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A Four-Year Experience with Patient Individualized Heparin and Protamine Dosing Using the Hemochron® RxDx™ System

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Abstract: Cardiac surgical case histories, collected over 4 years at Huntsville Hospital in Alabama, were reviewed for 2,293 patients. Patients were separated into two dosing groups for both heparin and protamine, hospital empirically dosed and Hemochron RxDx dosed. Review of the heparin dosing information found that incomplete data were collected for 47 patients, leaving 2,246 patients eligible to be evaluated for heparin dose comparison. Both RxDx recommended and empirically calculated doses were recorded, as well as the actual dose given. Of the 2,246 patients, 1671 were administered heparin according to the RxDx calculated dose, and the remaining 575 patients were dosed according to the hospital's empirical protocol. The average RxDx calculated heparin dose was 17% greater then the empirically calculated heparin dose (350 U/kg) ($p < .001$). Anticoagulation to target ACT (480 sec) was achieved in 92% of the patients dosed according to the RxDx recommended dose; whereas, in the empirically dosed patient group only 80% of the patients reached the target ACT after initial heparin bolus dose. Incomplete protamine dosing data was recorded for 336 patients, leaving a total of 1,957 patients available for protamine dose evaluation. All patients had an RxDx protamine calculation, empirical protamine calculation, and actual amount of protamine dosed recorded. Of the 1,953 patients, 1,764 were dosed according to the RxDx recommended dose, with the remaining 189 patients dosed empirically (1 mg protamine/100 U of heparin). In both the RxDx and the empirical groups, 96% of the patients returned to baseline following initial protamine infusion. The overall RxDx dose (293 mg) was 16% lower than the average empirical dose (348 mg). The RxDx system has been shown to be an effective method for determining patient-specific dosing for both heparin and protamine. This long-term clinical experience demonstrates the consistency and reliability of patient maintenance using this individualized dosing system, which has been shown, in other independent evaluations, to lead to improved patient outcomes. **Keywords:** activated clotting time, cardiac surgery, hemochron RxDx. *JECT. 2001;33:19–22*

During cardiac surgery requiring cardiopulmonary bypass (CPB), heparin is administered to prevent the formation of thrombus in the extracorporeal circuit and the patient's circulatory system. At the completion of surgery, protamine is administered to reverse the effects of heparin.

Optimizing heparin and protamine dosing for each patient helps avoid problems associated with insufficient or excessive pharmaceuticals. Too little heparin increases the risk of thrombosis; whereas, too much heparin might increase the likelihood of bleeding complications. The amount of heparin given also affects the amount of protamine needed to achieve complete neutralization. If too little protamine is administered, the patient runs the risk of bleeding complications, if too much protamine is given, there is an increased risk of such adverse effects of protamine as hypotension and shock or possibly postoperative platelet dysfunction (1).

In many hospitals, administration of heparin and protamine is done on an empirical basis. One commonly used protocol is a weight-adjusted heparin dosing algorithm (300–400 U/kg), with the protamine dosed as a ratio to the initial heparin bolus or the total amount of heparin given (1–1.4 mg protamine/100 U of heparin). The activated clotting time (ACT) is routinely performed to confirm the adequacy of heparin anticoagulation or heparin neutralization. Before CPB, if the target ACT time is not reached, subsequent doses of heparin are given until the ACT exceeds the desired minimal target time. However, additional doses of heparin do not produce the same effect as a single bolus dose, because there is a reduction in the patient's response to subsequent doses (2). Thus, for optimal anticoagulation predictability and decreased presurgical delay, it is desirable to achieve the target time with a single bolus injection.

Variability of patient response to heparin is well known.

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Commercial heparin preparations vary in potency across manufacturers and lots (3). Patient variability is significant. Heparin-sensitive patients require very little heparin to reach target; whereas, highly resistant patients require significantly larger doses to achieve a safe level of anticoagulation (4). Together, these factors plus preoperative anticoagulation status (i.e., prior heparin exposure), age, hemodilution, patient blood volume, and fat distribution make a standard dosing regimen inappropriate to use for all patients.

The Hemochron® RxDx™ (International Technidyne Corp., Edison, NJ) system is an in vitro method used during CPB to optimize the total amount of heparin and protamine administered to cardiac patients. The RxDx system quantifies heparin and protamine doses on a patient specific basis. RxDx is a dose–response assay system that contains matched pharmaceutical preparations of heparin and protamine. The heparin response test (HRT; International Technidyne Corp.) is run to determine the amount of heparin that a patient requires to reach a hospital specific ACT target time (generally 480 sec, range of 400–600 sec). The protamine response test (PRT; International Technidyne Corp.) quantifies the protamine dose required to neutralize the heparin and return the patient's ACT to baseline values (i.e., pre-CPB) can vary from patient to patient. At Huntsville Hospital (Huntsville, AL), the RxDx system was instituted as the standard method for patient dosing in 1995 based on the desire to individualize drug dosing. This article is a retrospective review of the performance of the system under routine clinical conditions.

MATERIALS AND METHODS

Patient case histories, from which all patient identification was removed, were collected for 2,293 patients undergoing cardiac surgery between April of 1996 and June of 2000 as part of Huntsville Hospital's surveillance policy. All ACT results (baseline through end of procedure) were recorded. In addition RxDx HRT and PRT assays were performed to calculate recommended heparin and protamine doses. All assays were performed using the Hemochron 8000 instrument, which calculated the required heparin and protamine doses based on patient demographics and clotting time test results. In addition to the RxDx calculated doses, empirical heparin and protamine doses were recorded for all patients. The empirical doses were based on common standard dosing protocols, with heparin bolus dose given at 350 U/kg and protamine at a 1:1 ratio to total heparin administered (1 mg protamine/100 U heparin). Statistical analyses using analysis of variance (ANOVA) and Student's *t*-tests were performed to compare the heparin and protamine doses of these two regimes.

RESULTS

Complete heparin dosing data were recorded for a total of 2,246 patients, 47 patients with incomplete data were excluded from analysis. All patients had an RxDx HRT performed poststernotomy to determine an RxDx calculated heparin dose. In addition to the RxDx calculated dose, an empirical heparin dose was recorded (based on the hospital's standard of 350 U/kg) for each patient. Heparin was given according to the RxDx recommended dose in 1,671 of these patients (74%), with the remaining 575 patients (26%) dosed according to the hospital empirical calculations, as per physician discretion. Demographics for the heparin-dosing groups, empirical and RxDx, are shown in Table 1. No statistical differences were observed in gender, weight, age, or estimated blood volume between the two dosing groups.

The average RxDx calculated heparin dose for the RxDx group was 33,991 U, with the actual heparin administered being 33,839 U (99.6% of recommended). Had these patients been dose empirically, the average heparin dose (29,430 U) would have resulted in patients receiving 13% less heparin.

The average heparin dose calculated for the empirical group was 29,653 U, with the actual heparin dose given being 31,079 U (105% of calculated dose). The average RxDx calculated dose for this group was 38,834 U, a significant increase (20%) over the empirical dose. On an individual basis, most empirically dosed patients received in excess of 9,000 U less heparin than indicated by the RxDx HRT.

Across all patients, regardless of dosing group, the average RxDx heparin dose (33,839 U) was statistically higher than the average empirical dose (31,078 U, $p < .001$). On average, the RxDx dose was 20% higher than the empirically calculated dose, (ratio = 1.20 ± 0.36, Fig. 1). The wide distribution of RxDx recommended to empirical doses (<0.5–2.9) indicates significant variability in a patient's dose response. Adequate anticoagulation was defined as the ACT reaching the hospital target of 480 sec or higher following heparin bolus. Anticoagulation was achieved in 1,538 patients (92%) dosed according to the RxDx recommended bolus dose; whereas, only 461 (80%) of the empirically dosed patient group reached the target ACT postheparin bolus. As the amount of heparin given

Table 1. Patient demographics.

Demographic	RxDx group	Empirical group	*p* value
Males/females	1,255/416	434/141	0.858
Weights	84.1 kg	84.7 kg	0.190
Age	62	62	0.652
Elevated Blood Volume	5.81	5.85	0.680
Pre-op medications			
ASA	4 (<1%)	3 (<1%)	N/A
Heparin	143 (8.6%)	42 (7.3%)	N/A
ASA/heparin	11 (<1%)	2 (<1%)	N/A

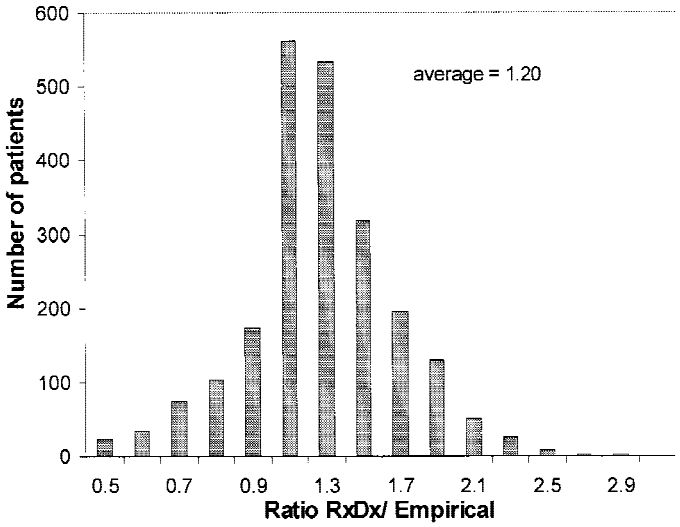

Figure 1. Heparin dosing: A comparison of empirical dose to the RxDx dose. When using the RxDx patient specific dosing system, there is an increase in dosing variability among patients for both heparin and protamine. The RxDx dosing system, on average, predicted a larger heparin dose than empirical. The percentage of patients that reached target when dosed as recommended was 92% in the RxDx group and only 80% in the empirical group. The RxDx dosing system significantly decreased the protamine dose given ($p < .01$) with 96% patients reaching baseline after initial protamine dose.

decreased below the RxDx recommended dose, there was a concomitant increase in the proportion of patients not achieving target anticoagulation (Table 2).

Complete datasets for protamine dosing were available for 1,957 patients. The remaining 336 patients had insufficient data recorded for analysis. All evaluable patients had an RxDx PRT performed to determine an RxDx calculated protamine dose. In addition to the RxDx calculated dose, all patients had a hospital empirical protamine dose calculated (based on the hospital's standard dosing protocol of 1 mg protamine/100 U total heparin given). The PRT recommended protamine dose was administered to 1,706 patients (87%); whereas, the remaining 251 patients (13%) were empirically dosed as per physician's discretion.

As seen for the heparin dosing, there was a wide variation in the RxDx recommended dose when compared to the empirically calculated dose (range: 30–190%). On average, the RxDx recommendation was only 87% of the empirical dose ($p < .001$).

The average protamine dose for the RxDx-dosed group was 301 mg with the actual protamine dose given being 312 mg, dosing (104% if recommended). The average empirically calculated protamine dose for this group was 353 mg, which would have resulted in a 15% increase in protamine given as compared to the RxDx recommendation ($p < .001$) (Fig. 2). Of the 1706 patients dosed as recommended by the RxDx PRT, 1,642 (96%) returned to baseline (baseline is defined as ≤ patient's preheparin ACT); whereas, 64 patients (4%) did not. Thirty-one of the 64 patients who did not reach baseline were given additional protamine (average dose = 55 mg).

The average protamine dose for the empirically dosed group was 305 mg with an average dose given of 290 mg, dosing within 5% of recommended. The average RxDx calculated protamine dose for this group was 237 mg, which would have resulted in an 18% reduction of protamine dosing as compared to the empirically given dose ($p < .001$). Of the 251 patients dosed according to the hospital empirical protocol, 241 (96%) returned to baseline; whereas, the remaining 10 patients (4%) did not. Six of these patients were given additional protamine (average dose 92 mg). The additional protamine dose in all cases was determined by physician discretion.

Table 2. Patients dosed less than RxDx recommended—percentage of patients not achieving target anticoagulation as a relationship to the amount of heparin given.

Heparin ratio: given/RxDx recommended	Total no. patients	Mean ACT	Lowest postbolus ACT	% of Patients that DID NOT reach target
0.3	2	369.5	247	1 (50%)
0.4	4	447.7	356	2 (50%)
0.5	24	463.8	301	16 (66.7%)
0.6	63	475.6	317	38 (60.3)
0.7	99	556.5	317	36 (36.4%)
0.8	200	544.9	311	70 (35%)
0.9	41	563.0	354	12 (29.3%)

DISCUSSION

As is common in many large volume cardiac surgical centers, the institution reviewed in this report had relied exclusively on empirical protocols for administration of heparin and protamine until 1995. From January of 1996

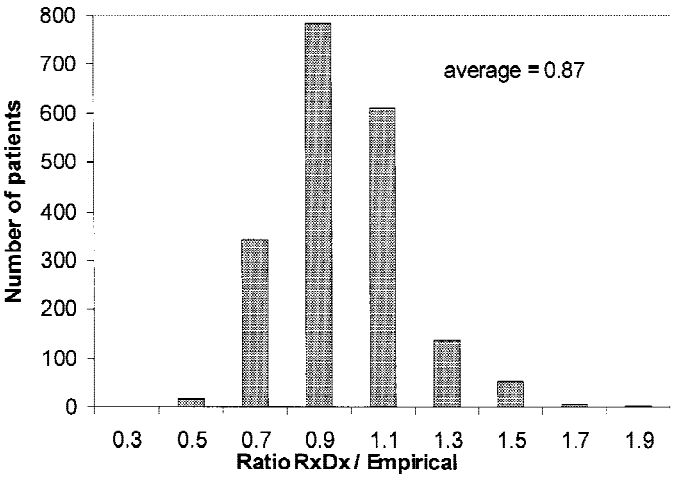

Figure 2. Protamine dosing: A comparison of empirical dose to the RxDx dose. The average RxDx recommended protamine dose for the population was 89% of the empirically calculated dose (1 mg/100 units total heparin). On an individual basis, a large difference in protamine dose variability was observed (30–190%, $p < .001$).

to June of 2000, data were collected for 2,293 patients who were to be dosed using the RxDx system. These anticoagulation records demonstrate the efficacy of the RxDx system as a method for the determination of patient-specific dosing for both heparin and protamine.

At this institution the RxDx system is a consistent and reliable method for maintaining safe anticoagulation. Examining the anticoagulation records of patients electively not dosed as recommended by the RxDx system provided an "internal control" for comparison to the RxDx-dosed group. Patients dosed as recommended by the RxDx system reached the target ACT significantly more often than the empirically dosed patients. For heparin dosing, 92% of patients dosed as recommended reached target as compared to 80% of those dosed empirically. Although both groups had a 96% return to baseline during protamine dosing, the empirically dosed group was given significantly more protamine than recommended by the RxDx system. Too much protamine has been documented to increased a patient's risk of such adverse outcomes as hypotension, shock, or possibly postoperative platelet dysfunction (1).

Consistent with other reports (5, 6) the average heparin RxDx heparin dose was significantly higher (35,231 U) than the overall empirically calculated dose (29,487 U). This reflects the patient-individualized response to heparin and emphasizes the lack of merit in employing empirical dosing for all patients (4). With large amounts of heparin being administered, it is reasonable to expect a correspondingly high dose of protamine would be required to return the patient's ACT to baseline. However, this evaluation found that the PRT recommended dose was less (293 mg) than the empirically calculated dose (348 mg), and patient individualized dose requirements were observed. Although both dosing regimens saw a 96% return to baseline, the empirical group received significantly more protamine than the RxDx group.

The efficacy of the RxDx system was unchanged across multiple lots of heparin and protamine. Five different lots of heparin and three different lots of protamine were used over the 4-year period. There was no difference in patients reaching target ACT with heparin or patients returning to baseline after administration of protamine, irrespective of the lot of pharmaceutical preparation and HRT or PRT assay used (data not shown).

The use of the RxDx system has been shown to provide improved clinical outcome. The use of patient individualized heparin and protamine dosing has been shown to reduce intraoperative transfusion requirement (6), as well as postoperative blood loss (5, 6), and transfusion requirements (5). In addition, the reduction in blood product usage led to a significant cost savings for all cardiac surgery patients (7), particularly those with the most complicated clinical course. This retrospective analysis of routine clinical use of the RxDx system provides further validation of the utility of the system as a standard patient management tool.

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