Melagatran anticoagulation during haemodialysis—‘Primum non nocere’

Michael J. Flanigan

University of Iowa Hospitals, Iowa City, USA

‘Primum non nocere’ or ‘First do no harm’ is attributed to Galen’s translation of the Hippocratic Corpus (Epidemics, Bk. I, Sect. XI.), ‘Declare the past, diagnose the present, foretell the future; practice these acts. As to diseases, make a habit of two things—to help, or at least to do no harm’ [1,2].

In this issue of Nephrology Dialysis Transplantation, Per-Ola Attman and colleagues describe an elegant, heparin-free, haemodialysis anticoagulation scheme using the direct thrombin inhibitor melagatran. They use dialysate as a drug delivery vehicle and thus regulate melagatran serum levels with precision. The authors define and monitor efficacy and safety end-points. Drug efficacy is assessed by inspecting the dialysis system for clotting, recording dialyser iohexol clearance and monitoring trans-dialyser pressure gradients. Drug safety is assessed by measuring post-dialysis needle puncture haemostasis times. The report includes both intra- and inter-dialysis pharmacokinetic data [3]. The authors note that melagatran is dialysable, has no antidote and might potentiate bleeding. They propose that the prolonged melagatran half-life following dialysis (14±4 h) may facilitate arteriovenous (A-V) fistula and central dialysis catheter patency. They do not, however, announce that surgery, trauma or dental work in the 24 h following dialysis could precipitate uncontrollable haemorrhage [4,5].

Dialysis anticoagulation has a long history. Early dialysis systems exposed blood to variously stagnant and turbulent flow characteristics, bioactive materials and pyrogenic dialysate. These dialysis...
systems were intensely thrombogenic, and successful dialysis required through anticoagulation. Initially, the thrombin inhibitor hirudin served this purpose; however, hirudin bio-extraction was laborious, its purity questionable and the leaches needed for extraction fell into shortage during the war years. Thus, human dialysis remained impractical until the description and extraction of heparin became reality [6–8]. Through the 1950s and into the 1980s, the dominant feature of dialyses anticoagulation was bleeding, and ‘uraemic bleeding’ was a major contributor to patient death [9]. Subdural haematomas, haemorrhagic periarteritis, retroperitoneal haematomas and gastrointestinal haemorrhage were believed to be manifestations of uraemic coagulopathy and, while currently less prevalent, remain important contributors to patient morbidity and mortality [10]. Over the last 20 years, improved equipment and nursing practices have permitted heparin doses to decrease from >20,000 units/dialysis to ~5000 units/dialysis, and ‘spontaneous’ bleeding complications have become unusual. Recent cases of spontaneous bleeding after recombinant hirudin haemodialysis anticoagulation illustrate the problems of protracted aggressive antithrombin therapy [4], and trials of xilomelagatran for the prevention of post-operative venous thrombosis report severe bleeding incidences as high as 5% when therapeutic doses of xilomelagatran are administered in the post-operative setting [11]. Of still greater concern is that neither dialysis patients nor their dentists and primary care physicians routinely consider haemodialysis synonymous with systemic anticoagulation. This is likely to result in the unexpected discovery of dialysis-induced coagulopathy and will endanger patient safety whether it occurs during accidental trauma, elective surgery or spontaneously [5].

It is important to maintain perspective and ‘Primum non nocere’. Dialysers are disposable, patients are not. Successful routine haemodialysis is readily achieved in >90% of treatments with no anticoagulant [12–15], while supervised, controlled anticoagulation of dialysis patients with aspirin, clopidogrel, heparin, warfarin, hirudin and low molecular weight heparins leads to excessive bleeding [5,16–22] in 5–10% of dialysis patients annually. It is imperative that innovators alert their readers not just to potential benefits but also to possible risks and hazards. Those who fail to educate their audience fully share responsibility for those adverse events encountered by their ‘trainees’.

Conflict of interest statement. None declared.

[See related Article by Attman et al., pp. 1889]

References
1. Primum non nocere. Viewed 5/7/05 @http://en.wikipedia.org/wiki/Primum_non_nocere.