Introduction

Zinc bacitracin is a mixture of high molecular weight polypeptides (bacitracin A, B and C and several minor components), first described in 1945 as a product of a Bacillus sp. (now recognized as Bacillus licheniformis), contaminating wounds. It has activity against some Gram-positive organisms, among which Staphylococcus aureus is somewhat less susceptible and Streptococcus pyogenes is highly susceptible. It is noteworthy that the high susceptibility of S. pyogenes, established by Maxted in 1953, still obtains and continues to be used as a diagnostic test for Lancefield Group A streptococci.1

Bacitracin acts bactericidally by binding to isoprenyl pyrophosphate, the lipid carrier that transfers N-acetyl-muramyl-N-acetylglucosamyl-amino acid cell wall building blocks across the cytoplasmic membrane, a mechanism unlike that of any other commercially available antibiotic. Aquired resistance is known, for example in S. aureus, but is uncommon. Other organisms, such as enterococci, seem always to have varied in their susceptibility. There is no cross-resistance with other antibiotics.

Upon introduction into clinical use in man, bacitracin was found to be nephrotoxic, and preparations for systemic use were soon withdrawn. However, it continued to be used topically, and is still used for the treatment of infected dermatoses and other skin infections, for infected wounds and the prevention of infection in dirty wounds, although to a diminished extent now other more effective agents have taken its place. The products containing bacitracin are ointments (including ophthalmic preparations) and various antibiotic sprays, in which it is mixed with such antibiotics as polymyxin and neomycin. The antibiotic sprays have rarely been favoured by microbiologists since they have been associated with both bacitracin and neomycin resistance, even though only the latter is of great clinical importance.

Acquired resistance to bacitracin

The determination of the in-vitro activity of bacitracin has been bedevilled by a lack of standardized reference methodology, by a lack of agreement on interpretive criteria and by the lack of any great interest in the antibiotic, particularly in human medicine. If these problems are taken into account, it appears that the prevalence of bacitracin resistance has not changed over time, regardless of the use of the drug in human and animal medicine. C. perfringens and S. pyogenes remain highly susceptible, while S. aureus is occasionally resistant, and enterococci more often so.3,4

Transmission of bacitracin-resistant Enterococcus faecium to man

Clearly, bacitracin-resistant enterococci colonize the faeces of animals, including poultry, pigs and cattle, and, equally...
clearly, resistant enterococci can contaminate animal carcases destined for human consumption. According to Danish data, the prevalence of bacitracin-resistant enterococci is lower in beef and pork products than in live cattle and pigs, being highest in live chickens and in chicken carcases from retail food outlets. A battoir handling might well increase and spread initial contamination, and some contamination persists during processing and distribution, though at what level is not clear.

Bacitracin-resistant enterococci are thus highly likely to reach human food. What happens next is pure surmise in the absence of valid experimental evidence. Experiments such as those of Berchieri, who ingested cultures of vancomycin-resistant enterococci from animal sources, tell us little because of deficiencies in design, as well as the unknown extrapolation factor linking ingestion of cultures and ingestion of naturally contaminated food. Contaminating enterococci might fail to pass the acid barrier of the stomach, or might colonize the gut transiently or semi-permanently. There is increasing evidence that enterococci, like S. aureus, are often species specific and might not readily colonize other hosts. Furthermore, if the resistant enterococci were to survive they would still need to avoid host immune mechanisms before opportunistic infection could take place. Reaches in defences are only likely when the gut is damaged, for example, intentionally during surgery or, unintentionally, as in severely immunocompromised patients. Resistant enterococci might also be expected to gain access to the bladder and thus to cause simple or complicated urinary tract infection. If bacitracin-resistant organisms were to cause infection, the fact is scarcely likely to be noticed, let alone to lead to difficulties of antibiotic therapy, since the antibiotic is not used in such circumstances.

Risk assessment

As far as I am aware, there has been no formal assessment to indicate the probability of the hazard of bacitracin-resistant enterococcal infection in man resulting from animal use of the antibiotic, being translated into actual risk. However, informal assessment suggests that the risk is so low as to be unmeasurable, and that it would be of trivial consequence even if it were to occur.

Risk management

There is a growing and clamorous belief that all that is needed to manage the risks—real or not—arising from antibiotic-resistant bacteria in animals as a consequence of the use of antibiotics for growth promotion, is to terminate the use of such agents. This may be so, although resistance, once it has arisen, seems loath to disappear, at least in the short term. Furthermore, discontinuance of any individual growth promoter may lead to the increased use of others, as was experienced in Denmark when avoparcin was discontinued and the use of macrolide growth promoters in animals increased, at least temporarily. Even less desirably, there might be a compensating increase in the use in animals of therapeutic agents such as aminopenicillins (with or without β-lactamase inhibitors), fluoroquinolones and macrolides, for the treatment or prevention of infection (not to be confused with growth promotion). This is particularly likely in the case of C. perfringens infection incidentally suppressed by the use of bacitracin as a growth promoter. The first two of these antibiotic groups are likely to add to the resistance burden already accumulating in salmonellae, and the latter two to increasing macrolide and fluoroquinolone resistance in campylobacters.

There is a danger that concentration on banning antibiotic feed additives in general might divert attention from other measures that might be more effective and have less unwanted consequences. For example, food irradiation—unfortunately equally contentious—would be expected to remove all microbial contamination, including enterococci. Less contentious would be an insistence on careful handling of potentially contaminated foods to prevent cross-contamination. If those who cook for us were to act after handling uncooked chicken as though they had handled faeces (in fact, the case!), another powerful remedy for this and other more important contaminants would be in place. Proper cooking would be another measure expected to be effective. Finally, those at greatest perceived risk could abstain from certain foods, as is the case with those with liver disease and certain cheeses and patés potentially contaminated with listeria. There is a great need for sociologically based research on how people might be persuaded to apply such measures.

There is also a real danger that over-concentration on animal sources of resistant organisms might divert attention from the consequences of antibiotic use in humans. Most agree that this is the source of most of our current problems. Sadly, and contrary to popular belief, microorganisms do not differentiate between prudent and non-prudent use of antibiotics, and there is little scientific evidence of the effect of prudence. There is an overwhelming case for the promotion of scientific research on the effects of prudent use and on alternative approaches to the solution of our antibiotic-resistance problems.

Risk of bacitracin resistance for humans

None of the clinical uses of topical bacitracin in humans, outlined above, is critical, since alternative and improved compounds are available. However, it has been suggested that there may be a new niche for bacitracin in the eradication of carriage of resistant enterococci from the faecal flora of humans. This is worth consideration in some detail, because if such an application were to be shown to be effective, there might be a case for reservation of bacitracin for human use. There is, I believe, only one fully published
A brief report from Chia et al.\(^8\) on eight patients colonized with vancomycin-resistant but bacitracin-susceptible \((\text{MIC} < 16 \, \text{mg/L})\) \(E.\) faecium, found that six patients became negative after treatment with oral bacitracin 25,000 IU twice daily for 10 days, one later relapsing, and two failed to respond. In the face of a failure rate of 35% they concluded that “this may be an effective way to eliminate vancomycin-resistant \(E.\) faecium from the intestine”. Three further abstracts complete the current literature on the subject. Weinstein et al.\(^9\) treated 15 colonized patients in a dialysis unit with bacitracin 25,000 IU four times daily plus doxycycline 100 mg daily for 10 days, and compared them with 21 untreated patients. A though all 15 patients were initially cleared, all either relapsed completely or continued to have intermittently positive cultures, thus differing little from untreated patients. The authors concluded that “antibiotics did not play a major role in changing the natural history of colonization of this population”. Monte-calvo et al.\(^10\) reported on quantitative \(E.\) faecium stool cultures before, during and after bacitracin therapy (25,000 IU twice daily for 10 days). Pre-treatment levels of \(10^6-8\) cfu/g faeces fell to undetectable levels in four patients (one of whom was lost to further follow-up, two remained negative at 7 days and 5 weeks, and one relapsed at 14 days). Six patients remained positive (two with no change, two with a \(1 \log_{10}\) increase and two with a \(2 \log_{10}\) decrease). They conclude that “oral bacitracin is minimally effective in reducing vancomycin-resistant enterococcal stool carriage”. Finally, Hachem and Rad\(^11\) treated 45 patients with faecal carriage of vancomycin-resistant enterococci with bacitracin \((25,000 \, \text{IU} \times 3 \, \text{times daily})\) plus gentamicin \((80 \, \text{mg} \times 3 \, \text{times daily})\) for 14 days. At follow-up after 2 months, 23/28 (82.2%) evaluable patients remained positive. They concluded that oral bacitracin and gentamicin was “not well tolerated and had little effect in reducing \(VRE\) colonization”.

Overall we must conclude, on the basis of these studies (most of them not really adequate or adequately reported), that oral bacitracin is more likely to be ineffective for clearing vancomycin-resistant enterococci from the faeces, and may on occasion be harmful. There remains confusion in relation to the effect of bacitracin resistance. A ny effect on this aspect of human medicine from resistance selected in animals seems likely to be minimal.

Conclusions

Although there is evidence for acquired resistance to bacitracin in enterococci isolated from animals and staphylococci, though not in \(C.\) perfringens or \(S.\) pyogenes, there is no evidence that the prevalence of such resistance has increased over time or in relation to the use of the antibiotic in man or in animals. The hazard of transmission of bacitracin-resistant organisms via the food chain remains a theoretical hazard rather than a quantified risk. If measures for control were thought to be needed, improved food handling and proper cooking would be expected to be effective. However, since the use of the agent in humans is either topical, for which many alternatives exist, or, in the case of gut carriage, experimental and of doubtful efficacy, the application of any control measures, including the banning of bacitracin for growth promotion will have no value. Indeed, it might even have adverse consequences for human health if it led to the use of alternative antibiotics, such as aminopenicillins, macrolides and fluoroquinolones, in animals, either for growth promotion or for therapy. There are no reasons, serious or trivial, to consider that the use of zinc bacitracin for growth promotion poses any current or foreseeable risk to human health. The conditions required for the withdrawal of bacitracin in the relevant \(E\)uropean \(U\)nion \(R\)egulation,\(^12\) amending an earlier \(C\)ouncil \(D\)irective,\(^13\) are quite simply not met.

If purity of practice is required, in accordance with the Swann Report,\(^14\) no great harm would ensue if bacitracin were to be reserved for use as a growth promoter in animals and its use in human medicine abandoned.

References

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