

Regulatory Matters

Deadly paediatric drugs: diethylene glycol again

Haiti — An Associated Press report widely featured in national newspapers on 4 July of this year implicates diethylene glycol, yet again, in the fatal poisoning of children.

The deaths of more than 50 pre-school children in Haiti from acute renal failure have been attributed to two locally-fabricated (and possibly counterfeit) liquid paediatric formulations of an antipyretic medicine. The Minister of Health is reported to have ordered the immediate destruction of all stocks of these products which are presumed to have been formulated with diethylene glycol, a highly toxic industrial solvent.

WHO has responded by sending dialysis equipment vital to the treatment of surviving children, and US nephrologists are on the ground assessing the situation and further investigating its causes.

Concerns have been expressed that the quality of locally manufactured pharmaceutical products is inadequately controlled. Deaths from renal failure of many previously healthy infants and children were first ascribed to use of diethylene glycol as a solvent in medicinal products in the United States in 1937. This resulted in legislation which set in place many of the basic tenets of drug regulation now enforced by the US Food and Drug Administration. In recent years, similar tragedies have been reported from Argentina, Bangladesh, India and Nigeria.

Until effective international initiatives are forthcoming — including the organization of a pool of technical support to advise small companies in less developed countries on the basic principles of quality assurance — further such catastrophes must be inevitable.

Albendazole: approved as a cysticidal agent

United States of America — The Food and Drug Administration has recently accorded "orphan drug" status to the anthelmintic drug, albendazole

(Albenza®: SmithKline Beecham), for treatment of neurocysticercosis and hydatid disease (1). The first of these diseases is acquired by ingestion of pork tape worm (*Taenia solium*) eggs in contaminated food or water. The second results from ingestion of eggs of one of two species of the *Echinococcus* tapeworm, which in North America is rarely harboured by dogs.

The agency estimates that, in patients with active neurocysticercosis, albendazole is active in 40 to 70% of cases, whereas it eliminates hydatid cysts in some 30% of patients and reduces their size in an additional 40%.

Impaired liver function, leukocytosis, and nausea/vomiting are cited as the most significant adverse systemic effects of albendazole. In patients with neurocysticercosis, oedematous inflammatory reactions are liable to induce headache, while abdominal pain is frequently reported by patients treated for hydatid disease.

The treatment of neurocysticercosis, which is highly prevalent in some developing countries, has been discussed *in extenso* in an earlier issue of this journal (2).

References

1. US Food and Drug Administration. *First treatment approved for rare parasitic infections*. Document T96-40, 13 June 1996.
2. *WHO Drug Information*, 9: 135-138 (1995).

Cancer therapies: accelerating the approval process

United States of America — Until now, the Food and Drug Administration has usually required evidence of improvement in survival time or quality of life before approving a proposed new cancer therapy. However, in order to accelerate access to promising new treatments, and after wide consultation with groups representative of patients, physicians, the pharmaceutical industry, and the research community, it has been decided that the following four initiatives will be adopted:

- approval time will be shortened by accepting evidence of tumour shrinkage as an early indicator of effectiveness;
- collaboration will be established with pharmaceutical companies to enable promising cancer therapies approved by other countries to be made available to cancer patients before the product is approved in the United States;
- all FDA advisory committees concerned with cancer therapy will now include an ad hoc member "who has personal experience with the illness for which a new product is being considered";
- administrative procedures will be changed to facilitate the investigation of new uses for cancer therapies already marketed in the United States.

These changes will not waive the responsibility of sponsoring companies to provide data relating to survival and quality of life after the product has been marketed. Approval may be withdrawn if postmarketing studies fail to demonstrate clinical benefit.

The possibility of extending such initiatives to therapies for patients with other serious and life-threatening conditions is under consideration.

Source: US Food and Drug Administration. *Cancer therapies: accelerating approval and expanding access.* Document BG 96-3. 29 March 1996.

Drug interactions predisposing to ventricular arrhythmias

United States of America/United Kingdom — Between 1990 and 1992, doctors in the United States (and subsequently in other countries) were alerted on several occasions to the finding that two non-sedating antihistamines, terfenadine (Seldane[®]; Hoechst Marion Roussel) and astemizole (Hismanal[®]; Janssen) could induce electrocardiographic changes, including prolongation of the QT interval, cardiac arrest, torsades de pointes and other ventricular arrhythmias when the maximum recommended drug plasma concentrations are exceeded (1-4). Blood concentrations of these drugs, it was noted, were greatly increased in individual patients who had concomitantly taken either a macrolide antibiotic (erythromycin or troleandomycin), or the imidazole systemic anti-

fungal agent, ketoconazole (3, 4). Doctors were advised to avoid prescribing these drugs to all patients taking non-sedating antihistamines.

Now, a similar warning has been issued in respect of cisapride (Prepulsid[®]; Janssen), a neuroleptic agent which is used primarily to reduce gastric stasis associated with diabetes and other causes of neuropathy of the autonomic system. When used alone, cisapride has not been associated with serious adverse effects. However, there is now evidence that, when imidazole antifungal drugs or macrolide antibiotics are taken concomitantly, plasma concentrations of cisapride rise and electrographic changes develop that predispose to ventricular arrhythmias (5).

A review of data relevant to cisapride has recently been provided by the UK Committee on Safety of Medicines (6). Some 25 cases of ventricular arrhythmia (of which two were fatal) have been reported worldwide in patients who have received antifungals or macrolide antibiotics while on cisapride. These cases, characterized by prolongation of the QT interval, torsades de pointes and/or ventricular fibrillation, have been associated with erythromycin (ten reports), fluconazole (nine), clarithromycin, (four), ketoconazole (two), itraconazole (two) and miconazole (one). In three instances individual patients received two of these drugs.

Most of these patients were also receiving other medicines and some had predisposing conditions including hypokalaemia. It is notable that the plasma concentration of cisapride was raised in three of four patients in whom it was measured, and that no reports of prolongation of the QT interval have been reported in patients taking cisapride alone.

The Committee has consequently recommended that:

- cisapride should not be co-administered with oral or parenteral formulations of the antifungals and antibiotics cited above.
- its use should be carefully considered in patients found to have a prolonged QT interval, whether this is related to a congenital syndrome or acquired as a result of electrolyte disturbances or other medication.
- the recommended maximum starting dose (40 mg daily) should not be exceeded.

In a broader context, these findings point to a need to review the possibility that other drugs extensively metabolized in the liver may interact adversely with imidazole antifungals and macrolide antibiotics.

More fundamentally, a study focused on terfenadine has recently illustrated the difficulty of ensuring that official messages regarding serious drug interactions are recalled and heeded by health professionals in the course of their routine duties (7). In the USA, starting in 1990, all practising doctors have received two letters alerting them to the problem, the product labelling has been revised to include a prominent warning, and case reports, warnings, commentaries, and clinical investigations have been reported in widely circulated journals. None the less, it is estimated that, during the first half of 1994, some 2–3% of several millions of persons in the USA who used terfenadine were likely to have taken either a macrolide antibiotic or an imidazole antifungal during this time (7).

References

1. Marion Merrell Dow Inc. *Important drug warning*. Cincinnati, Ohio, 6 August 1990.
2. Marion Merrell Dow Inc. *Important drug warning*. Kansas City, July 1992.
3. Nightingale, S. Warnings issued on non-sedating antihistamines terfenadine and astemizole. *Journal of the American Medical Association*, **268**: 705 (1992).
4. Safety of terfenadine and astemizole. *The Medical Letter*, **34**: 9–10 (1992).
5. Food and Drug Administration, *FDA Medical Bulletin*; 25 August 1995.
6. Committee on Safety of Medicines/Medicines Control Agency. *Current Problems in Pharmacovigilance*, Volume 22, March 1996.
7. Thompson, D., Oster, G. Use of terfenadine and contraindicated drugs. *Journal of the American Medical Association*, **275**: 1339–1341 (1996).

PCR test approved by FDA — but only to monitor progression of HIV infection

United States of America — The Food and Drug Administration has announced its first approval (1) of a polymerase chain reaction (PCR) test Amplicor HIV-1 Monitor Test[®]; Roche Diagnostic Systems

Inc.) for directly detecting proviral HIV-1 genetic material in peripheral blood mononuclear cells through a gene amplification technique (2).

Both the sensitivity and the selectivity of the test are considered to be high. Blood samples containing more than 800 copies of the target genetic material have been detected with 100% reliability in pre-marketing studies, and none of 495 samples from known HIV-1 negative donors tested false-positive.

At present, the test is approved only for predicting the risk of disease progression in HIV-infected patients. It is not labelled for use as a screening or confirmatory test for HIV infection. Two small clinical trials have indicated that if viral levels (as measured by the PCR DNA) are high prior to treatment, or if they increase by five-fold or more during the first eight weeks of therapy, the risk is high of further progression to AIDS, an AIDS-related infection, or death. Serial PCR tests undertaken on patients receiving combinations of antiretroviral drugs have demonstrated progressive reduction in the viral load but, as yet, these changes have not been related to clinical responses in drug therapy.

On grounds of cost alone, PCR tests are impractical to use for screening purposes. Prices charged for tests as yet unapproved for routine clinical use within the USA range from \$125 to \$200 (3). In contrast, most HIV serological screening tests — which detect antibodies to HIV and which have comparable sensitivity and specificity — cost as little as \$1 to \$2 to perform (4). Most of these latter tests are enzyme-linked immunosorbent assays (ELISAs) which require up to 3 hours to perform. Others, however, are simple agglutination and microdot assays which can be read within a few minutes, require little equipment, and are particularly appropriate for field testing in developing countries (5).

A particularly important potential application for PCR tests is in the early diagnosis of HIV infection in neonates and infants (3) since HIV serological tests are uninformative during the first year of life (6). As yet, however, the reliability of PCR tests in this setting remains uncertain. In some of the earlier published studies, unacceptable incidences of false-positive and false-negative results were reported (7, 8), and a recent multicentre quality control study suggests that low but clinically significant rates of false-positive and false-negative results continue to occur (9).

At present, within many clinical studies conducted in the USA, a working definition is used for the diagnosis of vertical HIV infection which requires that positive results be obtained from two separate blood samples, one by HIV culture (which is slow, labour intensive and expensive) and the other by culture, by PCR, or (in infants aged more than 4 weeks) by neutralizable plasma p24 antigen (9).

There is now a call to develop an alternative strategy, derived on evidence that approximately 30% to 50% of infected infants are positive at birth to PCR testing, and that most of the remainder become positive within seven days (10). The proposal is that infants at risk should be screened by PCR testing at birth and, as necessary, weekly thereafter during the first month of life, and that confirmatory testing be undertaken on those found positive (6). This strategy seeks to establish a diagnosis as rapidly as possible in order that antiviral therapy can be started at an early stage of viral replication and before opportunistic infections develop.

However, recent evaluations of sequential and combination test strategies suggest that PCR results during the first month of life are of value primarily if the test is negative (11), that a single PCR test is not sufficient to diagnose or exclude HIV infection, and that initial PCR results should be confirmed on samples drawn after a delay of a month or more (3). At present, it seems that although PCR is one of the most useful tests for diagnosis of HIV infection in neonates and infants, it is not definitive. A cautious reading of the situation is that PCR should be interpreted with the aid of careful follow-up examinations, preferably lasting until the HIV antibody status of the infant is resolved (3).

References

1. US Food and Drug Administration. *FDA approves new test to measure HIV levels in blood*. Document T96-38, 3 June 1996.
2. Guyer, R., Koshland, D. The molecule of the year. *Science*, **246**: 1543-1546 (1989).
3. Owens, D., Holodniy, M., McDonald, T. et al. A meta-analytic evaluation of the polymerase chain reaction for the diagnosis of HIV infection in infants. *Journal of the American Medical Association*, **275**: 1342-1348 (1996).
4. Van kerckhoven, Vercauteren, G., Piot, P., van der Groen, G. Comparative evaluation of 36 commercial assays for detecting antibodies to HIV. *Bulletin of the World Health Organization*, **69**: 753-760 (1991).
5. Spielberg, F., Ryder, R.W., Mulanga Kabeya, C. et al. Field testing and comparative evaluation of rapid, visually read screening assays for antibody to human immunodeficiency virus. *Lancet*, **1**: 580-584 (1989).
6. Luzuriaga, K., Sullivan, J. DNA polymerase chain reaction for the diagnosis of vertical HIV infection. *Journal of the American Medical Association*, **275**: 1360-1361 (1996).
7. Rogers, M., Ou, C., Ray field, M. et al. for the New York City Comparative Study of Maternal HIV Transmission and Montefiore Medical Center HIV Perinatal Transmission Study Groups. Use of the polymerase chain reaction for early detection of the proviral sequences of human immunodeficiency virus in infants born to seropositive mothers. *New England Journal of Medicine*, **320**: 1649-1654 (1989).
8. Eschaich, S., Wallon, M., Baginski, I. et al. Comparison of HIV detection by virus isolation in lymphocyte cultures and molecular amplification of HIV DNA and RNA by PCR in offspring of seropositive mothers. *Journal of the Acquired Immune Deficiency Syndrome*, **4**: 130-135 (1991).
9. Jackson, J., Drew, J., Lin, H. et al. Establishment of a quality assurance program for human immunodeficiency virus type 1 DNA polymerase chain reaction assays by the AIDS Clinical Trials Group, ACTG PCR Working Group, and the ACTG PCR Virology Laboratories. *Journal of Clinical Microbiology*, **31**: 3123-3128 (1993).
10. Bryson, Y., Luzuriaga, K., Sullivan, J. et al. Proposed definitions for *in utero* versus intrapartum transmission of HIV-1. *New England Journal of Medicine*, **327**: 1246-1247 (1992).
11. Paul, M., Tetali, S., Lesser, M. et al. Laboratory diagnosis of infection status in infants perinatally exposed to human immunodeficiency virus type 1. *Journal of Infectious Diseases*, **173**: 68-76 (1996).

Irinotecan provisionally released for metastatic colonic cancer

United States of America — The Food and Drug Administration has granted accelerated release to irinotecan (Camptosar®; Pharmacia/Upjohn) for the treatment of metastatic colonic or rectal cancer that has recurred or progressed after standard fluorouracil-based chemotherapy.

Irinotecan is the first of a new class of antimetabolites called camptothecins, which specifically inhibit the cellular enzyme topoisomerase-I. In open phase II studies infusion of the drug reduced tumour size in 39 of 304 patients for an average duration of six

months. Unwanted effects included leukopenia and diarrhoea — which was sometimes prolonged and severe and, in some cases, required supportive medical treatment.

The FDA notes, in taking this decision, that colorectal cancer is diagnosed in 134 000 people in the United States each year, and that in 50% of these patients the disease recurs after primary treatment with surgery, adjuvant chemotherapy or radiotherapy. At present, there is little that can be offered to help these patients.

This decision has been taken on the advice of FDA's Oncology Drugs Advisory Committee, which has provided advice on additional studies that should be conducted to evaluate further the safety and effectiveness of irinotecan.

Source: Food and Drug Administration. *FDA approves drug for advanced colorectal cancer.* Document T96-42, 17 June 1996.

Vasopressin for enuresis: danger of hyponatraemic convulsions

United Kingdom — The Committee on Safety of Medicines has advised that, since 1987, it has received 24 reports of hyponatraemic convulsions among patients (21 children and 3 adults) using an intranasal spray of vasopressin to control primary nocturnal enuresis (1).

Since symptomatic hyponatraemia can have dangerous consequences (2), the Committee emphasizes the need to take effective preventive measures, which should include:

- avoiding taking tricyclic antidepressants and other drugs which may increase the secretion of endogenous vasopressin;
- keeping to the recommended starting dose of 10 micrograms vasopressin in each nostril;
- warning patients to avoid excessive fluid intake;
- stopping treatment temporarily during illnesses that cause vomiting or diarrhoea to allow restitution of normal fluid and electrolyte balance.

References

1. Committee on Safety of Medicines/Medicines Control Agency. *Current Problems in Pharmacovigilance*, Volume 22, March 1966.
2. Arief, A., Ayus, J.C., Fraser, C.L. Hyponatraemia and death or permanent brain damage in healthy children. *British Medical Journal*, **304**: 1218–1222 (1992).