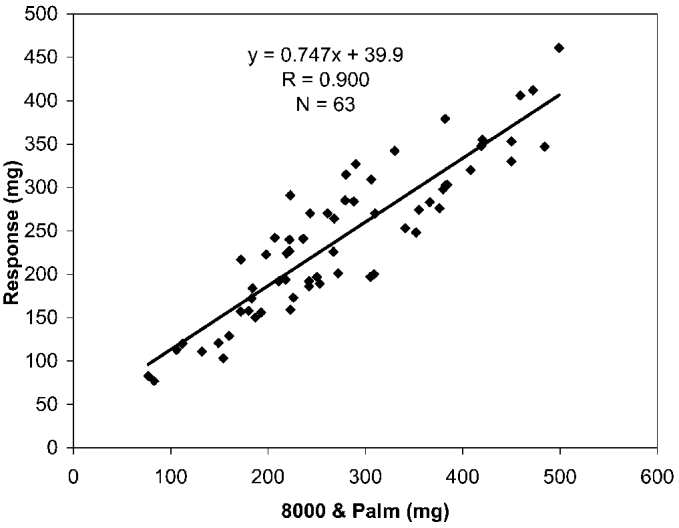


**Figure 3.** Protamine dose correlation between the Hemochron Response RxDx system and the combined data from the Hemochron 8000 and Response PDA RxDx systems. The combined data collected across five clinical sites showed excellent correlation. Of the 76 patients in the study, 8 were excluded because of out of range (>500 mg) doses calculated by the 8000 system.

achieve the target ACT when the bolus heparin dose failed to raise the ACT to the desired target time. The total amount of heparin given throughout the procedures by the Hemochron Response RxDx system compared favorably to the amount of heparin actually given to the patient as recorded on the case report form (data not shown). For the bolus heparin dose, a 10.3 ± 7.2% absolute percent difference was observed. For these studies the actual clotting times generated with the Response system vs. the 8000 system were used. Thus the percent difference reflects the total system bias, which is negligible.

Furthermore, at the end of the case, the protamine dose calculated using *in vitro* titration (11) with the Hemochron Response showed equivalence to the Hemochron 8000 and the Response PDA systems. For the protamine dose, a 15.3 ± 9.2% absolute percent difference was observed. Again, this value reflects total system bias as each instrument used discrete clotting times for these calculations.

The PDA-O is used to verify complete heparin neutralization following protamine administration at the close of cardiac bypass surgery. The PDA-O verification system was used in 68 patients of which, only 3 patients were given additional protamine. In the single case where the Response and 8000 differed in the additional protamine recommendation, no drug was administered. The additional doses required ranged from 22 to 50 mg. Although statistical analysis could not be performed on these data, clearly equivalent results were obtained.

The new Hemochron Response program offers additional user friendly options such as blood volume limits, expanded clotting time ranges for presetting default values and flexibility in test sequence, whereby the user may include specialty tests within the RxDx program. Ten RxDx cases can be stored for easy retrieval. Active case records with patient ID, operator ID and test results are retrievable for 8 hours after the last test and can be printed or downloaded to a PC via the Hemochron Response Data Management (HRDM) program.

This trial verifies the accuracy and precision of the Hemochron Response RxDx dosing system. It is equivalent to both the currently used Hemochron RxDx systems and the current results demonstrate its clinical utility in the cardiac surgery setting.

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