

Regulatory Matters

Measles/rubella vaccine: a favourable balance of risk and benefit

United Kingdom — To prevent an anticipated epidemic of measles, 8 million children aged 5 to 16 years were immunized with measles/rubella vaccine in the United Kingdom during the last months of 1994. Doctors were asked specifically to report all suspected adverse reactions. Some 1200 notifications, which described a total of 2735 events, were received in response to this appeal. These events were not necessarily causally-related to vaccination, and many were minor and self-limiting. At most, the risk of a vaccine-related adverse event was estimated to be 1:6700 (1).

Most frequent among these events were skin rashes, general symptoms including dizziness and malaise, and neurological signs. In all, 530 events were judged to be serious (0.007%). None of these was fatal, and in the few instances in which recovery was incomplete, there was no conclusive evidence of a causal association with vaccination.

Among 91 neurological events, were 11 cases of encephalitis, of which 6 were diagnosed definitively. This number of cases was within the background frequency estimated from epidemiological studies. The one child who was left with a residual neurological deficit had no antibody response to the vaccine, presumably because of pre-existing immunity, and a causal relationship was considered unlikely.

Convulsions that occurred within one hour of immunization were reported in 29 children and were mostly associated with syncope. Convulsions were reported after much longer intervals in 19 children with no previous history of epilepsy or other neurological disease. These were thought to be largely unrelated to vaccination since this number of cases was within the presumed background frequency, as were 3 cases of Guillain-Barré syndrome, and 5 cases of optic neuritis.

Six children were reported to have developed arthritis, all of whom recovered. Self-limiting arthritis

has previously been associated with rubella immunization in adolescents and adults (2), but this reported rate (1 in 300 000) indicates that the reaction is very rare in children of school age.

Signs of anaphylaxis or allergic reactions within 24 hours of vaccination were recorded in 123 children (1 in 65 000), all of whom recovered. However, there were also nine reports of erythema multiforme (1 in 900 000). The illness was protracted in one child but none developed Stevens-Johnson syndrome.

The Committee concludes that the balance of risks and benefits associated with measles/rubella vaccination in children of school age is highly favourable, even allowing for pre-existing immunity against measles in many children. Had the anticipated epidemic occurred, it was likely to have resulted in some 150 000 cases of measles, of which about 50 would probably have been fatal.

References

1. Committee on Safety of Medicines/Medicines Control Agency. Adverse reactions to measles/rubella vaccine. *Current Problems in Pharmacovigilance*, Volume 21, November 1995.
2. Weibel, R., Stokes, J. Buynak, E. et al. Influence of age on clinical response to HPV-77 duck rubella vaccine. *Journal of the American Medical Association*, **222**: 805-807 (1972).

Pancreatic enzyme supplements and fibrosing colonopathy

United Kingdom — Over a period of 14 months in 1993/94 the Committee on Safety of Medicines received 13 reports of large bowel strictures in children with cystic fibrosis aged 2 to 13 years who were receiving high-strength pancreatic enzyme supplements (1). In nearly all cases fibrotic strictures affected the ascending colon, and in some cases the lesion extended continuously from the ileo-caecal valve to the transverse colon. The condition, which is distinct from any intestinal pathology previously associated with cystic fibrosis, is now known as fibrosing colonopathy.

In order to obtain a comprehensive overview of the epidemiology of the condition within the UK, a case-control study was carried out using a national disease register (2). This identified a total of 7600 patients with cystic fibrosis who had been treated between 1984 and 1994. Of these, 14 patients (including the 13 previously notified) met the diagnostic criteria for fibrosing colonopathy. For each of these cases four patients with cystic fibrosis were selected from the registry as controls.

The first case of fibrosing colonopathy presented in 1992, about one year following the introduction in the UK of the first high-strength pancreatic preparation. High-strength (but not standard strength) preparations were strongly associated with the condition. Moreover, the mean daily intake of enzyme was 46 200 (range 15 250 – 84 560) lipase units/kg among the cases, compared with 21 500 (range 0 – 85 870) among the controls.

Most cases occurred in children aged between 2 and 8 years, and boys appeared to be more vulnerable than girls. Patients with more severe disease and those who were also using laxatives were shown to be at increased risk.

More recently, the condition has been diagnosed in two children aged 9 months and 2 years (3, 4). Both had received standard strength pancreatic enzyme preparations, but at doses in excess of 40 000 lipase units/kg daily. To accommodate these findings, two possibilities have been raised. Firstly, it has been suggested that if oro-caecal transit time is shortened, the contents of enteric-coated tablets may be released in the colon rather than in the small intestine (3). Secondly, it has been noted that no association has been documented between fibrosing colonopathy and one widely used high-strength supplement (Creon 25 000) (4). Moreover, it has been found that other high-strength supplements (but not Creon 25 000) all contain a methacrylic acid co-polymer in the enteric coating that could contain a monomer contaminant, ethyl acrylate, which is a potent gastro-intestinal irritant in laboratory animals (5).

At present, however, these suggestions are no more than speculative. Based on the evidence currently available, the Committee on Safety of Medicines has issued the following recommendations:

- The following brands of high-dose pancreatic enzyme — Pancrease HL, Nutrizym 22, and

Panzytrat 25 000 — should not be used in children with cystic fibrosis aged 15 years or less. (Creon 25 000 has thus far not been associated with fibrosing colonopathy).

- The total dose of supplementary pancreatic enzyme in these patients should not exceed 10 000 lipase units/kg daily.
- Any patient receiving a pancreatin preparation who complains of new or changed abdominal symptoms should be reviewed to exclude the possibility of colonic pathology.

References

1. *WHO Drug Information*, 9(1): 30 (1995).
2. Smythe, R., van Velsen, D., Smyth, A. et al. Strictures of ascending colon in cystic fibrosis and high-strength pancreatic enzymes. *Lancet*, 343: 85–86 (1994).
3. Jones, R., Franklin, K., Spicer, R., Berry, J. Colonic strictures in children with cystic fibrosis on low-strength pancreatic enzymes. *Lancet*, 346: 499 (1995).
4. van Velsen, D. Colonic strictures in children with cystic fibrosis on low-strength pancreatic enzymes. *Lancet*, 346: 499–500 (1995).
5. European Centre for Ecotoxicology and Toxicology of Chemicals. Joint assessment of commodity chemicals, No. 28: ethyl acrylate, CAS No 140–88–5. Brussels, September 1994.

Paracetamol overdose

United Kingdom — The Committee on Safety of Medicines has issued a statement to emphasize that, although paracetamol is a safe and effective analgesic at recommended doses, it has become the most frequently used medicine in self-poisoning.

Unintentional overdose has also occurred as a result of persons taking two or more preparations containing paracetamol at the same time. Doctors and pharmacists are consequently asked to warn patients, when they advise them about home medicines, to avoid taking more than one preparation containing paracetamol by carefully checking the label.

Wherever there is a possibility that a person prone to suicidal gestures might gain access to a medicine, it is suggested that a preparation containing a combination of paracetamol and methio-

nine should be chosen. Paracetamol overdose may be rapidly fatal unless promptly treated with methionine or N-acetylcysteine.

Source: Committee on Safety of Medicines/Medicines Control Agency. Paracetamol toxicity in overdosage. *Current Problems in Pharmacovigilance*, Vol. 21. November 1995.

Chlorzoxazone: strengthened warning on hepatotoxicity

United States of America — The Food and Drug Administration has announced (1) that the current warning regarding hepatotoxicity in the labelling for products containing chlorzoxazone has been strengthened to read as follows:

“Serious (including fatal) hepatocellular toxicity has rarely been reported in patients receiving chlorzoxazone. The mechanism is unknown but appears to be idiosyncratic and unpredictable. Factors predisposing patients to this rare event are not known. Patients should be instructed to report early signs and/or symptoms of hepatotoxicity such as fever, rash, anorexia, nausea, vomiting, fatigue, right upper quadrant pain, dark urine, or jaundice. Chlorzoxazone should be discontinued immediately and a physician consulted if any of these signs or symptoms develop. Chlorzoxazone use should also be discontinued if a patient develops abnormal liver enzymes (such as AST, ALT, alkaline phosphatase, and bilirubin). The concomitant use of alcohol or other central nervous system depressants may have an additive effect.”

Chlorzoxazole, a benzoxazole-derivative, is a centrally-acting skeletal muscle relaxant. It is a metabolite of zoxazolamine which is no longer commercially available because of its hepatotoxicity. It is used as an adjunct to analgesics and other conditions associated with acute, painful musculoskeletal conditions.

Source: From the Food and Drug Administration: chlorzoxazone warning on hepatotoxicity is strengthened. *Journal of the American Medical Association*, 274: 1903 (1995).

Information for institutional review boards and clinical investigators

United States of America — The Food and Drug Administration has published a new set of information sheets to assist institutional review boards and

clinical investigators in carrying out their responsibilities to protect the safety and welfare of human subjects involved in biomedical research. The sheets, which were last revised in 1989, are available on the FDA home page on the Internet World Wide Web (<http://www.fda.gov>).

The publication includes answers to questions that the FDA frequently receives regarding its regulations on institutional review boards and informed consent procedures. It emphasizes that institutional review boards, clinical investigators, contract research organizations and animal laboratories are each subject to on-site inspections by the FDA with a view to ensuring both the safety of human subjects and the quality and integrity of data submitted to the agency. It explains the procedures followed during such inspections and possible sanctions that can result from failure to satisfy mandatory responsibilities.

Annexed to the revised sheets are essential resource materials including relevant FDA regulations; a self-evaluation checklist for institutional review boards to use when considering studies of FDA-regulated drugs; and the full text of the Belmont Report on the conduct of research involving human subjects.

Source: From the Food and Drug Administration. *Journal of the American Medical Association*, 274: 1903 (1995).

FDA on the Internet

United States of America — Latest press releases, enforcement reports, summaries of relevant *Federal Register* notices and other information from the Food and Drug Administration are now available on the Internet's World Wide Web (<http://www.fda.gov>). The FDA's electronic bulletin board, which provided on-line information for more than a decade, was phased out at the end of 1995.

WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce

WHO is required to publish, for the convenience of national drug regulatory authorities and pharmaceutical manufacturers, updates of lists of competent national authorities. The following updates information contained in WHO/PHARM/82.4 Rev 4

(February 1994) "Certification Scheme on the quality of pharmaceutical products moving in international commerce". Copies of this document may be obtained on request from the Division of Drug Management & Policies, WHO, 1211 Geneva 27, Switzerland.

In order to assist in the revision of the list of competent authorities, we should appreciate receiving information about relevant changes of telephone and facsimile numbers from drug regulatory authorities.

Notified changes in addresses of competent authorities of participating countries:

Algeria

Direction de la Pharmacie
Ministère de la Santé et de la Population
125, Boulevard Laala Abderrahmane
El-Madania, 16000 Alger

Belgium

Service de l'Inspection générale de la Pharmacie
Ministère de la Santé publique et de la Famille
Cité administrative de l'Etat
Quartier Vésale, 1010 Bruxelles
Tel: 0032 2 2104918 Fax: 0032 2 2104922

Chad

La Direction des Pharmacies
Ministère de la Santé Publique
Direction des Pharmacies
B.P. 440, N'djamena
Tel: 00235 51 55 87, Fax: 00235 51 51

Denmark

The National Board of Health
Medicines Division
378 Frederikssundsvej
2700 Bronshøj
Tel: 0045 44 889314 Fax: 0045 42 847077

France

Agence du Médicament
143/147 Boulevard Anatole France
93285 Saint Denis Cedex
Tel: 0033 1 48 13 20 20 Fax: 0033 1 48 13 20 97

Kuwait

Drug Control and Registration Centre
Ministry of Public Health
P.O. Box 4575, 13046 Safat
Tel: 00965 4831038 Fax: 00965 4811267

Lao People's Democratic Republic

Le Directeur
Direction de l'Alimentation et de la Pharmacie
Ministère de la Santé
Vientiane

Malta

Department of Health
15 Merchants Street
Valletta VLT 03
Tel: 00356 224071 Fax: 00356 242884

Mongolia

Council of Drugs and Biopreparations
Ministry of Health
Karl Marx Street 2, Ulaanbaatar 11
Tel: 00976 1 320 916 Fax: 00976 1 321 278

Namibia, Republic of

Medicines Control Council
Ministry of Health and Social Services
P.B. 13366, Windhoek
Tel: 264 61 2032861/2032865 Fax: 264 61 2032988

The Netherlands

Chief Inspector for Pharmacy and Medical Technology
Public Health Supervisory Service of the Netherlands
The Inspectorate of Health Care
Sir W. Churchillaan 362
P.O. Box 5850, 2280 HW Rijswijk
Tel: 0031 70 3406169 Fax: 0031 70 3407159

New Zealand

Therapeutics Section
Department of Health
P.O. Box 5013, Wellington
Tel: 0064 4 496 2088 Fax: 0064 4 496 2340

Oman, Sultanate of

Directorate General of Pharmaceutical Affairs
and Drug Control
Ministry of Health
P.O. Box 393, 113, Muscat
Tel: 00968 602177 Fax: 00968 602287/604684

Peru

Dirección General de Medicamentos,
Insumos y Drogas del Ministerio de Salud
Av. Arenales 1302 08 318, Lima, 11
Tel: 0051 14 713801/716353 Fax: 0051 14 725028

Philippines

Bureau of Food and Drugs
Alabang 1702, Muntinlupa, Metro Manila
Tel: 0063 2 842 45 83 Fax: 0063 2 842 46 03

Portugal

INFARMED
Parque da Saude de Lisboa
Avenida do Brasil, 53, 1700 Lisbon
Tel: 00351 1 7908500 Fax: 00351 1 7959116

Singapore

The Drug Administration Division
Pharmaceutical Department
Ministry of Health
2 Jalan Bukit Merah
Singapore 0316
Tel: 0065 3209121 Fax: 0065 2242352