

Reports on Individual Drugs

Short-course zidovudine in perinatal HIV transmission

In 1994, a reduction of 67.5% in the relative risk of mother-to-child transmission of HIV was demonstrated in newborn infants treated before, during and after birth with zidovudine (1). Further data from a recent trial in Thailand suggest that an abbreviated regimen of oral zidovudine from 36 weeks of gestation until delivery, with no neonatal component, can reduce the relative risk of transmission by approximately 50% (2). Although the decrease was significant, it was understandably lower than the reduction in the relative risk of perinatal transmission reported in the 1994 study.

The results of a new study undertaken in the USA suggest that more abbreviated zidovudine prophylaxis can also reduce the rates of perinatal transmission of HIV (3). The timing and response to zidovudine therapy were analysed in 939 HIV-exposed infants below 180 days of age. When treatment was begun in the prenatal period, the rate of HIV transmission was 6.1%. However, when zidovudine was begun intrapartum the rate was 10%; begun within the first 48 hours of life 9.3%; and on day 3 of life or later 18.4%. In the absence of zidovudine prophylaxis, the rate of HIV transmission is 26.6%. These results confirm the efficacy of zidovudine prophylaxis and suggest that reductions in the rates of perinatal transmission of HIV can be achieved even with the use of abbreviated regimens that begin during labour or the first 48 hours of life.

These findings require further confirmation but, even without confirmation, the study offers hope that HIV infection can be prevented after exposure. It also indicates that HIV-infected women who do not receive zidovudine during pregnancy should be identified so that they can receive antiretrovirals during delivery and their infants can begin receiving zidovudine at birth. This study demonstrates that a less expensive preventive regimen (4) is available for routine use, particularly in those areas where HIV prevalence is high but resources are severely limited (5).

References

1. Connor, E.M., Sperling, R.S., Gelber, R. et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. *New England Journal of Medicine*, **331**: 1173–1180 (1994).
2. Centers for Disease Control and Prevention. Administration of zidovudine during late pregnancy to prevent perinatal HIV transmission — Thailand 1996–1998. *Morbidity and Mortality Weekly Report*, **47**: 151–153 (1998).
3. Wade, N.A., Birkhead, G.S., Warren, B.L. et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the human immunodeficiency virus. *New England Journal of Medicine*, **339**: 1409–1414 (1998).
4. McIntosh, K. Short (and shorter) courses of zidovudine. *New England Journal of Medicine*, **339**: 1467–1468 (1998).
5. World Health Organization. Recommendations on the safe and effective use of short-course ZDV for prevention of mother-to-child transmission of HIV. *Weekly Epidemiological Record*, **73**: 313–320 (1998).

Vitamin D supplements in adults

Vitamin D is an essential precursor of 1,25-dihydroxyvitamin D, the steroid hormone necessary not only for bone development and growth in children but maintenance of bone in adults. In particular, vitamin D deficiency is a risk factor for bone loss in osteoporosis and fracture. Correction of an even slightly low concentration of serum 25-hydroxyvitamin D with vitamin D (INN: colecalciferol) and calcium substantially reduces the risk of osteoporosis fractures and hip fractures (1, 2). The prevalence of hypovitaminosis D in residents of retirement and nursing homes and people over the age of 65 is generally between 25% and 54%, but can be as high as 79% (3, 4).

A recent study of 152 male and 138 female hospitalized patients with a mean age of 62 years (range 18 to 95 years) had measured low serum 25-hydroxy-vitamin D at 57% (3). In 22%, hypovitaminosis D was severe. Patients hospitalized in March had more hypovitaminosis than those hospitalized

in September. The patients in this study were younger than those in many previous studies and only a minority were housebound or residents of a nursing home. Thus the patients may have been more representative of the general population.

Hypovitaminosis D is associated with conditions such as poor dietary intake, inadequate sun exposure, chronic liver and renal diseases, malabsorption, and therapy with drugs that impair vitamin D activation, or accelerate its clearance such as glucocorticoids, phenytoin, carbamazepine and rifampicin.

Increased calcium intake by older people has an important role in prevention of osteoporosis but it is apparent that attention should also be focused on the need for increased intake of vitamin D (4). Vitamin D stimulates calcium absorption, thereby increasing the benefit of supplemental calcium. It also slows bone resorption and increases bone formation.

It is evident that more widespread screening for vitamin D deficiency is required especially in elderly people, and more frequent routine vitamin D supplementation should be considered. An increase in vitamin D intake is likely to have a greater effect on osteoporosis and fractures than many other interventions (4).

References

1. Chapuy, M.C., Arlot, M.E., Duboeuf, F. et al. Vitamin D and calcium to prevent hip fracture in elderly women. *New England Journal of Medicine*, **327**: 1637–1642 (1992).
2. Chapuy, M.C., Arlot, M.E., Delmas, P.D. et al. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. *British Medical Journal*, **308**: 1081–1082 (1994).
3. Thomas, M.K., Lloyd-Jones, D.M., Thadhani, R.I. et al. Hypovitaminosis D in medical inpatients. *New England Journal of Medicine*, **338**: 777–783 (1998).
4. Utiger, R.D. The need for more vitamin D. *New England Journal of Medicine*, **338**: 828–829 (1998).

Tacrine and Alzheimer disease

The present ageing of the world's population will lead to an increase in cases of elderly dementia, of which Alzheimer disease is a common form. The possibilities for prevention of Alzheimer are limited by the major determinants — age and genetic makeup — which cannot be modified. As a result,

treatment has thus far been directed to the symptomatic relief of the disease.

Although an effective treatment for Alzheimer disease has yet to be marketed, potent acetylcholinesterase inhibitors have been the dominant therapeutic strategy. Tacrine hydrochloride was the first in the generation of cholinesterase inhibitors to be widely marketed for impaired memory and reasoning ability of patients with Alzheimer disease. Several other drugs, such as donepezil, rivastigmine and metrifonate, have a similar mechanism of action.

Using the Cochrane Dementia Group registry of clinical trials, the Dementia Trialists Collaboration Group has now carried out a meta analysis of tacrine in patients with Alzheimer disease (1). The aim was to determine the effects of tacrine on symptoms in terms of cognitive performance, clinical global impression of change, behaviour and functional autonomy. The study analysed 12 randomized, double-blind, placebo controlled trials totalling 1984 patients. All patients enrolled in the trials had been diagnosed as having "probable" Alzheimer disease according to commonly accepted criteria (2). Duration of treatment varied from 3 to 36 weeks.

Cholinesterase inhibition with tacrine appears to reduce deterioration in cognitive performance during the first 3 months of treatment and an increase in the odds of overall clinical improvement. However, as measured by behavioural disturbances, the beneficial effects were of questionable clinical significance and functional autonomy was not significantly affected. Early withdrawal from studies was much higher for patients receiving tacrine compared with placebo and elevated transaminase levels were cited as the main reason for this in the two largest trials.

The benefits of cholinesterase inhibition remain controversial, and long-term trials with clinically relevant end points are required. Only 2 of the 12 trials had assessments beyond 12 weeks and it was therefore not possible to make reliable estimates of the long-term effects of tacrine. Neither was it possible to assess whether beneficial effects are obtained from continuous therapy, how long they endure, or when it is best to withdraw treatment. Efforts should thus continue to define the types of patients and the circumstances in which the newer cholinesterase inhibitors may be beneficial.

References

1. Qizibash, N., Whitehead, A. Higgins, J. et al. Cholinesterase inhibition for Alzheimer disease. *Journal of the American Medical Association*, **280**: 1777–1782 (1998).
2. McKanna, G. Drachman, D. Folstein, M. et al. Clinical diagnosis of Alzheimer disease: report of the NINCDS-ADRDA Working Group. *Neurology*, **4**: 939–944 (1984).

Anti-ulcer drugs may mask early gastric cancer

Dyspepsia, typically presenting as heartburn or gastrointestinal discomfort, is responsible for about 2–5% of patient visits to general health care physicians. In over 50% of cases, no firm diagnosis is possible because symptoms are of an uncertain origin. However, a significant proportion of patients with early gastric cancer experience symptoms typical of dyspepsia.

Following the availability of H₂ receptor antagonists such as cimetidine, famotidine, nizatidine and ranitidine to treat gastric ulcer, it became evident that their use could mask symptoms of cancer and delay diagnosis and appropriate treatment (1). Furthermore, the recently introduced and more powerful proton pump inhibitors such as omeprazole, lansoprazole, and pantoprazole produce significantly more rapid symptom control and healing of benign gastric ulcer.

It would appear that the action of these drugs masks symptoms of gastric cancer to such an extent that endoscopic diagnosis is difficult, thereby altering the prognosis from a probable cure to incurable disease (2–4). In some cases, ulcerated lesions which were visible at an initial gastroscopy are virtually undetectable less than four-weeks after treatment with a proton pump inhibitor (5). Patients with missed early cancers may alternatively be labelled as having non-ulcer dyspepsia and receive repeated courses of antisecretory drugs which will act to delay diagnosis even further (4, 5).

Antisecretory drugs, including H₂ receptor antagonists, are available in lower doses without prescription. At present, no studies are available to show whether these low-dose drugs are also able to heal the mucosal lesions associated with early gastric cancer.

In conclusion, it is recommended that dyspeptic patients over 45 years of age should undergo endoscopy before any antisecretory drugs are started (5). Inappropriate use and prescription of anti-ulcer drugs may delay or even prevent diagnosis of early gastric ulcer in two ways. The rapid control of dyspepsia may lead the patient or general practitioner to underestimate the importance of the symptoms and referral for endoscopy will be delayed or even deferred. If the patient should later undergo a gastroscopy, the prior treatment with antisecretory drugs could also mask signs. It remains to be seen whether the increased availability of these drugs over-the-counter and their expanding use for self medication requires reassessment.

References

1. Taylor, R.H., Menzies-Gow, N., Lovell, D. et al. Misleading response of malignant gastric ulcers to cimetidine. *Lancet*, **686**–687 (1978).
2. Wayman, J., Hayes N. Proton pump inhibitors delay the diagnosis of gastric cancer. *British Journal of Surgery*, **84**(Suppl. 1): 62 (1997).
3. Wayman, J., Hayes, N., Griffin, S.M. The response of early gastric cancer to proton-pump inhibitors. *New England Journal of Medicine*, **338**: 1924–1925 (1998).
4. Suvakovic, Z., Bramble, M.G., Jones, R. et al. Improving the detection rate of early gastric cancer requires more than open access gastroscopy: a five year study. *Gut*, **41**: 308–313 (1997).
5. Griffin, S.M., Raimes, S.A. Proton pump inhibitory may mask early gastric cancer. *British Medical Journal*, **317**: 1606–1607 (1998).