

Original Article

Evaluation of the Hemochron 8000 Rx/Dx System for Heparin Management

Howard D. Johnson, RRT, CCP; Marc S. Morgan, CCP; Gary R. Koenig, CCP; Joe R. Utley, MD; Steven A. Leyland, MD; Thomas B. Whittle, MD; John M. Conn, MD

Spartanburg Regional Medical Center, Spartanburg, SC

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ABSTRACT

The Hemochron Rx/Dx uses an ACT and a heparin response tube to calculate the heparin dose to identify heparin sensitive/resistant patients. We evaluated the Rx/Dx system in 37 patients to determine if the ACT after the predicted heparin loading dose was adequate to initiate CPB.

The mean heparin dose calculated by the Rx/Dx was 31,700 IU \pm 8,700 IU (370 IU/kg) with a mean post ACT of 463 \pm 124 sec. Our standard heparin dose (400 IU/kg) would have given an additional 2,800 IU over the Rx/Dx.

Four patients (6.5%) were predicted to be heparin sensitive and all four achieved an ACT over 450 sec. Twenty-one patients (56.8%) were predicted to be resistant and yet failed to raise the ACT over 450 sec in 17 (81.0%). Twelve patients (32.4%) were predicted to have a normal heparin response, and four (33.3%) did not achieve an ACT over 450 sec. In all, 21 patients (56.8%) did not achieve an ACT greater than 450 sec.

Each institution should evaluate their heparin loading dose and the resultant ACT. In this study, we found the number of times the Rx/Dx system did not raise the ACT over 450 sec too great to justify the additional expense.

Address correspondence to:
Howard D. Johnson, RRT, CCP
Physician's Center
Foothills Cardiothoracic Surgeons
Suite 300 101 East Wood Street
Spartanburg, SC 29303

INTRODUCTION

The use of the activated clotting time (ACT) has gained popularity in many centers for monitoring the anticoagulant effect of heparin during cardiopulmonary bypass (CPB). Measuring the ACT during CPB has been shown to be an improvement over administering a standard dose of heparin followed with additional heparin doses at fixed intervals. There is both a reduction in blood loss and a reduction in heparin rebound seen in patients post CPB (1-9).

The ACT may be influenced by many factors. Many variables have been noted by Mabry: 1) the molecular heterogeneity of the different species of heparin, 2) the wide spectrum of binding sites and their respective kinetic properties and the dissociation constants, 3) differences in methods for measuring the effect of heparin and its concentration, 4) the dose dependence of the drug's half-life, 5) the presence of ongoing thrombosis or infection, 6) the individual variation in response to heparin, 7) the level and binding of antithrombin III, and 8) drug interactions with heparin (10). In addition, other variable factors have been implicated as well, such as the platelet count (11), hypothermia (12, 13) and hemodilution (12-15). Stenbjerg and associates however, did not see any changes with hemodilution in their study (16). The ACT machine itself has been shown to have variations ranging from 10% (17, 18) to 25% (19, 20), indicating that there may be a need for two samples to be drawn each time. The technique used by the perfusionist may cause the results to vary as well, which would include the time of the sampling (pre vs. post skin incision) (21), the amount of time the heparin is allowed to circulate (22), manual vs. automated (10), the site where the sample is drawn from (13, 14, 16), and the technique used to shake the tube (20). All of these factors indicate the need for a standardized technique during each case.

Anderson described possible causes of heparin resistance: 1) infective endocarditis 2) intra-aortic balloon pump 3) hypereosinophilic syndrome 4) oral contraceptives 5) shock 6) low grade intravascular coagulation 7) previous heparin therapy 8) previous streptokinase 9) presence of a clot within the body 10) congenital antithrombin III deficiency 11) pregnancy 12) neonatal respiratory distress syndrome 13) increased platelet count 14) increased Factor VIII levels 15) secondary decrease in antithrombin III levels 16) ongoing clotting and utilization of heparin (26).

Patients exhibiting heparin resistance can be a challenge in that additional heparin is required and in severe cases, the level of the patient's antithrombin III may need to be increased with either fresh frozen plasma (FFP) or Thrombate III (antithrombin III)^a (23-25). Both of these measures add additional time delays, and will ultimately add to the overall cost to the patient.

Our primary concern has been in the patient exhibiting heparin resistance and thus, we are more interested in the results of the heparin calculation by the Rx/Dx system than with the protamine requirements. Hence, the protamine results are not discussed here. It is because of the need for standardization, and the added cost to the heparin resistant patient, that we decided to investigate the International Technidyne Hemochron 8000 Rx/Dx system^b.

MATERIALS AND METHODS

The Rx/Dx system uses two blood sample ports to calculate a heparin and protamine dose. To determine the heparin dose, one port is used for the ACT (CA510 black top tube), while the other port uses an Rx/Dx Heparin Response Time tube (HRT) (mint top tube) with six units of heparin within the tube. Both tubes require 2 mls of whole blood drawn at the same time prior to heparinization as a baseline. The CA510 will yield the baseline ACT level while the HRT will measure the effect with the six units of heparin inside the tube. The Hemochron 8000 will then measure the difference between the two and calculate the heparin dose based on values of body weight, height, and gender, all of which the perfusionist programs into the Rx/Dx system.

The desired level of anticoagulation can also be entered for a level of 300 or 480 seconds for the target end point. Heparin bottles are supplied to match the heparin within the HRT tubes with the lot number of heparin solution administered to the patient to minimize any possibility of variation in heparin lot potency. Following heparinization, a post heparin ACT is drawn. If this ACT is below the desired level of 480 sec, the Rx/Dx system will calculate the additional heparin necessary to achieve 480 sec. The amount of heparin per body weight predicted by the Rx/Dx was recorded and compared to the amount of heparin per body weight that would have been used with our standard dose of 400 IU/kg, or to that of 300 IU/kg.

Forty-one patients were selected for trial of the Hemochron 8000 Rx/Dx system, specifically for the heparin calculation. In four patients, the Hemochron system aborted the test prematurely, which in turn, did not give a calculated heparin dose. Due to the somewhat time-consuming element of acquiring a second baseline HRT, which would have resulted in an immediate delay in giving the heparin dose and continuing on with the operation, another set of blood samples were not drawn in these four patients, but rather our standard heparin protocol dose of 400 IU/Kg was given. Thirty-seven patients were ultimately completed within this study group.

The patient's case number, height, weight, and gender were entered into the Hemochron 8000, as well as the target ACT of 480 sec for the acceptable level of anticoagulation along with the type of ACT tube (CA510). Following the manufacturer's guidelines for sampling, all samples were drawn just prior to heparinization with enough time to avoid a delay in the calculation by the Rx/Dx system. Blood samples were withdrawn from

a Miles, Inc., West Haven, CT 06516-4175

b International Technidyne Corporation, Edison, NJ 08820

the patient's radial arterial line. Two milliliters of whole blood was used in the CA-510 black top ACT tube and an additional 2 ml in the HRT (mint top tube). The Rx/Dx system measured the end point of the ACT and HRT and then provided the calculation of the heparin dose. After the heparin dose was determined, heparin was drawn up from the provided heparin vials matching the HRT tubes to the heparin vial lot numbers and administered to the patient.

A heparin dose response calculation was used in order to determine whether a patient would be resistant, sensitive, or achieve a normal heparin response, where Heparin Concentration would be: Heparin (units)/ Patient Blood Volume (ml), and Heparin Dose Response would be: (Post heparin ACT – Pre heparin ACT)/ Heparin Concentration. Sixty to eighty sec/unit/ml would be considered a normal heparin response. Anything less than 60-80 sec/unit/ml would be considered to be heparin resistant, and anything greater would be heparin sensitive.

A post heparin ACT was drawn 5 minutes later to verify adequate heparinization. If the post heparin ACT was less than 450 sec, additional heparin necessary to achieve an ACT of 480 sec was calculated by the Rx/Dx system and administered to the patient. The t-tests for paired samples were used to evaluate statistical significance, with P < 0.05.

RESULTS

There were 26 male and 11 female patients enrolled in the study. The mean age was 61.7 ± 10.7 years, the mean body weight was 85.7 ± 16.9 kg, and the mean body surface area (BSA) was 1.99 ± 0.22 m². (Table 1).

Table 1: Patient demographic information

WEIGHT (mean)	85.7 ± 16.9 kg
BSA (mean)	1.99 ± 0.22 m ²
NUMBER OF MALE	26
NUMBER OF FEMALE	11
AGE (mean)	61.7 ± 10.7 yrs

Table 2: ACT/HRT values

PRE ACT	133.3 sec
POST ACT	463.0 sec
HRT	348.0 sec

Table 3: Heparin Dose Comparison

Rx/Dx Heparin Dose	31,700 ± 8,700 IU
400 IU/kg Heparin Dose	34,500 ± 6,800 IU
300 IU/kg Heparin Dose	25,800 ± 5,200 IU
Rx/Dx compared to 400 IU/kg: p < 0.017 (significant)	
Rx/Dx compared to 300 IU/kg: p < 0.001 (significant)	
400 IU/kg compared to 300 IU/kg: p < 0.001 (significant)	

The mean pre-heparinization ACT value was 133 sec (range 100-194) with an HRT of 348 sec (range 276-454) (Table 2), calculating a mean heparin dose of 31,700 IU (range 15,000-50,000). The mean patient weight of 85.7 kg gave a mean heparin dose of 370 IU/kg. The Rx/Dx system dose called for 2,800 IU less heparin when compared to our standard dose of 400 IU/kg (p < .017). The Rx/Dx system dose called for 5,900 IU more heparin when compared to a dose of 300 IU/kg (p < .001) (Table 3). The mean post heparin ACT was 463 sec (range 309-1000), just 17 sec below the target of 480 sec (NS) (Table 2).

Four of the 37 patients (6.5%) were predicted to be heparin sensitive, with all four achieving an ACT of 450 sec or greater. Heparin resistance was predicted in 21 of the 37 patients (56.8%), and failed to adequately raise the ACT over 450 sec in 17 (81.0%) of these patients. Twelve of the 37 patients (32.4%) were predicted to fall within the normal heparin response, and 4 (33.3%) failed to adequately raise the ACT over 450 sec. Of the 37 patients, 21 (56.7%) had an ACT of less than 450 sec (17 patients from the heparin resistant group, and 4 from the normal heparin response group).

DISCUSSION

Cost saving has certainly become increasingly vital in all areas of health care. No longer is it sufficient to compare cost between different manufacturers to seek the lowest price or the most convenient device. The ability of a device (or technique) to reduce operating room time is an issue more and more manufacturers are stating in their sales agenda to the perfusionist and health care administrators.

One must carefully evaluate the efficiency in every aspect of surgical technique and individual products for any possible reduction of cost related to the time savings. With respect to this issue, we sought to evaluate the Hemochron Rx/Dx system in order to see if we would be able to identify patients that may be heparin resistant and/or sensitive. Our primary concern was to identify the heparin resistant patient in order to cut down on the pre-CPB period of waiting for FFP/Thrombate III. In addition to calculating the heparin dose, the Rx/Dx system will also give a calculated protamine dose, which was not our primary objective.

Despite the popularity of the ACT, there is still debate over its usefulness. Several studies have found that the ACT does not show a good correlation with the plasma heparin levels (13, 27), and that the ACT had little value on residual heparin levels (28, 29). Dietrich, on the other hand, found that the plasma heparin level itself was not a good indicator of anticoagulation (25). Others have found that the ACT does correlate with heparin levels (1, 2) but varies between patients (2). Verska found that the patient's weight, body surface area, and age did not correlate with the ACT (3).

In this study we made no attempt to determine any correlation between the ACT and heparin levels, nor with blood loss

or utilization. Our primary concern has been with patients that exhibit marked variable responses to heparin prior to CPB, with particular interest in those with heparin resistance. If the perfusionist is able to identify these patients and is able to adjust the initial heparin dose accordingly, he/she may be able to eliminate the need for an additional dose of heparin, prior to initiating CPB. One may also be able to establish a protocol to order FFP or Thrombate III to elevate the antithrombin levels in order to treat heparin resistance immediately. Naturally, such a machine would have to be shown to be extremely accurate and reliable in establishing a pre-heparin protocol for anti-thrombin III administration.

The results of the "mean" ACT data were found to be straightforward when comparing the end point ACT (463 sec) to the desired ACT (480 sec). However, determining the overall efficacy of just how well the machine will alert the perfusionist to the possibility of an abnormal response to a standard heparin dose is more difficult.

Mollitt describes the ideal characteristics of a laboratory monitor of heparinization: 1) quantitate the anticoagulant effect 2) reflects the logarithmic curve of heparin disappearance and 3) be simple to perform and therefore available at all hours (30). The advantages and disadvantages of the ACT have been listed elsewhere (31).

Looking at the mean values, one could conclude that the Rx/Dx system achieved satisfactory results, especially if one were giving a fixed heparin dose based on weight and never measured the post heparin ACT, but gave fixed doses at set intervals. However, the primary objective was to identify all patients that would be heparin resistant, and to adjust the heparin dose to achieve an ACT of 480 sec prior to CPB. Our heparin protocol is to use 400 IU/kg, had 300 IU/kg been used, the amount of heparin required would have been lower and the results may be somewhat different. Ultimately, each institution should evaluate their own heparin dose protocol before making any necessary modification.

The Rx/Dx predicted 4 patients (6.5%) to be heparin sensitive, and the calculated heparin dose raised the ACT over 450 sec in all patients. Heparin resistance was predicted in 21 patients (56.8%), and the heparin dose failed to raise the ACT over 450 sec in 17 patients (81.0%). A normal heparin response was predicted in 12 patients (32.4%), yet the heparin dose failed to raise the ACT over 450 sec in 4 patients (33.0%). A total of 21 patients (56.8%) did not achieve an ACT of 450 sec, prompting us to administer additional heparin.

The target ACT was set at 480 sec; anything less than 450 sec would prompt us to administer additional heparin to achieve an ACT of 480 sec. Many centers may choose to go with an ACT of 400 sec as acceptable to initiate CPB; however, we feel more comfortable with an ACT of 450 sec based on previous study slides showing gross deposits of platelets and fibrin on arterial filters at 400 sec, and much less of an effect was seen at 450 sec (32). Thus, we feel inclined to make every effort to have the ACT greater than 450 sec. Strictly speaking, a post heparin ACT less

than 480 sec (instead of 450) could possibly be considered heparin resistant when one considers that an automated (computerized) system was employed, while it also implied the resultant ACT of 480 sec should be achieved.

The amount of heparin required for our standard heparin dose (400 IU/kg) would have been just 2,800 IU more than the amount given by the Rx/Dx system ($P < 0.017$). Had this additional dose been able to sufficiently raise the ACT over 450 sec is merely speculation. With a heparin dose of 300 IU/kg, the amount of heparin given would have been 5,900 IU less than the Rx/Dx system ($P < 0.001$). Having a standard dose of 3 mg/kg in these patients would most likely have increased the number of patients responding with an ACT of less than 450 sec.

Twenty-one of the 37 patients (56.8%) did not achieve an ACT above 450 sec. This failure to bring the target ACT to an acceptable level was felt to be extremely high and kept us from purchasing this machine. We could not justify the cost of the Rx/Dx system knowing that in over half of the patients the results would be less than satisfactory.

In conclusion, our primary objective was to identify heparin resistant patients and to achieve an ACT of 480 sec in a standardized fashion. We felt that the inability of the Rx/Dx to raise the ACT over 450 sec in 21 of 37 patients (56.8%) of the predicted heparin resistant patients, and 56.8% of the total patient population, is too great to justify the added expense of the machine and the disposable tubes necessary to operate the system.

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