The pharmacokinetics of the oral cephalosporins—a review

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The pharmacokinetics of the older and more recent oral cephalosporins are reviewed. With the exception of cefadroxil the older agents (cephalexin, cephradine and cefaclor) have serum elimination half-lives of ≤ 1 h and hence have to be administered three to four times daily. The urinary recovery of these agents is high (> 80% of oral dose) with the exception of cefaclor (54%). Cefaclor is also chemically unstable.

The newer agents can be divided into those that are prodrugs (cefodoxime proxetil and cefuroxime axetil) and compounds that are absorbed as such (cefixime, cefprozil and ceftibuten). They all have half-lives > 1-25 h and can be given once or twice daily. The penetration of these agents into an inflammatory exudate was studied and found to be cefixime 132%, ceftibuten 113%, cefpodoxime 104%, cefuroxime 92% and cefprozil 79% of the serum concentration. The penetration of cefpodoxime and cefixime into the respiratory tract was also studied; the mean percentage bronchial mucosal penetration was 52% for the former and 38% for cefixime. The urinary recovery of these newer agents (with the exception of ceftibuten) tends to be less than that of the earlier agents.

There was a relationship between the serum elimination half-life of these agents and the degree of tissue penetration, those agents with longer half-lives penetrating to a greater extent.

Introduction

Orally absorbed cephalosporins have been in clinical use for more than twenty years. Although the number of available oral agents is now increasing, it is still small in comparison with the injectable cephalosporins. β-Lactam antibiotics are generally poorly absorbed from the gastro-intestinal tract. They are either inactivated by gastric acid or highly hydrophilic and hence not able to traverse the mucosal barrier of the small intestine. However, the cephalosporin nucleus (Figure 1) is readily modified or substituted at a number of points. Substitution at position 3 tends to affect the pharmacokinetic properties of the agent and the carboxylic acid residue at position 4 has the potential for esterification and pro-drug development.

In this brief review I wish to divide the agents, somewhat artificially, into those agents that are well known and have been available in many countries for a number of years and those that have recently appeared—or are about to appear on the clinical scene.

The pharmacokinetics of the earlier oral cephalosporins

The first oral cephalosporin to be widely used was cephalexin and this has been followed by cefadroxil, cefaclor, cephradine and in certain countries, cefroxadine (CGP 9000).
The earliest attempts to produce an oral cephalosporin mimicked the approach taken to develop an oral penicillin. Phenoxymethylpenicillin (penicillin V) is moderately well absorbed from the gut because it is acid-stable. It was proposed that the addition of a non-polar side chain might enable cephalosporins to be absorbed (Abrahams, 1987), although this approach did not produce orally administrable analogues of cephalothin and cephaloridine. Cephalexin, however, which borrows the D-a-aminobenzyl side chain from ampicillin, did achieve high serum levels (Griffiths & Black, 1968) (see Figure 2). Pivaloyl prodrug esters of cephalexin were then produced but not commercially—presumably because of the high bioavailability of the parent compound.

Table I compares the pharmacokinetics of these earlier agents and in Figure 3 the
Pharmacokinetics of oral cephalosporins

Table I. Pharmacokinetics of older oral cephalosporins

<table>
<thead>
<tr>
<th></th>
<th>Serum half-life (h)</th>
<th>Protein binding (%)</th>
<th>Cmax (mg/l) after 500 mg</th>
<th>Urinary recovery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalixin</td>
<td>0.9</td>
<td>18–20</td>
<td>5.8</td>
<td>88</td>
</tr>
<tr>
<td>Cephradine</td>
<td>0.9</td>
<td>10–20</td>
<td>16.0</td>
<td>86</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>0.6</td>
<td>25</td>
<td>14.0</td>
<td>54</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>1.6</td>
<td>18–20</td>
<td>9.5</td>
<td>88</td>
</tr>
<tr>
<td>Cefroxadine</td>
<td>0.9</td>
<td>10</td>
<td>11.5</td>
<td>80</td>
</tr>
</tbody>
</table>

Based on Wise (1982), and Bergan (1987)

serum levels following a 1 g dose of four of these agents are shown (Lode, Stahlmann & Koepp, 1979).

It can be seen that their half-lives are all less than 1 h, with the exception of cefadroxil. This suggests that they should be given four times a day, except cefadroxil, which should be given three times a day; the pharmacokinetic case for its twice daily use being arguable. There is however, clinical evidence that twice daily cefadroxil is satisfactory for a wide range of infections (Phillips & Wise, 1982).

Food does not have a significant impact on the absorption of these agents, with the exception of cefaclor of which the maximum serum concentration is halved but the half-life prolonged (Glynne, Goulbourn & Ryder, 1978). This is in contrast to the prodrugs which will be discussed below. With the exception of cephaloglycin, a very early and now no longer used oral cephalosporin, none of these agents is metabolized. Cephaloglycin shares with the parenteral agents cephalothin, cefotaxime, cephalotriile and cefapirin an acetoxymethyl group at the 3 position which can be desacetylated to a less microbiologically active compound.
All the agents are excreted predominantly by the renal route. Table I shows that the urinary recovery of cefaclor is considerably lower than that of the other agents. The most likely explanation for this is the chemical instability of this compound compared with the other agents. The half-life of cefaclor when 'spiked' in serum at 37°C is 2-3 h (see Figure 4). No doubt this factor also partially accounts for the shorter elimination half-life.

Biliary elimination of these cephalosporins is usually minimal, about 1% of the drug being recovered in the bile. However even this may be sufficient to achieve the levels in bile necessary to inhibit potential pathogens.

There is minimal elimination of these agents in human breast milk or transfer via the placenta. The pharmacokinetics in infants and children are similar to those in adults but full term or premature neonates have elimination half-lives three- to four-fold greater than their older counterparts (Bergan, 1987).

There is little comparative information on the tissue penetration of these earlier agents. Cephalexin and cefroxadine achieved levels in a non-inflammatory exudate comparable with those found in serum, in a study employing a dermabrasion technique (Gillett & Wise, 1978). CSF levels are low; for example 1-3 mg/l of cephalixin was found 3-4 h after a 750 µg dose (Bergan, Midtvedt & Eriksen, 1970). The penetration into the respiratory tract is similar to that of other β-lactams. For example the mean cefaclor level in the middle ear in otitis media is a mere 0-5 mg/l following a 14 mg/kg dose and that of amoxycillin 0-3 mg/l after the same dose (McLinn, 1978).

These agents penetrate sputum to a modest extent. Simon & Gatzemeier (1979) reported only 2%-8% penetration by cefaclor. The mean cephaloxin sputum level following 500 mg in infected patients is 0-3 mg/l which represents a 4%-6% penetration (Halprin & McMahon, 1973; Light & Wyle, 1983).

The pharmacokinetics of the newer agents

Those agents at present marketed and under clinical trial in Europe and the USA can be divided into two groups:
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Table II. Pharmacokinetics of the newer oral cephalosporins: mean (s.D.)

<table>
<thead>
<tr>
<th>Drug and dose</th>
<th>Elimination half-life (h)</th>
<th>C_{max} (mg/l)</th>
<th>T_{max} (h)</th>
<th>24 h urinary recovery</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefixime, 400 mg single</td>
<td>3.8 (0.3)</td>
<td>3.7 (1.3)</td>
<td>3.7 (0.7)</td>
<td>19.9 (5.3)</td>
<td>Stone et al. (1989)</td>
</tr>
<tr>
<td>Cefibuten, 200 mg bd, 5 days</td>
<td>2.5 (0.3)</td>
<td>10.9 (1.2)</td>
<td>1.8 (0.4)</td>
<td>53-68</td>
<td>Wise et al. (1990)</td>
</tr>
<tr>
<td>Cefprozil, 500 mg single</td>
<td>1.4 (0.3)</td>
<td>9.6 (2.2)</td>
<td>1.9 (0.9)</td>
<td>63-6 (8.2)</td>
<td>Nye et al. (1990)</td>
</tr>
<tr>
<td>Cefuroxime, 500 mg single</td>
<td>1.1 (0.1)</td>
<td>6.4 (1.6)</td>
<td>2.5 (1.2)</td>
<td>30-0 (19.2)</td>
<td>Wise, Bennett &amp; Dent (1984)</td>
</tr>
<tr>
<td>Cefpodoxime, 200 mg single</td>
<td>2.2 (0.3)</td>
<td>2.1 (0.4)</td>
<td>2.9 (0.8)</td>
<td>32.2 (5.8)</td>
<td>O'Neill et al. (1990)</td>
</tr>
<tr>
<td></td>
<td>2.31 (0.15)</td>
<td>2.60 (0.16)</td>
<td>2.42 (0.15)</td>
<td>39.2 (1.8)</td>
<td>Tremblay et al. (1990)</td>
</tr>
</tbody>
</table>

*0-8 h excretion.

(a) those orally absorbed as the parent compound—cefixime, cefibuten and cefprozil; and

(b) those absorbed from a prodrug formulation—cefuroxime axetil and cefpodoxime proxetil.

Some of these agents exist in differing tautomeric or isomeric forms. For example cefprozil is 90% cis and 10% trans in the galenic formulation; cefibuten on the other hand undergoes metabolism from its original cis form to a trans-isomer which is present in serum at about 5%-7% that of the cis-form (Wise et al., 1990). How renal or hepatic disease affects these ratios is not yet known.

The oral absorption of the agents shows considerable differences (Table II). The rapidity of absorption, as measured by the time of maximum serum concentration (T_{max}) varied from cefibuten, the most rapidly absorbed with a T_{max} at 1.8 h, to cefixime, the most slowly absorbed, at 3.7 h. There is some evidence that the prodrug agents are better absorbed after food. In the case of cefuroxime axetil the urinary recovery increases from 30% when a 500 g dose is given in the fasting state to 42% when given with food (Harding, Williams & Ayrton, 1984). The figures for cefpodoxime are c.41% and c.64% (Hughes et al., 1989). It has been suggested that this is related to the inhibition of intraluminal esterases by food which might allow de-esterification prior to absorption.

Table III. Inflammatory fluid penetration of newer oral cephalosporins: mean (s.D.)

<table>
<thead>
<tr>
<th>Drug and dose</th>
<th>T_{1} (h)</th>
<th>C_{max} (mg/l)</th>
<th>T_{max} (h)</th>
<th>% penetration</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefixime, 400 mg single</td>
<td>4.1 (0.4)</td>
<td>3.2 (1.0)</td>
<td>6.7 (1.0)</td>
<td>132.6 (12.2)</td>
<td>Stone et al. (1989)</td>
</tr>
<tr>
<td>Cefibuten, 200 mg bd, 5 days</td>
<td>3.2 (1.1)</td>
<td>9.2 (2.2)</td>
<td>3.7 (1.9)</td>
<td>113.4 (18.6)</td>
<td>Wise et al. (1990)</td>
</tr>
<tr>
<td>Cefprozil, 500 mg single</td>
<td>1.4 (0.4)</td>
<td>4.9 (1.3)</td>
<td>3.5 (1.1)</td>
<td>79.0 (23.7)</td>
<td>Nye et al. (1990)</td>
</tr>
<tr>
<td>Cefuroxime, 500 mg single</td>
<td>1.9 (0.6)</td>
<td>4.1 (1.7)</td>
<td>3.3 (1.2)</td>
<td>92 (24.8)</td>
<td>Wise, Bennett &amp; Dent (1984)</td>
</tr>
<tr>
<td>Cefpodoxime, 200 mg single</td>
<td>3.6 (1.6)</td>
<td>1.7 (0.7)</td>
<td>3.5 (1.2)</td>
<td>103.7 (14.3)</td>
<td>O'Neill et al. (1990)</td>
</tr>
</tbody>
</table>
Although the urinary recovery of cefixime is low, the absolute bioavailability is higher, 40% for the 400 mg capsule (Faulkner et al., 1988). Therefore, the non-prodrug agents tend to be better absorbed than the prodrug formulations. If one divides the maximum serum concentration ($C_{\text{max}}$) by the dose to obtain a $C_{\text{max}}/100\text{ mg dose}$ then cefitibuten (5:5 mg/l/100 mg) achieves the highest serum concentration per unit dose, and the corresponding value for cefprozil is 1:9 mg/l/100 mg dose, for cefuroxime 1:1 mg/l/100 mg dose, for cefpodoxime 1:1 mg/l/100 mg dose and for cefixime 0:9 mg/l/100 mg dose.

All the agents penetrate well into inflammatory exudate (Table III). In Figure 5 it can be seen that the peak inflammatory fluid level following 200 mg of cefpodoxime was 1:7 mg/l and the mean percentage penetration 104%. In Figure 6 it can be seen that there is a good correlation between the serum half-life and the percentage penetration in this model, namely that agents with longer serum half-lives tend to penetrate more rapidly. It is possible that agents that are more lipophilic are more readily reabsorbed by the renal tubules (hence more slowly excreted) and also, because of their lipophilicity, tend to penetrate tissue more rapidly. The degree of penetration of cefprozil was
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Table IV. Penetration of cephalosporins into bronchial mucosa

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>n</th>
<th>% penetration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefpodoxime proxetil</td>
<td>200 mg po single</td>
<td>11</td>
<td>52</td>
</tr>
<tr>
<td>Cefixime</td>
<td>200 mg po bd</td>
<td>10</td>
<td>37</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>500 mg po single</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Cefpirome</td>
<td>1 g iv single</td>
<td>27</td>
<td>57</td>
</tr>
<tr>
<td>Cefepime</td>
<td>2 g iv single</td>
<td>20</td>
<td>60</td>
</tr>
</tbody>
</table>

the lowest at a mean of 79% and greatest for cefixime at 132-6% although in all cases there was considerable intersubject variation.

We have studied the penetration of three of these oral compounds in comparison with two injectable cephalosporins into the bronchial mucosa of patients undergoing fiberoptic bronchoscopy. As can be seen in Table IV the percentage penetrations were 37%-60%.

As these cephalosporins are all primarily excreted by the renal route, urine levels are high and with the extended half-life (compared with earlier agents) a single oral dose should be sufficient for the therapy of uncomplicated cystitis. For example, the mean 8–12 h urine concentration following 200 mg of cefpodoxime was 19-8 mg/l and from 12–24 h, 3-9 mg/l (R. Wise, unpublished observation).

As many of these agents are still under investigation there is little information on the effects of disease on the pharmacokinetics. A decrease in renal function is accompanied by a longer serum elimination half-life—for example, in the case of cefpodoxime a creatinine clearance of 10–39 ml/min is associated with a $T_{1/2}$ of 7-67±0-69 h (O. Nilsen, personal communication). In the case of cefixime, the elimination half-life increases to 11-5 h when the creatinine clearance is reduced to < 10 ml/min (Guay et al., 1986). Age also affects the pharmacokinetics, for example in otherwise healthy elderly patients the AUC following cefixime dosing increased 20% in comparison with the results in younger volunteers (Silber et al., 1988); however no dosing alteration is likely to be recommended on the basis of age alone.

In conclusion, the newer oral cephalosporins are characterized by larger elimination half-lives, which, when combined with their intrinsically greater antimicrobial activity, suggests that these compounds can be used in once to thrice daily dosing regimens for the therapy of a wide range of infections.

References


