Factors affecting the oral absorption of esterified antibiotics

PETER E. O. WILLIAMS*
Human Pharmacology Department, Glaxo Group Research Ltd, Greenford, Middlesex UB6 0HE, U.K.

Many ester prodrugs are better absorbed after oral administration than their parent molecules. This report describes some of the effects which can be achieved by esterification of β-lactam antibiotics, and the differences which result between ester prodrugs of cephalosporins and those of penicillins. The majority of the data relate to studies in man, which are relatively rare for cephalosporin esters.

Absorption mechanisms

It is presumed that antibiotics such as cefuroxime are not absorbed from the gastrointestinal tract after oral administration because of their anionic state at physiological pH and their low lipid solubility. The addition of an ester moiety to the C-4 carboxylic acid group, as in cefuroxime axetil for instance (Fig. 1), may enable the prodrug to diffuse across the mucosal epithelial cell membranes in the intestine, although the strategy is not always successful (Ferres, 1980). Thereafter, the prodrug may also cross the basal membranes, and appear in the blood intact. For example, the levels of the propionate ester of erythromycin are higher than those of erythromycin base in the plasma of volunteers given oral doses of erythromycin estolate (erythromycin propionate lauryl sulphate) according to Welling et al. (1979).

To achieve clinical efficacy, cefuroxime axetil must be hydrolysed after absorption since the intact ester has no antimicrobial activity, in common with other cephalosporin esters (Murphy & Webber, 1972). Detailed studies on the hydrolysis of cefuroxime axetil have not been reported, but experiments on the intestinal absorption and metabolism of pivampicillin, the pivaloyloxymethyl ester of ampicillin (Shindo et al., 1978), illustrate principles which may apply to cefuroxime axetil as well. Pivampicillin is hydrolysed by one of the many non-specific esterases because they are inhibited by organophosphates such as di-isopropylfluorophosphate, but not by cholinesterase inhibitors such as eserine (Krisch, 1971). The hydrolysis of pivampicillin yields ampicillin, which passes into the systemic circulation, and formaldehyde and pivalic acid, which may be incorporated directly into the metabolic pathways of the mucosal cells. There is a wide distribution of non-specific esterases in mammalian plasma, liver and intestinal mucosa, but the spectrum of activity of these enzymes is species-dependent. Simple alkyl esters of some penicillins are broken down by mice and rats but are not readily hydrolysed by man (Agersborg et al., 1966). However, some acyloxyalkyl esters are hydrolysed enzymically in man to unstable oxyalkyl esters, which undergo further chemical breakdown to release the parent drugs. Despite a half-life of 3.5 min in human blood, no intact cefuroxime ester could be detected in the peripheral venous blood of volunteers after single oral doses of cefuroxime axetil (1.5 g) (Harding et al., 1984). This result indicates rapid hydrolysis in the intestinal mucosa and portal blood. If a large proportion of a dose of cefuroxime axetil had reached the portal blood unhydrolysed, detectable levels of intact ester would have been expected in the systemic circulation.

Prodrug versus parent drug

The improvement in absorption due to esterification can be measured by comparison of the serum levels of active antibiotic in volunteers given oral doses of ester prodrugs or their parent drugs (Fig. 2). After 1 g of cefuroxime sodium given orally, serum levels did not exceed the limit of assay sensitivity (broken line in Fig. 2a) at any time after dosing. Esterification increases the percentage urinary recovery of cefuroxime about 40-fold from 1% (Foord, 1976) to more than 40% (Williams & Harding, 1984), in contrast to ampicillin which is only increased 3-fold from 20-40% to 70-90% (Verbiest, 1974). Esters of several cephalosporins other than cefuroxime have been described (Wright et al., 1979; N. Kakeya, K. Nishimura, A. Yoshimi, S. Nakamura, S. Nishizawa, S. Tamaki, H. Matsui, T. Kawamura,
either group of drugs, including the presence of esterase
continuous shedding of cellular debris from the tips of the
lumen. Luminal esterase activity would release non-
absorbable mecillinam from pivmecillinam but not
mucosal epithelial cell is less than
explain the near complete availability of ampicillin from
absorbable ampicillin from ampicillin esters. This might
increase in the rate of transfer of pivampicillin from lumen
to mucosal cell but a considerable increase in transfer from
cell to blood, suggesting an effect of the inhibitor in the
cytosol but not in the lumen. However, the heterogeneity of
non-specific esterases militates against any rejection of the
importance of luminal esterases for the absorption of
different ester prodrugs in another species, i.e. man.

Acid stability. The instability of ampicillin at low pH
has been suggested as a factor limiting its absorption (Bergan,
1978), but this does not apply to cephalosporins and the
ester prodrugs, which are relatively stable at low pH. Thus,
ampicillin is not extensively broken down in the stomach
after oral administration and nor is cefuroxime axetil. The
improvement in cefuroxime bioavailability due to esterifi-
cation does not arise from increased stability to acid.

The influence of food. A further difference between
cephalosporin and penicillin esters has been noted in that
the absorption of cefuroxime axetil in volunteers is
significantly improved by dosing after a meal (Williams &
Harding, 1984), whereas absorption of ampicillin esters is
unaffected by food intake (Foltz et al., 1971; Jones et al.,
1978). Ampicillin itself is usually absorbed more slowly and
less completely after food (Welling & Tse, 1982). If
significant quantities of ampicillin are released from
ampicillin esters in the gastrointestinal lumen, food
would be expected to decrease the availability of ampicillin from
the esters as well. The improved absorption of cefuroxime
axetil after a meal could be due to the effects of food on drug
dispersion, gastrointestinal motility, gastric pH or inhibi-
tion of luminal esterases. A series of volunteer trials have
been conducted to investigate these possibilities. The
improvement was consistent for two different tablet
formulations and an aqueous suspension of cefuroxime
axetil, which suggests that dispersion was not important.
Agents such as loperamide, diphenoxylate and castor oil,
which alter intestinal motility, produced no significant
change in the absorption of cefuroxime axetil. Co-
administration with the histamine2-receptor blocker, raniti-
dine, decreased rather than increased absorption. This
suggested that low gastric fluid volume after ranitidine
might be more important than low gastric pH as a limiting
factor in the fasting state. Unfortunately, the lack of
available inhibitors of non-specific esterases for use in
humans makes it impossible to reach firm conclusions about
the interaction between luminal esterases and food. In
summary, the improvement of cefuroxime axetil absorption
after meals may be due to increased gastric fluid volume
and/or inhibition of luminal esterases.

Physicochemical properties. The potential importance of
gastric fluid volume mentioned above prompts a compari-
sion of the physicochemical properties of cefuroxime axetil
and an ampicillin ester (Table 1). Data on bacampicillin,
the oxycarbonyloxyethyl ester of ampicillin, are taken from
a recent review (Ekstrom, 1981). Esterification increases
the octanol/water partition coefficient by several
orders of magnitude. The pH-dependence of bacampicillin
partitioning may be related to the decreasing ionization
of the α-amino group (pKα, around 7) with increasing pH.
Mecillinam has a tertiary amino group in its side-chain,
which should give pivmecillinam a pKα around 8.9 and pH-
dependent partitioning. Both ampicillin and cefuroxime have predominantly anionic character at physiological pH since their carboxyl groups have $pK_a$ values around 2. Cefuroxime axetil is uncharged and so partitions independently of pH.

Similar points apply to aqueous solubility. This tends to increase with increasing ionization, with the notable exception that bacampicillin, unlike cefuroxime axetil, is more soluble at low pH than its highly ionized parent drug. Therefore, esterification has influenced the physical chemistry of a cephalosporin ester and a penicillin ester in different ways, and this could help to explain the discrepancy between the percentage absorption of the two drugs. It is possible that aqueous solubility in the pH range 4–7 is one of the factors limiting absorption of esterified antibiotics.

The antibacterial activity of cefuroxime against ampicillin-resistant organisms may confer considerable advantages in the treatment of infections. This broad antibacterial spectrum together with the favourable pharmacological properties of cefuroxime axetil, render the ester prodrug a promising new oral antibiotic.

### Table 1. Physicochemical properties of two ester prodrugs and their parent antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Octanol/water partition coefficient ($pK_a$)</th>
<th>Aquous solubility (g/l)</th>
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<tbody>
<tr>
<td>Bacampicillin</td>
<td>pH 4 0.2</td>
<td>190</td>
</tr>
<tr>
<td></td>
<td>pH 7 12.0</td>
<td>1</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>pH 4 0.01</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>pH 7 0.01</td>
<td>25</td>
</tr>
<tr>
<td>Cefuroxime axetil</td>
<td>5.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>0.003</td>
<td>150</td>
</tr>
</tbody>
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HARISH M. PATEL
Department of Biochemistry, Charing Cross Hospital Medical School, Fulham Palace Road, London W6 8RF, U.K.

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**Liposomes as a controlled-release system**

In vivo.

Their multilamellar structure, taken together with properties that can easily be identified such as size, charge, fluidity, permeability, pH and thermal sensitivity, and biodegradability, etc., gives great flexibility, when these vesicles are adapted for the controlled release of drugs. The controlled release of drugs from liposomes could occur:

At the site of injection

Many drugs, and peptide hormones like insulin, are routinely administered subcutaneously or intramuscularly for medical reasons. However, they are then rapidly absorbed into the circulation and produce ‘peak’ blood levels which do not last long, due to rapid removal of the administered substances from the circulation by organs such as the liver and kidney. These substances would be more effective if they were delivered to the bloodstream at a constant rate. Since the transport mechanism of lymphatic capillaries can clearly small-diameter vesicles much more rapidly than large multilamellar liposomes of a diameter greater than 100 nm, liposomes of this latter size will be retained at the injection site and act as a ‘local depot’, releasing the entrapped drug as they are gradually disinte-