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Angiotensin-II-receptor antagonists in diabetic nephropathy

The end-organ damage caused by type 2 diabetes mellitus causes concern and poses public health problems worldwide. Of particular interest in three recently published papers was nephropathy, which causes almost 40% of all incident dialysis cases in the USA. Average survival once end-stage renal disease (ESRD) has developed is 2 years, most of the deaths being from renal disease.

Microalbuminuria precedes overt diabetic nephropathy, and this stage is readily detectable. It is also potentially reversible. Irbesartan 300 mg per day was shown in a trial[1] to reduce progression to overt nephropathy at 2 years. Lower doses were ineffective. The benefits were superior to those of placebo, and were independent of blood pressure (BP) lowering and glycaemic control. In addition, it was more likely than placebo to cause regression to normoalbuminuria.

In the second study,[2] the Irbesartan Diabetic Nephropathy Trial (IDNT), Lewis and colleagues showed that in patients with type 2 diabetes, nephropathy and hypertension irbesartan was more effective than amlodipine or placebo in reducing progression of nephropathy, independent of the effect on BP.

In the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study,[3] the results showed that losartan was renoprotective in patients with type 2 diabetes and nephropathy. The effect was beyond that attributable to BP control.

Christian Rabbat of McMaster University, Ontario, Canada, commenting on these trials,[4] says that both the IDNT and RENAAL studies used prespecified secondary outcome clusters to measure morbidity and mortality from cardiovascular causes. Secondary outcomes occurred in 24% of patients in the IDNT study and 34% in the RENAAL study. Neither losartan nor irbesartan reduced the risk for this composite outcome. Losartan was, however, associated with a lower rate of first hospitalisation for congestive heart failure.

'Patients and clinicians must now consider using these drugs', continues Rabbat. 'The treatment of type 2 diabetes should start early in the course of the disease process.'

At the normoalbuminuric or microalbuminuric stage, ACE inhibitors can be considered as first-line agents because of their proven efficacy in preventing progression to overt nephropathy, and reducing cardiovascular events. Once nephropathy has developed, the importance of renin-angiotensin system blockade persists, but the choice of drug is less clear. Clinicians should expect to have to use three or four different drugs to achieve a good BP reading. Dual blockade of the renin-angiotensin system with a combined ACE inhibitor and angiotensin-II-receptor antagonist seems promising. It may offer the best treatment strategy and result in lower incidence rates of microvascular and macrovascular complications in type 2 diabetes.

1. Parving H-H *et al. N Engl J Med* 2001; **345:** 870-878.
2. Lewis EJ *et al. N Engl J Med* 2001; **345:** 851-860.
3. Brenner BM *et al. N Engl J Med* 2001; **345:** 861-869.
4. Rabbat CG. *ACP J Club* 2002; **136(3):** 82-84.

Aircraft recirculation and the common cold

It has been thought that aircraft cabins may be high-risk environments for transmission of infectious disease. Space confinement, limited ventilation, prolonged exposure times, and recirculated air have been demonstrated to be risk factors for transmission of upper respiratory tract infections in other settings. It was not known whether air recirculation increased rates of transmission. A study was conducted to evaluate the role of air recirculation as a predictor of postflight upper respiratory tract infections (URTIs).

Passengers (N = 1 100) travelling from San Francisco, California to Denver, Colorado completed a questionnaire before boarding

the flight, and received a follow-up telephone interview 5 - 7 days later.

The first questionnaire collected baseline data about the passengers, which included health status, history of allergies, sinus problems, asthma, recent flu vaccination, sick contacts before first questionnaire, as well as knowledge and beliefs about the risks of URTIs and air recirculation.

The second set of questions investigating possible URTI symptoms included a range from a runny nose to headache, sneezing, chills, sore throat, malaise, nasal discharge, nasal obstruction and cough.

Forty-seven per cent travelled aboard aircraft using 100% fresh air for ventilation, and 53% on aircraft that recirculated cabin air.

In commenting on this research, the authors say that there are limitations to the study. Firstly, the study's size was limited. Secondly, the intergroup differences in some baseline variables were greater than expected. People aboard planes that recirculated air were more likely to be older and have a history of sinus problems, characteristics which might have made them more likely to report colds. Another issue was the duration of the flight — the possibility exists that there is a dose-dependent effect of air recirculation which would become evident on flights that were longer than 2 hours. Longer flights could not be studied as older airplanes which do not recirculate air are used almost exclusively on shorter routes.

The high incidence of subjectively reported symptoms that became apparent in this study could in part have been due to a travel effect involving factors such as stress, sleep loss, crowding, and poor eating, which were not controlled for in the design.

This 'natural experiment' took advantage of the passengers' lack of awareness of the air mixture in different aircraft, to replicate a blinded study.

The results indicated that cabin air recirculation was not a risk factor for developing symptoms of a cold during the week after a flight.There was no difference in the likelihood of a self-reported cold during the week after a flight between passengers travelling aboard an aircraft using 100% fresh air and those travelling on a plane which recirculated up to 50% of the cabin air. The widespread practice of recirculating air therefore does not seem to increase the risk of transmission of URTIs, at least on flights lasting up to 2 hours.

(Zitter J *et al. JAMA* 2002; **288**(4): 483-486.)

Faecal calprotectin for assessing disease activity in inflammatory bowel disease

Calprotectin is a calcium-binding protein which is found in abundance in neutrophils and in lower concentrations in monocytes and reactive macrophages. It has the potential of representing a surrogate marker of neutrophil influx into the bowel lumen and in turn to act as a marker of intestinal inflammation. Studies to date indicate that increased levels of faecal calprotectin are found in inflammatory bowel disease, colonic cancer and non-steroidal anti-inflammatory drug (NSAID) treatment.This suggests that it is a sensitive but nonspecific marker of intestinal inflammation.

Faecal calprotectin correlates well with endoscopic and histological grading of disease activity in ulcerative colitis. It correlates more closely to histology than to macroscopic findings, suggesting that it is more sensitive than endoscopy in inflammatory bowel disease.

Methods currently used to monitor disease activity in Crohn's disease include monitoring faecal excretion of radiolabelled white cells (indium-111-labelled granulocytes) and the Crohn's disease activity index (CDAI). A strong positive correlation between faecal calprotectin and faecal excretion of indium-111-labelled neutrophils has been shown. Faecal calprotectin has been proposed as an ideal marker of disease activity in Crohn's disease.The test is cheap, easy to perform, with a marker that is stable at room temperature for up to 7 days, thereby permitting postage of samples.

Faecal calprotectin cannot replace invasive tests for the diagnosis of Crohn's disease, as it is too nonspecific. However, it has real potential to evolve as a simple, cheap, non-invasive and sensitive marker of disease activity and/or response to treatment in those who already have a firm diagnosis of inflammatory bowel disease.

The CDAI is used to assess the activity of the disease and the response to treatment. It has certain shortcomings, e.g. interobserver variability, and subjectivity, in that it depends on the patient's perception of the disease. A study comparing faecal calprotectin, radiolabelled white cell scanning and the CDAI is currently being done.

A potential important use of faecal calprotectin measurement is to reveal treatment failure, thereby avoiding prolonged ineffective steroid therapy. One would

also hope to prevent relapse by regular monitoring. This raises the question of whether one should consider treating a patient on the basis of the inflammatory component of Crohn's disease, irrespective of symptoms, in order to alter the natural history of the disease. We do not yet know if it would be in the patient's best interests to treat asymptomatic bowel inflammation. For the foreseeable future, treatment decisions will therefore remain symptom/sign-based.

(Gaya DR *et al. QJM* 2002; **95:** 557-558.)

Admission body temperature predicts long-term mortality after acute stroke

Body temperature is considered crucial in the management of acute stroke patients. Recently, hypothermia applied as a therapy for stroke has been demonstrated to be feasible and safe in acute stroke patients. In the Copenhagen Stroke Study the authors investigated the predictive role of admission body temperature in long-term mortality in stroke patients.

They studied 390 patients with acute stroke admitted within 6 hours of stroke onset. Admission clinical characteristics (age, sex, stroke severity, blood glucose, cardiovascular risk factor profile, and stroke subtype) were recorded for patients with hypothermia (body temperature 37°C) and for those with hyperthermia (body temperature >37°C). Univariately the mortality rates for all patients were studied by Kaplan-Meier statistics. To find independent predictors of long-term mortality for all patients, Cox proportional-hazards models were built. All clinical characteristics and body temperature as a continuous variable were included.

Results

In patients with hyperthermia there was a higher incidence of severe strokes and diabetes, whereas no difference was found for the other clinical characteristics. For all patients mortality rate at 60 months after stroke was higher for patients with hyperthermia (73 per 100 cases v. 59 per 100 cases, $p = 0.001$). When body temperature was studied in a multivariate Cox proportional-hazards model, a 1°C increase in admission body temperature independently predicted a 30% relative increase in long-term mortality risk. For 3-month survivors the authors found no association between body temperature and long-term survival when studied in a multivariate Cox proportional-hazards model.

Conclusion

Low body temperature on admission is considered to be an independent predictor of good short-term outcome. The present study suggests that admission body temperature seems to be a major determinant, even for long-term mortality after stroke. Hypothermic therapy in the early stage in which body temperature is kept low for a longer period after ictus could be a long-lasting neuroprotective measure.

(Kammersgaard LP *et al. Stroke* 2002; **33:** 1759-1762.)

SINGLE SUTURE

Is your waiting room a DUMP?

The acronym DUMP (according to Margaret Sutherland, research co-ordinator, Department of Public Health and General Practice, University of Otago, New Zealand (*BMJ* 2002; **324:** 1443)) stands for depressing, uninteresting medical practice. She says that the waiting rooms of doctors' practices (those she has visited, anyway) often have tired and neglected décor, with faded paint and curtains, and dog-eared posters on the walls, with depressing medical messages. Untidy piles of dated, tatty, tawdry magazines (including pornography in one practice) possibly donated by well-meaning patients, are not uncommon. Dirty, torn, well-chewed children's books, old broken toys and incomplete puzzles provide 'unlimited boredom for younger victims', she says. Patient satisfaction surveys ask about waiting times, not waiting rooms. Why not ask your patients what they would like to be available to them while they wait?