Clinical opinions in general medicine

In this issue of clinical opinions Higgins highlights the importance of early intervention in chronic renal disease and raises the possibility of a combination of aspirin, an ACE inhibitor and a statin as a renoprotector super pill. Ferguson and Hayes look at the safety profile of statins in patients with liver disease. Finally, dipping into the world of undergraduate medical education, MacLeod tells us that, yes, medical students' attitudes are slipping. Hopefully something of interest for everyone and as always we invite comment and encourage readers to submit opinions of their own.

Clinical opinion: Renoprotection – a road to the 'super pill' for chronic nephropathies

TITLE: The history and future of renoprotection.
KEYWORDS: ACE inhibitors, angiotensin receptor blockers, chronic renal disease, renoprotection, vasopeptidase inhibitors.
AUTHOR: Brenner BM.
JOURNAL: *Kidney Int* 2003; **64:**1163–6.

SUMMARY

This article summarises the work of Brenner and others since his seminal paper in 1982 showing that progressive deterioration in renal function is due to compensatory glomerular haemodynamic changes in response to renal injury.[1] Briefly, following renal injury, the remaining nephrons undergo hypertrophy, increased glomerular blood flow, and reduced arteriolar resistance. Since the afferent arterial tone decreases more than the efferent tone, the intraglomerular pressure rises and the amount of filtrate per nephron rises. Angiotensin II is the main mediator of these vascular changes; other non-vascular actions of angiotensin II on chemokines and renal mesangial cells are probably also important causes of renal damage.

Using experimental models and subsequently by observation in human disease, it has been shown that angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are both highly effective in reducing glomerular capillary hypertension, reducing proteinuria and reducing the rate of loss of glomerular filtration rate. Brenner reviews a number of trials of ACE inhibitors and ARBs in renal disease due to diabetes mellitus (Types 1 and 2) and non-diabetic renal disease, showing a reduction in proteinuria and a slowing of the rate of loss of glomerular filtration rate. These effects cannot be attributed to coincidental control of blood pressure. The article further describes the seductive possibility of even better renoprotection using vasopeptidase inhibitors, which act like ACE inhibitors to reduce angiotensin II mediated vasoconstriction and which also enhance vasodilatation by inhibiting the inactivation of bradykinin, brain natriuretic peptide and atrial natriuretic peptide.

Brenner emphasises that renoprotective treatment should not be seen in isolation but as an addition to treatments such as moderate dietary protein restriction, which independently preserves renal function, blood pressure control, reduction of blood lipids and tight glycaemic control in diabetes mellitus.

OPINION

Brenner's review is a timely reminder that physicians should not take a passive or negative view of treatment in chronic renal disease prior to the need for dialysis or renal transplantation. The addition of renoprotection to already potentially complex therapy may be daunting, but the goal of a better quality of life from reduced cardiovascular morbidity and postponement of dialysis is an obvious patient benefit. Moreover, the worldwide growth of dialysis for end-stage renal disease will cost more than US$1 trillion in the next decade. This prediction may even be exceeded if the survival of patients treated by dialysis continues to improve, and there appears to be no chance of providing sufficient renal transplants to reduce this burden.

Accordingly, it behoves us to concentrate our efforts in the early treatment of renal disease to reduce the rate of progression to renal failure. The importance of this article lies in the clear pointers it gives for treatment strategies offered primarily by the control of systematic and glomerular hypertension using ACE inhibitors and ARBs, protein restriction, and lipid control. Brenner recognises the cost of such

treatment, particularly in resource-constrained developing countries, and he closes the article with a suggestion similar to that of Wald and Law for cardioprotection[2] using a low-dose combination tablet of aspirin, a statin and an ACE inhibitor as low-cost renoprotection. These proposals together could act as guidelines for developed and less-developed countries to reduce the burden of end-stage renal disease.

REFERENCES

1 Brenner DM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of renal disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation and intrinsic renal disease. *N Engl J Med* 1982; **307:**652–9.

2 Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. *BMJ* 2003; **326:**1419–24.

DECLARATIONS OF INTERESTS

Dr Higgins has shares in Pfizer.

MR Higgins, Consultant Nephrologist, Scarborough Regional Hospital, Tobago, West Indies

Clinical opinion: Are statins safe in patients with elevated liver enzymes?

TITLE: Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicty.
KEYWORDS: Hepatotoxicty, hyperlipidaemia, liver enzymes, statin.
AUTHORS: Chalasani N, Aljadhey H, Kesterson J *et al.*
JOURNAL: *Gastroenterology* 2004; **126:**1287–92.

SUMMARY

Often known as 'statins', HMG Co-A reductase inhibitors are commonly prescribed and are potent lipid-lowering agents. These agents are well tolerated but can occasionally lead to liver and muscle injury. Manufacturers recommend that they should not be prescribed in patients with persistently elevated transaminases. This study aimed to evaluate whether patients with elevated baseline liver enzymes are at a higher risk of statin induced hepatotoxicty.

The authors utilised a powerful medical electronic database that captures demographic, clinical, laboratory and prescription data from three hospitals and 30 clinics in the Indianapolis area of the US. They identified three cohorts of patients: cohort 1 (n=342) consisted of individuals with elevated baseline liver enzymes (ALT >35 IU/L) who were prescribed a statin; cohort 2 (n=1,437) consisted of individuals with normal baseline liver enzymes who were prescribed a statin; and cohort 3 (n=2,245) consisted of individuals with elevated liver enzymes who did not receive a statin. Mild to moderate hepatotoxicity was defined as elevations of AST and/or ALT up to ten times the upper limit of normal (ULN). Severe hepatotoxicity was defined as the development of a serum bilirubin >3 mg/dl or elevations of AST and/or ALT greater than ten times the ULN.

They found that cohort 1 had a higher incidence of mild to moderate, but not severe, elevations in liver biochemistry than cohort 2. However, no difference in the frequency of elevation of mild to moderate or severe elevations in liver enzymes was found between cohort 3 and cohort 1. They therefore suggest that individuals with elevated liver enzymes do not have increased susceptibility to hepatotoxicity from statins.

OPINION

If paracetemol is excluded, most severe drug induced liver injury (DILI) is idiosyncratic. Conventional wisdom has suggested caution when administering a drug capable of causing a DILI to patients with coexisting liver disease. However, this recent study suggests that this approach may be wrong in the case of statins. This is important, as currently regulatory authorities are considering whether statins should be available without prescription in the US and UK.

There are certain aspects of this study that deserve consideration. First, patients with hepatitis B or C and those with a history of alcohol abuse were excluded. Therefore the results may not be

applicable to these groups of patients. Second, the study only examined the course of transaminases within a six-month period and therefore did not examine trends after this time. Last, findings with statins cannot be generalised to other drug classes.

In the future we would hope that the genetic and environmental factors behind DILI will be elucidated. However, at present this study provides useful guidance; patients with elevated liver enzymes of unknown aetiology are not at higher risk of hepatotoxicty from statin use.

JW Ferguson, Clinical Research Fellow and PC Hayes, Professor of Hepatology,
Liver Unit, Royal Infirmary of Edinburgh, Little France, Edinburgh, Scotland

Clinical opinion: Attitude decline in medical students – real or imagined?

TITLE: Attitude change during medical school: a cohort study.
KEYWORDS: Attitudes, behaviour, medical students, unintended curriculum.
AUTHORS: Woloschuk W, Harasym P, Temple W.
JOURNAL: *Med Educ* 2004; **38:**522–34.

SUMMARY
Attitudes are important because they are viewed as a link between clinical competence (knowledge and skills) and clinical performance. Attitudes influence what a doctor does in real life practice yet there is little published evidence examining attitude shifts amongst medical students as they progress through medical school. This cohort study sought to do this by following students from three consecutive classes (1999–2001) at the University of Calgary Medical School. The authors also sought to determine whether gender influenced attitude shifts. Attitudes were assessed using two validated questionnaires administered at three milestones during medical school training – entry to medical school, end of preclinical training and end of clerkship.

Reliability estimates for attitudinal scores were in the acceptable range. Multivariate analyses of scores showed a persistent decline in several attitude scores as students progressed through the programme. Females consistently demonstrated higher attitude scores than males.

The authors offer no clear reasons for such a decline but speculate it may be the result of unusually high attitude scores at entry combined with loss of idealism over time and the impact of what they call the 'unintended' curriculum.

OPINION
At first glance this study is rather depressing – bright, idealistic young people with highly positive attitudes on entry to medical school leave a few years later less idealistic and with a poorer attitude. However, it is important to note that, despite a significant decline in attitude scores, overall the total and subscale scores on both assessment instruments indicate that positive attitudes persist. In other words, at the end of medical training students still retained a positive attitude, albeit somewhat less so than on entry to medical school.

The difference between males and females is not new and therefore not surprising. What is interesting is the finding that females consistently outscored males on the social desirability subscale – in other words, females may respond in a way they hope will reflect more positively on them whereas males may feel less compelled to do so.

Also of interest is the authors' speculation about the impact of the 'unintended' curriculum, which itself may be broken down into the 'hidden' and the 'null' curriculum. The hidden curriculum is all that which is taught but does not appear in course and class syllabi, lecture notes and handouts or among the volumes of documentation produced for the purposes of accreditation. The hidden curriculum comprises the student's exposure to role models and to professionalism and reminds us of the crucial, yet largely informal, role seniors have in shaping the doctors of tomorrow. The 'null' curriculum is that

material which is either left out completely, or discontinued at some point during the undergraduate curriculum, and which transmits a message of unimportance. One thinks of the importance attached to communication skills in the early years of many undergraduate curricula and its absence in the senior and final years.

This paper gives us much to think about and hopefully will stimulate further study. In the meantime we would do well to reflect on the quotation the authors include from Anderson's paper on the hidden curriculum, 'Our teachings reflect our attitudes, prejudices, honesty and humility. It is our example that will be remembered long after the differential diagnoses are forgotten.'

C MacLeod, Consultant Paediatrician & Honorary Senior Lecturer, Antrim, Northern Ireland

NOTICE

IN THE COURT OF SESSION

in the

Petition of the Royal College of Physicians of Edinburgh as Trustees of a Trust by Sir John Pringle for authority to vary Trust purposes and approval of a Cy Pres Scheme.

An Action has been brought in the Court of Session, Edinburgh, Scotland by The Council of the Royal College of Physicians of Edinburgh in which they seek authority to vary the terms of a Trust by Sir John Pringle. The Council also seek approval of a Cy Pres Scheme. By virtue of an Order of Lord Marnoch, 26th June 2004, all parties claiming interest should lodge answers, if so advised, with the Office of Court, Court of Session, 2 Parliament Square, Edinburgh EH1 1RP within 21 days after the date of publication of this notice.

John B Stirling WS
Agent for the Petitioner
Bennett & Robertson LLP
25 George IV Bridge
Edinburgh
0131 225 4001