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MODIFICATIONS OF BIOLOGICAL PARAMETERS DURING TREATMENT OF PULMONARY EMBOLISM BY A VERY LOW MOLECULAR HEPARIN FRAGMENT (CY 222). B. DELAHOUSSE (1), Y. GRUEL (1), P. MOALIC (1), L. QUILLIET (2), F. TOULEMONDE (3), J. LEROY (1). (1) Lab. Hématologie, Pr J Leroy. (2) Clin Cardiologie, Pr M Brochier, CHU Trousseau, Tours. (3) Institut Choay, Paris - France.

45 patients with pulmonary embolism (PE) were treated by a very low molecular weight heparin fragment (CY 222, Institut CHOAY - France) in an open range dose study. Patients were included into three groups (I, II and III) and received respectively 500, 750 or 1000 IC (Institut Choay) antiXa units/ kg/day by continuous intravenous infusion for ten days. The laboratory screen carried out at Day 0 and at 2 - 8 - 12 - 24 - 36, 48 hours and then every day until Day 10, included : Platelet count, Thromboelastography (TEG) on platelet rich plasma (PRP), Amidolytic assays for anti Xa (CBS 3139 STAGO) and anti IIa (S2238 KABI) activities (Calibration with Hepanorm STAGO), Heptest (Diamed, France), Amidolytic assay for tissue plasminogen activator (t-PA) and its inhibitor (PAI, Verheijen's method). Results showed no modification of platelet count and t-PA or PAI levels; An hypocoagulability was demonstrated with TEG on PRP (r+k > 35 mn) in 20 cases (3 patients from group III with haemorrhagic manifestations and 17 cases from groups II and III without complication). Anti-IIa activities were always lower than 0.15 U/ml. Anti-Xa activities and Heptest (Control adult values = 12.75 sec ± 1.15) were (Mean ± SD):

		Group I (500)	Group II (750)	Group III (1000)
ANTI Xa (U/ml)	Day 1	0.44 ± 0.15	0.48 ± 0.14	0.83 ± 0.2
	Day 5	0.55 ± 0.12	0.63 ± 0.15	1.19 ± 0.3
	Day 10	0.61 ± 0.17	0.76 ± 0.18	1.49 ± 0.3
HEPTEST (Sec)	Day 1	51 ± 7.5		61 ± 13
	Day 5	54 ± 7.3	Not tested	75 ± 14
	Day 10	57 ± 11		86 ± 23

Any significant biological difference between patients who have good or poor clinical results was observed, excepted for 1 patient who had a high level of PAI at Day 0 and recurrence of PE.

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DOSE FINDING STUDY OF LOW MW HEPARIN (LMWH) CY222 IN HAEMODIALYSIS FOR CHRONIC RENAL FAILURE: RELATIONSHIP BETWEEN ANTI-FACTOR XA ACTIVITY AND ANTICOAGULANT EFFECT. H. Ireland, D.A. Lane, A.M. Flynn, A.C. Pegrum and J.R. Curtis. Departments of Haematology and Medicine, Charing Cross and Westminster Hospital and Medical School, London W6 8RP.

A dose finding study of the LMWH CY222 (MW~2800) in patients (n=8) has been carried out to (i) establish an effective dose and (ii) determine the relationship between ex vivo anti-factor Xa levels in plasma and the anticoagulant effect (in vivo suppression of FPA levels). Doses of CY222 were compared to a dose (5000 iu bolus+1500 iu/hr) of unfractionated heparin (UFH) that has been shown to suppress FPA levels during prolonged (>5hr) dialysis (Ireland et al, J Lab Clin Med 103, 643, 1984). CY222 given iv in doses (a) 5000 IC (Institute Choay)u bolus+1500 ICu/hr (b) 10000 ICu bolus (c) 10000 ICu bolus+ 1500 ICu/hr (d) 15000 ICu bolus+1500 ICu/hr (e) 20000 ICu bolus (f) 20000 ICu bolus+1500 ICu/hr produced a dose related increase in anti-factor Xa levels (measured with CY222 as standard) and suppression of FPA levels. Dose (f) did not alter KCCT, produced FPA levels that were statistically indistinguishable from those of the UFH regime (indicating comparable anticoagulant effect), but had anti-factor Xa Levels (ICu) that were 2-3 times those of UFH. All samples were also assayed against the proposed LMWH Standard. Plasma levels of CY222 were then found to be 2-3 times lower, so that dose (f) had very similar anti-factor Xa levels to those of UFH. Clinically, doses (c), (d), (e) and (f) were all effective, although increasing amounts of fibrin were visible in the dialyser circuit with decreasing dose. It is concluded that CY222 has comparable anticoagulant effect to UFH when present at similar anti-factor Xa concentration (measured against the LMWH Standard). CY222 may prove to be an effective alternative to UFH for use in haemodialysis.

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TREATEMENT OF PULMONARY EMBOLISM BY A VERY LOW MOLECULAR WEIGHT HEPARIN FRAGMENT (CY 222), A DOSE RANGE STUDY. L. QUILLIET (1), B. CHARBONNIER (1), PH. RAYNAUD (1), B. DELAHOUSSE (2), F. TOULEMONDE (3), M.L. BROCHIER (1).
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Experimental studies showed that CY 222 (MW 2500 - 250 U AXAIC/ mg - 25 UI/mg) kept the profibrinolytic properties of heparin with a considerable reduction of bleeding risk and that the optimal dose was about 1 000 U AXAIC/kg/day in rabbits. We have tested the dose related effectiveness and tolerance of this drug in 47 patients (pts) with acute pulmonary embolism (PE) less than 5 days. Pts were divided into 3 groups receiving : Group I : 500 (n = 16), Group II : 750 (n = 17), Group III : 1 000 (n = 14) U AXAIC/kg/day by continuous intravenous infusion for ten days. Effectiveness was appreciated by Miller's index with pulmonary angiography (PA) performed before, on the 5th day and on the 10 th day of treatment. The decrease of Miller's index mean value was comparable in the 3 groups. But the improvement was faster in the group III

	Group I (500)	Group II (750)	Group III (1 000)
Miller Day 1	16.9 + 1.5	15.9 + 1.9	19.5 + 1.3
Miller Day 5	12.5 + 1.8	11.8 + 2.0	12.9 + 2.0
Miller Day 10	5.11+ 1.3	5.5 + 1.6	6.4 + 1.7
% Revascularisation Day 1 - Day 10	64.6 + 9.9	71 + 6.8	68.0 + 8.5

* : p<.05 ; ** : p<.02 ; *** : p<.002

We noticed 5 recurrent PE (2 in Group I, 1 in Group II and 2 in Group III) of which one was fatal (Group I), and 2 hematoma at the venous punction site in Group III.

In conclusion, CY 222 is a safe treatment of PE and the most effective dose seems to be 1 000 U AXA IC/kg/day in spite of minor bleeding.

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PLASMA EXCHANGE WITH A VERY LOW MOLECULAR WEIGHT (VLMW) HEPARIN FRAGMENT CY 222. EVOLUTION OF THE COAGULATION FACTORS. B. Crespo (1) U. Assogba (2) B. Bayrou (3) F. Rouffi (1) J.P. Durande (2) J. Rottembourg (2). Laboratoire d'Hématologie (1) and Service de Néphrologie (2) G.H. Pitié-Salpêtrière, 75651 Paris Cédex 13, Institut Choay (3) 75782 Paris Cédex 16, FRANCE.

In a randomized, between-patient study we investigated the effects of a VLMW Heparin fragment (CY 222) versus standard Heparin (SH) in plasma exchanges (n = 8) on coagulation factors (CF): Fibrinogen (FGN), II, V, VII+X, IX, XI, XII, VIIIc, VIIIRag,VIIIvwf and ATIII, Prot C, Prot S, Plasminogen (PGN), APTT, Prothrombin time (PT), TT, anti factor Xa (AXa), D-Dimer, Platelet Count. Heparin was administered as a bolus and an infusion during the session, CY 222 as a bolus dose only. 1 to 1.5 plasma volume was exchanged substituted by 5% albumin. The preliminary results (mean, s.d.) at the end of the session (End) and 4 hours later (T4) are summarized below. No differences were found between treatment groups at the baseline (data not shown).

		XII %	II %	V %	PT %	AXa u/ml	APTT sec.	FGN g/l
CY 222	End: mean	39	45	58	53	1.50	79	1.05
	s.d.	16	19	23	37	0.38	25	0.68
	T4 : mean	61	58	69	65	0.78	50	1.34
	s.d.	22	16	11	12	0.16	11	0.77
S.H.	End: mean	31	39	41	41	0.58	108	1.13
	s.d.	14	11	12	8	0.22	5	0.59
	T4 : mean	48	41	62	57	0.18	51	1.18
	s.d.	18	14	11	6	0.04	2	0.49

CF are similar in both groups except Factor XII levels at the end of the session, and Factors II, V, XII at T4 (paired t-test: $p < 0.05$). High APTT levels in all samples seem related to low FGN ($p < 0.01$). Significant differences in AXa activities were found in each treatment compared with its own standard suggesting different ranges of activities of both drugs. Evolution in D-Dimer levels seems different during the session and at T4 according to the tested drugs and could be related to their mode of administration. Clinical efficiency and tolerance were excellent either with CY 222 or with SH.