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QUALITY ASSURANCE OF THERAPEUTIC HEPARIN/ORAL ANTICOAGULANT THERAPY IN A GENERAL TEACHING HOSPITAL. W. Brien, M. Inwood, K. Dillon. Department of Medicine and Department of Clinical Laboratory Medicine, St. Joseph's Health Centre of London and the University of Western Ontario, London, Ontario, Canada.

In preparation for the development of a standard anticoagulation protocol and as part of a quality assurance programme, a retrospective analysis of anticoagulation therapy in a teaching hospital was undertaken. The results of this audit were compared to the results of other workers who have previously emphasized controversial areas of anticoagulation therapy and potential benefits of a standard anticoagulation protocol.

Charts from seventy-nine patients with a diagnosis of venous thrombosis were analyzed. Fifty-five percent of the patients were at increased risk of bleeding and forty-five percent had an extensive proximal vein thrombosis, but not apparent consideration of a heparin dose adjustment was noted. Patients received heparin for an average 9.7 days, with concomitant coumadin therapy for an average 4.8 days. Patients on heparin were over/ or undercoagulated on average 5.4 days and ninety-four percent of patients on coumadin had a PT (rabbit brain) greater than 18 seconds for at least one day. Sixty percent of patients had their dose changes noted in a tabular form for easy reference. Less than fifty percent had their hemoglobin or platelet counts followed while on heparin. The APTT and TCT are used to follow heparin therapy and discrepant results were noted in thirty-three percent. All patients' discrepancies were investigated automatically by the coagulation laboratory. Less than thirty percent of patients received formal teaching from the clinical pharmacist concerning coumadin therapy.

We feel that these results show a need for a standard protocol for heparin coumadin therapy. It has been shown that a standard protocol can provide favourable chemical, financial and therapeutic benefits.

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DO APTT AND ANTI IIa ACTIVITY PERMIT THE PREDICTION OF THE EFFICIENCY OF HEPARIN THERAPY IN PATIENTS WITH PROXIMAL DEEP VEIN THROMBOSIS ? Ph Villain, JL Bouvier, G Le Corff, A Elias, I Juhan-Vague, A Serradimigni, Service de Cardiologie, CHU TIMONE 13385 MARSEILLE CEDEX 05, FRANCE

One hundred and forty two patients admitted for proximal deep venous thrombosis (PDVT) from 01.01.85 to 12.20.86 were treated with Na-heparin. After an initial bolus (100 units/kg), a continuous intravenous infusion was started (500 units/kg/24h). Heparin activity in daily drawn blood samples was determined by two different assays = APTT (general diagnostic) and anti IIa activity (clotting method). Doses of heparin were adjusted to maintain APTT ratio between 2 and 3.

A phlebography was performed for each patient at D0 and D10. Two groups of patients with PDVT were identified :

- Group I : n = 14 increased thrombosis
- Group II : n = 26 partly or fully cleared thrombosis

No difference in localization or etiology of PDVT was found between the two groups. Thrombocytopenia was excluded in the two groups by platelet counts (D0,D5,D10).

Daily mean values and mean of mean values were analyzed in each group for APTT ratio and anti IIa activity :

		I n = 14	II n = 26
MEAN OF MEAN VALUES (± SD)	APTT (ratio)	2.92 ± 0.31	2.87 ± 0.25
	ANTI IIa ACTIVITY (UI/ml)	0.25 ± 0.03	0.27 ± 0.02

Statistical analysis (student's T test) shows no difference between the two groups.

It can be concluded that mean values of APTT and anti IIa activity in therapeutic range are not predictive of heparin efficiency for the treatment of PDVT

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PHARMACOKINETIC BEHAVIOUR OF ANTITHROMBOTIC AND BLEEDING ENHANCING EFFECTS OF VARIOUS HEPARIN(OID)S IN RATS: THEIR RELATION WITH INTERACTIONS WITH FACTORS IIa AND Xa. P.M.J. Hobbelen, G.M.T. Vogel and D.G. Meuleman. Organon Scientific Development Group, 5340 BH Oss, The Netherlands.

The effects on thrombus formation and bleeding of various heparin(oid)s were studied at several time-intervals: in addition, the αXa-, αIIa-, and thrombin generation inhibitory (IIaGI)-activities were measured amidolytically in plasma from these animals. The following substances were studied: heparin (HEP), the fraction of heparin with high affinity for ATIII (HA-HEP), a low molecular weight fraction of heparin (LMW-HEP), nitrous acid degraded heparin (NAD-HEP), Fragmin^{R} (FRA), Org 10172 and the fraction of Org 10172 with high affinity for ATIII (HA-10172). The substances were given in a dose of 800 αXa U/kg i.v. in the thrombosis model and in the double dose (1600 αXa U/kg i.v.) in the bleeding model because of the lower intrinsic effect on bleeding. The initial magnitude and the duration of the anti-thrombotic and bleeding enhancing effects of these substances are summarized in the table together with the half-lives of the αXa-, αIIa- and IIaGI-activities.

Substance	Antithrombotic effect		Bleeding effect		$T_{\frac{1}{2}}$		
	initial effect (% of inh. of plac)	duration (hrs)	initial effect (% of plac)	duration (hrs)	αXa	αIIa (hrs)	IIaGI
HEP	92	4	1198	>2	1	1	1
HA-HEP	90	4	798	>2	1	1	1
LMW-HEP	68	3	504	>2	2	1	1,5
NAD-HEP	53	2	279	1	2	0,5	1
FRA	82	4	380	1	1,5	0,5	0,75
Org 10172	72	8	328	1	3	NE	1,5
HA-10172	64	8	171	0,5	2	NE	1

NE: not estimated due to too low αIIa-activities.

The following conclusions could be drawn concerning the duration of the effects: 1. in contrast with HEP most lower molecular weight substances showed different time courses of the anti-thrombotic and the bleeding enhancing effect 2. the duration of the anti-thrombotic effect of Org 10172 and HA-10172 is considerably longer than that of the other substances 3. the duration of the bleeding enhancing effect of Org 10172, HA-10172, NAD-HEP and Fragmin^{R} is shorter than that of HEP, HA-HEP and LMW-HEP. Additional conclusions could be drawn by inspecting the time response curves and taking the magnitude of the effects into account: 4. Org 10172 and its high affinity fraction have a better benefit/risk ratio in comparison with the other substances, which even increases in time 5. the time-response curves of the anti-thrombotic effects seem to be associated with those of the αXa-activities and 6. the time-response curves of the bleeding enhancing effects seem to be related to those of thrombin inactivation.

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COMPARATIVE PHARMACODYNAMICS OF SUBCUTANEOUSLY ADMINISTERED HEPARIN (HEP) AND A LOW MOLECULAR WEIGHT HEPARIN (LMWH) AS STUDIED BY AN EX VIVO FIBRINOPEPTIDE A (FPA) GENERATION TEST. B. Spyropulos, J. Fareed, R.M. Emanuele, and D. Hoppensteadt. Loyola University Medical Center, Maywood, IL 60153.

Subcutaneously administered heparins do not produce any sizeable effects on the global tests and their activities are currently measured using amidolytic anti Xa and anti IIa assays. These methods are sensitive only to the individual enzyme and do not reflect other biologic actions. We have used a thromboplastin C activated FPA generation test to measure the pharmacodynamic effects of subcutaneously administered HEP and a LMWH in primates. 400 µl of citrated plasma was equilibrated at 37°C for 2 minutes and was activated with 100 µl thromboplastin diluted in .020M $CaCl_2$. FPA was generated for 2 min, inhibited with 50 µl of an inhibitor cocktail and measured using an RIA kit (Mallinckrodt, St. Louis, MO). Marked dose dependent suppression of the FPA generation was noted for varying periods of time by both HEP and LMWH. Stronger effects were observed with LMWH suggesting better subcutaneous bioavailability and functional effects. Significant FPA generation inhibition was observed even when there was no circulating antiprotease activity present in the plasma. These results suggest that FPA generation test is a sensitive test to measure the pharmacologic effect of heparins. Furthermore the FPA generation tests can be modified to activate the coagulation system at certain sites to study the effect of heparins.