

# Reports on Individual Drugs

## Spread of quinolone-resistant salmonella

Food-borne salmonella infections have become a major problem in many industrialized countries (1, 2). *Salmonella enterica* serotype typhimurium (DT104) is now resistant to five drugs: ampicillin, chloramphenicol, streptomycin, sulfonamides, and tetracycline. An increasing proportion of DT104 isolates also have reduced susceptibility to fluoroquinolones. The concomitant use of these and other antimicrobial agents at sub-therapeutic concentrations to enhance growth in animals and for farming purposes is causing obvious concern and national and international recommendations on the use of antimicrobials for disease control in humans and animals have been proposed (3, 4).

A recent study in Denmark has demonstrated the spread of an unusually resistant strain of typhimurium, through the food chain, from food-producing animals to humans (5). The surveillance of salmonella in farms in Denmark covers nearly all commercial food-producing animal facilities and slaughterhouses. In 1998, the first community outbreak of quinolone-resistant salmonella occurred. The outbreak included 25 culture-confirmed cases which were difficult to treat: eleven patients were hospitalized and two died. The investigators succeeded in tracing the source of infection in most of the 25 cases. During microbiological investigation, an unusual resistance pattern was found in isolates from all patients, the slaughterhouse, two samples of pork originating from food inspection agencies and two swine herds. Nine patients had eaten pork originating from a slaughterhouse where two herds tested positive for multidrug-resistant salmonella. The molecular epidemiological data from patients confirmed that the primary source of all cases was a Danish swine herd.

Fluoroquinolones were licensed in Denmark for veterinary use in 1993 and by 1998 accounted for 400 kg of a total of 57 300 kg of antimicrobial agents consumed by food-producing animals. No indication of fluoroquinolone use was found in the implicated herds. It is therefore suggested that resistant salmonella may have originated as a result of use of fluoroquinolones prior to 1998 or

through introduction from pigs not bred in Denmark, and thereafter spread through wild animals or equipment.

A further case of ceftriaxone resistant salmonella infection acquired by a child from cattle has also been reported from the United States (6). The ceftriaxone-resistant isolate from the child was indistinguishable from one of the isolates from cattle, which was also resistant to ceftriaxone. Furthermore, both isolates were resistant to 13 antimicrobial agents; all but one of the resistance determinants were on a conjugative plasmid of 160 kb that encoded the functional group 1 beta-lactamase CMY-2. This study provides additional evidence that antibiotic-resistant strains of salmonella evolve primarily in livestock. Resistance to ceftriaxone is a concern, especially with respect to children, since fluoroquinolones are not approved for use in children in the United States.

Fluoroquinolones remain the empirical treatment for suspected intestinal salmonella infection. They are crucial for the treatment of severe concomitant diseases and health conditions. The increased presence of quinolone-resistant salmonella strains in food producing animals is therefore of public health concern. Fluoroquinolones should not be used in food-producing animals to enhance growth or for other purposes. They should be used in veterinary practice for therapeutic indications only when other options are not possible.

Antimicrobial resistance was the topic of a conference of Health Ministers from the European Union countries in 1998 (4, 7). The majority of participants considered the use of antimicrobials as growth promoters in animals unjustified and recommended that safer alternatives such as improved farming practices should be developed. The follow-up of these recommendations is increasingly important.

### References

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### Evidence for the role of zinc in childhood survival

Although the theoretical basis for a potential role of zinc has been postulated for quite some time, convincing evidence for its importance in child health has come only recently from randomized controlled trials of zinc supplementation. Episodes of childhood diarrhoea that last 14 days or more are associated with increased morbidity and growth retardation. Children who experience such episodes are more likely to have other serious infections and to die (1).

Zinc is essential for many cellular functions, including transcription of DNA and cell division (2) and is required for normal immune function (3). It has been shown to hasten mucosal recovery after diarrhoea. Zinc deficiency, as indicated by low plasma zinc concentrations, is associated with both an increased risk of diarrhoeal episodes and greater severity of these illnesses (4, 5).

The data from 10 trials evaluating preventive effects of zinc supplementation; three trials evaluating the therapeutic effects on acute diarrhoea; and four trials in therapy of persistent diarrhoea have now been subjected to a pooled analysis (6). This evaluation assessed studies carried out on the effects of zinc supplementation in the prevention of diarrhoea and pneumonia. Trials included those that provided oral supplements containing at least one half of the United States Recommended Daily Allowance of zinc in children under 5 years of age and evaluated the prevention of serious infectious morbidity. The effects of supplements on diarrhoea

and pneumonia were analysed overall and in subgroups, defined by age, baseline plasma zinc concentration, nutritional status, and sex. The analysis used random effects hierarchical models to calculate odds ratios and confidence interval.

This analysis indicated that there is significant homogeneity in the results across the studies conducted throughout 10 developing countries. Zinc supplementation in these children in developing countries is associated with substantial reductions in the rates of diarrhoea and pneumonia, the two leading causes of death in these settings. These studies also provide by far the best evidence of widespread prevalence of zinc deficiency among preschool children.

However, although the available evidence is promising, it is still insufficient to formulate public health policies. Extrapolation of mortality impact from morbidity trial data is fraught with problems of both underestimating and overestimating the impact. Therefore, given its substantial potential to become a powerful intervention to promote child survival, the World Health Organization, in collaboration with UNICEF backed by funding from the United Nations Foundation, has initiated two large studies to determine whether zinc supplementation truly has an important role in decreasing child mortality and morbidity. These studies should provide conclusive new evidence on which to base interventions within the next 30 months and allow recommendations concerning the benefit of zinc supplementation in young children to be made.

#### References

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## Increased risk of gastrointestinal bleeding: SSRIs and NSAIDs

Antidepressants with selective serotonin re-uptake inhibitory action such as fluoxetine, fluvoxamine, paroxetine and sertraline have been associated with bleeding disorders including purpura, ecchymose, epistaxis, prolonged bleeding time, thrombocytopenia, platelet dysfunction, and haemorrhage (1–3). Serotonin released from platelets has an important role in regulating the haemostatic response to vascular injury. Selective serotonin re-uptake inhibitors (SSRIs) diminish transportation of serotonin from circulation to platelets creating a haemostatic defect with increased risk of bleeding. New data show that concurrent use of SSRIs with nonsteroidal anti-inflammatory drugs (NSAIDs) greatly increases the risk of upper gastrointestinal bleeding.

A population-based case-control study has been carried out using the United Kingdom General Practice Research Data Base (1). The study identified 1651 cases of upper gastrointestinal bleeding against 10 000 controls. Current exposure to SSRIs was found in 3.1% of patients with upper gastrointestinal bleeding and only 1% in controls. The estimated absolute risk of upper gastrointestinal bleeding was 1 case in 8000 prescriptions which was similar to that of low-dose ibuprofen, a commonly used NSAID.

In contrast, the nonselective serotonin re-uptake inhibitors such as amitriptyline, imipramine, lofepramine and doxepin showed only a small trend toward gastrointestinal bleeding with a ratio of 1.4. No increased risk was shown with nortriptyline, protriptyline, desimipramine or mianserin. The concomitant use of SSRIs with NSAIDs increased significantly the risk of upper gastrointestinal bleeding to a ratio of 15.6 which was beyond the sum of their independent effects.

These data show that the SSRIs have an increased risk of gastrointestinal bleeding but the older antide-

pressants with no action on serotonin mechanisms lack this risk. Moreover, there is clinically relevant interaction between SSRIs and anti-inflammatory drugs. Their concurrent use significantly increases the risk of upper gastrointestinal bleeding. Since many of these drugs such as acetylsalicylic acid, ibuprofen and ketoprofen are available over-the-counter it is important to warn patients using SSRIs of this risk.

## References

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## Clozapine and venous thromboembolism

Data from the Swedish Adverse Drug Reaction Committee suggest that use of clozapine is associated with venous thromboembolic complications. Until now, use of clozapine, an atypical antipsychotic agent, has been limited by agranulocytosis, and the existence of other potentially fatal adverse effects such as myocarditis and thromboembolism has also been suggested.

Between April 1989 and March 2000, six cases of pulmonary embolism and six of venous thrombosis were reported. In all cases, the diagnosis of the adverse drug reaction was supported by clinical findings. In eight patients, symptoms occurred in the first 3 months of treatment. Massive pulmonary embolism was confirmed in the five patients who died, and in three of these patients no other factors contributed to death.

The mechanism by which clozapine can induce thromboembolism remains to be established. The assumed risk would be at least one per 2000–6000 treated patients and could be higher because of under-reporting. This potentially fatal effect seems to occur mainly during the first 3 months of clozapine treatment and the drug should not be used in any patient in whom this reaction may be suspected.

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## ACE inhibitors improve cardiovascular outcome

Angiotensin converting enzyme (ACE) inhibitors have been shown to improve outcome among patients with left ventricular dysfunction, whether or not they have heart failure. ACE inhibitors block the activation of the renin-angiotensin system and may retard the progression of both heart failure and atherosclerosis. In a meta-analysis of three studies (1–3) that included more than 9000 patients with low ejection fractions, treatment with ACE inhibitors reduced the risk of myocardial infarction by 23% suggesting that ACE inhibitors may have a role in preventing myocardial infarction in a wide range of patients. ACE inhibitors may also reduce the risk of stroke by lowering blood pressure and may prevent complications related to diabetes (4).

A recently reported (5) trial has now evaluated the role of ramipril, an ACE inhibitor, in patients at high risk for cardiovascular events not having left ventricular dysfunction or heart failure.

The Heart Outcomes Prevention Evaluation (HOPE) study was carried out in centres in Argentina, Brazil, Canada, Mexico, USA and western Europe. A total of 9297 high-risk patients of 55 years of age or older who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor were randomly assigned to receive ramipril or matching placebo and vitamin E for a mean of five years. A substudy compared low-dose ramipril (2.5 mg daily) with a full dose (10 mg daily). A total of 3578 patients in the study had diabetes, and 8160 had cardiovascular disease. The event rate in this group for those receiving placebo was about half that in patients with cardiovascular disease receiving placebo.

The magnitude of the benefit of treatment with ramipril was at least as large as that observed with other proven secondary prevention measures. Treatment with ramipril significantly reduced rates of death from cardiovascular causes, myocardial infarction, stroke, death from any cause, revascularization procedures, cardiac arrest heart failure, and complications related to diabetes.

The study concluded that ramipril is beneficial in a broad range of patients without evidence of left

ventricular systolic dysfunction or heart failure who are at high risk for cardiovascular events.

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## Ticlopidine and thrombotic thrombocytopenic purpura

The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has recently received its first report of thrombotic thrombocytopenic purpura (TTP) in association with ticlopidine (Ticlid®).

TTP is a life-threatening syndrome of thrombocytopenia and microangiopathic haemolytic anaemia commonly associated with fluctuating neurological abnormalities, renal dysfunction, and fever. A central feature is widely disseminated platelet aggregates, which have been observed in the adrenal glands, brain, heart, kidneys, and pancreas.

The association of TTP with ticlopidine has been the subject of two recent publications (1, 2). In the report to ADRAC (3), a 56-year-old female was admitted to hospital with spontaneous bruising on the arms, chest and legs after about 3 weeks use of ticlopidine for coronary stenting. Laboratory investigations showed thrombocytopenia (platelets  $9 \times 10^9$  /L [reference range:  $150\text{--}400 \times 10^9$  /L]) and declining haemoglobin (haemoglobin 88 g/L [refer-

ence range: 115–165 g/L]). Microangiopathic red cells consistent with TTP were present on full blood examination. The patient's highest recorded temperature was 38 °C and involved haematuria in addition to spontaneous bruising. Neurological signs and symptoms included severe headaches and neck stiffness. Recovery was achieved after aggressive treatment which included plasmapheresis. TTP is a rare and often fatal disorder with an estimated incidence of 3.7 cases per million people (0.0004%).

Since mortality exceeds 20%, this complication needs to be recognized promptly and treatment commenced rapidly.

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### Miltefosine: effectiveness in visceral leishmaniasis explored

There is currently no effective orally administered medication against visceral leishmaniasis, a parasitic disease affecting 500 000 people a year and occurring mainly in India, Brazil and Sudan. Symptoms of infected patients are hepatosplenomegaly and pancytopenia, while the disease is usually fatal if left untreated.

Traditionally, four weeks of injections of pentavalent antimonial agents has been the mainstay of treatment. In 1997, liposomal amphotericin B was licensed for visceral leishmaniasis but because of its high cost and need for parenteral administration it has not been successfully deployed in the developing world.

Miltefosine, originally developed as an antitumour compound, has now shown promise in use against visceral leishmaniasis and successful reports have been received following a phase II trial conducted in India.

The study was an open-label, multicentre trial in which four 30-person cohorts received 50 mg, 100 mg or 150 mg of miltefosine per day for four or six weeks. The 120 patients, who ranged in age from 12 to 50 years, had anorexia, fever and splenomegaly as a result of confirmed leishmania infection. Parasitological cure was defined by the absence of parasites in a splenic aspirate obtained two weeks after completion of treatment.

In all 120 patients there was an initial parasitological cure. Six patients had clinical and parasitological relapse, but the remaining 114 had not relapsed by six months follow up. This represents a cure rate of 95%. The regimen of 100 mg per day produced the best cure rate. Gastrointestinal side effects were frequent (62%) but mild to moderate in severity and no patient discontinued therapy. A phase III trial is under way in adults in India.

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