Lack of In Vitro Efficacy of Oral Forms of Certain Cephalosporins, Erythromycin, and Oxacillin against *Pasteurella multocida*

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The in vitro susceptibility of human isolates of *Pasteurella multocida* to oral antimicrobial agents from our current study and from a review of the literature suggests that dicloxacillin (oxacillin), erythromycin, clindamycin, cephalixin, cefaclor, and cefadroxil should not be used for empiric therapy of animal bite wounds. Agents that were consistently active against *P. multocida* were penicillin, ampicillin, amoxicillin-clavulanic acid, tetracycline, minocycline, chloramphenicol, trimethoprim-sulfamethoxazole, and cefuroxime. Possible reasons for the confusion regarding the activity of oral cephalosporins are addressed.

*Pasteurella multocida* is an important pathogen in human infections due to dog and cat bites (2, 9, 10, 12, 14, 15, 17, 23). These wounds account for approximately 1% of emergency room visits (6) and over $30 million in health care costs annually (7). Many of these patients are given oral antimicrobial therapy and are followed as outpatients.

While penicillin is considered to be the drug of choice, alternative therapy must be considered when *Staphylococcus aureus* either is suspected to be or is present in the wound or when the patient gives a history of penicillin allergy. In these situations, the selection of alternative therapy has been varied. The use of penicillin-resistant penicillins such as oxacillin or dicloxacillin has been advocated (3, 7, 8, 16). In the penicillin-allergic patient either oral cephalosporins or erythromycin is often used.

To clarify the potential utility of oral agents for empiric therapy, we report the comparative activities of some commonly used oral antimicrobial agents against strains of *P. multocida* recently isolated (1986) from humans with infected animal bite wounds, and we also review the published English-language data on *P. multocida* susceptibility.

MATERIALS AND METHODS

Literature review. Using the MEDLARS computer search (National Library of Medicine) and references cited in recent articles, we reviewed the English-language literature of the past 5 years on the susceptibility of *P. multocida*.

Susceptibility studies. Standard laboratory powders were kindly supplied by the following companies: penicillin G, cephalixin, and erythromycin, Eli Lilly & Co., Indianapolis, Ind.; ampicillin and oxacillin, Bristol Laboratories, Syracuse, N.Y.; minocycline, Lederle Laboratories, Pearl River, N.Y.; sulfamethoxazole-trimethoprim (SXT), Hoffmann-La Roche Inc., Nutley, N.J.; amoxicillin-clavulanic acid, Beecham Pharmaceuticals, Bristol, Tenn.; tetracycline, Pfizer Inc., New York, N.Y.; cefadroxil, Mead Johnson, Evansville, Ind.; cefuroxime, Glaxo Inc., Research Triangle Park, N.C.

Strains were taken from frozen cultures and transferred twice to ensure purity and good growth. Mueller-Hinton agar supplemented with hemin (10 μg/ml) was used as the basal medium. Plates for testing the activity of SXT were supplemented with 5% laked horse blood. Freshly prepared solutions of twofold dilutions of antimicrobial agents were incorporated into the media described to yield final concentrations of 64 to 0.06 μg/ml. SXT was prepared in a sulfamethoxazole-to-trimethoprim ratio of 19:1.

The plates were inoculated with a Steers replicator (Craft Machine Inc., Chester, Pa.) using a standard inoculum corresponding to a 0.5 McFarland standard no. 1 and were further diluted 1:10 (10⁴ CFU/ml, final concentration). Control plates without antimicrobial agents were inoculated before and after each series of drug-containing plates. Plates were incubated at 35°C in an aerobic environment for 24 h and then examined. The control strain (*S. aureus* ATCC 25923) was tested simultaneously. The MIC was defined as the lowest concentration of an agent that yielded no growth or one discrete colony.

RESULTS

Eighty-five references were cited in the literature search, of which 33 described the susceptibility of human isolates to oral antimicrobial agents (11, 21, 23). An additional report (22) was found in the literature cited by these articles. The remainder of the references either concerned animal isolates, did not study the activity of oral antimicrobial agents, or did not report quantitative susceptibilities of the human isolates studied. The results of these reports are compared with our present study in Table 1.

In these studies, *P. multocida* isolates were uniformly susceptible to penicillin, ampicillin, tetracycline, minocycline, SXT, and chloramphenicol. Isolates were uniformly resistant to dicloxacillin, cephalxin, cefadroxil, cefaclor, erythromycin, and clindamycin. A broad-spectrum cephalosporin with a new oral formulation, cefuroxime, showed good activity (MIC for 90% of isolates, <0.25 μg/ml) against all 20 strains of *P. multocida* tested in our current study.

DISCUSSION

The continued use of oral erythromycin, oxacillin, and cephalosporins such as cephalixin may be based upon confusion about susceptibility data and on extrapolations of "class susceptibility" to other specific members of that class of antibiotic.

From our review, several points appear to be underappreciated. The majority of reports concerning *P. multocida* are related to animal diseases, veterinary isolates, anecdotal

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TABLE 1. Comparative susceptibilities of human isolates of Pasteurella multocida to oral antimicrobial agents

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (µg/ml) obtained from indicated reference (no. of isolates):</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td></td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
<td>0.8</td>
<td>0.25</td>
</tr>
<tr>
<td>Amoxicillin-clavulanic acid</td>
<td></td>
<td>0.2</td>
<td>0.25</td>
</tr>
<tr>
<td>Diloxacin</td>
<td></td>
<td>12.5</td>
<td>6.2</td>
</tr>
<tr>
<td>Cephalaxin</td>
<td></td>
<td>6.3</td>
<td>3.1</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td></td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Cefaclor</td>
<td></td>
<td>3.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td>0.09</td>
<td>0.8</td>
</tr>
<tr>
<td>Tetracycline</td>
<td></td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>Minocycline</td>
<td></td>
<td>1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td></td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>SXT</td>
<td></td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Clindamycin</td>
<td></td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

* 50% and 90%, MICs for 50% and 90% of isolates, respectively.

case reports, or studies which have used isolates from nonspecified sources (e.g., references 1, 4, 13, 18–20). While human isolates from bite wounds also have animals as their ultimate source, there are a variety of biotypes of Pasteurella multocida with various degrees of pathogenicity (5, 19). Consequently, susceptibility data from studies using non-human isolates might not be applicable to the clinical situation encountered in human infections.

Another source of confusion may be the extrapolation of data obtained by the less quantitative and possibly less accurate disk diffusion method rather than MICs. Physicians are unable to correlate the zone of inhibition around the disk with the achievable antibiotic levels at the site of infection. Discrepancies between the disk diffusion method and broth dilution (MIC) method for the activity of erythromycin against Pasteurella multocida have been noted (22): disk diffusion gave larger zones that suggested falsely low MICs. Unfortunately, 10% horse serum was used in the microdilution trays, which may have increased the pH and altered erythromycin activity.

A third cause of confusion may be the disparity in susceptibility of Pasteurella multocida to intravenous and oral antimicrobial preparations even in the same class of drugs. This is particularly true of first-generation intravenous cephalosporins, which achieve higher levels and to which Pasteurella multocida isolates are more likely to be susceptible, and of the first-generation oral cephalosporins, to which Pasteurella multocida is usually resistant (18, 21, 22). A broad-spectrum cephalosporin with an oral form, cefuroxime axetil, was much more active than its predecessors against Pasteurella multocida.

Our current review noted that four prior reports (11, 21–23), using human clinical isolates and quantitative susceptibility methodologies to determine MICs, as well as our current in vitro data, all showed most Pasteurella multocida strains to be resistant to oxacillin, dicloxacin, cephalexin, cefaclor, cefadroxil, and erythromycin.

Weber et al. (23) noted that, "based on susceptibilities in vitro, an orally absorbed semisynthetic penicillin (dicloxacin) and two orally absorbed cephalosporins (cephalexin and cefaclor) would not achieve blood levels sufficient to treat Pasteurella multocida infections reliably." Stevens et al. (22) and Noel and Teele (18) confirmed "the poor in vitro activities of erythromycin and oxacillin against Pasteurella multocida." Elenbaas et al. (8), who advocate the use of oxacillin in cat bite wounds, also reported a failure to cure an abscess from which Pasteurella multocida was isolated in a dog bite.

On the basis of these data, we caution physicians not to use dicloxacin, oxacillin, erythromycin, clindamycin, cephalexin, cefadroxil, or cefaclor in the treatment of animal bite wounds. If these agents must be used in an individual patient, then careful monitoring for progression of infection and therapeutic failure would be prudent.

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LITERATURE CITED


