

# Reports on Individual Drugs

## Lamivudine: impressive benefits in combination with zidovudine

The value of zidovudine and other first generation antiretroviral nucleoside analogues has been seriously compromised by rapid emergence of resistant variants of HIV (1–5). In some cases, clinically-evident drug resistance has developed within a matter of weeks. Several clinical studies have suggested that the clinical response might be prolonged by using these analogues in combination. Gains obtained with combinations of zidovudine and didanosine (6–8) were initially reported to be modest. However, a preliminary report of results obtained in a European/Australian multicentre study indicates that, after some two years of use, zidovudine administered in combination with either didanosine or zalcitabine, confers "substantial and significant advantage in survival and disease-free survival" over zidovudine monotherapy (9). Meanwhile, impressive early results have recently been reported with a combination of zidovudine and lamivudine among patients in the early stages of HIV infection (10).

The nucleoside analogues act by inhibiting HIV-1 reverse transcriptase after phosphorylation *in vivo* (11). This viral enzyme is crucial to the replication of HIV since it transmutes the single-stranded RNA genome of HIV-1 into double-stranded DNA which integrates into the chromosomal apparatus of the cell. This inserted DNA (or provirus) generates new retroviral RNA through the normal mechanisms of cellular transcription. The gene that expresses the reverse transcriptase enzyme is subject to a high frequency of mutations (12, 13) and, in the presence of zidovudine, mutants that confer resistance to the drug are preferentially selected. Typically, resistance to zidovudine develops progressively, since it results from the accumulation of several independent mutations (14).

*In vitro*, lamivudine has activity against a wide range of isolates of HIV-1 including variants resistant to zidovudine (15–17). However, when given as monotherapy to patients with early HIV-1 infection, a marked decline in viral load (serum HIV-1 RNA) is consistently followed within a few weeks by a rise that is coincident with the

emergence of highly resistant mutant virus (18). *In vitro* selection experiments have shown that a 500-fold increase in resistance to lamivudine is conferred by a mutation at a single site (codon 184) of the HIV-1 reverse transcriptase gene (19–21).

The clinical value of lamivudine in combination therapy arises because, not only do virions resistant to lamivudine remain sensitive to zidovudine *in vitro* (21, 22), but introduction of this mutation resensitizes virions previously resistant to zidovudine (21), and mutations conferring resistance to zidovudine appear more slowly in patients who are also receiving lamivudine (23). Moreover, both drugs act synergistically against primary clinical isolates *in vitro* (24); they may target different populations of infected cells (25); and lamivudine is well tolerated in comparison with other nucleoside analogues (26).

The recently reported clinical study (10), which was conducted at 26 hospital centres in North America, was a double-blind, randomized, placebo-controlled trial lasting 24 weeks, with a blinded extension phase lasting an additional 28 weeks. Patients received one of four regimens: lamivudine, 300 mg every 12 hours; zidovudine, 200 mg every 8 hours; or zidovudine 200 mg every 12 hours in combination, respectively, with lamivudine 150 mg or lamivudine 300 mg.

Despite the expectation that lamivudine resistance would rapidly emerge, there was no significant difference in time-related changes in plasma levels of CD4 cells or of HIV-1 RNA between the two groups receiving monotherapy. Adding lamivudine to zidovudine strongly potentiated immunological and antiviral activity, as measured by these two indicators, without altering the safety profile associated with zidovudine. After one year, patients remained significantly more responsive to the combination regimens:

- the mean CD4 cell count had fallen among patients receiving zidovudine monotherapy by  $-53 \pm 14$  cells/mm<sup>3</sup>, whereas among patients receiving each of the combination therapies, the count had risen by a mean of approximately  $+60 \pm 20$  cells/mm<sup>3</sup>.

- in a subgroup of 224 patients whose plasma initially contained more than 20 000 copies of HIV RNA/ml, the mean reduction was estimated to be some 35% among patients receiving zidovudine monotherapy, as opposed to some 99% among those receiving either of the combination regimens.

As yet, it is too early to speculate what impact this potentiation will have on mortality or symptom-free survival. Such interaction may not be unique since both didanosine and zalcitabine have recently been reported to inhibit emergence of one of the mutations that confers resistance to zidovudine (27). Moreover, no mutations associated with didanosine or zalcitabine were detected in patients who had received these drugs in combination with zidovudine for some two years (27). Further prospective studies are needed that will examine clinical endpoints. At this stage, these results are highly impressive. Given recent success in the development of potent non-nucleoside antiretroviral compounds (28), the prospect of tangible achievement in the management of HIV infection through combination therapy has been suddenly and dramatically advanced.

#### References

- Larder, B., Darby, G., Richmann, D. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. *Science*, **243**: 1731–1734 (1989).
- Rooke, R., Tremblay, M., Soudéyins, H. et al. Isolation of drug-resistant variants of HIV-1 from patients on long-term zidovudine therapy. *AIDS*, **3**: 411–415 (1989).
- Richman, D., Grimes, J., Lagakos, S. Effect of stage of disease and drug dose on zidovudine susceptibilities of isolates of human immunodeficiency virus. *Journal of the Acquired Immune Deficiency Syndrome*, **3**: 743–746 (1990).
- Kozal, M., Shafer, R., Winters, M. et al. A mutation in human immunodeficiency virus reverse transcriptase and decline in CD4 lymphocyte numbers in long-term zidovudine recipients. *Journal of Infectious Diseases*, **167**: 526–532 (1993).
- Ioannidis, J., Cappelleri, J., Lau, J. et al. Early or deferred zidovudine therapy in HIV-infected patients without an AIDS-defining illness. *Annals of Internal Medicine*, **122**: 856–866 (1995).
- Callendo, A., Hirsch, M. Combination therapy for infection due to human immunodeficiency virus type 1. *Clinical Infectious Diseases*, **18**: 516–524 (1994). [Erratum: *ibid*, **19**: 379 (1994)].
- Collier, A., Coombs, R., Fischl, M. et al. Combination therapy with zidovudine and didanosine compared with zidovudine alone in HIV-1 infection. *Annals of Internal Medicine*, **119**: 786–793 (1993).
- Yarchoan, R., Lietzau, J., Nguyen, B. et al. A randomized pilot study of alternating or simultaneous zidovudine and didanosine therapy in patients with symptomatic human immunodeficiency virus. *Journal of Infectious Diseases*, **169**: 9–17 (1994). [Erratum: *ibid*, **170**: 260 (1994)]
- Gazzard, B. on behalf of the International Coordinating Committee. Further results from the European/Australian Delta trial. *Abstracts of the Third Conference on Retroviruses and Opportunistic Infections*. Washington, DC, 1996, p. 161.
- Eron, J., Benoit, S., Jemsek, J. et al. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. *New England Journal of Medicine*, **333**: 1662–1669 (1995).
- Furman, P., Fyfe, J., St Clair, M. et al. Phosphorylation of 3'-azido-3'-deoxythymidine and selective interaction of the 5'-triphosphate with human immunodeficiency virus reverse transcriptase. *Proceedings of the National Academy of Sciences, USA*, **83**: 8333–8337 (1986).
- Japour, A., Welles, S., d'Aquila, R. et al. Prevalence and clinical significance of zidovudine resistance mutations in human immunodeficiency virus isolated from patients after long-term zidovudine treatment. *Journal of Infectious Diseases*, **171**: 1172–1179 (1995).
- Loveday, C., Kaye, S., Tenant-Flowers M. et al. HIV-1 RNA serum-load and resistant viral genotypes during early zidovudine therapy. *Lancet*, **345**: 820–824 (1995).
- Larder, B., Kemp, S. Multiple mutations in HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT). *Science*, **246**: 1155–1158 (1989).
- Schinazi, R., Chu, C., Peck, A. Activities of the four optical isomers of 2', 3'-dideoxy-3'-thiacytidine (BCH-189) against human immunodeficiency virus type 1 in human lymphocytes. *Antimicrobial Agents and Chemotherapy*, **37**: 875–881 (1993).
- Coates, J., Cammack, N., Jenkinson, H. et al. (-)-2'-deoxy-3'-thiacytidine is a potent, highly selective inhibitor of human immunodeficiency virus type 1 and 2 replication *in vivo*. *Antimicrobial Agents and Chemotherapy*, **36**: 733–739 (1992).
- Coates, J., Cammack, N., Jenkinson, H. et al. The separated enantiomers of 2'-deoxy-3'-thiacytidine (BCH 189) both inhibit human immunodeficiency virus replication *in vitro*. *Antimicrobial Agents and Chemotherapy*, **36**: 2025 (1992).

18. Schuurman, R., Nijhuis, M., van Leeuwen, R. et al. Rapid changes in human immunodeficiency virus type 1 RNA load and appearance of drug-resistant virus populations in persons treated with lamivudine (3TC). *Journal of Infectious Diseases*, **171**: 1411–1419 (1995).
19. Gao, Q., Gu, Z., Hiscott, J. et al. Generation of drug-resistant variants of human immunodeficiency virus type 1 by *in vitro* passage in increasing concentrations of 2',3'-dideoxycytidine and 2',3'-dideoxy-3'-thiacytidine. *Antimicrobial Agents and Chemotherapy*, **37**: 130–133 (1993).
20. Boucher, C., Cammack, N., Schipper, P. et al. High level resistance to (-)-enantiomeric 2'-deoxy-3'-thiacytidine (3TC) *in vitro* is due to one amino acid substitution in the catalytic site of HIV-1 reverse transcriptase. *Antimicrobial Agents and Chemotherapy*, **37**: 2231–2234 (1993).
21. Tisdale, M., Kemp, S., Parry, N., Larder, B. Rapid *in vitro* selection of human immunodeficiency virus type 1 resistant to 3'-thiacytidine inhibitors due to a mutation in the YMDD region of reverse transcriptase. *Proceedings of the National Academy of Sciences, USA*, **90**: 5653–5656 (1993).
22. Schinazi, R., Lloyd, R., Nguyen, M. et al. Characterization of human immunodeficiency viruses resistant to oxathiolane-cytosine nucleosides. *Antimicrobial Agents and Chemotherapy*, **37**: 875–881 (1993).
23. Larder, B., Kemp, S., Harrigan, P. Potential mechanism for sustained antiretroviral efficacy of AZT-3TC combination therapy. *Science*, **269**: 696–699 (1995).
24. Mathez, D., Schinazi, R., Liotta, D., Leibowitch, J. Infectious amplification of wild-type human immunodeficiency virus from patients' lymphocytes and modulation by reverse transcriptase inhibitors *in vitro*. *Antimicrobial Agents and Chemotherapy*, **37**: 2206–2211 (1993).
25. Gao, W., Shirasaka, T., Johns, D. et al. Differential phosphorylation of azidothymidine, dideoxycytidine, and dideoxyinosine in resting and activated peripheral blood mononuclear cells. *Journal of Clinical Investigation*, **91**: 2326–2333 (1993).
26. van Leeuwen, R., Katlama, C., Kitchen, V. et al. Evaluation of safety and efficacy of 3TC (lamivudine) in patients with asymptomatic or mildly symptomatic human immunodeficiency virus infection: a phase I/II study. *Journal of Infectious Diseases*, **171**: 1166–1171 (1995).
27. Loveday, C. on behalf of the Delta Virology Group. Genotypic and phenotypic resistance in Delta patients. *Abstracts of the Third Conference on Retroviruses and Opportunistic Infections*. Washington, DC, 1996, p. 162.
28. Update on AIDS. *WHO Drug Information*, **9**: 196–209 (1995).

## Lamivudine: encouraging experience in chronic hepatitis B infection

Notwithstanding its high cost, the need for parenteral administration over several months, troublesome adverse effects, and a low rate of prolonged remissions, recombinant interferon alfa-2b has long remained the only established treatment for chronic hepatitis B infections (1–4). Recently, nucleoside analogues — which inhibit reverse transcriptase — have been shown to interfere with replication of hepatitis B virus (HBV) as well as human immunodeficiency virus (HIV) *in vitro* (5, 6). Although, unlike HIV, HBV is not a retrovirus, reverse transcription of an RNA pre-genome to the minus strand of DNA is a vital step in its mechanism of replication (6). The therapeutic expectation created by these findings, however, was not realized in clinical studies with the first generation of these compounds: vidarabine, aciclovir, zidovudine, zalcitabine, didanosine, and ribavirin were found to be either largely ineffective in chronic hepatitis or too toxic for prolonged use (7–11).

Interest in nucleoside analogues in the therapy of chronic hepatitis B infections was more recently revived with the demonstration that newer compounds in this series, including fialuridine and lamivudine, are particularly potent inhibitors of HBV *in vitro* (5). However, confidence in their safety was unexpectedly undermined when, in a recent clinical study (12, 13), treatment with fialuridine was associated with several fatalities resulting from refractory lactic acidosis, hepatic and renal failure, pancreatitis and myopathy (14).

Before this setback occurred, promising results had been reported from preliminary clinical studies of lamivudine in patients with chronic hepatitis. In one of these, the patients were concomitantly treated for HIV infection (15). In the other, 75 patients were treated with lamivudine for four weeks at doses ranging from 5mg/day to 600 mg/day (16). Daily doses of 100 mg or more resulted in complete suppression of pre-existing serum levels of HBV DNA but, in all but three patients enrolled in the latter study, rebound rapidly followed cessation of treatment (16).

More promising results have now been obtained with extended courses of lamivudine (17). In a

multicentre study conducted in the USA, 32 patients with chronic hepatitis B — half of whom had not responded to previous treatment with interferon — received either 25, 100, or 300 mg lamivudine daily for 12 weeks, and each was followed for a further 24 weeks. By 12 weeks HBV DNA had been suppressed to undetectable levels in all patients who received either 100 mg or 200 mg lamivudine daily. This suppression was maintained in 6 of the patients. Among these latter patients serum aminotransferase remained within normal limits after completion of treatment, and in four of them the Be antigen also became undetectable within the period of follow-up. One of the two patients in whom the Be antigen remained detectable — and who was consequently considered to have an indeterminate response — relapsed after some 57 weeks of observation.

Lamivudine caused none of the adverse effects ascribed to fialuridine. Minor perturbations in biochemistry were in no case associated with symptoms. Treatment was stopped prematurely in only one case: a patient in the low-dose group whose serum alanine aminotransferase level rose transiently two fold above baseline. Liver biopsy revealed no change, in this instance, from a pre-treatment sample. Lesser rises in alanine aminotransferase levels were recorded in a total of 13 patients either during or shortly after the period of treatment. These rises — which have also been described during treatment with interferon alfa (1, 2) — were unlikely to have resulted from a hepatotoxic effect since they were inversely rather than directly related to the dose.

Lamivudine, like all nucleoside analogues, exerts its antiviral effect by becoming incorporated into viral DNA and arresting its replication. All the nucleoside analogues developed thus far are also incorporated to a greater or lesser extent into the genomic and mitochondrial DNA of the host. But, at concentrations required to block the synthesis of HBV DNA, lamivudine, unlike other dideoxynucleosides, has not been detected in mitochondrial DNA, nor has it been found to inhibit the proliferative activity of marrow progenitor cells (18). In this respect it behaves in striking contrast to fialuridine: it is the facility with which fialuridine is incorporated into mitochondrial DNA which provides a persuasive but as yet hypothetical explanation of the toxicity of the compound (19, 20).

All patients who relapsed in the lamivudine trial are now being retreated with 100 mg lamivudine daily

(17). Already, Be antigen is reported to have become undetectable in three additional patients. In an associated development, patients unresponsive to previous treatment with interferon are being treated either with lamivudine alone or in combination with interferon. In the meantime, it remains important to retain all treated patients in whom there is no evidence of relapse under open-ended surveillance to ensure that any possible recrudescence of infection is investigated and recorded.

#### References

1. Hoofnagle, J., Peters, M., Mullen, K. et al. Randomized, controlled trial of recombinant human alpha-interferon in patients with chronic hepatitis B. *Gastroenterology*, **95**: 1318–1325 (1988).
2. Perrillo, R., Schiff, E., Davis, G. et al. A randomized, controlled trial of interferon alpha-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. *New England Journal of Medicine*, **323**: 295–301 (1990).
3. DiBisceglie, A., Fong, T., Fried, M. et al. A randomized controlled trial of recombinant alpha-interferon therapy for chronic hepatitis B. *American Journal of Gastroenterology*, **88**: 1887–1892 (1993).
4. Wong, D., Cheung, A., O'Rourke, K. et al. Effect of alpha-interferon treatment in patients with hepatitis B: a meta-analysis. *Annals of Internal Medicine*, **119**: 312–323 (1993).
5. Korba, B., Gerin, J. Use of a standardized cell culture assay to assess activities of nucleoside analogues against hepatitis B virus replication. *Antiviral Research*, **19**: 55–75 (1992).
6. Doong, S., Tsai, C., Schinazi, R. et al. Inhibition of the replication of hepatitis B virus *in vitro* by 2', 3'-dideoxy-3'-thiacytidine and related analogues. *Proceedings of the National Academy of Sciences, USA*, **88**: 8495–8499 (1991).
7. Garcia, G., Smith, C., Weissberg, J. et al. Adenine arabinoside monophosphate (vidarabine phosphate) in combination with human leukocyte interferon in the treatment of chronic hepatitis B: a randomized, double-blind, placebo-controlled trial. *Annals of Internal Medicine*, **107**: 278–285 (1987).
8. Alexander, G., Fagan, E., Hegarty, J. et al. Controlled clinical trial of acyclovir in chronic hepatitis B infection. *Journal of Medical Virology*, **21**: 81–87 (1987).
9. Fried, M., Korenman, J., DiBisceglie, A. et al. A pilot study of 2', 3'-dideoxyinosine for the treatment of chronic hepatitis B. *Hepatology*, **17**: 383–388 (1993).

10. Janssen, H., Berk, L., Heijtkink, R. et al. Interferon-alpha and zidovudine combination therapy for chronic hepatitis B: results of a randomized, placebo-controlled trial. *Hepatology*, **17**: 383–388 (1993).
11. Fried, M., Fong, T., Swain, M. et al. Therapy of chronic hepatitis B with a 6-month course of ribavirin. *Journal of Hepatology*, **21**: 145–150 (1994).
12. McKenzie, R., Fried, M., Sallie, R. et al. Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B. *New England Journal of Medicine*, **333**: 1099–1105 (1995).
13. Nucleoside analogues: premonitory experience in therapy of viral hepatitis. *WHO Drug Information*, **9**: 212–215 (1995).
14. Stevenson, W., Gaffey, M., Ishitani, M. et al. Clinical course of four patients receiving the experimental antiviral agent fialuridine for the treatment of chronic hepatitis B infection. *Transplantation Proceedings*, **27**: 1219–1221 (1995).
15. Benhamou, Y., Dohin, E., Lunel-Fabiani, F. et al. Efficacy of lamivudine on replication of hepatitis B virus in HIV-infected patients. *Lancet*, **345**: 396–397 (1995).
16. Tyrrell, D., Mitchell, M., De Man, R. et al. Phase II trial of lamivudine for chronic hepatitis B (abstract). *Hepatology*, **18**: 112A (1993).
17. Dienstag, J., Perrillo, R., Schiff, E. et al. A preliminary trial of lamivudine for chronic hepatitis B infection. *New England Journal of Medicine*, **333**: 1657–1661 (1995).
18. Lau, D., Mostowski, H., Hoofnagle, J., Sallie, R. Nucleoside analogue toxicity and mitochondria (abstract). *Hepatology*, **20**: 189A (1994).
19. Lewis, W., Meyer, R., Simpson, J. et al. Mammalian DNA polymerases, alpha, beta, gamma, delta and epsilon incorporate fialuridine (FIAU) monophosphate into DNA and are inhibited competitively by FIAU triphosphate. *Biochemistry*, **33**: 14620–14624 (1994).
20. Swartz, M. Mitochondrial toxicity — new adverse drug effects. *New England Journal of Medicine*, **333**: 1146–1148 (1995).

## Pyronaridine: yet another promising antimalarial substance from China

The successful development of derivatives of artemisinin as antimalarials within China, and the synthesis of the Colombian anti-malarial vaccine have turned a page of history in drug development. They have shown, against all current trends, that

important innovative contributions to new drug development can still be made from outside the internationally-operative research-based pharmaceutical companies.

First synthesized in China some 25 years ago, pyronaridine is an acridine derivative which, like mepacrine and floxacrine, has antimalarial activity (1–4). It has been used clinically to treat *Plasmodium falciparum* and *P. vivax* malaria in China for the past 20 years, but only in the past few years has information on its performance been published in journals circulated internationally (5, 6). On the basis of clinical experience gained in some 1000 patients claims have been staked that it is effective against multidrug-resistant *P. falciparum*; that discernible cross-resistance has not yet emerged with chloroquine, quinine or mefloquine; and that it is well tolerated at the dosage regimens (1.2–1.6 g over 2–3 days) used in China.

Results have now been published of the first clinical study of pyronaridine to be undertaken outside China (7). In an open trial conducted in Yaoundé, Cameroon, 96 adult patients with acute uncomplicated falciparum malaria were randomly assigned either to a total dose of chloroquine 25 mg/kg or of pyronaridine 32 mg/kg (a somewhat higher dose than has been used in China) administered orally over a period of three days. Their progress was subsequently followed for a further 14 days on an outpatient basis.

Eleven of the patients (6 in the chloroquine group and 5 who had taken pyronaridine) were lost to follow-up, and 4 others who were found to be additionally taking quinine were excluded from analysis. Among the remaining 81 patients, thick blood smears were free of parasites at the end of follow-up in 24 of 41 patients in the chloroquine group and all 40 patients who had received pyronaridine. All patients in the trial who responded positively to treatment were afebrile within 3 days and all had a negative blood smear by day 4.

The incidence of chloroquine-resistant parasites in pretreatment blood samples was shown to be similar in the two groups. As expected in Cameroon, pruritus requiring treatment with chlorphenamine was considerably more frequent among patients who received chloroquine (44% vs 18%). In contrast, mild abdominal pain and diarrhoea were more common among patients taking pyronaridine (30% vs 3%). More troublesome nausea and vomiting occurred in some 55 patients in each

group. One patient who had taken pyronaridine developed a localized herpetiform eruption which resolved within 7 days. However, much of the basic pharmacological and toxicological investigation which has come to be regarded as a vital element in the routine development of every new pharmaceutical product apparently remains outstanding in the case of pyronaridine, and dosage schedules have been devised empirically (8). Every precaution will need to be taken to assure its safety in pregnant women and small children who are particularly susceptible to malaria wherever the disease is endemic. Pyronaridine is clearly a highly promising compound for the treatment of falciparum malaria, but if it is to be developed to the standards now generally required of drugs moving in international commerce, substantial investment will be required.

The need for such investment is compelling, particularly for Africa where malaria is estimated to cause more than one million deaths annually (8). Chloroquine-resistant strains of *P. falciparum* continue to proliferate, and strains resistant to pyrimethamine/sulfadoxine (the only alternative treatment that is cheap and effective) are likely to spread across the continent within the next few years (9). Quinine remains available as a treatment of last resort, but other effective drugs — mefloquine, halofantrine and artemisinin derivatives remain far too expensive for generalized use.

#### References

1. World Health Organization. *Practical chemotherapy of malaria*. WHO Technical Report Series No. 805, WHO, Geneva, 1990.
2. Childs, G., Hausler, B., Milhaus, W. et al. *In vitro* activity of pyronaridine against field isolates and reference clones of *Plasmodium falciparum*. *American Journal of Tropical Medicine and Hygiene*, **38**: 24–29 (1988).
3. Basco, L., Le Bras, J. *In vitro* activity of pyronaridine against African strains of *Plasmodium falciparum*. *Annals of Tropical Medicine and Parasitology*, **86**: 447–454 (1992).
4. Peters, W., Robinson, B. The chemotherapy of rodent malaria XLVII: studies on pyronaridine and other Mannich-base antimalarials. *Annals of Tropical Medicine and Parasitology*, **86**: 455–456 (1992).
5. Fu, S., Xiao, S. Pyronaridine: a new antimalarial drug. *Parasitology Today*, **7**: 310–313 (1992).
6. Chen, C., Tang, L., Jantanaviat, C. Studies on a new antimalarial compound: pyronaridine. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **86**: 7–10 (1992).
7. Ringwald, P., Bickii, J., Basco, L. Randomised trial of pyronaridine versus chloroquine for acute uncomplicated falciparum malaria in Africa. *Lancet*, **347**: 24–28 (1996).
8. Winstanley, P. Pyronaridine: a promising new drug for Africa? *Lancet*, **347**: 2–3 (1996).
9. UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Disease (TDR). *Twelfth Programme Report*. WHO, Geneva, 1995.

## Acellular pertussis vaccines: more persuasive evidence of efficacy

The development of acellular pertussis vaccines was first envisaged some 20 years ago after the existing whole-cell vaccines had been linked with cases of encephalopathy, some of which — as it was thought at the time — had resulted in permanent neurological damage and death (1, 2). In the midst of this concern, several health authorities reacted by dropping pertussis vaccination from their national programmes (3). These decisions were reversed, however, as it became apparent that the risk of chronic neurological damage following pertussis vaccination, if it really exists, is vanishingly small (4, 5); that effective national vaccination programmes had reduced morbidity and mortality associated with the disease more than 100-fold (6, 7); and that pertussis remains an important public health problem wherever vaccination coverage is inadequate (8).

Work was none the less sustained within several pharmaceutical companies on a new generation of acellular vaccines which contain various anti-genic components of *Bordetella pertussis* including, most commonly, pertussis toxin, filamentous haemagglutinin (an outer membrane protein), and other agglutinins. Comparative studies on those products that are now in clinical use have shown them to be reliably immunogenic at the recommended dosages and to be less likely than the whole-cell vaccines to cause local reactions, fever and febrile convulsions (9–13).

The first assessments of protective efficacy were undertaken in Japan on two locally-manufactured products. When these were used for the primary vaccination of two-year-old children, they were judged to be as effective as the whole-cell vaccines (14–17). In retrospective household contact studies their efficacy in preventing typical pertussis was estimated as 98% (95%CL: 84% to 99%) (17) and 79% (14), respectively.

In contrast, less encouraging results were obtained in Sweden in 1988 with two Japanese products. Neither was accepted for primary vaccination by the licensing authority (18). Their reported efficacy when administered in two doses to infants aged from 5 to 11 months — 54% (95%CI: 26% to 72%) and 69% (95%CI: 67% to 87%) — was regarded as inadequate. No group was given a whole-cell pertussis vaccine in this study, but since it was assumed that these long-established vaccines were over 80% effective, doubts were aroused internationally about the potential of acellular products to protect infants from pertussis at the age when they are most vulnerable to the infection.

Confidence was to some extent restored after the children admitted to the Swedish studies had been observed for an additional three years. When the results were then reworked the estimated efficacy of the two products was found to have risen to 79% (95%CI: 67% to 87%) and 92% (95%CI: 84% to 96%), respectively (19). None the less, when the first acellular products were subsequently licensed in the United States in 1992, they were approved exclusively for boosting the immunity of previously vaccinated children who were at least 15 months old (20).

Decisive evidence has recently been presented that specific candidate acellular preparations, when delivered in a triple diphtheria/tetanus/pertussis vaccine to infants at two, four and six months of age, are immunogenic, strongly protective against pertussis infection, and safe within the limits of detection of the studies. This evidence derives largely from the results of three prospective efficacy trials undertaken in areas of Sweden (21), Italy (22), and Germany (23) where previous uptake of cellular pertussis vaccines was known to have been low and where pertussis retains a relatively high prevalence. The studies undertaken in Sweden and Italy were prospective, randomized, double-blind studies which included, for comparison, groups which received whole-cell vaccine and placebo (diphtheria/tetanus vaccine), while the German investigation was a community study which involved blind surveillance of vaccinated and unvaccinated children who were contacts of index cases of pertussis. In each of the studies, surveillance was maintained for some two years after vaccination.

The basis on which efficacy was determined differed between the trials, but the conclusions were consistent. Whereas a widely-licensed whole-cell vaccine was found to protect only about half of

the vaccinated children (21, 22), the efficiency of the acellular preparations ranged from 70% to over 90%. Only one vaccine, a bivalent product containing pertussis toxin and filamentous haemagglutinin, was estimated to be substantially less effective (21). The addition of pertactin, it has been suggested, may substantially increase the efficacy of the simpler bivalent products (24). However, there is no secure explanation for this difference since, within a smaller efficacy study, a monovalent vaccine containing only pertussis toxin has been estimated to be some 70% effective (25).

Given the consistency of more recent findings, there is optimism that it may now prove feasible to define reliable serological markers for protection against pertussis, which have been singularly lacking thus far throughout the development of the acellular vaccines (26). In default of this, it will remain necessary to conduct large-scale prospective clinical studies to estimate the protective potential of each product within a given immunization schedule. Beyond this, there will be the need — given the chequered history of pertussis vaccination — to maintain assiduous postmarketing surveillance of the safety of these products for many years to come.

#### References

1. Kulenkampff, M., Schwartzman, J., Wilson, J. Neurological complications of pertussis inoculation. *Archives of Diseases of Children*, **49**: 46–49 (1974).
2. Department of Health and Social Security. *Report of the Committee on Safety of Medicines and Joint Committee on Vaccination and Immunisation*. London, (1981).
3. Cherry, J., Brunell, P., Golden, G., Karzon, D. Report of the Task Force on Pertussis and Pertussis Immunization — 1988. *Pediatrics*, **88**: 1019–1023 (1991).
4. Howson, C., Howe, C., Fineberg, H. eds. and the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines. Division of Health Promotion and Disease Prevention, Institute of Medicine, National Academy of Sciences. *Adverse Effects of Pertussis and Rubella Vaccines*. Institute of Medicine, Washington, DC. 1991.
5. Sutter, R., Cochi, S. Pertussis hospitalizations and mortality in the United States, 1985–1988. Evaluation of the completeness of national reporting. *Journal of the American Medical Association*, **267**: 386–391 (1992).
6. National Office of Vital Statistics. Reported incidence of selected notifiable diseases: United States, 1920–1950. US Department of Health, Education and Welfare. Washington, DC, 1953.

7. Centers for Disease Control. Summary of notifiable diseases, United States, 1989. *Morbidity and Mortality Weekly Report*, **38**: 51–59 (1989).
8. Howson, C., Fineberg, H. Adverse events following pertussis and rubella vaccines: summary of a final report of the Institute of Medicine. *Journal of the American Medical Association*, **267**: 392–396 (1992).
9. Edwards, K., Lawrence, E., Wright, P. Diphtheria, tetanus and pertussis vaccine: a comparison of the immune response and adverse reactions to conventional and acellular pertussis components. *American Journal of Diseases of Children*, **140**: 867–871 (1986).
10. Ad Hoc Group for the Study of Pertussis Vaccine. Placebo-controlled trial of two acellular pertussis vaccines in Sweden: protective efficacy and adverse events. *Lancet*, **1**: 955–960 (1988).
11. Blumberg, D., Mink, C., Cherry, J. et al. Comparison of an acellular pertussis-component diphtheria-tetanus-pertussis (DTP) vaccine with a whole cell pertussis component DTP vaccine in 17 to 24-month-old children, with measurement of 69-kilodalton outer membrane protein antibody. *Journal of Pediatrics*, **117**: 46–51 (1990).
12. Edwards, K., Meade, B., Decker, M. et al. Comparison of 13 acellular pertussis vaccines: serologic response. *Pediatric Research*, **96**: 548–557 (1995).
13. Decker, M., Edwards, K., Steinhoff, M. et al. Comparison of thirteen acellular pertussis vaccines: adverse reactions. *Pediatric Research*, **96**: 557–566 (1995).
14. Aoyama, T., Murase, Y., Kato, T., Iwata, T. Efficacy of an acellular pertussis vaccine in Japan. *Journal of Pediatrics*, **107**: 80–83 (1985).
15. Kimura, M., Kuno-Sakai, H. Pertussis vaccines in Japan. *Acta Paediatrica Japonica*, **30**: 143–153 (1988).
16. Kato, T., Goshima, T., Nakajima, N. et al. Protection against pertussis by acellular pertussis vaccines (Takeda, Japan): household contact studies in Kawasaki City, Japan. *Acta Paediatrica Japan*, **31**: 698–701 (1989).
17. Mortimore, E., Kimura, M., Cherry, J. et al. Protective efficacy of the Takeda acellular pertussis vaccine combined with diphtheria and tetanus toxoids following household exposure of Japanese children. *American Journal of Diseases of Children*, **144**: 899–904 (1990).
18. Ad Hoc Group for the Study of Pertussis Vaccines. Placebo controlled trial of two acellular pertussis vaccines in Sweden: protective efficacy and adverse events. *Lancet*, **1**: 955–960 (1988).
19. Storsaeter, J., Olin, P. Relative efficacy of two acellular pertussis vaccines during three years of passive surveillance. *Vaccine*, **10**: 142–144 (1992).
20. Immunization Practices Advisory Committee. Pertussis vaccination: acellular pertussis vaccine for reinforcing and booster dose use — supplementary ACIP statement. *Morbidity and Mortality Weekly Report*, **41**: 1–10 (1992).
21. Gustafsson, L., Hallander, H., Olin, P. et al. A controlled trial of a two-component acellular, a five-component acellular, and a whole-cell pertussis vaccine. *New England Journal of Medicine*, **334**: 349–355 (1996).
22. Greco, D., Salmaso, S., Mastrantonio, P. et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. *New England Journal of Medicine*, **334**: 341–348 (1996).
23. Schmitt, H-J., von König, C., Neiss, A. et al. Efficacy of acellular pertussis vaccine in early childhood after household exposure. *Journal of the American Medical Association*, **275**: 37–41 (1996).
24. Edwards, K., Decker, M. Acellular pertussis vaccines for infants. *New England Journal of Medicine*, **334**: 391–392 (1996).
25. Trollfors, B., Taranger, J., Largargård, T. et al. A placebo-controlled trial of a pertussis-toxoid vaccine. *New England Journal of Medicine*, **333**: 1045–1050 (1995).
26. Storsaeter, J., Blackwelder, W., Hallander, H. Pertussis antibodies, protection, and vaccine efficacy after household exposure. *American Journal of Diseases of Children*, **146**: 167–172 (1992).

## Childhood morbidity, immunity and micronutrients

Over the past two decades, the development and use of oral rehydration salts has palpably lowered the mortality of acute diarrhoea among infants and children in developing countries. However, despite this success, diarrhoea remains a widespread and formidable public health problem. Many of the children who are most vulnerable are undernourished, retarded in growth, and at high risk from measles and respiratory infections. In these children diarrhoea is often prolonged (1–4), apparently as a result of multiple infection (5), and it seems that signs of impaired cellular immunity may be characteristic (4, 6, 7).

Since dietary improvement is a remote prospect for the vast majority of these children, much research has focused on the correction of specific micronutrient deficiencies. The spectacular reduction in mortality reported to result from repletion of vitamin A reserves in undernourished children has overshadowed other developments in nutritional

research in recent years. But this discovery has not lessened the importance of assuring adequate access to other vitamins. Nor should it distract attention from the need for other essential micro-nutrients.

Elemental zinc, for instance, is a vital catalyst for many enzymatic reactions, but it is highly vulnerable to depletion since there is no reserve storage capacity within the body. Both vitamin A and zinc have been shown to be important to the integrity of the immune system, and this review examines their contributions to physiological defences against diarrhoeal illness and other acute childhood infections.

### Vitamin A supplements

The association between xerophthalmia — the classical indicator of vitamin A deficiency — and raised morbidity from measles, diarrhoea and respiratory infections was first demonstrated some 10 years ago (8–11). This discovery was soon followed by evidence from controlled studies that supplements of vitamin A reduced total mortality among preschool children in developing countries by amounts ranging from 20% to over 50% (12–15). Initial assumptions that these supplements would counter all the complications associated with vitamin A deficiency, possibly by restoring failing immune mechanisms (16–18), have since been called into question.

There is now a general acceptance that the most profound and consistent effect of vitamin A is to reduce the morbidity and mortality associated with measles (19), even in situations of marginal deficiency (20). In contrast, in several studies in which vitamin A supplements have significantly reduced total mortality, they have not reduced morbidity and mortality associated with respiratory infection (15, 21, 22). Indeed, in at least two studies, high-dose supplements have been associated with an increased prevalence of acute lower respiratory tract infections (23, 24).

Several studies have indicated that vitamin A supplements reduce mortality attributed to diarrhoea (9, 15, 21, 22). In contrast, negative results have been reported from two large prospective, placebo-controlled studies undertaken in India (25, 26). It is notable, but possibly coincidental, that in both of these studies, massive oral loading doses of 200 000 IU vitamin A were administered (27–29). However, these findings raise the possibility — based on evidence from

animal models (30, 31) — that in children who are not highly deficient in vitamin A, massive single doses may temporarily attenuate the immune response. This possibility is strengthened by independently generated concern that high-dose vitamin A supplements are associated with an attenuated immune response to measles vaccine and possibly — by implication — to other live virus vaccines, including oral poliovirus vaccine (32, 33). This finding brings into question the current practice of administering routine high-dose vitamin A supplements to infants simultaneously with measles vaccine, and it points to the need for further investigation of this apparent and disadvantageous interaction.

### Zinc treatment

Zinc is a trace element which is vital to many enzyme systems, to cellular metabolism and division, and to efficient immune function (34). There is also histological, morphological, and physiological evidence to show that zinc deficiency compromises intestinal function. It has been shown to be vital to the structure and function of biomembranes (35), to the ultrastructure of the small intestine (36), to its permeability characteristics and glucose transport (37–40), and (in animal models) to its response to infection (41).

Zinc deficiency, whether it is a primary or secondary consequence of disease, is associated with chronic diarrhoea, stunting of growth, and immune deficiency (28, 42–46). Conversely, since there are no appreciable zinc stores in the body, episodes of diarrhoea commonly result in immediate and substantial falls in plasma zinc concentrations (47–51), particularly where dietary intake is low and absorption is reduced (52). Foods rich in readily absorbable zinc, which include red meat, liver, poultry, fish and other sea food, are far from plentiful in developing countries. Moreover, the phytates in fibre and lignin form insoluble complexes with zinc which impede its absorption from cereals and vegetables (53).

Zinc supplements have been used with success to restore plasma concentrations in children receiving intensive hospital treatment for kwashiorkor (54). Zinc deficiency is also recognized to be a consistent feature of diarrhoeal infection in developing countries (55), and there is evidence (56) to link this deficiency with suppression of cell-mediated immunity that has been detected in some children during episodes of acute diarrhoea (4). More recently, zinc supplements (20 mg elemental zinc daily as zinc

gluconate) have been shown, in a randomized, blind, prospective study involving over 900 preschool-age children in India, to reduce significantly both the intensity (23%; 95%CI: 12% to 32%) and the duration (39%; 95%CI: 6% to 70%) of episodes of acute diarrhoea (57).

### Implications for routine practice

The evidence is now conclusive that, among children in developing countries, vulnerability to diarrhoea is a consequence not only of gastrointestinal infection, but also of impaired immunity to infection. Both vitamin A and elemental zinc, it seems, contribute to this protective immunity. However, these discoveries have been made empirically, and the mode of action of these substances is essentially unknown.

Since other micronutrients may well contribute to the physiological integrity of such complex biological systems, it follows that, whenever possible, dietary inadequacies should be remedied by dietary adjustment. When — as is all too frequently the case — effective adjustment is not feasible, dietary supplements provide a vital but not necessarily optimal alternative.

Improving vitamin A status in very young children with clinical evidence of deficiency is undoubtedly saving many lives. However, there is now recognition of a need to explore the possible negative effects of very high oral doses of vitamin A on the immune response to live vaccines, and on immune mechanisms in general, particularly in infants with little or no clinical evidence of deficiency.

Much less experience has as yet been gained with zinc supplements, and many basic questions remain to be answered about how or whether these findings might be exploited for treatment or prophylaxis of diarrhoea in routine practice. More needs to be known about dosage requirements in different settings, and about the possible facilitatory effects of vitamin A or other food constituents on the therapeutic response. Cost may be a decisive consideration, not least because options are limited by the need for daily dosing. In the last analysis, it has been suggested, more might be achieved by determined commitment to fundamentals: effective use of oral rehydration solutions, promotion of breast-feeding, and meticulous concern with hygiene (56). The imperative of respecting economies, priorities and practicalities in the management of infections endemic throughout the developing world is the central issue in the following review on the use of bismuth salts in diarrhoeal disease.

### References

1. Black, R., Brown, K., Becker, S. Malnutrition is a determining factor of diarrheal duration, but not incidence, among young children in a longitudinal study in rural Bangladesh. *American Journal of Clinical Nutrition*, **39**: 87–94 (1984).
2. Sazawal, S., Bhan, M., Bhandari, N. et al. Evidence for recent diarrhoeal morbidity as a risk factor for persistent diarrhoea: a case-control study. *International Journal of Epidemiology*, **20**: 540–545 (1991).
3. Bhandari, N., Bhan, M., Sazawal, S. Mortality associated with acute watery diarrhea, dysentery and persistent diarrhea in rural north India. *Acta Paediatrica*, **381**: 3–6 (1992).
4. Black, R., Lanata, C., Lazo, F. Delayed cutaneous hypersensitivity: epidemiologic factors affecting and usefulness in predicting diarrheal incidence in young Peruvian children. *Pediatric Infectious Diseases*, **8**: 210–215 (1989).
5. Lanata, C., Black, R., Muartua, D. et al. Etiologic agents in acute vs persistent diarrhea in children under three years of age in peri-urban Lima, Peru. *Acta Paediatrica*, **381**: 32–38 (1992).
6. Baqui, A., Black, R., Sack, R. et al. Malnutrition, cell-mediated immune deficiency, and diarrhea: a community-based longitudinal study in rural Bangladeshi children. *American Journal of Epidemiology*, **137**: 355–365 (1993).
7. Baqui, A., Sack, R., Black, R. et al. Cell-mediated immune deficiency and malnutrition are independent risk factors for persistent diarrhea in Bangladeshi children. *American Journal of Clinical Nutrition*, **58**: 543–548 (1993).
8. Sommer, A., Katz, J., Tarwatjo, I. Increased risk of respiratory disease and diarrhoea in children with pre-existing vitamin A deficiency. *American Journal of Clinical Nutrition*, **40**: 1090–1095 (1984).
9. Milton, R., Reddy, V., Naider, A. Mild vitamin A deficiency and childhood morbidity — an Indian experience. *American Journal of Clinical Nutrition*, **46**: 823–829 (1987).
10. Tomkins, A., Hussey, G. Vitamin A, immunity and infection. *Nutritional Research Reviews*, **2**: 17–28 (1989).
11. Bloem, M., Wedel, M., Egger, R. et al. Mild vitamin A deficiency and risk of respiratory tract diseases and diarrhoea in preschool and school children in north-eastern Thailand. *American Journal of Epidemiology*, **131**: 332–339 (1990).
12. Sommer, A., Tarwatjo, I., Djunaedi, E. et al. Impact of vitamin A supplementation on mortality: a randomized controlled community trial. *Lancet*, **1**: 1169–1173 (1986).

13. Muhilal, Permeisih, D., Idjradinata, Y. et al. Vitamin A-fortified monosodium glutamate and health, growth and survival of children: a controlled field trial. *American Journal of Clinical Nutrition*, **48**: 1271–1278 (1988).
14. Rahmathullah, L., Underwood, B., Thulasiraj, R. et al. Reduced mortality among children in southern India receiving a small weekly dose of vitamin A. *New England Journal of Medicine*, **323**: 929–935 (1990).
15. West, K., Pokhrel, R., Katz, J. et al. Efficiency of vitamin A in reducing preschool child mortality in Nepal. *Lancet*, **338**: 69–71 (1991).
16. Thurnham, D. Vitamin A deficiency and its role in infection. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **83**: 721–723 (1989).
17. Ross, C. Vitamin A status: relationship to immunity and the antibody response. *Proceedings of the Society of Experimental Biology and Medicine*, **200**: 303–320 (1992).
18. Semba, R., Muhilal, Ward, B. et al. Abnormal T-cell subset proportions in vitamin-A deficient children. *Lancet*, **341**: 5–8 (1993).
19. Latham, M. Vitamin A and childhood mortality. *Lancet*, **342**: 549 (1993).
20. Hussey, G., Klein, M. A randomized controlled trial of vitamin A in children with severe measles. *New England Journal of Medicine*, **323**: 160–164 (1990).
21. Daulaire, N., Starbuck, E., Houston, R. et al. Childhood mortality after a high dose of vitamin A in a high-risk population. *British Medical Journal*, **304**: 207–210 (1992).
22. Ghana VAST Study Team. Vitamin A supplementation in northern Ghana: effects on clinical attendances, hospital admissions, and child mortality. *Lancet*, **342**: 7–12 (1993).
23. Dibley, M., Sadjimin, T., Kjolhede, C. Impact of high-dose vitamin A supplementation on incidence and duration of episodes of diarrhea and acute respiratory infections in preschool Indonesian children (abstract). *FASEB Journal*, **6**: A1787 (1992).
24. Standfield, S., Louis, M., Lerebours, G., Augustin, A. Vitamin A supplementation and increased prevalence of childhood diarrhoea and acute respiratory infections. *Lancet*, **342**: 578–582 (1993).
25. Vijayaraghaven, K., Radhaiah, G., Prakasam, B. et al. Effect of massive dose vitamin A on morbidity and mortality in Indian children. *Lancet*, **336**: 1342–1345 (1990).
26. Bhandari, N., Bhan, M., Sazawal, S. Impact of massive dose of vitamin A given to preschool children with acute diarrhoea on subsequent respiratory and diarrhoeal morbidity. *British Medical Journal*, **309**: 1404–1407 (1994).
27. Sommer, A., Muhilal, Tarwojto, I. et al. Oral versus intramuscular vitamin A in the treatment of xerophthalmia. *Lancet*, **1**: 557–559 (1980).
28. Islam, A., Molla, A., Jahan, F. Change in serum vitamin A concentration after an oral dose in children with acute diarrhea. *Journal of Pediatrics*, **103**: 1000–1002 (1983).
29. Reddy, V., Raghuramulu, N., Arunjiyoti, et al. Absorption of vitamin A by children with diarrhoea during treatment with oral rehydration salt solution. *Bulletin of the World Health Organization*, **64**: 721–724 (1986).
30. Friedman, A., Sklan, D. Antigen-specific immune response impairment in the chick as influenced by dietary vitamin A. *Journal of Nutrition*, **119**: 790–795 (1989).
31. Friedman, A., Meidovsky, A., Leitner, G., Sklan, D. Decreased resistance and immune response to *Escherichia coli* in chicks with high or low intakes of vitamin A. *Journal of Nutrition*, **121**: 395–400 (1991).
32. Semba, R., Munasir, Z., Beeler, J. et al. Reduced seroconversion to measles in infants given vitamin A with measles vaccination. *Lancet*, **345**: 1330–1332 (1995).
33. Vitamin A supplementation and measles vaccination. *WHO Drug Information*, **9**: 139–141 (1995).
34. Walsh, C., Stanstead, H., Prasad, A. et al. Zinc: health effects and research priorities for the 1990s. *Environmental Health Perspectives*, **102** (suppl 2): 5–46 (1994).
35. Bettger, W., O'Dell, B. A critical physiological role of zinc in the structure and function of biomembranes. *Life Sciences*, **28**: 1425–1438 (1981).
36. Arcasoy, A., Akar, N., Ors, U. et al. Ultrastructural changes in the mucosa of the small intestine in patients with geophagia (Prasad's syndrome). *Journal of Pediatric Gastroenterology and Nutrition*, **11**: 279–282 (1990).
37. Ghishan, F. Transport of electrolytes, water, and glucose in zinc deficiency. *Journal of Pediatric Gastroenterology and Nutrition*, **3**: 608–612 (1984).
38. Moran, J., Lewis, J. The effects of severe zinc deficiency on intestinal permeability: an ultrastructural study. *Pediatric Research*, **19**: 968–973 (1985).
39. Ford, R., Menzies, I., Phillips, A. et al. Intestinal sugar permeability: relationship to diarrheal disease and small bowel morphology. *Journal of Pediatric Gastroenterology and Nutrition*, **4**: 568–574 (1985).
40. Weaver, T., Chapman, P., Madeley, C. et al. Intestinal permeability changes and excretion of micro-organisms in stools of infants with diarrhea and vomiting. *Archives of Diseases of Children*, **60**: 326–332 (1985).

41. Fenwick, P., Aggett, P., Macdonald, D. et al. Zinc deficiency and zinc depletion: effect on the response of rats to infection with *Trichinella spiralis*. *American Journal of Clinical Nutrition*, **52**: 166–172 (1990).
42. Moynahan, E. Acrodermatitis enteropathica: a lethal inherited zinc-deficiency disorder. *Lancet*, **1**: 399–400 (1974).
43. Kay, R., Tasman-Jones, C. Zinc deficiency and intravenous feeding. *Lancet*, **2**: 605–606 (1975).
44. Beisel, W. Single nutrients and immunity. *American Journal of Clinical Nutrition*, **35** (suppl): 417–468 (1985).
45. Golden, M., Golden, B. Zinc and delayed hypersensitivity responses. *Nutritional Research*, **5** (suppl 1): 700–709 (1985).
46. Allen, L. Nutritional influences on linear growth: a general review. *European Journal of Clinical Nutrition*, **48** (suppl 1): 75–89 (1994).
47. Naveh, Y., Lightman, A., Zinder, O. Effect of diarrhea on serum zinc concentrations in infants and children. *Journal of Pediatrics*, **101**: 730–732 (1982).
48. Guerrieri, A., Catassi, C., Pasquini, E. et al. Plasma zinc levels in children with chronic diarrhea. *European Journal of Pediatrics*, **145**: 563–564 (1986).
49. Ruz, M., Solomons, N. Fecal zinc excretion during oral rehydration therapy for acute infectious diarrhea (abstract). *Federal Proceedings*, **46**: 748 (1987).
50. Castillo-Duran, C., Vial, P., Uauy, R. Trace mineral balance during acute diarrhea in infants. *Journal of Pediatrics*, **113**: 452–457 (1988).
51. Zinc and copper wastage during acute diarrhea. *Nutritional Reviews*, **48**: 19–22 (1990).
52. Murphy, S., Beaton, G., Calloway, D. Estimated mineral intakes of toddlers: predicted prevalence of inadequacy in village populations in Egypt, Kenya, and Mexico. *American Journal of Clinical Nutrition*, **56**: 565–572 (1992).
53. Walsh, T., Sandstead, H., Prasad, A. et al. Zinc: health effects and research priorities for the 1990s. *Environmental Health Perspectives*, **102** (suppl 2): 5–46 (1994).
54. Gatheru, Z., Kinoti, S., Alwar, J., Mwita, M. Serum zinc levels in children with kwashiorkor aged one to three years at Kenyatta National Hospital and the effect of zinc supplementation during recovery. *East African Medical Journal*, **65**: 670–679 (1988).
55. Tomkins, A., Behrens, R., Roy, S. The role of zinc and vitamin A deficiency in diarrhoeal syndromes in developing countries. *Proceedings of the Nutrition Society*, **52**: 131–142 (1993).
56. Penny, M., Lanata, C. Zinc in the management of diarrhoea in young children. *New England Journal of Medicine*, **333**: 873–874 (1995).
57. Sazawal, S., Black, R., Bhan, M. et al. Zinc supplementation in young children with acute diarrhea in India. *New England Journal of Medicine*, **33**: 869–874 (1995).

### Bismuth salts in diarrhoea: modest benefit at substantial cost

Bismuth salts have been used in proprietary anti-diarrhoeal preparations for the best part of a century (1), yet systematic investigation of their gastrointestinal effects has only begun in recent years. As a result, their efficacy has now been scientifically established in peptic ulcer disease as well as diarrhoea. In peptic ulcer, colloidal bismuth salts not only bind to the base of the ulcer and protect against erosion by acid and pepsin (2), they are also bactericidal to *Helicobacter pylori* (3, 4) and they are now extensively used in combination with antibiotics and metronidazole to eradicate *H. pylori* during therapy of duodenal ulcer.

Very little bismuth is absorbed since all preparations are largely insoluble in the gastrointestinal contents. Taken over long periods at high dosage, however, the subnitrate and subgallate salts were found some 20 years ago, both in Australia (6) and in France (7), to be associated with cases of encephalopathy. Neurotoxicity, it has been estimated, is unlikely to occur at a threshold plasma bismuth concentration of some 100 nanograms/ml (8). There is no evidence that, in normal circumstances, short-term use at recommended dosages presents a tangible risk, but it is possible that patients with AIDS are more vulnerable to acute neurotoxic effects (9).

The salicylate moiety of bismuth subsalicylate also presents a potential risk of intoxication in children (10, 11). Clinically-evident salicylate intoxication from this source seems not to have been reported in clinical practice (12). However, a single case of Reye's syndrome in a child who had received the recommended dose of a preparation containing bismuth subsalicylate to treat diarrhoea and nausea during an influenza-like illness has resulted in a requirement for a labelled warning in the United States (13).

All bismuth salts have a broad spectrum of activity against enteropathic bacteria and enterotoxins (14, 15). They have also been shown *in vitro* to inhibit

replication of several strains of rotavirus in tissue culture (16). The subsalicylate salt may additionally exert an antisecretory action (17) and it has been shown to protect against experimental infection with enterotoxigenic strains of *Escherichia coli* (18). Controlled studies undertaken in adults suggest that it is of modest benefit in preventing and treating travellers' diarrhoea (5, 19–22) and in treating viral diarrhoea due to Norwalk agent (23). More recently, controlled studies in children have shown bismuth subsalicylate to attenuate chronic nonspecific diarrhoea (24), and acute watery diarrhoea (25, 26).

In the most recent of these studies, undertaken in Lima, Peru, bismuth subsalicylate 100 mg/kg daily in 6 divided doses was judged to be a safe and effective adjunct to oral rehydration therapy for infants and young children with acute watery diarrhoea (26). Diarrhoea stopped within 120 hours of admission in 74% of patients given placebo and 89% of those given bismuth. Total stool output, total intake of oral rehydration solution and duration of hospitalization were also significantly reduced by margins ranging from 20 to 33%. In comparative terms the results are significant. However, the length of hospital stay was decreased by less than one day and the reduction in diarrhoea did not become apparent until the third day. There is no mention of whether bismuth subsalicylate was associated with any change in treatment failure rate or stool frequency.

It is clearly important to question whether such therapy is feasible, safe and cost effective within a developing-world economy. Feasibility is also in question on grounds of practicability. A four-hour dosage schedule is proposed, starting as soon as symptoms develop. Because the severity of the illness is not predictable at the outset, all episodes of diarrhoea qualify for treatment. However, where acute diarrhoeal disease is endemic, children frequently have several episodes within a year. Safety might then be at issue, because of cumulative absorption of bismuth (9).

The greatest concern relates to the implications of providing adjunctive therapy at considerably greater cost than sachets of oral rehydration salts. A leading article in the *New England Journal of Medicine* (27) concludes that "emphasizing the use of adjunctive therapy may divert attention and resources away from the use of oral rehydration therapy and early appropriate feeding", which are the essential components of effective therapy (28).

## References

1. Bierer, D. Bismuth subsalicylate: history, chemistry, and safety. *Reviews of Infectious Diseases*, **12** (suppl 1): 3–8 (1990).
2. Lee, S. A potential mechanism of action of colloidal bismuth subcitrate: diffusion barrier to hydrochloric acid. *Scandinavian Journal of Gastroenterology*, **17**: 17–21 (1982).
3. Marshall, B., Hislop, I., Glancy, R., Armstrong, J. Histological improvement of active chronic gastritis in patients treated with Denol. *Australian and New Zealand Journal of Medicine*, **14** (suppl 4): 907 (1984).
4. McNulty, C., Gearty, J., Grump, B. et al. *Campylobacter pyloridis* and associated gastritis: investigator-blind, placebo-controlled trial of bismuth subsalicylate and erythromycin ethylsuccinate. *British Medical Journal*, **293**: 645–649 (1986).
5. Tytgat, G., Axon, A., Dixon, M. et al. *Helicobacter pylori*: causal agent in peptic ulcer disease? Working Party Reports, World Congresses of Gastroenterology. Sydney, Australia. Oxford: Blackwell, 1990, pp. 36–45.
6. Burns, R., Thomas, D., Barron, V. Reversible encephalopathy possibly associated with bismuth subgallate ingestion. *British Medical Journal*, **1**: 220–223 (1974).
7. Lagier, G. Encéphalopathies bismuthiques: situation dans les pays autre que la France. *Thérapie*, **35**: 315–317 (1980).
8. Hillemand, P., Pallière, M., Laquais, B., Bouvet, P. Traitement bismuthique et bismuthémie. *Séminaires Hôpitaux de Paris*, **53**: 1663–1669 (1977).
9. Mendelowitz, P., Hoffman, R., Weber, S. Bismuth absorption and myoclonic encephalopathy during bismuth subsalicylate therapy. *Annals of Internal Medicine*, **112**: 140–141 (1990).
10. Feldman, S., Chen, S., Pickering, L. et al. Salicylate absorption from a bismuth subsalicylate preparation. *Clinical Pharmacology and Therapeutics*, **29**: 788–792 (1981).
11. Pickering, L., Feldman, S., Ericsson, C., Cleary, T. Absorption of salicylate and bismuth from a bismuth subsalicylate-containing compound (Pepto-Bismol). *Journal of Pediatrics*, **99**: 654–656 (1981).
12. Gryboski, J., Hillemeier, A., Grill, B., Kocoshis, S. Bismuth subsalicylate in the treatment of chronic diarrhoea of childhood. *American Journal of Gastroenterology*, **80**: 871–876 (1985).
13. US Food and Drug Administration. Reye's syndrome associated with bismuth subsalicylate. *Federal Register*, **58**(85): 26886–26888 (1993).

14. Manhart, M. *In vitro* antimicrobial activity of bismuth subsalicylate and other bismuth salts. *Reviews of Infectious Diseases*, **12** (suppl I): 11–15 (1990).
15. Ericsson, C., Evans, D., DuPont, H. et al. Bismuth subsalicylate inhibits activity of crude toxins of *Escherichia coli* and *Vibrio cholerae*. *Journal of Infectious Diseases*, **136**: 693–696 (1977).
16. Ward, R., Sander, D., Knowlton, D. *In vitro* activities of bismuth salts against rotaviruses and other enteric viruses. *Antimicrobial Agents and Chemotherapy*, **27**: 306–308 (1985).
17. Ericsson, C., Tannenbaum, C., Charles, T. Anti-secretory and antiinflammatory properties of bismuth subsalicylate. *Reviews of Infectious Diseases*, **12** (suppl I): 16–20 (1990).
18. Graham, D., Estes, M., Gentry, L. Double-blind comparison of bismuth subsalicylate and placebo in the prevention and treatment of enterotoxigenic *Escherichia coli*-induced diarrhoea in volunteers. *Gastroenterology*, **85**: 1017–1022 (1983).
19. DuPont, H., Sullivan, P., Pickering, L. et al. Symptomatic treatment of diarrhea with bismuth subsalicylate among students attending a Mexican University. *Gastroenterology*, **73**: 715–718 (1977).
20. Du Pont, H., Sullivan, P., Evans, D. et al. Prevention of travelers' diarrhea (emporiatric enteritis): prophylactic administration of bismuth subsalicylate. *Journal of the American Medical Association*, **243**: 237–241 (1980).
21. Steffen, R., Mathewson, J., Ericsson, C. et al. Travelers' diarrhea in West Africa and Mexico: fecal transport systems and liquid bismuth subsalicylate for self-therapy. *Journal of Infectious Diseases*, **157**: 1008–1013 (1988).
22. DuPont, H., Ericsson, C., Johnson, P., de la Cabada, F. Use of bismuth subsalicylate for the prevention of travelers' diarrhea. *Reviews of Infectious Diseases*, **12** (suppl I): 64–67 (1990).
23. Steinhoff, M., Douglas, R., Greenberg, H., Callahan, D. Bismuth subsalicylate therapy of viral gastroenteritis. *Gastroenterology*, **78**: 1495–1499 (1980).
24. Gryboski, J., Kocoshis, S. Effect of bismuth subsalicylate on chronic diarrhoea in childhood: a preliminary report. *Reviews of Infectious Diseases*, **12** (suppl I): 36–40 (1990).
25. Soriano-Brücher, H., Avendano, P., O'Ryan, M. et al. Bismuth subsalicylate in the treatment of acute diarrhea in children: a clinical study. *Pediatrics*, **87**: 18–27 (1991).
26. Figueroa-Quintanilla, D., Salazar-Lindo, E., Bradley Sack, R. et al. A controlled trial of bismuth subsalicylate in infants with acute watery diarrheal disease. *New England Journal of Medicine*, **328**: 1653–1658 (1993).

27. Snyder, J. Can bismuth improve the simple solution for diarrhoea? *New England Journal of Medicine*, **328**: 1705–1706 (1993).

28. The rational use of drugs in the management of acute diarrhoea in children. World Health Organization, Geneva (1990).

## Oral rehydration: variations on a traditional theme

The widespread adoption of oral rehydration solutions in the management of acute diarrhoea of infants and children has saved many lives in developing countries over the past 20 years (1). The general principles at issue are to replace the electrolyte deficit in sodium and potassium adequately and safely; to enhance intestinal absorption of sodium and water by including glucose or other carbohydrate; to counter acidosis by including citrate or bicarbonate as an alkalinizing agent; and to assure the ready availability of a preparation that meets these requirements and that is simple to use within the home.

Notwithstanding the massive use of oral rehydration over many years, there has been uncertainty about the optimum composition of the solution, particularly with regard to its osmolarity and the nature of the carbohydrate. For all children with acute diarrhoea who are able to drink and who are not severely dehydrated, WHO has recommended a standard solution. This is slightly hypertonic with a total osmolarity of 311 mmol/L, a sodium content of 90 mmol/l, and a glucose content of 111 mmol/l (2, 3). This formulation has been considered particularly effective in treating clinically-evident dehydration commonly encountered in developing countries, and it is generally agreed that any danger of hypernatraemia is remote when it is given with additional fluids and breast-feeding, as appropriate.

In many developed countries, and notably in Europe, concern that the WHO formulation might carry a demonstrable risk of hypernatraemia when fed to well-nourished marginally-dehydrated infants (4) has resulted in the adoption of a solution of reduced osmolarity — between 200 and 250 mmol/L — and containing only 60 mmol/l sodium (5). Use of this latter formulation has been supported by clinical experience in Finland (6): young children with acute diarrhoea who were allocated to a reduced osmolarity solution passed fewer stools and were able to leave hospital earlier than children who received the standard solution. More tellingly, it

has been reported from Egypt that some children, when given the standard solution and little else to drink during maintenance therapy, develop mild hypernatraemia with worsening diarrhoea and persistent thirst (7). This clinical response, it is claimed, is not seen in children treated with reduced-osmolarity solutions or with intravenous rehydration.

A further comparison of the response of some 450 young children to standard (311 mmol/l) and reduced-osmolarity (224 mmol/l) solutions has since been undertaken in centres in Brazil, India, Mexico and Peru (8). This has confirmed the findings of the earlier trials. On average, among the children who received the standard solution, the stool output was some 40% higher (95% confidence interval: 11–75); the duration of diarrhoea was 20% longer (2–45), the intake of oral solution was 20% greater (3–33); and the need for intravenous infusion was some 40% higher overall (relative risk 1.4; 95% CI: 0.9–2.4) than among children who received the reduced-osmolarity solution. Among children who were not breast-fed, the need for intravenous infusion was doubled among children who received the standard solution.

The authors conclude, none the less, that the two solutions are comparably safe on the grounds that no excess risk of developing or worsening of hypernatraemia was demonstrated in this study among the children who received the standard solution. They also question whether a reduced-osmolarity solution would be as satisfactory as the standard solution for the treatment of cholera (8), in which faecal concentrations of sodium are higher (9).

Further studies are planned to define the best formulation for patients with cholera. In the meantime it has been shown in a meta-analysis of 13 clinical trials that substitution of cooked rice for glucose in the standard solution reduces fluid loss in cholera by an average of one third over the first 24 hours (10). It has been suggested that carbohydrate and peptide constituents in rice may enhance fluid reabsorption within a nutrient-linked cotransport system (10). However, given that this effect only achieves clinical importance in cholera, it is alternatively possible that the mechanism is specific to this disease. *In vitro*, a specific hydrophobic low-molecular-weight fraction of rice exerts a direct anti-secretory effect on intestinal crypt cells by acting as a chloride channel blocking agent (11). It is this channel that is the target of adenosine 3'5'-cyclic monophosphate, the major mediator of intestinal secretion in cholera (12).

Thus far, it seems that rice-based solutions hold advantage sufficient to warrant their use, where it is convenient, in specialized treatment centres for cholera (10). There is no reason to propose wider use of these solutions since they hold no advantage over low-osmolarity glucose-based solutions in other forms of diarrhoea and the cost of commercially prepared oral rehydration salts based on precooked rice would be about three times greater than the cost of standard packets of WHO oral rehydration salts (10).

Meanwhile, the failure of the standard solution to reduce the rate of stool loss or to shorten the duration of the illness in cholera, as in other types of diarrhoea, remains a matter of concern (13–15). Not only is there lingering doubt about the possibility of hypernatraemia (5), there are also claims that failure of rehydration therapy to redress the symptoms of diarrhoea may account for widespread use of ineffective "antidiarrhoeal" drugs (16). To date, the only solutions that significantly reduce stool output, duration of diarrhoea and need for supplemental intravenous fluids in children with acute non-cholera diarrhoea, are reduced-osmolarity glucose-based solutions. Reduced-osmolarity solutions containing either cooked rice powder, or starch-like maltodextrins — both complex carbohydrates that yield glucose when digested — do not perform better than standard solutions (17). It seems that transient glucose malabsorption occurs frequently among children with acute diarrhoea (18–20). When this happens, glucose liberated from complex carbohydrates is not fully absorbed, intraluminal osmolarity rises to equal or exceed that of standard solutions, and the potential benefit of the reduced osmolarity solution is lost (21, 22).

Further studies of reduced-osmolarity glucose-based oral rehydration solutions are currently receiving support from WHO. The aim is to define a formulation that minimizes the risk of osmotic diarrhoea while ensuring adequate and timely replacement of water and electrolytes. When this series of studies is completed, formal recommendations will be made (17). In the meantime, WHO advises giving liberal amounts of water, breast-milk or other low-solute drinks during treatment with the standard rehydration solution (23).

#### References

1. Rahaman, M., Patwari, Y., Aziz, K et al. Diarrhoeal mortality in two Bangladeshi villages with and without community-based oral rehydration therapy. *Lancet*, **2**: 809–812 (1979).

2. Treatment and prevention of acute diarrhoea. Practical guideline. World Health Organization, Geneva, 1993. *American Journal of Clinical Nutrition*, **33**: 637–663 (1980).
3. Avery, M., Snyder, J. Oral therapy for acute diarrhea: the underused simple solution. *New England Journal of Medicine*, **323**: 891–894 (1990).
4. Finberg, L. Hypematremic (hypertonic) dehydration in infants. *New England Journal of Medicine*, **289**: 196–198 (1973).
5. Report of an ESPGAN Working Group. Recommendations for composition of oral rehydration solutions for the children of Europe. *Journal of Pediatric Gastroenterology and Nutrition*, **14**: 113–115 (1992).
6. Rautanen, T., El-Radhi, S., Vesikari, T. Clinical experience with a hypotonic oral rehydration solution in acute diarrhoea. *Acta Paediatrica*, **82**: 52–54 (1993).
7. El-Mougi, M., El-Akkad, N., Hendawi, A. et al. Is a low osmolarity ORS solution more efficacious than standard ORS solution? *Journal of Pediatric Gastroenterology and Nutrition*, **19**: 183–186 (1994).
8. International Study Group on Reduced-osmolarity ORS Solutions. Multicentre evaluation of reduced-osmolarity oral rehydration salts solution. *Lancet*, **345**: 282–285 (1995).
9. Mahalanabis, D., Wallace, C., Kallen, R. et al. Water and electrolyte losses due to cholera in infants and small children: a recovery balance study. *Pediatrics*, **45**: 374–385 (1970).
10. Gore, S., Fontaine, O., Pierce, N. Impact of rice-based oral rehydration solution on stool output and duration of diarrhoea: meta-analysis of 13 clinical trials. *British Medical Journal*, **304**: 287–291 (1992).
11. Macleod, R., Bennett, H., Hamilton, J. Inhibition of intestinal secretion by rice. *Lancet*, **346**: 90–92 (1995).
12. Field, M., Semrad, C. Toxigenic diarrheas, congenital diarrheas and cystic fibrosis in disorders of intestinal ion transport. *Annual Reviews of Physiology*, **55**: 631–655 (1993).
13. Pierce, N., Barnwell, J., Mitra, R. et al. Effect of intragastric glucose-electrolyte infusion upon water and electrolyte balance in Asiatic cholera. *Gastroenterology*, **55**: 333–343 (1968).
14. Hirschhorn, N., Kinzie, J., Sachar, D. et al. Decrease in net stool output in cholera during intestinal perfusion with glucose-containing solutions. *New England Journal of Medicine*, **279**: 176–180 (1968).
15. Mahalanabis, D., Sack, R., Jacobs, B. et al. Use of a glucose oral-electrolyte solution in the treatment of pediatric cholera: a controlled study. *Journal of Tropical Pediatrics and Environmental Child Health*, **20**: 82–87 (1974).
16. Programme for the Control of Diarrhoeal Diseases. *Seventh Programme Report, 1988–1989*. World Health Organization, Geneva, 1990.
17. El-Mougi, M., Hendawi, A., Koura, H. et al. Effect of sugar malabsorption on efficacy of standard glucose-based and reduced-osmolarity maltodextrin-based oral rehydration solutions. *Bulletin of the World Health Organization* (in press).
18. Maki, M. A prospective clinical study of rotavirus diarrhoea in young children. *Acta Paediatrica Scandinavica*, **70**: 107–113 (1981).
19. Kjellman, B., Ronge, E. Oral solutions for gastroenteritis — optimal glucose concentration. *Archives of Diseases of Children*, **57**: 313–315 (1982).
20. Manuel, P., Mukhtar, D., Walker-Smith, J. Transient monosaccharide intolerance in infants with acute and protracted diarrhoea. *Journal of Pediatric Gastroenterology and Nutrition*, **3**: 41–45 (1984).
21. Sandhu, B., Jones, B., Brook, C., Silk, D. Oral rehydration in acute infantile diarrhoea with a glucose-polymer electrolyte solution. *Archives of Diseases of Children*, **57**: 152–160 (1982).
22. Meeuwisse, G. High sugar worse than high sodium in oral rehydration solutions. *Acta Paediatrica Scandinavica*, **72**: 161–166 (1983).
23. Programme for the Control of Diarrhoeal Diseases. *The treatment of diarrhoea*. WHO/CDD/SER/80.2 Rev 3. World Health Organization, Geneva, 1990.

### **Parkinsonism: an under-recognized complication of metoclopramide use**

Metoclopramide hydrochloride acts both peripherally and centrally on the upper intestinal tract in a way that offers valuable symptomatic relief in several situations. Its anti-emetic effect, which may result from blockade of dopamine receptors in the chemoreceptor trigger zone in the medulla, is used to inhibit vomiting associated with migraine and cancer chemotherapy. It is most widely used, however, to increase muscular tone and peristaltic activity in disorders of upper gastrointestinal

motility: post-surgical and diabetic gastric stasis (1), and gastro-oesophageal reflux (2). Again, its mode of action is uncertain. It may reflect stimulation of intramural cholinergic neurones or antagonism of dopaminergic neurotransmission.

Like the phenothiazines and other dopamine receptor, metoclopramide can also cause unwanted extrapyramidal signs. Dystonic reactions can occur suddenly, typically at the outset of high-dose parenteral anti-emetic therapy, in children and young adults. Chronic tardive dyskinesia, which may be unresponsive to treatment, has occasionally been reported in elderly patients on prolonged therapy, but classical symptoms of Parkinsonism have generally been regarded as uncommon. This has now been placed in question by the results of a case control study reported from the United States (3).

Drug prescription records available from a state health insurance programme were obtained for 1253 patients over 65 years old who were started on dopaminergic drugs for Parkinson's disease between 1981 and 1990. Fifty-four of these patients had filled a prescription for metoclopramide in the three months prior to starting antiparkinsonian drugs and the association was strongest among patients receiving high doses of metoclopramide. Overall, metoclopramide use was three fold higher among these patients with Parkinsonism than among control patients who were assigned random index dates within the period under review (odds ratio=3.09; 95% confidence interval: 2.25 to 4.26). Most surprisingly, prescriptions for metoclopramide continued to be issued to two-thirds of the patients who were placed on antiparkinsonian drugs.

The results are remarkable in that that they suggest:

- many doctors do not associate extrapyramidal symptoms in the elderly with use of metoclopramide;
- this association is likely to be much stronger than is demonstrated within this study, since patients with extrapyramidal symptoms who were managed by other methods or simply by withdrawal of metoclopramide were not identified within the study;
- metoclopramide is consequently associated more frequently with extrapyramidal signs in elderly patients than was formerly recognized.

## References

1. Snape, W., Battle, W., Schwartz, S. et al. Metoclopramide to treat gastroparesis due to diabetes mellitus: a double-blind controlled trial. *Annals of Internal Medicine*, **96**: 444-446 (1982).
2. Durazo, F., Valenzuela, J. Effect of single and repeated doses of metoclopramide on the mechanisms of gastro-oesophageal reflux. *American Journal of Gastroenterology*, **88**: 1657-1662 (1993).
3. Avorn, J., Gurwitz, J., Bohn, R. et al. Increased incidence of levodopa therapy following metoclopramide use. *Journal of the American Medical Association*, **274**: 1780-1782 (1995).

## Selegiline in Parkinsonism: a need for radical reappraisal

The cause of the damage within the basal ganglia of the brain which results in the syndrome of Parkinsonism remains unknown. Cell loss and depigmentation within the substantia nigra is accompanied by diffuse changes in neural transmission, particularly within the corpus striatum, which result in the characteristic signs of the disease. Hypokinesia is associated with reduced dopaminergic activity, while tremor and rigidity result from over-activity within the cholinergic system. The disease often first becomes evident in persons aged between 50 and 60 years. About one quarter of the patients die within 6 years and over half die within 12 years (1)

Treatment of the condition is directed essentially to correcting the imbalance in neuronal transmission. This does not prevent progression of the disease, but it greatly improves the quality of life for many patients. Drug therapy, however, is not free from problems. Anticholinergics, which were the first drugs found to be beneficial in Parkinsonism, are still widely used. Benhexol (INN: trihexyphenidyl) and orphenadrine are effective in reducing tremor and excessive salivation, but they can cause an array of adverse effects ranging from dryness of the mouth and constipation, to precipitation of glaucoma or urinary retention in men with prostatic enlargement. They also worsen dyskinesias induced by levodopa — but they lessen the morning dystonia that can be troublesome as its effects wear off (2). More seriously, they can impair memory and concentration and, particularly in elderly patients, induce a confusional state with visual hallucinations (3, 4).

For the past 25 years, more effective symptomatic improvement has become possible by augmenting the pool of dopamine within the central nervous system. The dopamine precursor, levodopa, is used for this purpose since, unlike dopamine, it readily crosses the blood-brain barrier. To prevent wasteful metabolism of levodopa to dopamine before it enters the brain — and to minimize nausea and vomiting caused by circulating dopamine — levodopa is now generally combined with a peripheral (extracerebral) decarboxylase inhibitor (benserazide or carbidopa) which does not cross the blood-brain barrier.

Because levodopa fails to halt the underlying progression of Parkinsonism, its effect is time-limited. It does not substantially increase life expectancy (5), and it has even been suggested — on the basis of experimental evidence (6) and theoretical considerations (7, 8) — that it could accelerate neurological deterioration. Sooner or later, its effect is compromised by fluctuations in motor performance and mood, psychiatric disturbances, and abnormal hyperkinetic movements (9, 10).

Because of these limitations, various possibilities have been explored of either deferring the use of levodopa or extending the stage of the disease during which it remains effective. Among alternative drugs that are used in the early phases of the disease are three compounds — bromocriptine, lisuride, and pergolide — which stimulate both peripheral and central dopamine receptors for a few hours following an oral dose. These dopamine agonists, which are more appropriate for younger patients (2), are commonly given several times daily together with domperidone, a peripheral dopamine receptor blocking agent that attenuates peripheral dopamine activity and the resulting nausea and vomiting. However, domperidone cover does not prevent the occurrence of less common but more serious adverse effects, including vasospasm and rare cases of retroperitoneal and pleuropulmonary fibrosis (2). It has been estimated that some 5% to 10% of patients can be maintained on monotherapy with one of these agonists for several years while dopamine is held in reserve (11–14)

Greater potential has been ascribed to selegiline, a selective inhibitor of type B monoamine oxidase (the main catabolic enzyme for dopamine within the brain). Two large multicentre studies conducted respectively in North America (15, 16) and France

(17), and other smaller studies (18, 19) have indicated that selegiline defers the need for levodopa therapy by some 9 months among patients in the early phases of the disease. Whether this response reflects a neuroprotective effect or a symptomatic dopamine-like effect remains uncertain. Evidence that benefit is of limited duration favoured a symptomatic effect (20–23), but the claim made on the basis of an open, uncontrolled, retrospective survey that mortality was reduced by some 30% when selegiline was used as an adjunct to levodopa therapy supported a neuroprotective action (24).

A fundamental reappraisal of selegiline has now been forced by the unanticipated results of an open, prospective, randomized, multicentre study which involved over 500 patients with early, mild Parkinson's disease who were attending 93 hospitals throughout the United Kingdom. The objective was to compare the effects of three different treatment regimens on the course of the disease: levodopa and a decarboxylase inhibitor; levodopa and a decarboxylase inhibitor in combination with selegiline; and the dopamine agonist, bromocriptine. An interim report based on three years' follow-up indicated that each of the treatments improved baseline disabilities after one year, but that functional disability and physical signs had deteriorated after three years (25). Bromocriptine was shown to be less effective and to produce more adverse effects within the first months of treatment. Subsequently, it was associated with fewer dyskinesias and motor fluctuations in performance. No difference in mortality was discernible between the treatment groups.

The final report, based on an average of 5.6 years' follow-up of the patients allocated to the levodopa and levodopa/selegiline regimens, conveyed totally unexpected and highly disappointing results (26). Not only did selegiline fail to confer any detectable clinical benefit, notwithstanding a marked levodopa-sparing effect, but its use was associated with a five fold increase in the incidence of reported adverse effects and a 60% increase in mortality: 76/271 vs 44/249 (mortality ratio 1.57; 95% confidence interval 1.09 to 2.30). This increased mortality resulted principally from an excess of deaths attributed to Parkinson's disease (26 vs 7) and cerebrovascular disease (11 vs 2). Only in a few instances were these diagnoses confirmed at autopsy.

Whether this excess mortality is causally related to selegiline is, as yet, unproven. Such an association

has not been established in any other trial; but no other trial has involved such prolonged follow-up. The levodopa-sparing effect, which was anticipated and has been noted in other trials (19, 23), seems unlikely to hold relevance (27). The possibility that selegiline induces cardiac dysrhythmias has been raised in an earlier trial (15) but, despite this awareness, no such hazard was noted.

Mortality will be closely monitored in other ongoing studies involving selegiline. Meanwhile, patients in the British trial have been advised to relinquish using selegiline, to have their requirements for levodopa reassessed, and to attend for annual re-assessment. Many clinicians who have prescribed selegiline in routine practice are doubtless also following this course of action.

#### References

1. Shaw, K., Lees, A., Stern, G. The impact of treatment with levodopa on Parkinson's disease. *Quarterly Journal of Medicine*, **49**: 283–293 (1980).
2. Quinn, N. Drug treatment of Parkinson's disease. *British Medical Journal*, **310**: 575–579 (1995).
3. DeSmet, Y., Ruberg, M., Serdaru, M. et al. Confusion, dementia and anticholinergics in Parkinson's disease. *Journal of Neurology, Neurosurgery and Psychiatry*, **45**: 1161–1164 (1982).
4. Dubois, B., Danze, F., Pillon, B. et al. Cholinergic-dependent cognitive deficits in Parkinson's disease. *Annals of Neurology*, **22**: 26–30 (1987).
5. Clarke, C. Does levodopa therapy delay death in Parkinson's disease? A review of the evidence. *Movement Disorders*, **10**: 250–256 (1995).
6. Mena, M., Pardo, P., Casarejas, M. et al. Neurotoxicity of levodopa on catecholamine-rich human neuroblastoma cells. *Movement Disorders*, **5**: 62–73 (1992).
7. Fahn, S., Cohen, G. The oxidant stress hypothesis: evidence supporting it. *Annals of Neurology*, **32**: 804–812 (1992).
8. Calne, D. The free radical hypothesis in idiopathic parkinsonism: evidence against it. *Annals of Neurology*, **32**: 799–803 (1992).
9. Marsden, C., Parkes, J. "On-off effects" in patients with Parkinson's disease on chronic levodopa therapy. *Lancet*, **1**: 292–295 (1976).
10. Riley, D., Lang, A. The spectrum of levodopa-related fluctuations in Parkinson's disease. *Neurology*, **43**: 1459–1464 (1993).
11. Hely, M., Morris, J., Rail, D. et al. The Sydney Multi-centre Study of Parkinson's Disease: a report on the first three years. *Journal of Neurology, Neurosurgery and Psychiatry*, **52**: 324–328 (1989).
12. Rinne, U. Lisuride, a dopamine agonist in the treatment of early Parkinson's disease. *Neurology*, **39**: 336–339 (1989).
13. Bergamasco, B., Benna, P., Scarzella, L. Long-term bromocriptine treatment of *de novo* patients with Parkinson's disease. A seven-year follow-up. *Acta Neurologica Scandinavica*, **81**: 383–387 (1990).
14. Montastruc, J., Rascol, O., Senard, G., Rascol, A. A randomized controlled study comparing bromocriptine to which levodopa was added, with levodopa alone in previously untreated patients with Parkinson's disease: five year follow-up. *Journal of Neurology, Neurosurgery and Psychiatry*, **57**: 1034–1038 (1994).
15. Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *New England Journal of Medicine*, **321**: 1364–1371 (1989).
16. Parkinson Study Group. Effects of tocopherol and deprenyl on the progression of disability in early Parkinson's disease. *New England Journal of Medicine*, **328**: 176–183 (1993).
17. Allain, H., Cougnard, J., Neukirch, H. Selegiline in *de novo* Parkinson patients: the French selegiline multicenter trial (FSMT). *Acta Neurologica Scandinavica*, **82**: 73–78 (1991).
18. Tetrud, J., Langston, J. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science*, **245**: 519–522 (1989).
19. Myllyla, V., Sotaniemi, K., Vuorinen, J., Heinonen, E. Selegiline as initial treatment in *de novo* parkinsonian patients. *Neurology*, **42**: 339–343 (1992).
20. Schulzer, M., Mak, E., Calne, D. The antiparkinson efficacy of deprenyl derives from transient improvement that is likely to be symptomatic. *Annals of Neurology*, **32**: 795–798 (1992).
21. Ward, C. Does selegiline delay the progression of Parkinson's disease? A critical re-evaluation of the DATATOP study. *Journal of Neurology, Neurosurgery and Psychiatry*, **57**: 217–220 (1994).
22. Elizan, T., Yahr, M., Moros, D. et al. Selegiline as an adjunct to conventional levodopa therapy in Parkinson's disease. *Archives of Neurology*, **46**: 1280–1283 (1989).
23. Brannan, T., Yahr, M. Comparative study of selegiline plus L-dopa-carbidopa versus L-dopa-carbidopa alone in the treatment of Parkinson's disease. *Annals of Neurology*, **37**: 95–98 (1995).

24. Birkmayer, W., Knoll, J., Riederer, P. et al. Increased life expectancy resulting from addition of L-deprenyl to Madopar treatment in Parkinson's disease: a long-term study. *Journal of Neural Transmission*, **64**: 113–127 (1985).

25. Parkinson's Disease Research Group of the United Kingdom. Comparison of therapeutic effects of levodopa, levodopa and selegiline, and bromocriptine in patients with early, mild Parkinson's disease: three-year interim report. *British Medical Journal*, **307**: 469–472 (1993).

26. Lees, A. on behalf of the Parkinson's Disease Research Group of the United Kingdom. Comparison of the therapeutic effects and mortality data of levodopa and levodopa combined with selegiline in patients with early, mild Parkinson's disease. *British Medical Journal*, **311**: 1602–1607 (1995).

27. Poewe, W., Lees, A., Stern, G. Low dose L-dopa therapy in Parkinson's disease: a six-year follow-up study. *Neurology*, **36**: 1528–1530 (1986).

### Rheumatoid arthritis: corticosteroids reassessed

It is almost 50 years since corticosteroids were first proposed as a treatment for rheumatoid arthritis (1) but their use for this purpose remains controversial (2). There is no doubt that, in the short term, they provide striking symptomatic benefit (3) and it seemed, at first, that they might also prevent joint destruction (3–5). Enthusiasm waned, however, when it was found that prolonged treatment, even at moderate dosage, was associated with serious adverse effects (6, 7). Patients were at increased risk of osteoporotic fractures (8, 9), cataracts and glaucoma (10, 11), diabetes (12), systemic infections (13), gastrointestinal bleeding (14, 15), and atherosclerotic vascular disease (16).

After this setback, attention reverted to acetylsalicylic acid and to the rapidly extending range of other nonsteroidal anti-inflammatory drugs. When these first-line anti-inflammatory drugs failed, sequential monotherapy with slow-acting anti-rheumatic drugs such as antimalarial agents, gold salts, penicillamine, or sulfasalazine — and more recently, ciclosporin and methotrexate — became widely advocated (17). Use of steroids was largely relegated to low-dose "bridging therapy" to prevent exacerbation of the disease while one slow-acting drug was substituted for another (18, 19).

Monotherapy was soon recognized to have its limitations, however (20–22). The slow-acting drugs were found to have significant toxicity (23, 24) and

doubts, which still persist, emerged as to whether they exert a lasting influence on the course of the disease (25, 26). This has resulted in a resurgence of interest in combination therapy (27, 28), including the use of corticosteroids, which had never been entirely relinquished (2, 29, 30), and which are now being used more frequently under specialist supervision when standard treatment with slow-acting drugs has failed (28, 31).

Given this resurgence of interest in corticosteroids, the safety of prolonged low-dose steroid therapy has been re-explored by several groups in recent years. In general, the results of clinical studies have been reassuring. In particular, serious adverse effects, including osteoporosis, have rarely been reported within the context of carefully controlled and executed clinical trials (31, 32). Most recently published are the results of the largest of these studies, a multicentre trial organized by the British Arthritis and Rheumatism Council. This was designed to assess the effect of adding either a low, fixed daily dose of prednisolone (7.5 mg) or placebo to the pre-existing treatment regimen of over 100 adult patients with active rheumatoid arthritis of less than 2 years' duration (33). The most impressive finding was that the rate of radiological deterioration was greatly slowed throughout the first year among the patients treated with steroids. The disappointment was that symptomatic benefit, which was significant during the first six months of treatment, was not sustained into the second year.

Despite this apparent dissociation in the relationship between radiological changes and functional deterioration, and tenuous evidence that any treatment can lastingly attenuate the progression of joint damage in rheumatoid arthritis (28, 34, 35), there is cautious optimism from this and other trials that long-term benefits may be obtained by more intensive therapy during the early stages of the disease (36). It is at this time that irreversible joint damage progresses most rapidly (34), and that the retarding effect of the slow-acting drugs is most evident (37). The inadequacy of traditional approaches, it is now realized, may allow extensive refractory disease to develop in some patients before adequate therapy has even been started (36).

Even at this stage, however, a final verdict is still outstanding on the safety of long-term corticosteroid therapy. Analysis of an historical cohort of more than 100 patients with rheumatoid arthritis who had been receiving prednisone in doses no

greater than 15 mg daily (mean±SD: 6.1±3.1mg/day) for at least one year (mean±SD:6.2±4.6 years) is reported to indicate that steroid-specific adverse events occur in a dose-dependent distribution down to dosages as low as 5 mg daily (38). It is vital that the potential risks and benefits of any intensive approach to the treatment of early rheumatoid arthritis involving either corticosteroids or combinations of slow-acting drugs be meticulously assessed before it is accepted into routine use.

#### References

- Hench, P., Kendall, E., Slocumb, C., Polley, H. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions. *Archives of Internal Medicine*, **85**: 545–566 (1950).
- Byron, M., Mowat, A. Corticosteroid prescribing in rheumatoid arthritis — the fiction and the fact. *British Journal of Rheumatology*, **24**: 164–166 (1985).
- The Joint Committee of the Medical Research Council and Nuffield Foundation on Clinical Trials of Cortisone, ACTH and Other Therapeutic Measures in Chronic Rheumatic Diseases. A comparison of prednisolone with aspirin or other analgesics in the treatment of rheumatoid arthritis. *Annals of Rheumatic Diseases*, **18**: 173–187 (1959).
- Idem. A comparison of prednisolone with aspirin or other analgesics in the treatment of rheumatoid arthritis. *Annals of Rheumatic Diseases*, **19**: 331–337 (1960).
- West, H. Rheumatoid arthritis: the relevance of clinical knowledge to research activities. *Abstracts of World Medicine*, **41**: 401–417 (1967).
- Bollet, A., Black, R., Bunim, J. Major undesirable side-effects resulting from prednisolone and prednisone. *Journal of the American Medical Association*, **158**: 459–463 (1955).
- Truhan, A., Ahmed, A. Corticosteroids: a review with emphasis on complications of prolonged systemic therapy. *Annals of Allergy*, **62**: 375–391 (1989).
- Lukert, B., Raisz, L. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Annals of Internal Medicine*, **112**: 352–364 (1990).
- Michel, B., Bloch, D., Fries, J. Predictors of fractures in early rheumatoid arthritis. *Journal of Rheumatology*, **18**: 804–808 (1991).
- Furst, C., Smiley, W., Ansell, B. Steroid cataract. *Annals of Rheumatic Diseases*, **25**: 364–368 (1966).
- Francois, J. Corticosteroid glaucoma. *Annals of Ophthalmology*, **9**: 1075–1080 (1977).
- Olefsky, J., Kimmerling, G. Effects of glucocorticoids on carbohydrate metabolism. *American Journal of Medical Sciences*, **271**: 202–210 (1976).
- Stuck, A., Minder, C., Frey, F. Risk of infectious complications in patients taking glucocorticoids. *Reviews of Infectious Diseases*, **11**: 954–963 (1989).
- Messer, J., Reitman, D., Sacks, H. et al. Association of adrenocorticosteroid therapy and peptic-ulcer disease. *New England Journal of Medicine*, **309**: 21–24 (1983).
- Gabriel, S., Jaakkimainen, L., Bombardier, C. Risk for serious gastrointestinal complications related to use of nonsteroidal antiinflammatory drugs. *Annals of Internal Medicine*, **115**: 787–796 (1991).
- Kalbak, K. Incidence of arteriosclerosis in patients with rheumatoid arthritis receiving long-term corticosteroid therapy. *Annals of Rheumatic Diseases*, **31**: 196–200 (1972).
- Williams, J. Rheumatoid arthritis: treatment. In: *Primer on rheumatic diseases*, 10th edn. Schumacher, H. ed. The Arthritis Foundation, Atlanta, 1993, pp. 96–99.
- Harris, E., Emkey, R., Nichols, J., Newberg, A. Low-dose prednisone therapy in rheumatoid arthritis: a double-blind study. *Journal of Rheumatology*, **10**: 713–721 (1983).
- Masi, A. Low-dose glucocorticoid therapy in rheumatoid arthritis: transitional or selected add-on therapy. *Journal of Rheumatology*, **10**: 675–678 (1983).
- Wilske, K., Healey, L. Remodelling the pyramid — a concept whose time has come. *Journal of Rheumatology*, **16**: 565–567 (1989).
- Bensen, W.G., Bensen, W., Adachi, J., Tugwell, P. Remodelling the pyramid: the therapeutic target of rheumatoid arthritis. *Journal of Rheumatology*, **17**: 987–989 (1990).
- Pincus, T., Callahan, L. Remodeling the pyramid or remodeling the paradigms concerning rheumatoid arthritis. *Journal of Rheumatology*, **17**: 1582–1585 (1990).
- Felson, D., Anderson, J., Meenan, R. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. *Arthritis and Rheumatism*, **33**: 1449–1461 (1990).
- Singh, G., Fries, J., Williams, C. et al. Toxicity profiles of disease modifying antirheumatic drugs in rheumatoid arthritis. *Journal of Rheumatology*, **18**: 188–194 (1991).
- Iannuzzi, L., Dawson, N., Zein, N., Kushner, I. Does drug therapy slow radiographic deterioration in rheumatoid arthritis? *New England Journal of Medicine*, **309**: 1023–1027 (1983).

26. Kushner, I. Does aggressive therapy of rheumatoid arthritis affect outcome? *Journal of Rheumatology*, **16**: 1–4 (1989).
27. Paulus, H. The use of combinations of disease-modifying antirheumatic agents in rheumatoid arthritis. *Arthritis and Rheumatism*, **33**: 113–120 (1990).
28. Felson, D., Anderson, J., Meenan, R. The efficacy and toxicity of combination therapy in rheumatoid arthritis: a meta-analysis. *Arthritis and Rheumatism*, **37**: 1487–1491 (1994).
29. Caldwell, J., Furst, D. The efficacy and safety of low-dose corticosteroids for rheumatoid arthritis. *Seminars in Arthritis and Rheumatism*, **21**: 1–11 (1991).
30. Friesen, W., Hekster, Y., van der Putte, L., Gribnau, F. Cross-sectional study of rheumatoid arthritis treatment in a university hospital. *Annals of Rheumatic Diseases*, **44**: 372–378 (1985).
31. Sambrook, P., Eisman, J., Yeats, M. et al. Osteoporosis in rheumatoid arthritis: safety of low-dose corticosteroids. *Annals of Rheumatic Diseases*, **45**: 950–953 (1986).
32. van Schaardenburg, D., Valkema, R., Dijkmans, B. et al. Prednisone treatment of elderly-onset rheumatoid arthritis: disease activity and bone mass in comparison with chloroquine treatment. *Arthritis and Rheumatism*, **38**: 334–342 (1995).
33. Kirwan, J. and the Arthritis and Rheumatism Council Low-Dose Corticosteroid Study Group. The effect of glucocorticoids on joint destruction in rheumatoid arthritis. *New England Journal of Medicine*, **333**: 142–146 (1995).
34. Kirwan, J., Currey, H. Rheumatoid arthritis: disease-modifying antirheumatoid drugs. *Clinics of Rheumatic Diseases*, **9**: 581–599 (1983).
35. van der Heijde, D., van Leeuwen, M., van Riel, P. et al. Biannual radiographic assessments of hands and feet in a three-year prospective follow-up of patients with early rheumatoid arthritis. *Arthritis and Rheumatism*, **35**: 26–34 (1992).
36. Breedveld, F. New perspectives on treating rheumatoid arthritis. *New England Journal of Medicine*, **333**: 183–184 (1995).
37. van der Heijde, D., van Riel, P., Nuvér-Zwart, I. et al. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet*, **1**: 1036–1038 (1989).
38. Saag, K., Koehnke, R., Caldwell, J. et al. Low-dose long-term corticosteroid therapy in rheumatoid arthritis: an analysis of serious adverse effects. *American Journal of Medicine*, **96**: 115–123 (1994).

## Sumatriptan: does it have a place in the routine treatment of migraine?

The treatment of migraine remains imperfect. The headaches often respond to simple analgesics such as acetylsalicylic acid and paracetamol. In other patients the condition is highly resistant to treatment. In many cases, therapeutic failure may result from poor absorption caused by vomiting, delayed gastric emptying or impaired peristalsis. Dispersible or effervescent analgesic preparations are claimed to promote absorption (1), which is further assisted by phenothiazine or histamine antiemetics, or by metoclopramide — which also promotes gastric emptying and intestinal peristalsis (2–4).

Until recently, the ergot alkaloid, ergotamine, which is believed to act by constricting cranial arteries, offered the only widely-available alternative to analgesic therapy. It relieves headache in many patients, particularly when it is taken early in an attack. However, as is the case with the analgesics, metoclopramide may be needed to inhibit vomiting and promote absorption. Ergotamine has distinct limitations, however: it does not attenuate visual or other prodromal symptoms and, given too frequently, it can provoke headache. More serious is the risk of habituation and the danger of chronic overdosage. It should not be taken more frequently than twice a month and it should never be used for prophylaxis.

The introduction some five years ago of the 5-hydroxytryptamine agonist, sumatriptan, first in a parenteral formulation and subsequently in an oral preparation, aroused wide expectation of a substantial improvement in the management of migraine. The US Food and Drug Administration announced, when it registered parenteral sumatriptan succinate in 1993, that in clinical trials involving more than 1000 patients, approximately 82% improved within 2 hours of treatment, and 65% remained pain-free (5). It was already evident, however, that sumatriptan is not without risk: angiographic studies had shown that it induces coronary vasoconstriction and that this response is potentiated by ergot alkaloids (6).

A review of published controlled clinical studies of sumatriptan has since provided a less encouraging estimate of its efficacy: overall, it was estimated that no more than half to two-thirds of migrainous attacks are responsive (7). Large multicentre comparative studies have indicated that oral sumatriptan is significantly more effective than a com-

bination of ergotamine and caffeine (8), but that, in comparison with a combination of acetylsalicylic acid and metoclopramide, such superiority is evident only on the first occasion that it is used (9).

A further European multicentre comparative study has now been reported (10) in which the responses to three regimens — 100 mg oral sumatriptan; a combination of 10 mg metoclopramide and 1620 mg lysine acetylsalicylate (equivalent to 900 mg acetylsalicylic acid); and placebo — were compared in 428 patients who met international diagnostic criteria for migraine (11). The respective success rates for these regimens (estimated as the proportion of attacks in which headache was judged to have been reduced from severe to moderate or mild) were 53%, 57% and 24%.

The two active treatments were thus similarly effective. However, reported adverse effects were almost three fold more frequent among the patients taking sumatriptan. Among the latter, over 11% complained of nausea and vomiting compared with only 2% taking the acetylsalicylate combination product. Chest pain, which was reported by almost 5% of patients taking sumatriptan, was not associated with the other treatments.

The authors question whether it is still reasonable to regard sumatriptan — which typically costs some ten fold more than proprietary analgesic/antiemetic preparations — as a candidate drug for routine initial treatment of a migraine attack.

#### References

1. Volans, G. Absorption of effervescent aspirin during migraine. *British Medical Journal*, **4**: 265–269 (1974).
2. Volans, G. The effect of metoclopramide on the absorption of effervescent aspirin in migraine. *British Journal of Clinical Pharmacology*, **2**: 57–63 (1975).
3. Wilkinson, M. Treatment of the migraine attack — current status. *Cephalalgia*, **3**: 61–67 (1983).
4. Chabriat, H., Joire, J., Danchot, J. et al. Combined oral lysine acetylsalicylate and metoclopramide in the acute treatment of migraine: a multicentre double-blind placebo-controlled study. *Cephalalgia*, **14**: 297–300 (1994).
5. US Food and Drug Administration. *Medical Bulletin*, Vol. 23, March 1993.
6. UK Committee on Safety of Medicines. *Current Problems*, No. 34, June 1992.
7. Tfelt-Hansen, P. Sumatriptan for the treatment of migraine attacks — a review of controlled clinical trials. *Cephalalgia*, **13**: 238–244 (1993).
8. Multinational Oral Sumatriptan and Cafergot Comparative Study Group. A randomized, double-blind comparison of sumatriptan in the acute treatment of migraine. *European Neurology*, **31**: 314–322 (1991).
9. Oral Sumatriptan and Aspirin plus Metoclopramide Study Group. A study to compare oral sumatriptan with oral aspirin with oral metoclopramide in the acute treatment of migraine. *European Neurology*, **32**: 177–184 (1992).
10. Tfelt-Hansen, P., Henry, P., Mulder, L. et al. The effectiveness of combined oral lysine acetylsalicylate and metoclopramide compared with oral sumatriptan for migraine. *Lancet*, **346**: 923–926 (1995).
11. Headache Classification Committee of the International Headache Society. Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. *Cephalalgia*, **8** (suppl. 7): 1–96 (1988).