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ANCROD PROPHYLAXIS AFTER SURGERY FOR FRACTURED NECK OF FEMUR: A STUDY OF FATAL PULMONARY EMBOLISM. C.R.M. Prentice & H.A. Townsend, for the Ancrod Collaborative Study Group. University Department of Medicine, The General Infirmary, Leeds LS1 3EX, UK.

A pilot multi-centre randomized controlled trial was carried out to compare ancrod (Arvin, Knoll) versus no medical treatment in 453 patients having surgery for fractured neck of femur to assess prevention of fatal post-operative pulmonary embolism (PE). Ancrod was given subcutaneously by 5 daily injections starting immediately post-operatively; initially 4u/kg bw were given followed by 4 injections of 1u/kg bw, to reduce fibrinogen levels to 80mg/dl. The primary objective of the study was to record mortality due to PE, as shown by the Death Certificate, within 3 months after surgery. Death Certificates were analysed by 2 medical assessors, unaware of the patient treatment group. Of 239 control patients, not given ancrod, there were 5 deaths due to PE and 2 deaths where PE may have been contributory. Total deaths were 30 (12.5%). In 214 ancrod treated patients there were 2 deaths due to PE and a further 3 where it may have been contributory. Total deaths were 31 (14.5%), not significantly different from the control group. Deaths from PE occurred between 16 and 66 days after surgery. Although in this study there was a beneficial tendency for ancrod to reduce fatal PE it is likely that at least 6,000 patients would be needed to demonstrate that any drug significantly reduces by 50% the incidence of fatal PE compared to the control group. Wound infection was recorded in 16 patients in both groups. Wound haematomas were seen in 26 ancrod patients compared to 6 controls ($p < 0.02$) but were not sufficiently serious to warrant re-exploration or prolonged hospital stay. The low mortality due to PE in our patients with fractured neck of femur (2%) is contrasted with the figures of Sevitt & Gallagher, 1959 (8%). The low incidence of fatal PE in the high risk group studied here should be taken into account when assessing future antithrombotic prophylaxis after surgery. Advances in anaesthetics, surgery and rehabilitation may have contributed to the decline in fatal post-operative PE. Effective assessment of drugs for prophylaxis against post-operative venous thrombosis is best carried out by large scale simple controlled trials using fatal PE as the primary end point. Collaborative Centres were located in Portsmouth, Cape Town, Glasgow, Belfast and Leeds.

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ORGANON 10172 VS. WARFARIN TO PREVENT VENOUS THROMBOSIS AFTER HIP FRACTURE. T. Gerhart, H. Yett, A. Donovan, M.A. Lee, M. Smith, and E.W. Salzman. Beth Israel Hospital and Harvard Medical School, Boston, MA, U.S.A.

Deep venous thrombosis (DVT) remains a serious and frequent complication after fracture of the hip, and even the most efficacious prophylactic agents, e.g., warfarin, may fail to prevent DVT in up to 20% of cases. There is evidence that low molecular weight heparin or heparin-like agents may have advantages in antithrombotic prophylaxis with reduced hemorrhagic side effects in patients at risk of DVT. We are engaged in a randomized prospective trial comparing the antithrombotic effect of warfarin (PT 1.5x control) with that of Organon 10172, a mixture of sulfated low molecular weight glycosaminoglycans (750 anti-Xa u b.i.d. sc., begun preop and continued 9 days, followed by warfarin). Diagnosis is by 125-I fibrinogen scan and impedence plethysmography with confirmatory phlebography. At present 71 patients have been admitted, and patient groups are comparable in age, sex, type of fracture, and all other significant respects. DVT has been diagnosed in 7 of 36 patients given warfarin and in 1 of 35 patients who received Organon 10172. Pulmonary embolism has not been encountered. GI bleeding has occurred twice on warfarin and once on Organon 10172. There has been no difference in estimated operative blood loss, transfusion requirements, or other major bleeding complications. One patient on warfarin died of myocardial infarction and pneumonia. There were no other adverse reactions.

The study is still in progress. The present trend in the results suggests that the heparinoid Organon 10172 may be a promising new agent to prevent DVT in high risk patients, such as those with fractures of the hip.

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PREVENTING VENOUS THROMBOSIS (VT) WITH HEPARIN ALONE OR WITH HEPARIN/DIHYDROERGOTAMINE AFTER ELECTIVE HIP REPLACEMENT, A DOUBLE-BLIND, RANDOMISED, VENOGRAM END-POINT COMPARISON. J.F. Cade (1), K.W. Mills (1), A.S. Gallus (2) and W. Murphy (2). Epworth Hospital, Victoria (1) and Flinders Medical Centre, South Australia (2).

Dihydro-ergotamine (DHE) appears to be synergistic with small doses of heparin when used to prevent VT after general surgery. However, doubt remains whether DHE has this effect in patients with elective hip replacement (THR). We have therefore compared the results of VT prophylaxis using sub-cutaneous (sc) low-dose heparin alone or sc heparin plus sc DHE in a double-blind, randomised, study of 126 patients having elective THR, 98 at centre (1) and 28 at centre (2). All received 5000 iu sodium heparin, 8 hourly for 7 days, starting 2 hours before surgery at centre (1), or immediately after surgery at centre (2). Patients also received a separate 0.5 ml (0.5 mg) DHE or placebo injection each time they received heparin. Patients had bilateral ascending venography on the 7th postoperative day, and venograms were read before the treatment code was broken.

Results from Centre		(1)		(2)		combined	
Heparin plus:		DHE	plac	DHE	plac	DHE	plac
Number (No.):		48	50	13	15	61	65
All VT:	No.	14	9	4	5	18	14
	%	29%	18%	31%	33%	30%	22%
calf VT:	No.	8	6	2	4	10	10
	%	17%	12%	15%	27%	16%	15%
proximal VT:	No.	6	6	4	1	10	7
	%	13%	12%	31%	7%	16%	11%

These results do not support the presence of synergism between heparin and DHE in this situation.

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DIHYDROERGOTAMINE-HEPARIN PROPHYLAXIS OF DVT IN TOTAL HIP REPLACEMENT PATIENTS: A MULTICENTER TRIAL. A.A. Sasahara (1), F.J. DiSerio (2), and the Multicenter Investigators. West Roxbury-Brockton VA Hospitals and Harvard Medical School, Boston, MA (1), Sandoz Research Institute, Hanover, NJ (2), U.S.A.

We report on the results of a controlled, blinded, U.S. multicenter trial in the prophylaxis of postoperative DVT in total hip replacement patients. One hundred and forty-eight (148) patients were enrolled in this evaluation of two parallel treatment groups: (1) dihydroergotamine 0.5 mg with heparin 5000 units (DHE/5000), or (2) matching placebo. Treatment was administered subcutaneously preoperatively and continued three times a day (Q8h) for at least seven days. One hundred and twenty-eight (128) of these were valid protocol compliers.

Daily radiofibrinogen leg scans performed for the duration of treatment were followed by venographic evaluation on postoperative Day 7 or when the RFUT indicated a sustained positive reading for 48 hours. In 12 patients venography was not performed and these patients are not included in the efficacy analysis, as were eight other protocol violators. The venographically confirmed positive DVT rates for the consultant's review (protocol compliers) were 25% (16/63) for DHE/5000 and 52% (32/65) for placebo, a statistically significant difference in effective prevention of DVT ($p=0.0021$, two tailed Fisher's exact test). The incidence of proximal thrombi (popliteal and above) was reduced from 18.5% (12/65 patients) in the placebo group to 4.8% (3/63 patients) in the group treated with DHE/Heparin ($p=0.0255$), while the incidence of extensive thrombi (>25% occlusion) was reduced from 24.6% (16/65 patients) to 9.5% (6/63 patients) in the respective groups ($p=0.0399$).

The most common side effect was injection site hematoma occurring in seven of the DHE/5000 patients and two of the placebo patients. One DHE/5000 patient discontinued treatment due to a side effect (injection site hematoma) attributable to drug and three placebo patients discontinued treatment due to side effects (two of these had confirmed pulmonary embolism).

These data confirm previous investigations supporting the efficacy and safety of DHE/5000 for the prevention of postoperative DVT in patients undergoing total hip replacement.