Does the use in animals of antimicrobial agents, including glycopeptide antibiotics, influence the efficacy of antimicrobial therapy in humans?

Sir,

In their article, Bates, Jordens and Griffiths (1994) drew attention to the possibility that vancomycin-resistant (VR) Enterococcus faecium may have entered the community via the foodchain but stated that, because of their high cost and clinical use, glycopeptides are not used in animal feeds. While true of vancomycin and teicoplanin which are only used for medical purposes, the glycopeptide, avoparcin (Avotan, Cyanamid International) is available exclusively as a feed additive for livestock bred for their meat in every country of the world with the notable exception of the USA and Canada. The drug is not absorbed and 5—40 mg/kg avoparcin is incorporated in animal feed (Feed Additive Directive 70/524 of the EC). First licensed in 1975, the use of the drug has become progressively more widespread to promote the growth of broiler chickens, turkeys, pigs, beef and dairy cattle, veal calves, sheep and goats.

It is not known what impact, if any, the use of avoparcin has had on the development of glycopeptide resistance amongst the enterococci of animals exposed to the drug, but both they and man are potential reservoirs of VR E. faecium harbouring the vanA gene. Such strains have been isolated from the faecal samples of 3 (2%) of 184 patients based in the community around Oxford (Jordens, Bates & Griffiths, 1994), from the stools of 7 (35%) of 40 people living in Charleroi, Belgium, who had no association with health care (Van der Auwera P., Murray B. E. & Leclercq R., unpublished observations) as well as from the faeces of 22 (3.5%) of 636 patients within two days of entering hospital in Belgium (Gordts et al., 1994). The vanA gene cluster has got into several links in the food chain involving poultry as E. faecium possessing the vanA gene have been isolated from the manure of broiler chickens on a farm employing avoparcin in the feed and from chicken carcasses delivered to a hospital's kitchen (Klare et al., 1995) as well as from uncooked chicken obtained from retail outlets (Bates et al., 1994). There is also some evidence of wider dissemination since E. faecium carrying the vanA have also been isolated from 5 of 13 samples of minced meat obtained from separate butchers and in the faecal samples of 12 of 100 people living in the same area in Germany where avoparcin was used in livestock food (Klare, I. & Witte, W., unpublished observations). Similar strains have also been found in sewage (Bates, Jordens & Selkon, 1993; Torres et al., 1994).

The origin of vanA gene responsible for most of the resistance encountered in human isolates is unknown but it may have spread from humans to farm animals. VR E. faecium appears a more common nosocomial isolate in North American than here in Europe, despite the fact that avoparcin is not permitted in the USA, suggesting that these organisms may have originated in the patients' intestines and were, perhaps, selected by treatment with vancomycin. Alternatively, these resistant organisms may have entered the food chain via animals as suggested by Bates et al. (1993) who detected strains with the same ribotype in sewage and pig faeces, sewage and in blood cultures of a patient, and in faeces from a pig and a patient seen in general practice.

Whatever the original source of vanA, the gene seems widely disseminated in the faecal enterococci of man and his animals. Enterococci harbouring vanA also appear to be completely cross resistant to vancomycin, teicoplanin and avoparcin (Klare et al., 1995). Moreover, there are also signs that we are already in danger of losing an effective family of antibiotics for some of our illest patients due to VR enterococci and we can ill afford further expansion of the reservoirs of the vanA gene cluster. It therefore seems essential to trace the movements of the highly mobile vectors responsible for glycopeptide resistance throughout the food chain and to establish whether an open channel exists allowing
enterococci to move between hosts. We also should know whether the enterococci in livestock fed with avoparcin are becoming resistant to glycopeptides since these organisms may well end up in the meat we consume. If there is evidence of a link between the use of avoparcin in animal feed and the presence of VR enterococci, the drug may have to be withdrawn altogether from the market as has just occurred in Denmark. In the meantime, it seems reasonable to expect farmers to curb their use of avoparcin just as we must learn to do with glycopeptides in human medicine if we are to preserve an important class of therapeutic agents.

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References


Sir,

Dr Donnelly and his colleagues raise a fundamental question; does the use of antimicrobial agents in animals adversely affect the efficacy of those antimicrobial drugs which are used in humans? This has been one of the most thoroughly considered questions in animal agriculture. The possible relationship between antibiotic resistance in the enteric flora of food producing animals and antimicrobial efficacy in the treatment of infections of humans has been studied exhaustively. This issue has been investigated in Europe by the Swann and Netherthorpe Committees, and in the USA by task forces of the FDA, the Council of Agricultural Science and Technology, the Federal Office of Technology Assessment, and on two occasions by the National Academy of Sciences. These committees have invariably reached a decision that insufficient data exists to demonstrate a significant risk from the currently approved uses of antibiotics in the rearing of food animals in the European Union and the USA, respectively. Most scientists who have studied this issue would caution against the simplistic assumption that antibiotic resistance in animal enteric flora per se should be regarded as a threat to human health. There is a paucity of experimental evidence supporting the adverse effects on human health of the use of antibiotics in food animals. For this reason, the FDA in the USA and the analogous scientific and regulatory bodies in the member states of the EU and elsewhere have permitted the continued use of specific antimicrobial agents in food producing animals.

Such is the case with the glycopeptide antibiotics avoparcin and ardacin in the EU. Ardacin was licensed in the EU in late 1994 for use in the feed of broiler chickens. Avoparcin is licensed in the EU for oral administration exclusively in feed to improve the production efficiency of a range of animals raised for food, including broiler chickens, turkeys, pigs, beef cattle, veal calves, and lambs. Avoparcin is used throughout Europe, Australasia, and South America. With each assessment for