REVIEW

Fusidic acid resistance in *Staphylococcus aureus*

D Dobie, J Gray

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This review summarises current knowledge of the microbiological and clinical aspects of fusidic acid resistance in *Staphylococcus aureus*, and makes recommendations about fusidic acid prescribing and further research.

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Fusidic acid is a narrow spectrum antibiotic derived from *Fusidium coccineum* that has been used for over 35 years to treat infections with *Staphylococcus aureus*.[1] Fusidic acid resistance in *S aureus* can be readily selected for by in vitro exposure to the antibiotic, leading to the recommendation that for systemic therapy fusidic acid should only be given in combination with another agent. More controversial is the use of topical fusidic acid in the treatment of cutaneous and soft tissue infections. Many authors have suggested that the drug is effective as monotherapy in this setting. In the UK usage has of topical fusidic acid (alone or in combination with a glucocorticoid) almost doubled between 1995 and 2001,[2] which has coincided with reports of rapidly increasing fusidic acid resistance from many centres.[2–8]

Increasing fusidic acid resistance in *S aureus* might be important for three reasons. First, it might mean that systemic fusidic acid can no longer be used in situations where it is clinically indicated. Second, failure of topical treatment may be occurring, especially in primary care where treatment is often empiric, and third, resistance to fusidic acid might be linked to other antibiotic resistances, therefore favouring spread of multiply antibiotic resistant *S aureus* such as MRSA (methicillin resistant *S aureus*).

MODE OF ACTION OF FUSIDIC ACID

Elongation factor G (EF-G) is a bacterial protein that is necessary for translocation on the bacterial ribosome after peptide bond formation during protein synthesis. Fusidic acid binds to this protein and the ribosome thereby inhibiting further bacterial protein synthesis. Prokaryotes possess only one type of elongation factor. Eukaryotes, however, have other factors that are unaffected by the action of fusidic acid, which allow them to continue the process of protein synthesis.[9] The action of fusidic acid is largely bacteriostatic, but at high concentrations (2 to 32-fold higher than the MIC) the effect may be bactericidal.[1]

ANTIBACTERIAL SPECTRUM OF ACTION AND CLINICAL USES

Fusidic acid has an unusual spectrum of activity that includes corynebacteria, nocardia, anaerobes, and *Neisseria* species, but is used almost exclusively as an anti-staphylococcal agent.[9] Its main indications are:

- *Systemic treatment for severe staphylococcal infections*. Oral or intravenous fusidic acid may be used in combination with another anti-staphylococcal agent for the treatment of severe staphylococcal infections.[10] It is particularly valuable for the treatment of osteomyelitis and septic arthritis, because of its excellent bone penetration.[11]

- *Systemic treatment for colonisation and infection with MRSA*. Fusidic acid has proven useful when combined with agents such as vancomycin, but not as monotherapy, in the treatment of infections with MRSA.[12] Combined with rifampicin, it is used for attempted clearance of MRSA colonisation where topical agents such as mupirocin have failed.[13]

- *Topical treatment of skin infections*. Topical formulations of fusidic acid, now make up two thirds of the total usage[14] and are widely used as monotherapy for the treatment of superficial cutaneous infections, including impetigo, folliculitis, erythrasma, furunculosis, and infected traumatic wounds.[15 16] Unfortunately, good evidence of efficacy is lacking as few studies are randomised, double blinded, or controlled.[15]

- *Topical treatment of atopic dermatitis*. Topical preparations of fusidic acid and a glucocorticoid are widely used in the treatment of atopic dermatitis. Skin colonisation with *S aureus* is a characteristic feature of atopic dermatitis, and is believed to drive the inflammatory process, leading to the recommendation that fusidic acid-glucocorticoid preparations may be the treatment of choice for this condition.[17]

RESISTANCE TO FUSIDIC ACID

In vitro, resistance to fusidic acid can readily be selected from an initial high inoculum.[18] However, there has been surprisingly little detailed study of fusidic acid resistance mechanisms in *S aureus*.

All bacterial populations produce spontaneous single step chromosomal mutations in the gene coding for EF-G at a rate of 1 in 10^6–10^8 cell divisions. This occurs even with isolates from individuals who have never been exposed to fusidic acid. It has been postulated that resistant mutants are slower growing and less virulent, but it is not clear if this is true.[18] Resistance may also arise from plasmid mediated decreased cell wall or membrane permeability.[18 19] This resistance may be linked to resistance to heavy metals and to other antibiotic resistances, including

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pencillinase production.[19] The relative importance of these two resistance mechanisms is uncertain. Lacey and Rosdahl[20] determined the resistance mechanism in 26 patient isolates, and found plasmid mediated resistance in 18. Resistance in the other strains was assumed to be chromosomal. Various other resistance mechanisms have been reported, but are less well characterised.[18]

TRENDS IN FUSIDIC ACID RESISTANCE IN S AUREUS

There were a considerable number of reports of fusidic acid resistance rates in S aureus during the 1960s–1980s, which are summarised by Turnbridge and Collignon.[18] However, until recently there has been comparatively little contemporary data. Two types of data have been widely reported. Fusidic acid resistance rates in blood culture isolates relate to the potential application of systemic fusidic acid for deep seated staphylococcal infections, whereas data relating to isolates from skin and soft tissue sites pertain to possible indications for topical therapy.

Studies of S aureus bacteraemia up to the mid-1980s consistently showed fusidic acid resistance rates of 0–2.3%, with no significant difference between hospital and community acquired cases.[21–23] However, data from the UK suggest that there has subsequently been a rapid increase in the prevalence of fusidic acid resistance in blood culture isolates of S aureus. The rate of fusidic acid resistance in methicillin susceptible S aureus reported through the voluntary PHLS reporting scheme increased from 2.0% to 6.4% between 1990 and 2001.[14] MRSA were excluded from this analysis in order to eliminate the possible influence of clonal dissemination of MRSA. In our hospital, between 1995 and 2002, 18/322 (5.6%) blood culture isolates of S aureus were fusidic acid resistant (J Gray, unpublished data). The fusidic acid resistance rate in methicillin sensitive strains was 7.3%, whereas no MRSA were fusidic acid resistant. The increasing rate of fusidic acid resistance in blood culture isolates of S aureus is therefore not directly linked to the increase in MRSA bacteraemia that has occurred in the UK since the mid-1990s.[24]

Studies of fusidic acid resistance in isolates of S aureus from skin and soft tissue sites have shown much more variation in fusidic acid susceptibility, with resistance rates of 26–33% in burns, dermatology, and ITU patients.[18] Although in a recent Dutch study no fusidic acid resistance was detected in S aureus isolated from children presenting to primary care with impetigo,[25] in the UK fusidic acid resistance rates of between 11.5% and 18.5% have recently been reported,[2–8] with especially high rates in children.[3 5] While fusidic acid resistant strains are likely to be over-represented in these observational studies (because swabs from therapy resistant cases are more likely to be sent to the laboratory), resistance rates in laboratory isolates of S aureus have nevertheless increased by 50–200% during the 1990s.[2–8] A recent audit in our own hospital showed that 30 of 44 (68%) isolates of S aureus from children presenting to the Dermatology Department with impetigo were fusidic acid resistant. Even 50% of isolates from children with no history of fusidic acid treatment were fusidic acid resistant (SJ Beswick, unpublished data). Even more strikingly, in another study, where only two of the 46 children had received prior fusidic acid treatment, the resistance rate was 37.0%.[3]

FUSIDIC ACID PRESCRIBING AND THE EMERGENCE OF RESISTANCE

The ease with which fusidic acid resistance can be selected for in vitro is well established, and has led to the widely held view that fusidic acid as monotherapy risks treatment failure through selection of resistant mutants.[1 18] However, a limited number of studies, often involving relatively small numbers of patients, suggests that short term systemic or topical

treatment for acute infections is clinically and microbiologically effective. For acute skin and soft tissue infections, 5–10 day courses of fusidic acid have been associated with a low incidence(0–3.9%) of fusidic acid resistance emerging at the end of treatment.[18] However, these studies have rarely examined the impact of treatment on S aureus simultaneously present at carriage sites other than the site of infection. In one recent study, short term therapy was not associated with an increased fusidic acid resistance rate in post-treatment skin and nasal swabs.[26] However, only a small number of patients were studied, of whom 26% already had fusidic acid resistant S aureus in pretreatment swabs. Where treatment has been less successful is in hospitalised patients with chronic dermatological conditions, burns, or leg ulcers, where fusidic acid resistance rates of up to 43% following treatment have been reported.[27] This may be because the higher bacterial burden in patients with underlying skin disease and/or extensive infection may increase the risk of selection of resistant mutants; because microbiological cure is rarely achieved in such infections, again favouring the selection of resistant mutants; or because patient to patient transmission of fusidic acid resistant strains is occurring, favoured by the underlying skin condition and the selective pressure of fusidic acid use. Whatever the reason, hospital outbreaks can be successfully controlled by restricting the use of topical fusidic acid, coupled with improved infection control precautions.[28 29]

On the basis that short courses of fusidic acid as monotherapy have been reported to be effective, and that until recently most reports of high rates of fusidic acid resistance are in hospitals, it has been suggested that it is appropriate to use fusidic acid in primary care. A recent randomised trial in the Netherlands perpetuated this view, by concluding that fusidic acid as monotherapy was the treatment of choice for impetigo in children.[25] However, what the study actually showed was that topical fusidic acid administered together with povidone iodine was superior to povidone iodine alone: povidone iodine would have reduced the risk of selection of fusidic acid resistant mutants.

Recent evidence from the UK casts doubt on the view that fusidic acid use outside hospitals is justified. Although it must be borne in mind that samples are sent to the laboratory from only a small fraction of S aureus infections in primary care, there is evidence that the rate of fusidic acid resistance is increasing at least as rapidly in the community as in hospitals, and that this increase parallels increased prescribing of topical fusidic acid.[2–8] Moreover, a direct association between resistance rates and fusidic acid prescribing in different Welsh general practices has recently been reported.[30] Although fusidic acid resistance outside hospitals might be considered to be more likely to be due to selection of resistant mutants, rather than clonal dissemination, there are reports from the UK[3] and Sweden[31] of person to person transmission of fusidic acid resistant S aureus in the community.

The prevalence of MRSA in dermatology patients is increasing, raising concern that widespread use of topical fusidic acid may be a contributory factor.[32 33] In the UK, the predominant epidemic strains of MRSA have remained fusidic acid sensitive. However, a new epidemic strain (EMRSA-17) that is fusidic acid resistant has recently been identified in a number of centres, especially in southern England.[34] Thus while there is no direct evidence that fusidic acid use to date has promoted spread of epidemic strains of MRSA, it may become more important in the future.

RECOMMENDATIONS FOR THE USE OF FUSIDIC ACID IN TREATMENT OF INFECTIONS WITH S AUREUS

Topical antimicrobials are better tolerated than oral medication, which may improve compliance, particularly in

children.[35] For acute superficial skin infections, the efficacy of topical fusidic acid or mupirocin has been shown to be at least comparable to oral treatment, other than in more severe cases of impetigo.[36–40] A small number of studies comparing topical fusidic acid and mupirocin in staphylococcal skin infections have shown little difference in clinical outcome,[41 42] although in one study mupirocin was more effective in impetigo.[43]

Because of the perceived risk of promoting emergence and spread of resistance with topical antibiotic therapy, it is recommended that antibiotics used topically should be ones that are not used systemically.[44] While mupirocin fulfils this criterion, it is important also to recognise that mupirocin is the cornerstone of MRSA eradication therapy, and that widespread use risks affecting the ability of hospitals to control the spread of MRSA.[13]

Clinical Evidence, the UK Department of Health/BMJ information resource, concluded that there is no evidence to support the general use of antibiotic therapy in atopic dermatitis,[45] a view that has subsequently been endorsed by other authors.[46 47] Topical antibiotics are best avoided in any chronic skin condition, because of both doubtful efficacy and the higher risk of resistance emerging during therapy, at least with fusidic acid.[27–29] For acute superficial infections, the convenience of topical antibiotic therapy needs to be balanced against the risks of promoting clinically important resistance. Neither fusidic acid nor mupirocin are ideal from this point of view, especially in hospitals, and either agent must be used with caution. There are few data on alternative agents.

The use of systemic fusidic acid is much less controversial in that, where it is clinically indicated, it is already used almost exclusively as combination therapy.

CONCLUSION

In the UK at least, we are witnessing a rapid increase in the fusidic acid resistance rate in both the community and hospitals. Although this has happened at the same time as the incidence of MRSA has increased, the two observations are not directly related. The increase in resistance threatens to render fusidic acid ineffective for clinically important indications, such as the treatment of deep seated infections and the control of MRSA. Resistance can also lead to failure of topical therapy in primary care, which may in turn be leading to children presenting to hospital with worsening infections.

We have only a limited understanding of fusidic acid resistance at the genetic, epidemiological, and clinical level, and too many of our prescribing practices are based on outmoded data obtained from observational studies of small numbers of patients. There is a lack of good quality studies examining the clinical efficacy of topical fusidic acid in skin and soft tissue infections. We do not understand the impact of fusidic acid prescribing in the community on the emergence and spread of resistance, and whether any duration of monotherapy is safe. We do not know the relative importance of the different mechanisms of fusidic acid resistance, or the extent to which clonal spread in the community is contributing to the increase in fusidic acid resistance. Further studies are required to address questions such as these. In the meantime, given the paucity of suitable alternatives to fusidic acid for topical administration, it is difficult to recommend completely outlawing its use. However, we believe that it is sensible to restrict use of topical fusidic acid to short courses for patients outside hospital without underlying skin conditions, together with close monitoring of local antibiotic susceptibility patterns. Systemic fusidic acid should continue to be used only in combination with other agents where clinically indicated, and where the infecting bacteria are susceptible.

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