The Metabolism of Cimetidine in the Rat, Dog and Man
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The metabolism of metiamide (1, Scheme 1), the first orally active histamine H2-receptor antagonist, has already been described (Taylor, 1973). Cimetidine (2, Scheme 1) is a new H2-receptor antagonist described by Brimblecombe et al. (1975), in which the thioureido group of metiamide (1) is replaced by a cyanoguanidino group. The present communication reports some initial studies on the metabolism of cimetidine, labelled in the 2-position of the imidazole ring with either 3H or 14C in rat, dog and man.

When cimetidine was given orally to male rats, 58% of the dose (30mg/kg) of 14C was excreted in the urine in 24h, and approx. 50% of this was unchanged cimetidine; after intravenous dosing, 71% of 14C was excreted in the urine, 55% of which was unchanged compound. Similarly, female rats excreted 64% of the 14C oral dose and 73% of the intravenous dose in the urine in 24h but metabolized the compound to a lesser extent, about 74% of the urinary radioactivity being present as unchanged drug. T.l.c. and radioautography showed the presence of unchanged compound together with one major and two minor metabolites. The difference in metabolism between male and female rats was due largely to the greater conversion into the major metabolite by the male rats. Whereas this metabolite represented only about 12% of the urinary radioactivity from female rats, it accounted for 30% of the radioactivity in male rat urine.

This major metabolite was isolated from rat urine by extracting the urine at pH9 with ethyl acetate (3 vol.), to remove unchanged cimetidine, and then isolating and purifying the compound by column chromatography and t.l.c.; n.m.r. (nuclear-magnetic-resonance) analysis showed it to have a spectrum identical with that of synthetic sulphoxide (structure 3, Scheme 1).

A second metabolite which accounted for 5 and 8% of the radioactivity in female and male rat urines respectively was provisionally identified as the hydroxymethyl compound (structure 4, Scheme 1) by its similarity to authentic material in t.l.c. characteristics and reaction with alkaline diazotized sulphanilic acid.

\[ \text{Scheme 1.} \]

* Position of labelling (3H or 14C).
Table 1. Metabolites of cimetidine in rat, dog and man after oral administration of [2-14C]-cimetidine

<table>
<thead>
<tr>
<th>Species</th>
<th>Percentage of 14C excreted in 24h</th>
<th>Percentage of 14C excreted in 24h as</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(2)</td>
<td>(3)</td>
</tr>
<tr>
<td>Rat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>58</td>
<td>50</td>
</tr>
<tr>
<td>Female</td>
<td>64</td>
<td>74</td>
</tr>
<tr>
<td>Dog</td>
<td>72</td>
<td>75</td>
</tr>
<tr>
<td>Man</td>
<td>69</td>
<td>50</td>
</tr>
</tbody>
</table>

The third metabolite accounted for only about 2% of the excreted urinary radioactivity, was not detected in some of the urines examined, and has been provisionally identified by t.l.c. as the guany lurea (structure 5, Scheme 1). This compound (5) is probably formed non-enzymically, since it can be produced from cimetidine at acid pH. The sulphoxide (3), the major metabolite in the rat, was readily reduced to the parent compound by rat faecal homogenates.

To investigate the possibility of a 'first-pass' effect through the liver, four dogs were dosed orally with [3H]cimetidine (336mg/kg; 32μCi/mmol), followed 30 min later by 2mg of [14C]cimetidine (33.5μCi) by intravenous injection. A mean of 98% of the intravenous dose of [14C]cimetidine was recovered in the urine, showing this to be the principal route of elimination after intravenous dosing. A mean of 72% of the oral dose was recovered after 48h, indicating good absorption of the drug from the gastrointestinal tract. Investigation of the urines by t.l.c. showed that after oral dosing of [3H]cimetidine, a mean of 84% of the recovered urinary radioactivity was present as unchanged drug, whereas slightly less of the intravenous dose of [14C]cimetidine (81%) was excreted unchanged, suggesting that a 'first-pass' effect through the liver does not occur in the dog.

The pattern of metabolites in dog urine was similar to that found in the rat; the principal metabolite in the urine was the sulphoxide (3), characterized by n.m.r., together with smaller amounts of compounds (4) and (5).

The metabolism of cimetidine in man was studied in one volunteer who was given [3H]cimetidine orally (50mg; 100μCi), followed 0.5h later by an intravenous dose of [14C]cimetidine (50mg; 9.5μCi). Then 2 days later the routes by which the isotopes were given were reversed and the volunteer received 50mg of [14C]cimetidine (8.1μCi) orally, followed 0.5h later by 50mg of [3H]cimetidine by intravenous injection.

The volunteer excreted 70% of the oral 3H dose in his urine in 24h, 64% of the radioactivity being present as unchanged drug; 97% of the 14C intravenous dose was excreted in this period, 73% as unchanged drug. After intravenous administration of [3H]cimetidine, 89% of the radioactive dose was excreted in 24h, 64% of the urinary 3H representing unchanged drug. After oral administration of 14C-labelled compound, 69% of the 14C dose was excreted in the urine in 24h, 50% of the radioactivity representing the parent compound.

These results indicated a small 'first-pass' effect in this volunteer. The pattern of metabolites in urine as judged by t.l.c. was similar to that found for the rat and dog, except that a greater percentage of the urinary radioactivity, representing polar metabolites, remained at the origin of the t.l.c. plates; their nature has not been established.

The results of these experiments are summarized in Table 1, which shows the marked similarity between rat, dog and man in the metabolism of cimetidine.


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