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PRELIMINARY EVALUATION OF REPEATED USE OF A LOW MOLECULAR WEIGHT HEPARIN IN HAEMODIALYSIS FOR CHRONIC RENAL FAILURE

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Summary

In a randomized cross-over long-term study we compared our standard regime of unfractionated heparin (UFH), with a regime of a low molecular weight heparin (LMWH) during routine haemodialysis. At the first hour of dialysis, plasma anti factor X a (aFXa) activity was lower with the LMWH than with the UFH but became similar subsequently. There were no clinical problems with either regime. Minor fibrin deposits were more frequent during dialysis with the LMWH, but the standardized compression time for the 'venous' puncture site at the end of dialysis was less. An increased dose of LMWH resulted in plasma aFXa of 0.94–0.87U/ml which were maintained throughout dialysis, with a reduced frequency of fibrin deposits. It is concluded that trouble-free dialysis with LMWH can be achieved with a dose 50–60 per cent that of UFH.

Introduction

Heparin is the usual anticoagulant for haemodialysis, though alternatives, such as prostacyclin [1], citrate [2] or none [3], have been tried. The ideal anticoagulant should suppress completely any clotting in the extracorporeal circuit, whilst minimizing the risk of bleeding during or after the procedure.

Low molecular weight heparins (LMWH) have a longer half-life than unfractionated heparin (UFH) [4]. Their activity against coagulation factor Xa is comparable to UFH but is much lower when broad-based assays, such as the kaolin-cephalin clotting time (KCCT) are used. In animal experiments they have anti-thrombotic properties comparable to UFH but they cause less bleeding [5–7].

We present here the preliminary results of a study which compares different dosage regimes of a LMWH (KABI 2165) with our standard regime of UFH and also assesses the suitability of the LMWH for long-term routine haemodialysis.

Methods

Patients

Patients, excluding women of child-bearing age and patients who were seriously ill, undergoing twice-weekly haemodialysis were selected at random. Fully informed consent was obtained and the project was approved by the local ethical committee.

Haemodialysis

Acetate dialysis was with either Dylade D2 or Gambro AK10 machines. Dialysers were single-use disposable Gambro Lundia plate, surface area $1m^2$ or $1.36m^2$, Q_D 500ml/min, Q_B 250ml/min. Vascular access was either by arteriovenous fistulas, Scribner shunts or, for one patient, a central venous catheter. Patients dialysed for 4–7 hours twice weekly.

Heparin regimes

In all studies the haemodialysis lines and dialyser were primed with approximately 300ml of normal saline which contained approximately 1500 aFXa U or IU of LMWH or UFH, respectively. The heparin infusion was terminated one hour before the completion of dialysis for patients with Cimino-Brescia fistulas but continued until the completion of dialysis for the other patients.

Regime 1 Eight patients (7 with fistulas) each had an intravenous bolus of LMWH 4000 aFXa U at the start of dialysis, followed by an intravenous infusion of LMWH 750 aFXa U/hr.

Regime 2 Eight patients were entered into a randomized cross-over trial of the following regimes: (a) LMWH intravenous bolus of 3000 aFXa U at the start of dialysis, followed by an intravenous infusion of LMWH 750 aFXa U/hr. (b) UFH intravenous bolus of 5000 IU at the start of dialysis, followed by an intravenous infusion of UFH 1500 IU/hr.

Each patient had eight dialyses with each of the two regimes (2a and 2b). Five patients (3 with fistulas, 1 with a shunt, 1 with a central venous catheter) have completed both regimes (2a and 2b). Three other patients have completed part of the protocol at the time of writing. The total number of dialyses performed to date is as follows: (2a) LMWH – 85 dialyses (17 with blood samples). (2b) UFH – 95 dialyses (19 with blood samples).

Blood samples

These were taken, processed and stored as described previously [8,9]. Samples were timed as follows:

Regime 1 Immediately before the beginning of dialysis (pre), at one hour, at the mid-point of dialysis, at the end of the heparin infusion (1 hour before the completion of dialysis) and at the completion of dialysis.

Regime 2 For patients with fistulas, as for regime 1 but without a mid-point sample. For the other patients, samples were taken pre, at one hour and at the completion of dialysis (which was also the end of heparin infusion).

Clinical observations

Fibrin deposits Every hour during dialysis, the drip chamber was examined carefully. The presence or absence of any fibrin deposit (usually a wispy ring extending to less than half the circumference of the chamber) was recorded. The blood-level in the chamber was readjusted; each subsequent hour the drip chamber was re-examined similarly and only new deposits were recorded each time.

Compression time Three patients with fistulas completed both parts of the cross-over study (regimes 2a and 2b). Standardized measurements were taken on 17 occasions with LMWH and 20 occasions with UFH. At the end of dialysis, the 'venous' needle was taken out first and the 'arterial' needle one minute later. The puncture sites were compressed firmly and examined every two-and-a-half minutes until there was complete cessation of bleeding. The time was recorded for each site.

Results

Satisfactory haemodialysis was achieved with all three regimes. Routine haematological and biochemical parameters were monitored; there was no difference between the LMWH and UFH phases of the cross-over study. Though fibrin deposits were noted at times (see below), these were generally slight; at no time was it necessary to change the dialysis lines or the drip chamber, or to administer additional heparin.

The heparin levels attained with the three different regimes are shown in Table I. 'Pre' blood samples had no detectable aFXa activity.

TABLE I. Heparin levels attained during various heparin regimes, determined with the anti Factor Xa assay

Heparin regime	Bolus aFXa U	Infusion rate aFXa U/hr	Patients	Total dialyses	aFXa U/ml ± SEM 1 hr	Mid-point	End infusion	1 hr post infusion
1 KAB1 2165	4000	750	8	8	0.94 ±0.08	0.92 ±0.10	0.89 ±0.08 (n=6)	0.87 ±0.12 (n=6)
2(a) KAB1 2165	3000	750	7	17	0.77* ±0.08	–	0.93 ±0.11	0.73 ±0.13 (n=10)
2(b) UFH	5000	1500	7	19	1.03* ±0.09	–	0.98 ±0.13	0.65 ±0.17 (n=12)

*Statistically significant difference $p<0.05$ (unpaired 't' test)

TABLE II. Number of hours in which new fibrin rings were deposited expressed as a percentage of total hours of dialysis

	KABI 2165 Bolus 3000 aFXa U+Infusion 750 aFXa U/hr			UFH Bolus 5000 IU+Infusion 1500 IU/hr		
Patient	Hours with new deposits	Total hours of dialyses	%	Hours with new deposits	Total hours of dialyses	%
WB	11	35	31.4	11	35	31.4
JC	6	42	14.3	3	49	6.1
NR	7	36	19.4	2	42	4.8
WG	6	32	18.7	3	32	9.4
HS	3	36	8.3	2	48	4.2
Mean			18.42*			11.18*
±SEM			±3.8			±5.13

*Statistically significant difference $p<0.05$ (paired 't' test)

The frequency of fibrin deposition for the five patients who completed both phases of the cross-over study is shown in Table II. Fibrin rings were recorded more frequently during dialysis with the lower-dose LMWH than with UFH. With the higher-dose LMWH (regime 1), there were only two occasions when fibrin deposits were observed out of a collective total of 35 hours of dialysis.

Three patients with fistulas completed the cross-over study. The compression time for the 'venous' puncture site was 5.15±0.59 min (mean ± SEM, 17 dialyses) for the LMWH and 10±1.61 min (20 dialyses) for the UFH ($p<0.01$, unpaired 't' test). The corresponding mean compression times for the 'arterial' puncture site were similar at 10.30±2.16 min for the LMWH and 9.00±1.56 min for the UFH, respectively. With the higher-dose LMWH (regime 1:6 of the 8 patients, studied after a single dialysis) the 'venous' compression time was 4.58±0.42 min and the 'arterial' 5.83±0.83 min. These results cannot be compared directly with those of the cross-over study.

Discussion

Unfractionated heparin almost completely suppresses the generation of fibrin, assessed by visible observation and fibrinopeptide-A (FPA) generation, during prolonged haemodialysis [8]. In another study [9] we found that the LMWH, KABI 2165, also suppresses fibrin deposition and FPA generation when it is administered at the dose of intravenous bolus 5000 aFXa + infusion 15000 aFXa U/hr. However, continuously increasing plasma aFXa was observed with a maximum mean value exceeding 1.5 aFXa U/ml; there is possibly a risk of haemorrhagic complications at this dosage. In the same study, we found that if an intravenous bolus of LMWH 5000 aFXa U is given without a maintenance

infusion, FPA generation is suppressed for the first three hours but increases progressively from then on.

With a 3000 aFXa U bolus of LMWH and an infusion rate of 750 aFXa U/hr, the plasma values at one hour were lower than with our standard regime of UFH. Haemodialysis was carried out without severe clotting in either the haemodialysis lines or dialyser. With careful clinical monitoring, however, we were able to demonstrate that small fibrin deposits were more frequent with this regime (2a) than with UFH (2b) as shown in Table II. With a larger LMWH bolus at 4000 aFXa U (regime 1), a higher mean aFXa level was attained with a reduced frequency of fibrin deposition but we do not yet have enough data for statistical comparisons.

Despite the longer half-life of this LMWH, compared with UFH, there was no evidence of accumulation after multiple consecutive haemodialyses. There were no clinical, biochemical or haematological adverse reactions attributable to the LMWH.

We have also attempted to compare the potential for bleeding complications after LMWH and UFH by measuring the compression time at the puncture sites and we found that, at the 'venous' site, it was significantly less after LMWH than after UFH, despite similar plasma aFXa values at the end of dialysis. If confirmed, this will be important in vivo evidence of a reduced bleeding risk with LMWH compared with UFH. At the 'arterial' site there was no difference in compression times but this site is often close to the arteriovenous anastomosis of the Cimino-Brescia fistula and may reflect local haemodynamics more than disorders of coagulation.

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