Circadian changes in anticoagulant effect of heparin infused at a constant rate

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Abstract
Six patients with venous thromboembolism were treated with heparin, administered intravenously by a constant infusion pump. The initial daily dose of heparin was adjusted to keep the activated partial thromboplastin time, sampled at 0800, between 1:5 and 2.5 times the control level. Once that level was obtained, this dose was kept constant. Anticoagulation was thereafter measured, every four hours for 48 hours, by activated partial thromboplastin time, thrombin time, and coagulation factor Xa inhibition assay.

The results of all three coagulation tests showed a circadian variation in the six patients. Maximum values were achieved at night and minimum values in the morning. These circadian variations were reproduced for two consecutive days. Differences between night and morning values reached almost 50% for activated partial thromboplastin time, 60% for thrombin time, and 40% for factor Xa inhibition assay. This circadian variation resulted from two rhythms, a circadian rhythm lasting 24 hours and an ultradian rhythm lasting 12 hours, which were detected by cosinor analysis for each coagulation test (p<0.01). A circadian rhythm was detected individually in most of the patients for each coagulation test (p<0.05). All patients had a nocturnal peak in activated partial thromboplastin time on both days. In four patients this peak exceeded the upper desired limit of activated partial thromboplastin time.

These rhythms should be taken into account when evaluating the dosage of heparin to be administered.

Introduction
Heparin is the best anticoagulant for the initial treatment of venous thromboembolism. Continuous intravenous administration of heparin was proposed as a means of avoiding the acute variations in heparin anticoagulant effect that occur during discontinuous administration. Even so, in up to 30% of patients with venous thromboembolism treated with continuous intravenous administration of heparin bleeding complications occur or thrombosis recurs. At present there is no agreement on whether a coagulation test should be used to adjust heparin dosage. This suggests that factors other than those previously investigated may influence the effects of heparin. As the time at which a drug is administered often influences its effects we investigated this possibility for heparin administered intravenously by a constant infusion pump. Such a variation might explain some cases of bleeding or recurrence of venous thromboembolism, observed despite continuous intravenous administration of heparin. We studied six patients with venous thromboembolism treated with continuous intravenous administration of heparin. Activated partial thromboplastin time, thrombin time, and coagulation factor Xa inhibition assay were determined every four hours for 48 hours.

Patients and methods
Patients—Six patients entering our clinical study unit between February and April 1984 with the diagnosis of venous thromboembolism (without massive pulmonary embolism) participated in this study. Their informed consent was obtained. Two were men and four women. Their mean age was 62 (range 51–78) years and mean weight 67 (range 48–85) kg. None was a smoker or alcoholic; all had normal renal and hepatic function as assessed by serum creatinine,
TABLE I—Clinical data on six patients with venous thromboembolism and daily dose of heparin

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Venous thromboembolism</th>
<th>Anticoagulant</th>
<th>Heparin dose (U/kg/24 h)</th>
<th>Case No</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>M</td>
<td>78</td>
<td>Pulmonary embolism</td>
<td>Pulmonary embolism</td>
<td>590</td>
<td>1</td>
</tr>
<tr>
<td>78</td>
<td>F</td>
<td>62</td>
<td>Pulmonary embolism</td>
<td>Pulmonary embolism</td>
<td>590</td>
<td>2</td>
</tr>
<tr>
<td>53</td>
<td>M</td>
<td>52</td>
<td>Pulmonary embolism</td>
<td>Pulmonary embolism</td>
<td>590</td>
<td>3</td>
</tr>
<tr>
<td>64</td>
<td>F</td>
<td>71</td>
<td>Deep vein thrombosis</td>
<td>Pulmonary embolism</td>
<td>590</td>
<td>4</td>
</tr>
<tr>
<td>52</td>
<td>F</td>
<td>58</td>
<td>Deep vein thrombosis</td>
<td>Pulmonary embolism</td>
<td>590</td>
<td>5</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>85</td>
<td>Deep vein thrombosis</td>
<td>Pulmonary embolism</td>
<td>590</td>
<td>6</td>
</tr>
</tbody>
</table>

During the study antacid preparations were prescribed for cases 2, 4, and 6, calcium antagonists for case 3, H2 antagonists for cases 4 and 6, and thiazide diuretics for case 4.

TABLE II—Circadian rhythms in activated partial thromboplastin time (APTT), thrombin time (TT), and factor Xa inhibition assay (XaI) measured every four hours for 48 hours in six patients receiving continuous intravenous heparin treatment

<table>
<thead>
<tr>
<th>Coagulation tests</th>
<th>No of measurements</th>
<th>Circadian variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mesor (SEM)</td>
<td>Double amplitude (2 SEM)</td>
</tr>
<tr>
<td>Raw values:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APTT</td>
<td>78</td>
<td>53-9 (1-4 s)</td>
</tr>
<tr>
<td>TT</td>
<td>78</td>
<td>0-32 (0-020 U/ml)</td>
</tr>
<tr>
<td>XaI</td>
<td>78</td>
<td>0-38 U/ml</td>
</tr>
<tr>
<td>Percentage of individual 24 hour mean:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APTT</td>
<td>78</td>
<td>100 (2)</td>
</tr>
<tr>
<td>TT</td>
<td>78</td>
<td>100 (2)</td>
</tr>
<tr>
<td>XaI</td>
<td>78</td>
<td>100 (2)</td>
</tr>
</tbody>
</table>

* p test of null amplitude rejection hypothesis.
†Twenty-four hour rhythm adjusted mean.
‡Difference between peak and trough values of best fitting cosine function.
§Peak time location of best fitting cosine function. Mean time of acrophase in all six patients together with time 2 SEM before and after in parentheses.

Results

Table I gives clinical details for the six patients studied. During the study one (case 1) sustained mild bleeding (haemoptysis) at the end of the night. The main daily dose of heparin was 402 U/kg/24 h (range 237-595 U/kg/24 h). Table I gives the dose for each patient. When compared with the expected daily rate of infusion (48 ml/24 h) the pumps were fast on nine occasions (mean advance 1-9% (9-ml range 1-5%) and slow on three (1-0% (5-ml) for each patient). When the rate of infusion was checked every four hours no important fluctuation or systematic error was detected.
As figure 1 shows, whether the mean values for the six patients were expressed as raw values or as percentages of the individual 24-hour mean the anti-coagulant effect was not constant during the 24 hours. A circadian variation was observed, which was reproducible from one day to the next, with a peak at night and a trough in the morning. A similar pattern was observed with the results of the three coagulation tests. Differences between peaks (at 0400) and troughs (at 0800) reached almost 50%, for activated partial thromboplastin time, 60%, for thrombin time, and 40%, for coagulation factor Xa inhibition assay (paired t tests: p < 0.001). Table II gives results obtained with cosinor analysis. A circadian (24-hour) rhythm was detected for activated partial thromboplastin time and thrombin time expressed as raw values. This rhythm was also detected for factor Xa inhibition assay expressed as a percentage of individual 24-hour mean. Accrophases (peak times) occurred at the beginning of the night for the three tests. The double amplitude (difference between peak and trough) was considerable (almost 50%) for activated partial thromboplastin time and thrombin time. The good reproducibility of these rhythms from one day to the next was further validated by cosinor analysis performed on separate data from each study day (p < 0.01 for each day and for each coagulation test) with similar acrophases.

In addition to the 24-hour rhythm, an ultradian rhythm with a period of 12 hours was found for each coagulation test by the cosinor method (p < 0.01). The acrophases (peak times) of these ultradian rhythms occurred at 0210 and 1410 for activated partial thromboplastin time, at 0240 and 1430 for thrombin time, and at 0225 and 1425 for factor Xa inhibition assay. Their double amplitudes were smaller than those seen in the 24-hour rhythms—for example, 20% for activated partial thromboplastin time, 32% for thrombin time, and 14% for factor Xa inhibition assay. The algebraic sum of these two rhythmic components was computed as Fourier's transformation for each variable. Figure 2 shows the computed waveform of the circadian variation in activated partial thromboplastin time as an example.

![Figure 1](image1.png)

**FIG 1**—Time course of activated partial thromboplastin time, thrombin time, and factor Xa inhibition assay measured every four hours for 48 hours in six patients receiving continuous intravenous heparin treatment. Vertical bars represent mean (SEM). Periods of sleep (●) and wakefulness (□) are indicated. Significant circadian (24-hour) and ultradian (12-hour) rhythms were validated by cosinor analysis for the three coagulation tests.

![Figure 2](image2.png)

**FIG 2**—Computed waveform of circadian variation in activated partial thromboplastin time in six patients receiving continuous intravenous heparin treatment. A circadian rhythm with a period of 24 hours (∙—∙—∙—∙) and an ultradian rhythm with a period of 12 hours (— — —) were statistically validated by cosinor analysis. Their algebraic sum (— — — —) was computed as a Fourier's transformation.

Figure 3 shows variations in activated partial thromboplastin time in each patient. All patients had a high peak on both days, but the magnitude of the difference between peak and trough values varied from one patient to another. For example, night and morning activated partial thromboplastin time differed by more than 50 seconds in cases 1 and 2. A significant circadian rhythm (p < 0.05) was found by cosinor analysis in four patients (cases 1, 2, 3, and 4) for activated partial thromboplastin time and in three patients (cases 1, 2, and 3) for thrombin time (p < 0.08 in case 5). The circadian rhythm in factor Xa inhibition assay was statistically validated (p < 0.05) in four patients (cases 1, 2, 3, and 5). In all patients the acrophase occurred at the beginning of the night. The double amplitude was greatest in cases 1 and 2 for the results of all three coagulation tests. No evident correlation was found between the characteristics of the rhythm (detection or double amplitude, or both) and the clinical data on each patient (for example, heparin dose).

### Discussion

Continuous intravenous administration of heparin did not provide a constant anti-coagulant effect in the six patients. Indeed, results of the three coagulation tests showed a circadian variation, with a maximum anti-coagulation at night and a minimum in the morning, which was reproducible over two consecutive days (fig 1). Variations between night and morning were considerable, with a mean difference reaching almost 50% in activated partial thromboplastin time, 60% in thrombin time, and 40% in factor Xa inhibition assay (fig 1). This circadian variation resulted from two rhythms, a circadian rhythm lasting 24 hours and an ultradian rhythm lasting 12 hours,
The cause of these rhythms in the effect of heparin is not known at present. They may be circadian rhythms in the pharmacokinetics of this agent as has been shown for many drugs.14 Alternatively, a recent study in normal volunteers showed a spontaneous circadian variation in coagulation with an increased clotting tendency in the morning,15 which would be consistent with the circadian variation of the heparin effect reported here.

We believe that this circadian variation should be taken into account when evaluating the heparin dose to be administered. The time at which blood is taken for coagulation tests appears to be crucial, and the rate of heparin infusion might be adapted according to these biological rhythms. Further studies will be necessary before extrapolating our results to all patients receiving treatment with heparin. Such studies should also investigate the effects of variations in heparin administration on the incidence of bleeding and recurrence of venous thromboembolism.

We thank the nurses of our clinical department and the technicians from the transfusion centre, without whom this study could not have been performed; Professor J C Bertrand, Dr Y Page, and Professor C P Brizard for their collaboration; and M. M. Meckouri for his help with the data analysis; and Mrs M C Bres and Mrs E Chastel for typing the manuscript.

References

(Accepted 1 November 1984)