Pharmacological control of bleeding during cardiac surgery

Sir—The complex analysis of the pharmacological control of bleeding after cardiac surgery by Marcel Levi and colleagues (Dec 4, p 1940)[1] takes me back to a night in June, 1960, when a resident called to ask me to see a patient who had been bleeding all day after surgery to replace his aortic valve. Unable to control the bleeding or to close his chest (he had received 56 units of blood, mephyten, calcium chloride, and so on) the resident, a friend, called because he knew I had just received the first epsilon amino caproic acid for my research.

No dry analysis can do justice to the enormous excitement all of us felt when the bleeding stopped within minutes after injecting epsilon amino caproic acid, and the patient's chest could finally be closed.[2] This episode formed the basis of a study on the effect of open heart surgery on haemostasis at the University of Minnesota Hospitals, that would show the clinical usefulness but also some of the drawbacks of epsilon amino caproic acid.[3] When, a few years later, trasylol (now known as aprotinin) was developed and needed testing, its effectiveness in controlling the bleeding after open heart surgery was assessed and compared with epsilon amino caproic acid. We could not find much difference between the two.[4]

Since we had not visited the patient for over 30 years, I was curious to see what changes had occurred over the years in the use of these drugs. I noticed that despite the elaborate analysis of the trials on which the Amsterdam study was based, and hence the fact that our conclusions may not have had the same scientific validity, they were nevertheless the same.

What continues to puzzle me, however, is why one patient should bleed uncontrollably while others with the same fibrinolytic activity do not.

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Renal side-effects of cyclo-oxygenase-type-2 inhibitor use

Sir—Paul Emery and colleagues (Dec 18/25, p 2106)[1] showed that treatment with celecoxib caused fewer gastrointestinal side-effects than diclofenac. However, potential side-effects of cyclo-oxygenase (COX-2)-selective inhibitors may include impairment of renal function. In a study by Swan and colleagues,[2] rofecoxib reduced glomerular filtration rate (GFR) by about 12% in elderly patients with mild renal impairment (baseline creatinine clearance 30–80 mL/min; 10% reduction of GFR with indomethacin). Brooks and colleagues[3] found that in volume-depleted dogs, intravenous celecoxib reduced urine flow by 57%, sodium excretion by 70%, renal plasma flow by 65%, and GFR by 58% (reduction of 57%, 33%, 33%, 27%, respectively, for indomethacin). And Whelton and colleagues[4] found that celecoxib caused significant reductions of urinary sodium excretion on the first 2 days of treatment in healthy elderly patients, but did not significantly affect GFR (reduction of −1·1 mL/min). They also found that urinary prostaglandin E_2 and 6-keto prostaglandin F1α were decreased to the same extent by celecoxib and naproxen. In the study by Emery and colleagues, a small increase in serum creatinine concentration from 93·3 μmol/L at baseline to 95·5 μmol/L at the final visit, and of serum urea concentration from 6·0 mmol/L to 6·4 mmol/L was reported (serum creatinine 93·2 *vs* 97·2 μmol/L, serum urea 6·0 *vs* 6·7 mmol/L with diclofenac). With regard to changes in renal function during COX-2 inhibition, it would be of interest to know serum creatinine and urea concentrations measured at 4-weekly intervals, and the results of urine analyses. However, one has to keep in mind that in the study by Emery and colleagues, only patients with normal renal function were studied. In a larger study of 1149 patients, celecoxib versus naproxen was studied.[5] Baseline serum creatinine concentrations were as low as 66 μmol/L. Not surprisingly serum creatinine concentrations were unaffected by celecoxib or naproxen treatment in this study. Why there are such large differences in baseline serum creatinine concentrations between these two studies is not clear; the patients with rheumatoid arthritis studied were of nearly identical age and sex distribution.

Evidence suggests that COX-2 inhibitors impair renal function and cause sodium retention in patients with mild pre-existing renal failure and presumably also in some elderly patients with, for example, volume depletion. The published randomised trials have regularly excluded these patients. We feel that it is important for unpublished data from these trials to be made available to allow a better estimation of the renal risk conferred by COX-2 inhibitors. Furthermore, randomised trials that assess renal side-effects of COX-2 inhibition in patients with pre-existing renal failure are eagerly awaited.

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Male impotence

Sir—Abraham Morgentaler (Nov 13, p 1713)[1] provides a clear and concise account of the anatomy, physiology, and pathophysiology of male erectile dysfunction. The panel listing the medical risk factors associated with erectile dysfunction puts the problem in context, and it is important to stress that erectile dysfunction may presage cardiovascular disease because both have many risk factors in common.

Morgentaler's experience with sildenafil is surprising compared with our experience and that of others. He reports a 50% success rate whereas more than 80% of 500 men so treated in our clinic have been treated successfully. Certain subpopulations do have a lower response rate—ie, 62%