

Reports on Individual Drugs

Rotavirus vaccine nearing registration

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Rotavirus is responsible for more diarrhoeal disease than any other single agent. Most of the resulting 600 000 deaths each year are in the developing world, but rotavirus is a significant pathogen also in developed countries. Rotavirus diarrhoea is highly contagious and cannot be controlled by hygienic measures. This is a reason why rotavirus vaccination is attractive for both developed and developing countries. After fifteen years of studies, rotavirus vaccines are finally approaching registration status and may soon be considered for inclusion in the immunization programmes of many countries.

Rotavirus vaccination began by empirical use of the tissue-culture adapted bovine rotavirus strain RIT4237 in oral form. Studies in gnotobiotic piglets first showed cross-protection between bovine and human rotaviruses (1) and, thereafter, the vaccine was found safe, immunogenic, and efficacious during trials in human infants (2–3). In Finland, the RIT4237 vaccine induced 50–58% protection against any rotavirus gastroenteritis, and 82–88% protection against clinically significant forms (4). Thus, a high level of protection against severe rotavirus disease, moderate protection against mild disease, and no protection against rotavirus infection as such were seen. These findings have been consistent in most studies of oral rotavirus vaccines.

Despite the initial success in Finland, the RIT4237 vaccine was withdrawn. A report of a small study in Rwanda (5), and a preliminary analysis of a trial in Lima, Peru, indicated little or no protection and this led to the premature conclusion that the vaccine had failed in developing countries. Subsequently, a full analysis of the Peruvian trial showed protective efficacy of 40% against any rotavirus disease, and 58–75% against severe forms (6) — which was in

fact only slightly less than in Finland. Another bovine rotavirus vaccine strain, WC3, showed a promising 76% protective efficacy in the United States (7), but was withdrawn because of unsatisfactory efficacy (17%) in another US trial (8) and virtually no efficacy when administered in the Central African Republic (9).

A bovine-human reassortant rotavirus vaccine based on the WC3 strain has been developed more recently. This quadrivalent vaccine contains reassortant rotaviruses expressing human rotavirus surface proteins VP7 (G types) G1, G2 and G4, and VP4 (P type) protein P[8] and has demonstrated 67% protection against all rotavirus disease in one trial (10). The number of subjects studied so far is, however, insufficient to come to any firm conclusions. A major advantage of the previous bovine rotavirus vaccines, as well as this reassortant vaccine, is their lack of reactogenicity.

Rhesus rotavirus (RRV) vaccine is more immunogenic than the bovine rotaviruses in humans (11). The vaccine titre is 10^4 – 10^5 per ml, as compared with 10^7 (WC3) or 10^8 (RIT4237) for the bovine rotavirus vaccines. RRV vaccine relies on virus multiplication to produce a sufficient amount of viral antigens for induction of an immune response and, as a result, causes febrile reactions (but no diarrhoea) at 3 to 4 days post-vaccination (12). The reactions are more frequent and severe in children who lack maternally acquired antibody, and are more commonly observed in developed countries where infants are less likely to receive rotavirus antibodies from the mother than in developing countries. High titre RRV vaccine was, in fact, efficacious in a study in Sweden, but caused a high rate of reactions in 5–12-month-old children (13); in other studies there has been a great variation in efficacy (14–17).

RRV was further improved by development of the rhesus-human reassortant rotaviruses (18), which contain 10 RNA segments from the rhesus rotavirus and one, encoding for the VP7 (G-type) surface protein, from human rotaviruses corresponding to the G-types 1, 2 or 4. Rhesus rotavirus itself is close to the human G-type 3 rotavirus (18). A mixture of the four viruses is named the rhesus rotavirus tetravalent (RRV-TV) vaccine.

The performance of RRV-TV vaccine in clinical trials has been consistent. In a multicentre trial in the USA, RRV-TV vaccine at titre level 4×10^4 PFU showed a 57% protective efficacy against any rotavirus diarrhoea, and up to 92% protection against severe forms (19). In order to further improve vaccine efficacy a higher titre (4×10^5 PFU) RRV-TV vaccine was produced. In the USA, this high titre vaccine yielded a 49% efficacy for any rotavirus diarrhoea and 100% efficacy for dehydrating forms (20). In a recently completed trial in Finland, the high titre vaccine was 100% protective against hospitalization for rotavirus gastroenteritis*. In a large catchment trial in Caracas, Venezuela, the high titre RRV-TV vaccine showed good protection, with efficacy as high as in the USA and only slightly lower than in Finland**. This is perhaps the most encouraging result considering potential use in developing countries.

In contrast, the low titre RRV-TV was only 20% and 35% efficacious against any rotavirus diarrhoea in populations of low socioeconomic status in Lima, Peru (21), and Belém, Brazil (22), respectively, and, at best, 50–60% efficacious against severe diarrhoea. An apparent reason was that the immunogenicity was low at both of these study sites.

At the moment, field trials are the only way to judge the performance of RRV-TV and other candidate rotavirus vaccines, as there is no satisfactory surrogate marker for protection. Overall immunogenicity is certainly of importance for clinical protection, but the role of the human rotavirus G- or P-type surface antigens present in the RRV-TV or bovine reassortant vaccines is less clear (23).

It is likely that RRV-TV vaccine will be licensed in the near future. Thereafter, the vaccine may be used by paediatricians in private practice in the USA and, gradually, in Europe. Acceptance for public health immunization programmes will depend on national considerations of disease burden and cost-benefit in each country. For example, many Latin American countries are likely to be interested in the RRV-TV vaccine. In these countries, rotavirus diarrhoea is a seasonal epidemic disease, causing considerable morbidity with some mortality. Many of the countries may be able to afford the vaccine if the price is reasonable. What may be needed to convince the decision-makers is a large-scale demonstration project showing effectiveness, rather than efficacy, and cost-benefit at the same time.

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In many Asian and African developing countries, where rotavirus disease is less seasonal, transmission occurs by the faecal-oral route, and the infectious dose is presumably large, the challenge for rotavirus vaccine is greater, but perhaps not impossible to meet. Even an efficacy level of 50–60% demonstrated by the low-dose RRV-TV against severe rotavirus disease — modest as it may sound — could prevent a large number of deaths. It would, however, be crucial to identify means to further increase the uptake of the RRV-TV vaccine in developing-country conditions.

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Hearing loss from ototoxics

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Ototoxicity is the harmful effect of a drug or chemical substance on the organs of hearing and/or balance. Drugs and other chemicals that damage the cochlea — the organ of hearing in the inner ear — do so by destroying sound-sensitive hair cells, usually starting at the basal turn and progressing towards the apical turn. These drugs may also damage the end organs of balance in the semi-circular canals, utricle and saccule (vestibular apparatus). Ototoxic damage may be reversible initially but this generally depends on the particular agent and sometimes the dose. Aminoglycoside antibiotics, which are the commonest causes of drug-induced ototoxicity, usually produce permanent damage.

Most studies of ototoxicity have been hampered by difficulties in definition and measurement. A hearing loss of ≥ 15 dB at 2 or more frequencies or ≥ 20 dB at 1 or more frequencies following exposure to a potentially ototoxic substance is usually taken to indicate ototoxic damage. However, a recent study of aminoglycoside ototoxicity suggests that these levels could overestimate the incidence (1).

Cochlear toxicity often presents as tinnitus. Hearing loss may affect higher frequencies initially and patients may only become aware of a problem when their loss is at least 30 dB at frequencies from 3-4 kHz. Vestibular toxicity usually presents as unsteadiness (vertigo), or even oscillopsia (vertical "jiggling" of stationary objects). The vertigo may be so disabling that affected patients are often sick and bedridden (2).

Causes

The table below indicates the major causes of ototoxicity. Among systemically administered drugs, the aminoglycosides are probably the commonest cause, and some persons may have an inherited predisposition. Damage may be increased by poor renal function or during simultaneous administration of loop diuretics, which alone can also be ototoxic, especially when given by bolus injection. There is some evidence that aminoglycosides, especially streptomycin, may damage the fetus when given during pregnancy. The likelihood of this occurring may increase with the global resurgence of tuberculosis unless safer, alternative drug regimens are employed. Kanamycin given to pre-term infants has caused hearing loss and pre-term infants are hypersensitive to aminoglycoside ototoxicity during the period of anatomical and functional maturation of the inner ear. Neomycin, when used in the topical treatment of burns, may be absorbed and can cause irreversible ototoxic damage. Netilmicin may be less ototoxic than the other aminoglycosides.

Macrolide antibiotics such as erythromycin, and possibly azithromycin, can cause a reversible high-tone sensorineural hearing loss and tinnitus after high dosage (4 g/day for erythromycin). The risk is greater in the elderly or where there is kidney or liver dysfunction.

Salicylates, such as acetylsalicylic acid, have long been known to produce a reversible moderate

hearing loss and tinnitus. This is usually dose-dependent but idiosyncratic reactions have occurred. Some antimalarials are also ototoxic. Quinine, which is chemically similar to salicylates, can cause mild toxic symptoms — sometimes referred to as “cinchonism” — such as tinnitus, high-tone hearing loss, visual disturbances, nausea, giddiness and tremors when administered in therapeutic doses, and in excessive doses may cause permanent deafness or blindness as well as myocardial conduction abnormalities, hypoglycaemia and coma (3, 4). With the increase of chloroquine-resistant malaria, quinine is being used on a larger scale and in higher dosage, especially for cerebral malaria and the signs may be difficult to distinguish from quinine toxicity. Permanent hearing loss can also occur with high-dose chloroquine.

Anticancer agents, especially cisplatin, may be ototoxic. The hearing loss may not commence until many days after therapy, and occurs more commonly in adults with prior otologic disease. Affected patients may complain of otalgia, tinnitus and hearing loss. The chelating agent, deferoxamine, used to prevent iron overload in patients having multiple blood transfusions for conditions such as beta-thalassaemia, may produce auditory and visual neurotoxicity.

Many otological preparations, especially aminoglycosides, are potentially ototoxic. This has been demonstrated in animal studies, but the evidence in humans is less clear. Many otologists feel that the

Table of the main drugs causing ototoxicity

Aminoglycosides	gentamicin, streptomycin, kanamycin, amikacin, tobramycin, neomycin, netilmicin, polymyxin B
Macrolides	erythromycin, azithromycin, clarithromycin
Loop diuretics	furosemide, bumetanide, etacrynic acid
Salicylates	acetylsalicylic acid (aspirin)
Antimalarials	quinine, chloroquine (high dosage)
Nonsteroidal anti-inflammatory drugs	naproxen, indometacin (no definite findings)
Antineoplastic drugs	cisplatin, bleomycin, carboplatin
Chelating agents	deferoxamine
Topical otological preparations	antibiotic solutions: aminoglycosides, polymyxin B, chloramphenicol, fosfomicin anti-inflammatory: propylene glycol, hydrocortisone antiseptic: chlorhexidine, povidone iodine acidifying: acetic acid (2% solution)

risk of hearing loss from chronic otitis media is greater than from the ototopical antibiotics used to treat it. In fact, the ototoxic risk may be greater if such preparations are applied to a normal middle-ear mucosa, such as in a patient with a chronic perforation but only intermittent otorrhoea. The ototoxic potential of acetic acid and hydrocortisone has been questioned. Some traditional medicines may be ototoxic. For example infusions of various roots used as ear drops in Angola have been reported to be ototoxic (2).

Prevention

Ototoxic hearing loss and vestibulopathy are predominantly iatrogenic or self-induced conditions. Once ototoxic damage has occurred, it is frequently irreversible, and expensive and time-consuming audiological rehabilitation with hearing aids and speech training may be required. However, there is wide scope for prevention, and this is where the main activities for control should be targeted.

1. Health education and promotion

There is a general lack of knowledge and awareness of the potential ototoxic effects of certain drugs and chemicals. An increase in the public's understanding of the risk factors for ototoxicity and the improper use of such drugs could help to reduce the incidence of the problem, as was shown by a recent campaign in China (5).

2. Professional education

Much of the problem of ototoxicity results from the inappropriate and indiscriminate use of ototoxic drugs by health care providers, especially, but not only, at primary levels. Information on the dangers of potentially ototoxic drugs and the strategies for control should be included in basic and refresher training of all health professionals, particularly primary care workers, nurses, general practitioners, pharmacists, paediatricians, and internists. The importance of audiometric and other monitoring of patients at risk should be stressed. Lists of drugs published for use by health professionals and individual drug labelling and product information should include specific warnings of ototoxic potential.

3. Regulation and legislation

Many developing countries have inadequate control of the availability of potentially ototoxic drugs. In some countries, aminoglycosides and other antibiotics are available over-the-counter without the need for prescription. In others, there are regulations but they are not enforced. Regulations should

also include control of drugs donated for use in large-scale emergencies and disasters. Health authorities should ensure that adequate warnings written in the local language are provided with donated drugs.

4. Management and monitoring

If possible during treatment, ototoxic drugs should be avoided, particularly where other risk factors for ototoxicity are present. However this is not always possible because of the lack of alternative and affordable therapies. In situations where potentially ototoxic drugs must be used, the following precautions should be observed:

- Use the minimum effective dose and duration of therapy
- Use an appropriate route of drug administration; and
- Monitor the patient regularly and frequently.

This should be done by performing regular symptom checks, audiometric tests including high-frequency audiometry and otoacoustic emissions (if possible) and measurements of serum drug levels. Audiometry or serum testing may not be widely available in some developing countries, hence the need for constant clinical vigilance.

5. National surveillance systems

These should be set up, or integrated into other networks such as the WHO International Drug Monitoring Programme, in order to measure the extent and causes of the problem.

6. Research

The mechanism of ototoxicity and its incidence and prevalence, the development of affordable, alternative nontoxic drugs, and the need for substances that reduce damage caused by ototoxic drugs should be determined by research. The safe dosage and duration of treatment in high-risk patients need to be evaluated, in particular for those essential drugs that are potentially ototoxic.

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International study of hormone replacement therapy (HRT) announced

An international study involving more than 30 000 postmenopausal women will commence in 1997 to provide data on the long-term benefits and risks of HRT. The study is intended to complement the recent Women's Health Initiative study carried out in the United States. The Women's International Study of Long Duration Oestrogen after Menopause (WISDOM) will be coordinated in the United Kingdom by the Medical Research Council's Epidemiology and Medical Care Unit and will extend over 20 years.

Participants in the study will take HRT or placebo for 10 years, and be followed up for a further 10 years. The first results of the trial are not expected before 2012 and will study, in particular, the risks of developing heart and other cardiovascular diseases, stroke, breast cancer and bone fractures caused by osteoporosis, as well as provide information on the quality of life and economic implications of HRT.

Reference: *Script*, Number 2180, 1996. p. 27.

Betacarotene, vitamin A and E may not prevent cancer or cardiovascular diseases

Observations from epidemiological studies suggest that the risk of cancer and cardiovascular diseases is lower among persons who consume high dietary levels of vegetables, fruits and grains (1). A commonly accepted explanation for this, both among scientists and the public has been that antioxidant vitamins in vegetables and fruits prevent carcinogenesis and atherogenesis by interfering passively with oxidative damage to DNA and lipoproteins.

These theories have also been supported by observations in animal studies (2). As a result of these beliefs, many millions of dollars are spent annually on synthetic betacarotene and vitamin E (INN = tocofersolan) and A (INN = retinol) supplements.

Sceptics have long called for a large, long-term clinical intervention trial to demonstrate the benefits and risks of these prevention practices. and the results of four large-scale chemoprevention trials of betacarotene and related agents are now available. Their disappointing results reaffirm the importance of solid scientific evidence as a sound basis for any disease prevention strategies (3–6).

The Alpha-Tocopherol, Beta Carotene cancer prevention study (ATBC) (3) tested daily supplementation with 20 mg of betacarotene and 50 mg of tocofersolan in 29 133 male smokers (two-by-two factorial design). A total of 876 new cases of lung cancer were diagnosed and no reduction in the incidence of lung cancer was found among male smokers after five to eight years of dietary supplementation with tocofersolan or betacarotene. In fact the trial raised the possibility that these supplements may have both harmful and beneficial effects.

The Physicians' Health Study (4) tested supplementation with 50 mg of betacarotene on alternate days in 22 071 male physicians, 50% of whom were former smokers and 11 % of whom were currently smoking. In this trial, 170 new cases of lung cancer were diagnosed and 12 years of supplementation with betacarotene produced neither benefit nor harm in terms of the incidence of malignant neoplasms, cardiovascular disease, or death from all causes.

The betacarotene and retinol efficacy trial (CARET) tested daily supplementation with a combination of 30 mg betacarotene and 25 000 IU of retinol in a total of 18 314 smokers, former smokers and workers exposed to asbestos (5). There were 388 new cases of lung cancer and, after an average of four years of supplementation, the combination of betacarotene and retinol had no benefit and may have had an adverse effect on the incidence of lung cancer and on the risk of death from lung cancer, cardiovascular disease, and any cause in smokers and workers exposed to asbestos.

Finally, a study conducted in 34 486 postmenopausal women with no cardiovascular disease suggested that the intake of vitamin E from food is

inversely associated with the risk of death from coronary heart disease and that such women can lower their risk without using vitamin supplements (6). By contrast, the intake of retinol and ascorbic acid was not associated with lower risk of death from coronary disease.

In summary, the studies did not prove the value of antioxidant vitamin supplements for prevention of cancer or cardiovascular disease in a well-nourished population. Instead of buying and consuming antioxidant-vitamin supplements, people are advised to adhere to a healthy lifestyle. This is understood as eating sufficient fruit and vegetables, taking enough exercise, avoiding becoming overweight and refraining from smoking.

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Driving ability in cancer patients treated with morphine

Even a small single dose of an opioid in opioid-naive healthy volunteers is reported to reduce reaction speed and accuracy, muscular coordination, attentiveness and the ability to memorize, rendering the driver a traffic hazard. The question of whether stable doses of opioids in cancer treatment affect psychomotor functions in the same way is now raised in a study reported in the *Lancet* (1).

Two groups of cancer patients, one of 24 patients using slow-release morphine tablets in a mean daily dose of 209 mg, with dose stability established for at least two weeks, and a control group of 25 patients who had no pain and used no analgesics, performed a series of psychological, psychomotor and neurological tests originally designed to measure the vocational skills of professional drivers.

Although the morphine group did not perform quite as well as the control group in the tests, there were no significant differences between the two groups as far as measurement of intelligence, attentiveness, ability to concentrate, psychomotor speed and attention span were concerned. No significant drug effects were demonstrated in neurological tests measuring reaction speed, sensitivity to temperature variation, and keeping one's balance with the eyes open. The morphine group performed poorer only in the test for keeping balance with their eyes closed.

The authors concluded that the long-term use of stable doses of morphine does not essentially reduce driving skills. However, the observation relevant to driving was that there is a slight dose-dependent effect on the performance of tasks demanding special concentration.

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