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## Adverse reactions to Measles Rubella vaccine

*Serious adverse reactions are very rare.*

During late 1994, 8 million children aged 5 to 16 were immunised with measles rubella (MR) vaccine in order to prevent an expected measles epidemic<sup>1</sup>. The campaign received wide publicity and the Chief Medical Officers stressed to doctors the importance of reporting all suspected adverse reactions (ADRs). By the end of October 1995 we had received 1,202 reports from across the UK describing 2,735 suspected adverse reactions. A report of a suspected reaction does not necessarily mean it was caused by the vaccine. The estimated reporting frequency of suspected ADRs to MR vaccine was 1 per 6,700 children immunised and the ADRs reported are summarised in Figure 1. The most common were those affecting the skin, symptoms and signs such as dizziness and malaise, and neurological reactions.

Most reactions were minor and self-limiting. Five hundred and thirty children had a serious reaction (0.007%), none of which had a fatal outcome. Most children recovered completely, for those who did not there was no conclusive evidence to support a causal association with the vaccine.

There were 91 reports of serious neurological reactions. The reporting rates for these reactions are shown in Table 1. Of the 11 children reported with encephalitis, a definite diagnosis was made in only six. One boy with a residual hemiparesis had no change in antibody titres, suggesting he was already immune and it was unlikely that his condition had been caused by the vaccine viruses. The other 10 children recovered completely. No child had an identified cause for encephalitis. The number of reports of encephalitis is less than the background frequency estimated from epidemiological studies.

Figure 1: Proportion of 2,735 ADRs reported to MR vaccine categorised by body system affected

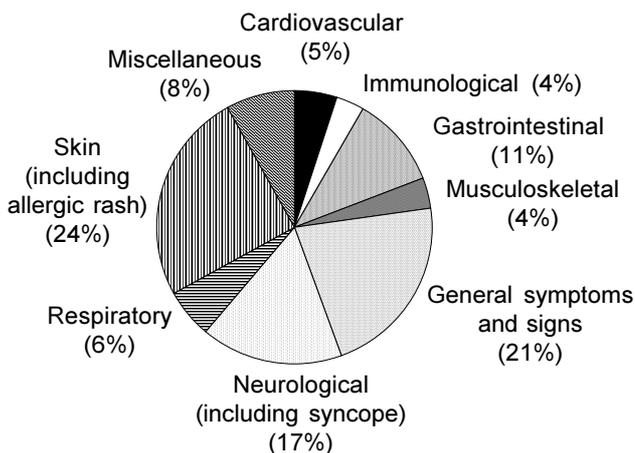


Table 1: Reporting rates for serious neurological reactions suspected to be due to MR vaccine

Serious reactions	Number of reports	Reporting rate
Encephalitis	11	1 in 730,000
Subacute Sclerosing Panencephalitis (SSPE)	1	1 in 8,000,000
Convulsions (within first hour of immunisation)	30	1 in 265,000
Convulsions (1 hour)	34	1 in 235,000
Optic neuritis	5	1 in 1,600,000
Guillain-Barré syndrome	3	1 in 2,500,000
Facial palsy	7	1 in 1,000,000
Miscellaneous neuropathies	3	-

One child with sub-acute sclerosing panencephalitis (SSPE) developed symptoms one month after

immunisation. The usual incubation period for SSPE is much longer and in this case there was a history of wild measles infection some years earlier, it is therefore most unlikely that the vaccine was responsible.

One child developed typical Guillain-Barré syndrome (GBS) which was probably associated with a respiratory infection present at the same time as immunisation. A second child had a rarer sensory form of GBS. The third case of GBS was incompletely documented. On the basis of UK epidemiological studies, between 1 and 7 cases of GBS would be expected to occur each month in this population in the absence of immunisation. The number of reported cases is therefore consistent with the background frequency of the disease.

Of the 29 reports of convulsions occurring within one hour of immunisation, most appeared to be associated with syncope. Thirty-two children had convulsions more than one hour after vaccination, 13 of whom had a past history of neurological disease, febrile convulsions or were known epileptics. Epidemiological data from the UK suggest that, on average, 35 new cases of epilepsy per million children over the age of 10 occur each month<sup>2</sup>. The reported rate of convulsions after MR vaccine was unexpectedly low compared to previous experience. This probably reflects the older age group that was immunised, with a lesser risk of febrile convulsions compared to children under the age of 5. The risk of MR vaccine causing convulsions and, in particular epilepsy, appears to be very low in the age group 5 to 16.

Two of the five children reported with optic neuritis had features suggesting multiple sclerosis. Facial palsy is not rare in children<sup>3</sup> and epidemiological data suggest that the numbers of reports for both these conditions are consistent with the expected background frequencies.

One hundred and twenty-three reports were identified which described symptoms and signs of anaphylaxis or allergic reactions occurring within 24 hours of vaccination. The estimated reporting rate for these reactions was 1 in 65,000. All the children recovered.

Six children were reported to have developed arthritis, all of whom recovered. Self-limiting arthritis is a recognised reaction to rubella immunisation in adolescents and adults<sup>4</sup>. The low reporting rate (1 in 1,300,000) suggests this reaction is very rare in children aged 5 to 16 given MR vaccine.

There were nine reports of erythema multiforme (reporting rate 1 in 900,000). Although one child had a protracted illness, no child developed Stevens-

Johnson syndrome. Epidemiological studies suggest between 1 and 4 cases per month would have occurred despite the campaign with MR vaccine<sup>5</sup>.

## CONCLUSIONS

The immunisation campaign successfully prevented an expected epidemic of measles during which it was predicted there would be around 150,000 cases of measles, 50 with a fatal outcome<sup>1</sup>. On the basis of spontaneous reporting, 1,202 children experienced a possible ADR, most of which were self-limiting. Serious suspected reactions were very rare and there were no fatalities. Even allowing for pre-existing immunity against measles in many children, the balance of risks and benefits associated with MR vaccine is highly favourable.

1. Department of Health. CMO's Update 1995; 8: 1.
2. Brown S. et. al. Seizure 1993; 2: 91-103.
3. Hauser WA. et. al. Mayo Clin Proc 1971; 46: 258-263.
4. Weibel RE. et. al. JAMA 1972; 222: 805-807.
5. Chan HZ. et. al. Arch Dermatol 1990; 126: 43-47.

A report on the background to the campaign, its implementation and impact is available from Dr David Salisbury, room 707, Wellington House, 133-155 Waterloo Road, London SE1 8UG.

## Reminder: Paracetamol toxicity in overdose



- Paracetamol is a safe and effective analgesic at the recommended doses but is now the most frequently used medicine in self-poisoning.
- A large paracetamol overdose may be fatal unless treated promptly with N-acetylcysteine or methionine.
- Unintentional overdose can occur if a patient takes several paracetamol preparations at the same time. A list of paracetamol-containing preparations on sale to the public is contained in section 4.7.1 of the *British National Formulary* and in the *OTC Directory*.
- When advising patients about self-medication, doctors and pharmacists should warn patients to check the label and avoid taking more than one preparation containing paracetamol.
- Those who use paracetamol and live with individuals prone to suicidal gestures should avoid keeping stocks of more than 25 tablets (12.5g) or 10 sachets. A paracetamol-methionine combination such as Pameton may be preferred in these circumstances.

# Fibrosing colonopathy associated with pancreatic enzymes

## *Dose-related strictures in children with cystic fibrosis.*

Between October 1993 and November 1994, 13 children with cystic fibrosis who were receiving high-strength pancreatic enzyme supplements were reported to have developed large bowel strictures<sup>1</sup>. The children were aged between 2 and 13 years and all required surgical excision of their lesions. The pathology of the resected specimens did not resemble any gastrointestinal pathology previously known to occur in cystic fibrosis. This new disease entity, identified by specific histological criteria, has been named fibrosing colonopathy.

A case-control study in the UK cystic fibrosis population was performed to investigate this novel adverse drug reaction<sup>2</sup>. Using a national disease registry, a cohort of 7,600 patients from centres treating cystic fibrosis was identified. This cohort consisted of almost the entire UK population of patients treated between 1984 and 1994. Using the histological criteria 14 cases of fibrosing colonopathy were identified. All but one had previously been reported to us. For each case 4 patients with cystic fibrosis matched for age were selected from the registry as controls.

It is striking that no case of fibrosing colonopathy was identified before 1993, the first high-strength pancreatic enzyme preparation having been introduced to the UK in April 1992. Use of high-strength, but not standard-strength, pancreatic enzymes in the two years prior to surgery was strongly associated with the development of this condition. Moreover, patients with fibrosing colonopathy were taking almost twice as many capsules (mean 35 capsules daily) as the controls. The average daily enzyme intake for cases was 46,200 (range 15,250 - 84,560) units of lipase per kg body weight compared to 21,500 (range 0 - 85,870) for the controls.

The data indicate that Nutrizym 22 and Pancrease HL were associated with the development of fibrosing colonopathy, whereas Creon 25,000 was not. There was only minimal use of Panzytrat 25,000 in the UK during the study period, although patients with cystic fibrosis in Denmark treated with an identical preparation have developed colitis and extensive colonic damage<sup>3</sup>.

Other risk factors in the development of fibrosing colonopathy identified by the study were gender (boys at greater risk than girls), more severe cystic

fibrosis and concomitant use of laxatives. The peak age was between 2 and 8 years.

Within the last few months there have been reports of two children (aged nine months and two years) with cystic fibrosis who have developed fibrosing colonopathy after being treated with a standard-strength pancreatic enzyme preparation, Nutrizym GR<sup>4,5</sup>. Both children had taken doses of pancreatic enzymes in excess of 40,000 units of lipase per kg body weight per day.

To review all the new evidence on this issue the Committee established a Working Party. Based on their findings, we currently recommend the following:

- Pancrease HL, Nutrizym 22 and Panzytrat 25,000 should not be used in children aged 15 years or less with cystic fibrosis.
- The total dose of pancreatic enzyme supplements used in patients with cystic fibrosis should not usually exceed 10,000 units of lipase per kg body weight per day.
- If a patient on any pancreatin preparation develops abdominal symptoms that are new to the patient or any change in existing abdominal symptoms, they should be reviewed to exclude the possibility of colonic damage.

Copies of the Pancreatic Enzymes Working Party report can be obtained from Dr Jill Steen, Medicines Control Agency, Market Towers, Room 1013, 1 Nine Elms Lane, London SW8 5NQ.

1. MCA/CSM Current Problems in Pharmacovigilance Vol 20: November 1994.
2. Smyth RL. et al. Lancet 1995; 346: 1247-1251.
3. Knabe N. et al. Lancet 1994; 343: 1230.
4. Jones R. et al. Lancet 1995; 346: 499.
5. van Velzen D. Lancet 1995; 346: 499-500.

## Summary of product characteristics (SPC)

Summaries of product characteristics (SPC) are gradually replacing product data sheets prepared by pharmaceutical companies and authorised by the Medicines Control Agency. For health professionals in the UK the difference will not be great: SPCs will contain much the same information as data sheets, but under different headings and in a different order. Newer medicines already have SPCs and these will be introduced over the next 5 years for other products and will progressively replace data sheets in the Data Sheet Compendium.

# Drugs and driving

*In some patients side-effects may impair driving: patients need to be warned.*

Certain drugs impair the ability of a patient to drive or operate machinery. This is well-recognised for anxiolytics but may also occur with various other medicines (see Table). Case-control studies of road traffic accidents have found that patients taking minor tranquillisers are 2 to 5 times more likely to have an accident than untreated controls<sup>1,2</sup>. A cohort study of drivers aged 65 or more found benzodiazepines and tricyclic antidepressants to be associated with dose-related increased risks. The risk of an accident was more than doubled in patients taking 20mg diazepam daily or its equivalent, and was 5-fold greater in patients taking 125mg amitriptyline daily<sup>3</sup>.

Drug-related effects which may interfere with driving  
**Table: Drugs which may impair driving**

Class of drug	Therapeutic group	Effect impairing driving
CNS*	Antidepressants	Drowsiness
	Opioid analgesics	Drowsiness
	Antipsychotics	Drowsiness
	Appetite suppressants	Drowsiness
	Benzodiazepines	Drowsiness
Anti-allergy	Antihistamines	Drowsiness (less common with newer agents)
Topical eye drops	Antibiotics Mydriatic agents	Blurred vision
Cardiovascular	Antihypertensives	Postural hypotension
Others	Insulins	Hypoglycaemia
	Oral anti-diabetic drugs	

\* Restrictions on driving in patients with epilepsy are shown in the BNF, Section 4.8.1 and in a booklet entitled *Medical aspects of fitness to drive*<sup>4</sup> available from: Health Publications Unit, Heywood Store, Manchester Road, Heywood, Lancashire OL10 2PX.

include drowsiness, blurred vision, impaired motor co-ordination, postural hypotension, fatigue and hypoglycaemia. Early stages of treatment may be associated with greater risk. The effects of many drugs with central actions are potentiated by alcohol.

Patients should be warned whenever their treatment could alter their ability to drive and, if affected, should be advised not to drive or operate machinery. The

British National Formulary, Appendix 9, includes all the drugs for which label warnings should be given.

1. MacPherson RD. et al. *Accid Anal Prev* 1984; 2: 139-148.
2. Skegg DCG. et al. *Brit Med J* 1979; 1: 917-919.
3. Ray W. et al. *Am J Epidemiol* 1992; 136: 873-883.
4. The Medical Commission on Accident Prevention 1995; 5th Edn.

## Medicines newly available for self-medication



In July 1995 the following medicinal substances were released for use without prescription:

**Fluconazole (oral)** for the treatment of vaginal candidiasis in adults between 16 and 60 years of age (maximum dose 150mg, maximum pack size 150mg).

**Hydroxyzine Hydrochloride (topical use)** for the management of pruritus associated with acute or chronic urticaria, atopic dermatitis or contact dermatitis in patients aged 6 years or over (maximum dose 25mg; maximum daily dose 75mg in adults, 50mg in children 6-12 years; maximum pack size 750mg).

**Ketoconazole (shampoo for topical use not more than once every three days)** for the prevention and treatment of dandruff and seborrheic dermatitis of the scalp (maximum strength 2%, maximum pack size 120ml, containing no more than 2400mg of ketoconazole).

**Pyrantel Embonate** for the treatment of threadworm (enterobiasis) in adults and children aged 2 years and over (maximum daily dose 750mg in adults, 500mg in children 6-12 years; 250mg in children 2-5 years; maximum pack size 750mg).

**Serious adverse reactions which are associated with any self-administered 'over-the-counter' medicine should be reported to us in the usual way.**

**Current Problems in Pharmacovigilance** is produced by the Committee on Safety of Medicines and the Medicines Control Agency.

**Editorial Board:** Professor M. D. Rawlins, Professor M. J. S. Langman, Dr S. M. Wood, Dr P. C. Waller and Dr M. L. A. Crawford (Secretary).

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**Doctors and dentists should notify a change of address** by writing to the Medical Direct Mail Organisation Ltd, Hazleton Industrial Park, Lakesmere Road, Horndean, Waterlooville, Hampshire PO8 9JU, or by dialling the hotline number 01705 571345. Addresses supplied in connection with mailings on behalf of CSM and MCA will not be used for other mailings without the permission of the doctor concerned. **Pharmacists in Great Britain and Northern Ireland** do not need to communicate a change of address provided that this has already been notified to the Pharmaceutical Society with whom they are registered.