British Journal of Dermatology 1998; 139: 37–40.

Fusidic acid in dermatology

J.D.WILKINSON

Department of Dermatology, Amersham General Hospital, Amersham, Bucks HP7 0JD, U.K.

Accepted for publication 27 October 1998

Summary Fusidic acid is an antibiotic that belongs to a group of its own, the fusidanes. The molecule has a steroid-like structure but does not possess any steroid activity. The structure is thought to be responsible for the steroid-like high penetration, and for the fact that no cross-resistance or cross-allergy has been seen with other antibiotics in routine clinical use. The anti-microbial activity of fusidic acid is specifically aimed at the most common skin pathogens, including *Staphylococcus aureus*, towards which it is one of the most potent antibiotics. The place of fusidic acid in dermatology is in the treatment of mild to moderately severe skin and soft-tissue infections, e.g. impetigo, folicullitis, erythrasma, furunculosis, abscesses and infected traumatic wounds, whereas it is of less use in conditions such as hidradenitis suppurativa, chronic leg ulcers, burns and pressure sores. The topical combinations of fusidic acid with either betamethasone or hydrocortisone are extremely useful in the treatment of atopic dermatitis/eczema whenever staphylococcal/secondary infection is suspected, and in more persistent cases of eczema where staphylococcal superantigen may be playing an important exacerbating role.

Most of the issues concerned with the role of *Staphylococcus aureus* and skin bacteria as a cause or as an aggravating factor in eczema have already been considered in earlier reports, as has the choice of antibiotic and the role of bacterial resistance and of *S. aureus* as superantigen. This paper concentrates on the key criteria with respect to choice and use of antibiotics in superficial skin infections and in infected eczema, with focus on fusidic acid. In essence, this relates to effectiveness (especially against *S. aureus*), differential bacterial resistance, tolerance (especially potential for allergic contact dermatitis) and comparative cost/cost effectiveness.

Effectiveness

With *S. aureus* being the dominant pathogen in most skin and soft-tissue infections, effectiveness against this bacteria is essential when choosing antibiotic treatment. Furthermore, choosing an antibiotic that is specifically effective against *S. aureus*, more than other bacteria, will be beneficial in reducing the risk of development of resistance. Fusidic acid is often used as a topical treatment in skin and soft-tissue infections. This is based on its high effectiveness against *S. aureus* (minimal inhibitory concentration = 0·06 mg/L),[1] as well as its good penetration at a level similar to that of steroids,[2,3] ensuring a high concentration at the site of infection.

The efficacy of topical fusidic acid has been established over many years. Some of the early clinical studies were uncontrolled.[4–6] This is not surprising since they were conducted many years ago, but there are several good comparative studies worthy of comment. For example, in impetigo, fusidic acid ointment was shown to be significantly more effective than its vehicle.[7] Another comparative study for the same indication showed that fusidic acid was superior to the older neomycin/bacitracin combinations.[8,9] The comparative clinical and bacteriological efficacy of fusidic acid and mupirocin has been investigated in several clinical studies.[10–16] In one study, mupirocin appeared more effective than fusidic acid with respect to bacteriological clearance;[13] however, this finding was not confirmed in other comparative studies.[10–12] Overall, therefore, it appears that the two preparations are likely to be equally effective in routine clinical use.

Topical fusidic acid has also been compared with oral antibiotics in the treatment of superficial infections.[6,17,18] It was found to be at least as effective as and, in one study, superior to oral antibiotics.[18] Naturally, systemic therapy is necessary in infections where there is evidence of systemic spread or in debilitated or immunocompromised patients, but in the typical patient with a localized superficial infection, topical fusidic acid is appropriate. With regards to eczema, it has already been discussed in the previous sessions that *S. aureus* can play an essential

role here as well. Clinical and bacteriological efficacy and patient acceptability of two fusidic acid/corticosteroid preparations has been evaluated in prospective, randomized, comparative studies in eczema.

The combination of fusidic acid and hydrocortisone has been compared with hydrocortisone alone in atopic eczema.[19] Combined therapy was significantly more effective in eradicating bacterial pathogens (almost exclusively *S. aureus*) and the clinical response appeared better in patients given the combination. Overall, fusidic acid/hydrocortisone treatment was significantly superior to hydrocortisone alone on combined clinical and bacteriological grounds. Fusidic acid and hydrocortisone has been shown to produce a faster clinical improvement than hydrocortisone + miconazole in clinically infected eczema, and the fusidic acid combination had advantages in terms of bacteriological efficacy and patient acceptability.[20]

Another fusidic acid/corticosteroid combination, this time with betamethasone, has been evaluated in the treatment of infected eczema.[21–25] Again, the combination was considered superior to the corticosteroid alone.[21] Fusidic acid/betamethasone and neomycin/betamethasone have been shown to be equally effective.[23,24] Comparative efficacy with a gentamicin/betamethasone combination was also established.[22] In a recently published 4-week study comparing fusidic acid/betamethasone and a clioquinol/betamethasone combination in patients with clinically infected hand eczema, a significantly better bacteriological outcome was seen with fusidic acid/betamethasone, although the two creams were equally effective clinically.[25] Patient acceptability for the fusidic acid cream was also superior to that of the clioquinol cream.[25]

When treating infected eczema where bacteria (particularly *S. aureus*) are known or suspected to be present, it is recommended to treat with an antibiotic/steroid combination for approximately 2 weeks, until the bacteria can be expected to be eradicated, and then continue treatment with steroid alone. An antibiotic/hydrocortisone combination is usually preferred over an antibiotic/betamethasone combination when treating children or treating eczema on the face.

In most countries fusidic acid is also available as tablets, giving the opportunity to choose systemic or combined treatment of staphylococcal skin infections if considered necessary. The dose of one tablet (250 mg) twice daily is recommended as it is as effective, both clinically and bacteriologically, as a higher dose and is better tolerated.[26,27] Whilst infections due to *S. aureus* is the area where fusidic acid is most widely used, it should not be overlooked that it is an effective topical treatment for erythrasma.[28,29] In a double-blind trial, topical fusidic acid proved as effective as erythromycin tablets and both were significantly better than placebo.[29]

Bacterial resistance

Development of resistance towards commonly used antibiotics is an issue of growing concern. When choosing antibiotics in dermatology it is important to target the specific bacteria involved in the lesions, thus reducing the risk of developing resistance. The tendency to induce resistance varies with the different antibiotics, depending on the mechanism involved when the bacteria develops resistance to the particular antibiotic.

Fusidic acid resistance can be selected readily *in vitro*, but as the mutants grow slower than the sensitive bacteria, they have a lower pathogenicity and revert to full sensitivity when fusidic acid is not present.[30] Naturally occurring resistance to fusidic acid has also been known, probably associated with a permeability barrier at the cell surface reducing entry of the antibiotic.[30] Shanson, after reviewing the published literature on the use of topical fusidic acid in treating skin infections, concluded that short courses where unlikely to be epidemiologically harmful.[30] Over more than 35 years of extended usage of fusidic acid, the level of resistance has remained low.[31–33]

There is no cross-resistance between fusidic acid and other antibiotics used clinically.[34] This might be due to the fact that fusidic acid belongs to a group of its own, the fusidanes, having a structure being very different from all other classes of antibiotics such as the beta-lactams, aminoglycosides and macrolides, thus reducing the likelihood of having the same mechanism of resistance (Fig. 1).

Sensitization

The capacity for allergic contact sensitization is an important consideration especially where topical antibiotics or steroid/antibiotic combinations are used repetitively on occluded or damaged skin. The incidence of allergic reactions to fusidic acid remains low[35] and cross-allergy has not been seen. Cross-resistance, however, might be explained by the structure of fusidic acid being different from all other antibiotics. Certain sites, such as the lower leg (in patients with leg ulcers and stasis eczema) and perineum, and patients with burns/pressure sores, otitis externa, etc., are notorious for their capacity to develop secondary contact sensitization. For

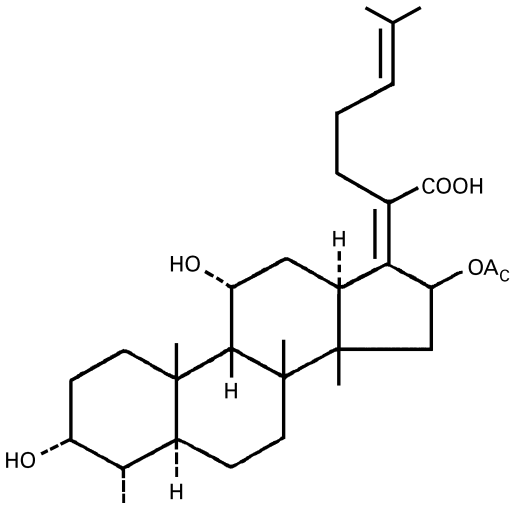

Figure 1. Structure of fusidic acid, a fermentation product of *Fusidium coccineum*.

this reason neomycin, soframycin and gentamicin containing topical preparations have to be used with great caution, especially in these vulnerable areas.

Cost-effectiveness

Rational prescribing of topical antibacterials must consider the relative cost-effectiveness of different preparations. Relative cost-effectiveness is of course dependent to a major degree on the local pricing situation. In the U.K., whilst topical fusidic acid remains more expensive than some of the older, more sensitizing topical antibiotics, the actual cost is still not great. For example, in a pharmacoeconomic analysis relating to the cost-effectiveness of treating superficial skin infections, the average cost at 1992 prices of successfully treating a patient (clinical 'cure' or 'improvement' and 'satisfactory overall acceptability') with superficial skin sepsis was just over GBP 3.[36] When comparing with a newer antibiotic such as mupirocin, topical fusidic acid is 40–80% more cost-effective.[36]

References

1 Godtfredsen W, Roholt K, Tybring L. Fucidin A new orally active antibiotic. *Lancet* 1962; 1: 928–31.
2 Stuttgen G, Bauer B. Penetration and permeation into human skin of fusidic acid in different galenical formulation. *Arzneimittelforschung* 1988; 38: 730–5.
3 Vickers CFH. Percutaneous absorption of sodium fusidate and fusidic acid. *Br J Dermatol* 1969; 81: 902–8.
4 Sobye P. Cutaneous *Staphylococcus aureus* infections treated with fucidin ointment. *Ugeskr Laeger* 1966; 128: 204–7.
5 Flemming JM, Mansfield AO. The place of topical oitment in the treatment of common skin infections. *Br J Clin Pract* 1967; 21: 529–31.
6 Jackson N, Verling W, Deasy DF *et al*. Treatment of cutaneous infections with fucidin ointment. *Clin Trials J* 1966; 3: 591–5.
7 Yasuda T. Double-blind study as the method of evaluation of the effect of antibiotic ointments. An experience with a new antibiotic, sodium fusidate. *Hifuka-No-Rinsho (Clinical Dermatology)* 1971; 13: 343–57.
8 Cassels-Brown G. A comparative study of Fucidin ointment and cicatrin cream in the treatment of impetigo. *Br J Clin Pract* 1981; 35: 153–5.
9 Baldwin RJT, Cranfield R. A multi-centre general practice trial comparing fucidin ointment and Fucidin cream. *Br J Clin Pract* 1981; 35: 157–9.
10 Morley PAR, Munot LD. A comparison of sodium fusidate ointment and mupirocin ointment in superficial skin sepsis. *Curr Med Res Opin* 1988; 11: 142–7.
11 Sutton JB. Efficacy and acceptability of fusidic acid cream and mupirocin ointment in facial impetigo. *Curr Ther Res* 1992; 51: 673–8.
12 Langdon CG, Mahapatra KS. Efficacy and acceptability of fusidic acid cream and mupirocin ointment in acute skin spesis. *Curr Ther Res* 1990; 48: 174–80.
13 White DG, Collins PO, Rowsell B. Topical antibiotics in the treatment of superficial skin infections in general practice – a comparison of mupirocin with sodium fusidate. *J Infect* 1989; 18: 221–9.
14 Ancill RJ. Double-blind comparison of mupirocin and fusidic acid in skin infections of the demented elderly. *Can J Dermatol* 1989; 1: 19–22.
15 Lewis-Jones S, Hart CA, Vickers CFH. Bactroban ointment versus fusidic acid in acute primary skin infections in children. In: *Bactroban (Mupirocin)* (Dobson RL, Leyden JJ, Noble WC, Price JD, eds). Excerpta Medica, 1985: 103–8.
16 Gilbert M. Topical 2% mupirocin versus 2% fusidic acid ointment in the treatment of primary and secondary skin infections. *J Am Acad Dermatol* 1989; 20: 1083–7.
17 Macotela-Ruiz E, Duran Bermudez H, Kuri Con FJ *et al*. Evaluation of the efficacy and toxicity of local fusidic acid compared with oral dicloxacillin in skin infections *Med Cut I LA* 1988; 16: 171–3.
18 Pakrooh H. A comparison of sodium fusidate ointment ('Fucidin') alone versus oral antibiotic therapy in soft-tissue infections. *Curr Med Res Opin* 1977/78; 5: 289–94.
19 Ramsay CA, Savoie LM, Gilbert M *et al*. The treatment of atopic dermatitis with topical fusidic acid and hydrocortisone acetate. *J Eur Acad Dermatol Venereol* 1996; 7 (Suppl. 1): S15–22.
20 Poyner TF, Dass BK. Comparative efficacy and tolerability of fusidic acid/hydrocortisone cream (Fucidin H cream) and miconazole/hydrocortisone cream (Daktacort cream) in infected eczema. *J Eur Acad Dermatol Venereol* 1996; 7 (Suppl. 1): S23–30.
21 Hjorth N, Schmidt H, Thomsen K. Fusidic acid plus betamethasone in infected or potentially infected eczema. *Pharmatherapeutica* 1985; 4: 126.
22 Strategos J. Fusidic acid-betamethasone combination in infected eczema: an open, randomized comparison with gentamicin-betamethasone combination. *Pharmatherapeutica* 1986; 4: 601–6.
23 Wilkinson JD, Leigh DA, Menday AP. Comparative efficacy of betamethasone and either fusidic acid or neomycin in infected or potentially infected eczema. *Curr Ther Res* 1985; 38: 177–82.
24 Javier PR, Ortiz M, Torralba M *et al*. Fusidic acid/betamethasone in infected dermatoses – a double-blind comparison with neomycin/betamethasone. *Br J Clin Pract* 1986; 40: 235–8.
25 Hill VA, Wong E, Corbett MF. Comparative efficacy of betamethasone/clioquinol (Betnovate-C) cream and betamethason/fusidic

acid (Fucibet) cream in the treatment of infected hand eczema. *J Dermatol Treat* 1998; 9: 15–9.
26 Carr WD, Wall AR, Georgala-Zervogiani S *et al*. Fusidic acid tablets in patients with skin and soft-tissue infection: a dose-finding study. *Eur J Clin Res* 1994; 5: 87–95.
27 Nordin P, Mobacken H. A comparison of fusidic acid and fluclox-acillin in the treatment of skin and soft-tissue infection. *Eur J Clin Res* 1994; 5: 97–106.
28 Macmillan AL, Sarkany I. Specific topical therapy for erythrasma. *Br J Dermatol* 1970; 82: 507–9.
29 Hamann K, Thorn P. Systemic or local treatment of erythrasma? A comparison between erythromycin tablets and Fucidin cream in general practice. *Scand J Prim Health Care* 1991; 9: 35–9.
30 Shanson DC. Clinical relevance of resistance to fusidic acid in *Staphylococcus aureus*. *J Antimicrob Chemother* 1990; 25 (Suppl. B): 15–21.
31 Speller DCE, Johnson AP, James D *et al*. Resistance to methicillin and other antibiotics in isolates of *Staphylococcus aureus* from blood and cerebrospinal fluid, England and Wales 1989–95. *Lancet* 1997; 350: 323–5.
32 Faber M, Rosdahl VT. Susceptibility to fusidic acid among Danish *Staphylococcus aureus* strains and fusidic acid consumption. *J Antimicrob Chemother* 1990; 25 (Suppl. B): 7–14.
33 Moorhouse B, Fenelon L, Hone R *et al*. Staphylococcus aureus sensitivity to various antibiotics – a national survey in Ireland 1993. *Ir J Med Sci* 1996; 165: 42–3.
34 Verbist L. The antimicrobial activity of fusidic acid. *J Antimicrob Chemother* 1990; 25 (Suppl. B): 1–5.
35 Wakelin SH, Shaw S, Marren S *et al*. Allergic contact dermatitis to newer topical anti-staphylococcal agents. *Br J Dermatol* 1996; 135 (Suppl. 47): 17.
36 Sutton JB, Langdon CG. An analysis of the cost effectiveness of fusidic acid cream and mupirocin ointment in the treatment of superficial skin sepsis in general practice. *Br J Med Econ* 1993; 6: 37–43.