Nadifloxacin: a quinolone for topical treatment of skin infections and potential for systemic use of its active isomer, WCK 771

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Nadifloxacin is a potent, broad-spectrum, quinolone agent approved for topical use in acne vulgaris and skin infections in Japan. As exposure of pathogenic and colonising bacteria to antibiotics results in drug resistance, it is not desirable to use an important, broad-spectrum antibiotic, which belongs to a class of agents widely used systemically to treat a wide variety of infections, as a topically applied preparation. On this basis, nadifloxacin is not a good option for topical treatment of acne when other effective non-antibiotic treatments are available. Nadifloxacin has potential as a topical agent for short-term treatment of skin infections. The arginine salt of its S-(-) isomer is being developed as a parenteral agent based on its potency against methicillin and quinolone-resistant Staphylococcus aureus.

Keywords: acne vulgaris, methicillin-resistant Staphylococcus aureus, MRSA, nadifloxacin, Propionibacterium acnes, quinolone-resistant Staphylococcus aureus, Staphylococcus epidermidis

1. Introduction

Nadifloxacin is a highly potent quinolone antimicrobial agent developed in Japan as compound OPC-7251 (Otsuka Pharmaceuticals, Tokyo, Japan) with broad-spectrum activity against a wide variety of pathogenic bacterial species [1]. Although the agent was initially investigated for oral or parenteral use as it was highly potent, its pharmacokinetic properties made it unsuitable for systemic administration. However, it was found to be very active in a 1% topical cream formulation, leading to the development of a topical formulation [2]. It received approval in Japan for use in acne vulgaris in 1993 and the indications were expanded in 1998 to include other skin infections, including those caused by methicillin-resistant staphylococci and, should they arise, staphylococci with raised glycopeptide minimum inhibitory concentrations (MICs) [1]. An arginine salt of the active isomer of nadifloxacin, WCK 771 (Wockhardt Limited, Aurangabad, India), has been developed, with good systemic pharmacokinetic properties, and this formulation is currently in human clinical trials in India for intravenous use [3].

Acne vulgaris, the primary indication for which topical nadifloxacin is approved, is a disease largely of adolescence and early adulthood, affecting > 80% of those between the ages of 12 and 24 years in developed countries [4,5]. Although not a life-threatening disease, it is responsible for a great deal of psychological distress during an already frequently difficult formative period [6,7]. Serious disease can result in scarring and disfigurement [8]. The disease is multifactorial, being associated with hormonal, dietary, genetic and bacterial interactions. With the onset of adolescence,
and increasing quantities of circulating androgens, sebum production increases. Abnormal follicular epithelial differentiation can lead to thickening in the upper follicle canal, causing a thickened stratum corneum and plugging of the follicle, leading to the precursor of acne, the microcomedo. The lipid-rich clogged follicle is an excellent growth medium for Propionobacterium acnes, the most common bacterial species associated with acne vulgaris. However, the role of P. acnes in the pathogenesis of acne is not clear, with current evidence indicating that this organism is not the initiating factor in acne, but seems to have a role in exacerbating tissue damage, possibly associated with stimulation of Toll-like receptors or IL-1α production [9]. It is not clear whether the effect of antibiotics on acne is the result of antibacterial or anti-inflammatory activity. Several other skin diseases can be similar in appearance to acne, but are caused by other mechanisms and are more likely to involve different bacteria. Nadifloxacin cream has been proposed for and been found to be useful in folliculitis, sycosis vulgaris, impetigo, infected wounds and atopic dermatitis with secondary infection [10-14]. Most of these infections are caused by staphylococci and pyogenic streptococci [15-19].

2. Market overview

There is, as of yet, no single treatment for acne vulgaris that works in all, or even most, cases. The choice of treatment is dependent primarily upon the extent of disease and probability of physical or psychological scarring. Mild disease is usually responsive to topical treatment, either with a retinoid, an anti-septic, such as benzoyl peroxide or azelaic acid, an antibiotic or a combination of these [20], whereas moderate-to-severe acne vulgaris must often be treated systemically [21,22].

Oral isotretinoin has proved effective, but has adverse effects that make its use contraindicated in many patients and necessitates close monitoring of liver function [23]. Long-term use of oral antibiotics is often accompanied by adverse side effects, as well as a high probability of selecting for resistant mutants. Topical antibiotics are somewhat effective and lack the systemic side effects, but also select for resistance. Topical clindamycin has been associated with pseudomembranous colitis due to toxins produced by Clostridium difficile in two patients [24,25]. The most effective acne treatments have been combinations of retinoids, anti-septics and, in some cases, antibiotics. Retinoids, either topical or oral, when used in combination with an antibiotic, can normalise the follicular epithelium, minimise inflammation and reduce bacterial proliferation [26]. Benzoyl peroxide is equally effective with or without an antibiotic, although it has been shown to decrease the development of antibiotic resistance when used in combination [27]. In addition, benzoyl peroxide and a retinoid can be used effectively as combination therapy without involving an antibiotic and all of the complicating sequelae involved with such agents, especially selective pressure for drug resistance.

Treatment of other skin infections is less complicated because of the shorter duration of treatment that is necessary, especially with antibiotics. Gram-positive bacteria, such as staphylococci and streptococci, are the most common cause of folliculitis, impetigo and skin infections, and are generally more responsive to antimicrobials than the anaerobic P. acnes found in acne. The caveat is that these bacteria, particularly staphylococci, are increasingly drug resistant, and empiric antimicrobial choices must be based on the local background rates of methicillin resistance in the community. As these diseases are not usually life threatening, culture of the affected area may be indicated prior to use of a high activity, broad-spectrum antibiotic, such as nadifloxacin.

An important principle that should be applied to the use of topical antimicrobial agents in acne vulgaris is that these agents should belong to different drug classes to systemic agents, so that use of topical agents does not compromise the use of systemic agents by inducing resistance to the latter group and vice versa [28]. However, use of systemic agents, including tetracycline and erythromycin, also induces resistance in skin flora. Prolonged or frequent intermittent use of topical agents results in increased resistance that is proportional to the duration of therapy. Resistant skin flora, such as Staphylococcus epidermidis, maintain a pool of resistance genes that can be transferred to other species.

3. Chemistry

Nadifloxacin is a chiral quinolone drug compound made up of a lipophilic tricyclic benzoquinolizine nucleus with a 4-hydroxyiperidine moiety at the C8 position. The levorotatory S-(-) compound is 64 – 256-times more potent than its R-(+) isomer and approximately two times as active as the racemate against Gram-positive and -negative bacteria [3]. The arginine salt of S-(-) nadifloxacin, WCK 771, has been investigated for parenteral use in animal models and is currently in Phase II human trials in India [29,30]. Structures of the isomers of nadifloxacin and the arginine salt of its active isomer, WCK 771, are shown in Figure 1.

4. Microbiology

Nadifloxacin is a chiral quinolone drug compound that is active against Gram-positive and -negative bacteria [3]. The topical compound uses RS-(+/-)-nadifloxacin with an approved indication for treatment of P. acnes acne vulgaris in Japan. The l-arginine salt of the (S-) isomer of nadifloxacin is currently being investigated in India for intravenous usage for treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections [3].

In vitro activity of nadifloxacin and the S-(-)-arginine salt isomer, WCK 771 is summarised in Table 1, and in comparison with other agents in Table 2. MICs of nadifloxacin against clinical isolates of P. acnes from patients with acne vulgaris were in the range of 0.1 – 0.78 µg/ml, with 50% of isolates
(MIC$_{50}$) being inhibited by 0.2 µg/ml and 90% (MIC$_{90}$) at 0.39 µg/ml for the 50 strains tested [31]. Nadifloxacin was among the more potent agents tested and compared favourably to ofloxacin, which had an MIC range of 0.39 – 3.13 µg/ml with an MIC$_{90}$ of 1.56 µg/ml. Only ampicillin, with an MIC range of 0.025 – 0.2 µg/ml and MIC$_{90}$ of 0.1 µg/ml, were more potent.

Staphylococcal isolates tested against nadifloxacin and other antimicrobial agents showed good in vitro activity for nadifloxacin against methicillin-resistant and susceptible strains [32]. Staphylococcus aureus had MIC ranges of 0.015 – 2.0 µg/ml and an MIC$_{90}$ of 1.0 µg/ml. S. epidermidis had MIC ranges of 0.03 – 2.0 µg/ml MIC$_{90}$ of 2.0 µg/ml. The 27 P. acnes tested in this study had an MIC range of 0.25 – 0.5 and an MIC$_{90}$ of 0.5 µg/ml [32]. A 2004 study of bacteria isolated from bacterial skin infections showed similar in vitro results [18].

As is the case with other quinolones, the molecular targets of nadifloxacin are DNA gyrase and topoisomerase IV, enzymes associated with DNA replication [33]. In staphylococci, DNA gyrase is encoded by $gyrA$ and $gyrB$ genes, whereas topoisomerase IV is encoded by $grlA$ and $grlB$ genes. The primary target of nadifloxacin in staphylococci is suggested to be DNA gyrase. Quinolone resistance mechanisms are mediated via mutations in the target enzymes and overexpression of the norA gene, which encodes an efflux pump. Nadifloxacin is not affected by norA expression, but is affected by DNA gyrase and topoisomerase IV mutations, with MICs increasing up to 2000-fold for strains with mutations in both enzymes [33].

A Japanese study by Nishijima et al. of S. aureus skin infection strains showed a small increase in the MIC$_{90}$ (from 0.05 to 0.1 µg/ml) for nadifloxacin over the course of the testing period July 1994 to May 1999, with the MIC$_{90}$ of ofloxacin
Nadifloxacin

Table 1. In vitro activity of nadifloxacin and its S-(-)-arginine salt, WCK 771.

<table>
<thead>
<tr>
<th>Data reference source/date</th>
<th>Species</th>
<th>Number of isolates tested</th>
<th>MIC range (µg/ml)</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/ml)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nishijima, 2002 [11]</td>
<td>Staphylococcus aureus</td>
<td>172</td>
<td>NP</td>
<td>0.025</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>130</td>
<td>NP</td>
<td>0.025</td>
<td>0.1</td>
</tr>
<tr>
<td>Haustein, 1997 [10]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td>24</td>
<td>0.05 – 0.2</td>
<td>0.05</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>Coagulase-negative staphylococci</td>
<td>65</td>
<td>0.05 – 3.13</td>
<td>0.05</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Propionobacterium acnes</td>
<td>34</td>
<td>0.05 – 0.78</td>
<td>0.2</td>
<td>0.39</td>
</tr>
<tr>
<td>Kurokawa, 1999[28]</td>
<td>P. acnes</td>
<td>50</td>
<td>0.1 – 0.78</td>
<td>0.2</td>
<td>0.39</td>
</tr>
<tr>
<td>Kurokawa, 1991[2]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yamakawa, 2002[29]</td>
<td>Streptococcus pyogenes</td>
<td>26</td>
<td>0.1 – 1.78</td>
<td>0.39</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>Streptococcus pneumoniae</td>
<td>42</td>
<td>0.39 – 3.13</td>
<td>0.78</td>
<td>1.56</td>
</tr>
<tr>
<td>Jacobs, 2004[30]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Quinolone-susceptible S. aureus</td>
<td>43</td>
<td>0.008 – 0.015</td>
<td>0.008</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>Quinolone-resistant S. aureus</td>
<td>73</td>
<td>0.06 – 4.0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Quinolone-susceptible S. epidermidis</td>
<td>44</td>
<td>0.008 – 0.12</td>
<td>0.015</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Quinolone-resistant S. epidermidis</td>
<td>70</td>
<td>0.25 – 4.0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Patel, 2004[32]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methicillin-susceptible S. aureus</td>
<td>244</td>
<td>0.015 – 0.25</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Methicillin resistant S. aureus</td>
<td>176</td>
<td>0.015 – 4.0</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Methicillin susceptible S. epidermidis</td>
<td>58</td>
<td>0.015 – 0.25</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Methicillin resistant S. epidermidis</td>
<td>22</td>
<td>0.03 – 1</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>

MIC<sub>50</sub>: Minimum inhibitory concentration inhibiting 50% of isolates; MIC<sub>90</sub>: Minimum inhibitory concentration inhibiting 90% of isolates; NP: Not provided.

Increasing from 0.78 to 3.13 – 12.5 µg/ml [11]. Agents from several antimicrobial classes, including ofloxacin, were tested and all had MIC<sub>90</sub> values greater than that of nadifloxacin and most of these increased over the course of the testing period, during which methicillin resistance increased from 10 to 20%. Vancomycin and fusidic acid MIC<sub>90</sub> values remained low and stable at 1.0 – 2.0 and 0.5 – 0.25 µg/ml, respectively, and no vancomycin-intermediate or -resistant strains were detected. Strains collected between June 1999 and November 2000 were also tested against all agents that were tested in the earlier periods, except for nadifloxacin; the MIC<sub>90</sub> of ofloxacin increased to 25 µg/ml during this period and it is likely that the MIC<sub>90</sub> of nadifloxacin would be between 0.5 and 1 µg/ml, based on other comparative studies [34].

WCK 771, the arginine salt of S-(-) nadifloxacin, has shown good in vitro activity against methicillin-susceptible and -resistant strains of S. aureus and coagulase-negative staphylococci, including strains considered resistant to quinolones (ciprofloxacin MIC > 2.0 µg/ml) [30]. In a study of 116 S. aureus isolates and 114 S. epidermidis isolates, WCK 771 MIC<sub>90</sub> values were 0.015 – 0.03 µg/ml against quinolone-susceptible, versus 1.0 µg/ml against quinolone-resistant, isolates (Table 2) [34]. Based on MIC<sub>90</sub> values, WCK 771 was 4-fold more potent than moxifloxacin, 8-fold more potent than gatifloxacin, and 8- to 16-fold more potent than levofloxacin against quinolone-susceptible staphylococci and 32-fold more potent than levofloxacin against quinolone-resistant staphylococci.
Whereas MIC\textsubscript{90} values of WCK 771 against quinolone resistant staphylococci were 32 – 64-fold higher than against quinolone-susceptible isolates, MIC\textsubscript{90} values of levofloxacin against quinolone-resistant staphylococci (32 µg/ml) were 128-fold higher than against quinolone-susceptible isolates (0.25 µg/ml). WCK 771 was also bactericidal against a vancomycin-resistant strain recently isolated in the US [35]. The high potency of WCK 771 against quinolone-resistant staphylococci suggests the agent’s potential value as an antimicrobial of last resort in highly resistant \textit{S. aureus} infections if its pharmacokinetic properties are favourable.

5. Pharmacokinetics, pharmacodynamics and metabolism

As pharmacokinetics, tissue penetration and rates of metabolism are not measurable for the topical formulations of agents, these values have not been determined for topical use of

### Table 2. 	extit{In vitro} activity of nadifloxacin and comparator agents. Table shows MIC\textsubscript{90} value in µg/ml or MIC range in µg/ml when \( n < 20 \).

<table>
<thead>
<tr>
<th>Species (n), data source, date</th>
<th>Nadifloxacin*</th>
<th>Levofloxacin</th>
<th>Gatifloxacin</th>
<th>Moxifloxacin</th>
<th>Vancomycin</th>
<th>Clindamycin</th>
<th>Minocycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{S. aureus} (172) [11] 1994 – 1995</td>
<td>0.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>2</td>
<td>0.39</td>
<td>0.39</td>
</tr>
<tr>
<td>\textit{S. aureus} (130) [11] 1998 – 1999</td>
<td>0.1</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>1</td>
<td>&gt;100</td>
<td>0.2</td>
</tr>
<tr>
<td>\textit{S. aureus} (116) [30]</td>
<td>1</td>
<td>32</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>1</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Quinolone susceptible (43)</td>
<td>0.015</td>
<td>0.25</td>
<td>0.12</td>
<td>0.06</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Quinolone resistant (73)</td>
<td>1</td>
<td>32</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Methicillin-susceptible \textit{S. aureus} (224) [32]</td>
<td>0.03</td>
<td>0.5</td>
<td>NS</td>
<td>0.12</td>
<td>2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Methicillin-resistant \textit{S. aureus} (176) [32]</td>
<td>1</td>
<td>16</td>
<td>NS</td>
<td>4</td>
<td>2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Vancomycin-intermediate \textit{S. aureus} (3) [30]</td>
<td>1</td>
<td>8 – 16</td>
<td>NS</td>
<td>4</td>
<td>4 – 16</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Vancomycin-resistant \textit{S. aureus} (1) [31]</td>
<td>0.5</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>32</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci (114) [30]</td>
<td>0.5</td>
<td>16</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Quinolone susceptible (44)</td>
<td>0.03</td>
<td>0.25</td>
<td>0.25</td>
<td>0.12</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Quinolone resistant (70)</td>
<td>1</td>
<td>32</td>
<td>&gt;4</td>
<td>&gt;4</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Methicillin-susceptible \textit{S. epidermidis} (58) [32]</td>
<td>0.03</td>
<td>0.5</td>
<td>NS</td>
<td>0.06</td>
<td>2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Methicillin-resistant \textit{S. epidermidis} (22) [32]</td>
<td>1</td>
<td>8</td>
<td>NS</td>
<td>2</td>
<td>2</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>\textit{P. acnes} (50) [28]</td>
<td>0.39</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>\textit{P. acnes} (39) [2]</td>
<td>0.2</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.1</td>
<td>0.39</td>
</tr>
<tr>
<td>\textit{Streptococcus pyogenes} (26) [29]</td>
<td>0.78</td>
<td>1.56</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>0.1</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Includes nadifloxacin and its S-(-)-arginine salt, WCK 771.

MIC\textsubscript{90}: Minimum inhibitory concentration inhibiting 90% of isolates; NS: Not studied.
nadifloxacin. However, topical use of nadifloxacin results in little systemic penetration [12].

The pharmacokinetics of the arginine salt of the active isomer of nadifloxacin, WCK 771, have been studied, as this agent is under development for parenteral administration. Phase I clinical studies of the intravenous formulation using a 1-h infusion of doses of 4800 mg showed linearity in C_max and AUC throughout the dose range [3]. A dose of 600 mg achieved a nonprotein-bound C_max value of 4.0 µg/ml with a half-life of 6 h. This level seems to be therapeutically adequate with twice-daily dosing to treat target pathogens, such as methicillin- and quinolone-resistant staphylococci and vancomycin-resistant enterococci, with WCK 771 MICs of 0.5 µg/ml.

6. Animal studies

The arginine salt of S(-) nadifloxacin, WCK 771, was examined in several animal models, including systemic infections and staphylococcal cellulitis with both methicillin-susceptible and -resistant strains, including those resistant to other quinolones. Both oral and parenteral routes were found to be effective in treating all of the infections [30].

5. Clinical efficacy

An early study included 28 patients with acne who were treated in a double-blind comparison of nadifloxacin (OPC-7251) 1% topical cream against the cream base. The patients showed a significant post-treatment effect in both clinical response and decreased P. acnes bacterial count when treated with the active agent [2]. Statistically significant reductions in viable P. acnes and S. epidermidis recovered after treatment were found. Nadifloxacin (OPC-7251) MICs for 39 P. acnes and 17 S. epidermidis strains isolated from patients in this study were 0.1 – 0.2 and 0.02 – 0.1 µg/ml, respectively.

Further studies have involved 31 – 85 patients with acne [36-38] and 35 – 101 patients with other bacterial skin diseases, including atopic dermatitis, folliculitis, sycois vulgaris and impetigo contagiosa [10,12,13]. A noncomparative study of nadifloxacin cream in 31 patients with facial acne found effectiveness in 71% [37]. Among these patients, 81% had bacteria detected before starting the medication, most (63.6%) of which were P. acnes; whereas S. epidermidis was detected in 18.2%. After treatment, the rate of bacterial detection was 40.9% for P. acnes and 4.5% for S. epidermidis. No drug resistance was detected in any of the bacteria isolated after treatment. A study of 35 acne patients using nadifloxacin cream on one side of the face and a benzoyl peroxide lotion on the other, applied twice daily for 2 – 12 weeks, showed improvement for 77.4% of the nadifloxacin-treated cheeks compared with 41.9% for the benzoyl peroxide lotion [38]. Another acne study, using 85 patients, found 81% clinical effectiveness [36]. In 76.5% of these patients a bacterial pathogen was isolated before initiation of treatment; P. acnes strains were found in 67.1%. No changes in MIC values were noted after completion of treatment.

Among the studies of nadifloxacin cream used to treat other bacterial skin diseases, most of which involved staphylococci, including methicillin-resistant strains, the drug was found to be very effective. Kimata reported use of nadifloxacin cream to treat atopic dermatitis casued by MRSA in children and found eradication in all 18 patients treated, whereas all of the 17 control patients had bacterial growth after the treatment period [13]. Likewise, Asada et al. reported eradication of 100% of Gram-positive cocci in single-species infections and an overall rate of all bacterial eradication of 86.9% for the 107 strains isolated from the 78 patients treated for folliculitis and sycois vulgaris infections [12]. The study of Haustein et al. reports on 101 patients with various skin infections treated with nadifloxacin cream [10]. A total of 77 different bacterial strains were isolated from these patients, most of which were coagulase-negative staphylococci (n = 47) or S. aureus (n = 24). After treatment, 74% of bacteria were eradicated. The one P. acnes strain was not eradicated and 15 of the 47 coagulase-negative staphylococci remained after treatment. Nadifloxacin MICs did not increase in any of the strains remaining following treatment.

The previously mentioned reports noted that nadifloxacin was well tolerated and that no cases of photosensitivity were reported. No photosensitivity was detected in toxicological studies in animals; no cases of photosensitivity were reported during pharmacovigilance in Japan between 1993 and 2005, where over 45 million units of topical nadifloxacin were used (pers. commun.: Otsuka Pharmaceuticals, Tokyo, Japan [2006]).

These studies show no evidence that topical use of nadifloxacin is associated with development of resistance to this agent or to other quinolones. Nevertheless, quinolone resistance has developed in staphylococci and the high level of quinolone resistance in S. aureus, which is ~30% in many countries at present, is the result of extensive systemic use of these agents [17]. However, it is important to note that the magnitude of the difference between quinolone-susceptible and -resistant staphylococci is similar for all quinolones studied to date, so that systemic use can compromise topical use and vice versa. The principle of using different classes of agents for topical and systemic use to minimise this problem should be applied [28]. Although new, potent quinolones have been developed, with activity against many isolates that are resistant to older quinolones, further development of resistance may result in isolates that are also resistant to the new agents.

6. Safety and tolerability

In the earlier studies, no adverse events were reported [2]. In one study involving 78 patients and another in 35, one patient in each of the studies complained of mild itching that did not necessitate discontinuation of the drug [12,38]. In the acne study involving 85 patients, three adverse events were reported, all of which were localised: mild irritation, flush and
increase, and throughout the world, rates of resistance have been observed. 

As such, fusidic acid is an important agent to maintain in the clinical challenge, as well as vancomycin-intermediate and -resistant staphylococci. Such resistant organisms will be resistant to all currently available quinolones and quinolones in development at present, as well as cephalosporins likely to be developed in the future.

In September, the FDA withdrew approval of the fluoroquinolone enrofloxacin for use in poultry after receiving convincing evidence of breakthrough human disease with quinolone-resistant strains of Campylobacter spp. The FDA Commissioner referred to the loss of the only ‘empiric treatment… currently available’ to treat enteric bacterial infections, which ‘may prolong the duration of disease and increase the risk of complications’.

9. Expert opinion

Although nadifloxacina has good efficacy against P. acnes and could prove useful for treatment of acne vulgaris, it is an extremely potent broad-spectrum quinolone antibiotic agent with activity against quinolone-resistant staphylococci. It is, consequently, far too valuable an agent for the treatment of resistant strains of S. aureus to ‘waste’ on diseases, such as acne vulgaris, that are effectively treated with other agents. Nadifloxacin holds promise for short-term topical use in treating more complicated skin or soft tissue infections, especially those known to be caused by resistant staphylococci. Success in the current clinical trials of the arginine salt of the active isomer of nadifloxacin, WCK 771, for parenteral use may provide an agent that is able to fill the extremely important niche of treating methicillin- and quinolone-resistant staphylococci, which have emerged as a major clinical challenge, as well as vancomycin-intermediate and -resistant staphylococci that have recently appeared and that are very likely to emerge as a major clinical problem in the near future.

Short-term use of topical agents of classes that are used systemically is acceptable for infections that are best treated topically, such as acne bacterial conjunctivitis, as the clinical benefits are high and the risk of inducing resistance is low. Arguments made in support of long-term, topical use of the quinolone nadifloxacin, as is the case for long-term, topical or systemic use of other classes of agents with important systemic applications, such as macrolides, lincosamides, aminoglycosides, tetracyclines and fusidic acid, are refuted by the continued, inexorable rise in resistance of major pathogens that cause life-threatening infections. Resistance to methicillin, macrolides, lincosamides, fusidic acid, quinolones and tetracyclines in staphylococci continues to increase and resistance to vancomycin, daptomycin and linezolid has now emerged. Judicious use of antimicrobial agents is the key to preserving the activity of these valuable agents.

Nadifloxacin is a broad-spectrum quinolone agent with good in vitro potency against P. acnes, the common causative agent of acne vulgaris [31]. It is also highly effective against the staphylococcal and streptococcal species most often associated with skin infections [11,12,39]. Nonetheless, quinolone usage for the treatment of simple skin infections is generally not recommended when less broad-spectrum agents are equally efficacious [40,41]. In addition, the risk of development of resistance to any topical antimicrobial agent used for prolonged periods in diseases such as acne vulgaris, in which the therapeutic role of such agents is highly questionable at best, is unacceptably high. Further development of quinolone resistance will compromise the utility of quinolones that are potent enough to overcome current levels of quinolone resistance in staphylococci.

An instructive model for the issues associated with topical use of an agent also used systemically is seen with fusidic acid. Fusidic acid is a bacteriostatic agent active against a variety of Gram-positive bacterial species, but is primarily noted for its activity against methicillin-susceptible and -resistant S. aureus. As such, fusidic acid is an important agent to maintain in the antimicrobial armamentarium. Unfortunately, it is widely used as topical monotherapy for chronic skin conditions, and resistance, which emerged not long after its release, has been increasing [42,43].

Throughout the world, rates of resistance vary widely, with the highest rates reported in Greece (49%), Kuwait (20%) and New Zealand (13%). As fusidic acid has not been approved for use in the US, resistance has remained very low [44]. Several studies have documented increasing and statistically significant rates of fusidic acid resistance in staphylococci in association with wide use of the drug as a topical treatment of chronic skin infections [45-51].

Although bactericidal rather than bacteriostatic, nadifloxacin presents many similarities to the issues associated with topical use of fusidic acid. It is one of the most potent quinolone agents ever developed and its arginine salt is currently under investigation for the treatment of infections, including those caused by methicillin- and quinolone-resistant staphylococci. Long-term or chronic usage of any antimicrobial agent is generally associated with increased development of resistance to that agent by both the target organism and, more importantly, normal resident flora. Widespread, long-term topical use of this agent is highly likely to result in the development of resistance in target pathogens, as well as resident skin flora, particularly staphylococci.

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Nadifloxacin

Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (***) to readers.


10. **NADIFLOXACIN:** An arginine salt of the active chiral benzoquinolizine-2-carboxylic acid, S-(+)-nadifloxacin has potential as a novel drug entity against hospital infections due to multi-drug-resistant S. aureus.


15. **PHARMACOTHERAPY:** Systemic therapy with a variety of β-lactams, macrolides and clindamycin have been the cornerstone of therapy of these infections for many years, and, with the exception of muromycin, topical therapy occupying a small therapeutic niche. The new antimicrobials, linezolid, minocycline, quinupristin/dalfopristin, gatifloxacin, gemifloxacin and oxifloxacin, are not a significant improvement upon older agents at this time.


27. **Although the pathogenesis of acne vulgaris remains a topic of considerable debate, oral retinoids is the treatment of choice in severe acne, and new developments include low-dose long-term isotretinoin, micronised isotretinoin, isotretinoin metabolites, insulin-sensitising agents, 5-α-reductase Type 1 inhibitors, antiinflammatory agents. 5-α-reductase Type 1 inhibitors, antiinflammatory agents.

28. **Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first- or second-generation oral cephalosporins, macrolides or clindamycin. Most community-acquired MRSA strains remain susceptible to trimethoprim-sulfamethoxazole despite development of community-acquired methicillin- and clindamycin-resistant S. aureus strains.**


31. WCK 771, administered orally and parenterally, was shown to be effective for the treatment of diverse staphylococcal infections in mice, including those caused by methicillin- and quinolone-resistant strains.


45. Fusidic acid monotherapy, both topical and oral, has led to resistance among S. aureus. Systemic fusidic acid should always be used with another antimicrobial, and topical use should either be abolished or restricted to prevent the loss of this agent.


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Website


Effectively 12 September 2005, the FDA Commissioner ordered the withdrawal of fluoroquinolones from poultry water as this caused the development of fluoroquinolone-resistant *Campylobacter* spp. in poultry and subsequent human infections with these poultry-derived strains.

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