Pharmacokinetics and urinary excretion of orally administered diiodotyrosine

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Abstract. Serum levels of diiodotyrosine (DIT) and urinary excretion rates of DIT and iodine were measured in 10 normal subjects after oral administration of 1.57 μmol of DIT corresponding to 400 μg of iodine. Serum DIT concentrations rose promptly from a mean endogenous basal level of 0.23 nmol/l to maximum values between 6.0 and 20 nmol/l within 30 min to 1 h after DIT ingestion. Decreasing DIT levels were found in all subjects 2 h after DIT intake. Urinary excretion of intact DIT was low, being less than 1% of the administered dose of exogenous DIT within 2 days. In contrast, 52% of the iodine administered in the form of DIT was excreted in the urine in the same time interval. The rapid absorption of DIT from the gastrointestinal tract combined with rapid and almost complete metabolic degradation by deiodination make orally applied DIT seem a suitable iodine carrier compound for therapeutic purposes.

In a recent comparative study on the effectiveness of iodine and thyroxine in the therapy of endemic goitre, the required iodine dose was administered in the form of 3,5-diiodo-L-tyrosine (DIT) instead of the usually applied potassium or sodium iodide (Hintze et al. 1985). DIT was chosen by these authors because some pharmaceutical quality aspects make it seem superior to iodide tablets, which require the presence of reducing agents to prevent oxidation of iodide to elementary iodine and to guarantee long-term pharmaceutical stability. Although DIT is known to be rapidly deiodinated in vivo and in vitro (Oswald 1910; Albert & Keating 1951; Tong et al. 1954; Stanbury et al. 1956), quantitative data on serum levels and urinary excretion rates after oral administration are scarce or lacking. In view of the suggested therapeutic application of DIT as pharmaceutical carrier compound of iodine, we used a specific radioimmunoassay to study the time course of its serum concentrations and urinary excretion after oral administration of a pharmacological dose of DIT to normal subjects.

Materials and Methods

Reagents
DIT was obtained in tablet form for oral administration from Henning Berlin GmbH (Berlin, FRG). Reagents used for the DIT radioimmunoassay previously developed in this laboratory have been described elsewhere (Meinhold et al. 1981).

Subjects
Studies were performed on 10 normal euthyroid volunteers (3 women, 7 men, aged 21 to 30 years). Euthyroidism was established on the basis of a normal TRH test (mean Δ TSH ± SD 10.3 ± 5.1 mU/l) after clinical investigation by palpation and sonography of the thyroid. Each subject gave written consent after having been informed of the purpose and nature of the study. The study protocol was reviewed and approved by the ethical committee of our hospital.
Study protocol
Each subject was orally given 1.57 μmol (680 μg) of DIT corresponding to 400 μg of iodine. Volunteers had an empty stomach at the time of DIT administration and remained without any food for at least 2 h. Blood samples were drawn at 15 min and immediately before as well as 0.5, 1, 2, 3, 5, 8, 12 and 24 h after DIT ingestion. 24-h urine specimens were collected 1 day before and for 2 days after DIT application. Serum and urine samples were stored at —20°C until analysed.

Analytical procedures
DIT was measured in serum by means of a specific radioimmunoassay after its immunochemical separation from serum as described previously (Meinhold et al. 1981). When DIT concentrations were related to the total serum volume of the volunteers, an estimated serum volume of 41 ml/kg body weight was used (Scientific Tables 1971). Urinary DIT concentrations were determined by a modified version of the method for serum DIT measurements. Methodological details and results of validation tests have recently been described elsewhere (Meinhold et al. 1987). Measurements of total urinary iodine excretion were kindly carried out in the laboratory of Dr D. Emrich (Göttingen) using a Technicon autoanalyzer with continuous wet washing of samples prior to quantitative analysis (Glöbel 1977). Creatinine in urine was determined by standard methods.

Table 1.
Urinary excretion of DIT and iodine in 10 normal subjects before and after oral administration of 1.57 μmol (680 μg) of DIT.

<table>
<thead>
<tr>
<th></th>
<th>DIT excretion*</th>
<th>Iodine excretion*</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>(nmol/24 h)</td>
<td>(nmol/mmol creatinine)</td>
</tr>
<tr>
<td>Basal</td>
<td>1.00 ± 0.38</td>
<td>0.082 ± 0.032</td>
</tr>
<tr>
<td>0—24 h after DIT</td>
<td>9.01 ± 3.80</td>
<td>0.583 ± 0.223</td>
</tr>
<tr>
<td>24—48 h after DIT</td>
<td>3.37 ± 1.83</td>
<td>0.233 ± 0.200</td>
</tr>
</tbody>
</table>

* Mean ± SD.
Table 2.
Percentage urinary excretion of exogenous DIT and iodine in 10 normal subjects after oral administration of 1.57 µmol (680 µg) of DIT.

<table>
<thead>
<tr>
<th>Urinary excretion (% dose)*</th>
<th>0–24 h</th>
<th>24–48 h</th>
<th>0–48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIT</td>
<td>0.51 ± 0.25</td>
<td>0.15 ± 0.15</td>
<td>0.66 ± 0.34</td>
</tr>
<tr>
<td>Iodine</td>
<td>51.8 ± 6.5</td>
<td>3.4 ± 3.8</td>
<td>55.2 ± 8.7</td>
</tr>
</tbody>
</table>

* Mean ± SD.

Results

The time course of serum DIT levels in each individual after oral DIT administration is shown in Fig. 1. DIT rose promptly from endogenous basal values between 0.09 and 0.53 nmol/l to peak levels of 6.0–20 nmol/l within 30 min to 1 h after DIT ingestion. Decreasing DIT levels were already observed in all subjects 2 h after DIT intake. The rate of DIT elimination from blood slowed down after 5 to 8 h, leading to serum concentrations which were still above baseline levels 24 h after administration.

Table 1 summarizes the results of DIT and iodine determinations in urine. Mean urinary DIT excretion was 1.00 nmol/24 h before DIT ingestion, increasing to 9.01 nmol/24 h on the first day and being 3.37 nmol/24 h on the second day after the administration. The urinary iodine excretion of 2376 nmol/24 h (302 µg/24 h or 176 µg/g creatinine) during the first day after DIT intake was more than four times higher than the basal excretion rate of 533 nmol/24 h (68 µg/24 h or 49 µg/g creatinine). On the second day after oral DIT, the iodine excretion of 678 nmol/24 h (86 µg/24 h or 62 µg/g creatinine) was only moderately increased. Marked differences between the percentage of DIT and iodine excretion became apparent after referring the excretion rates of exogenous DIT and iodine (after subtracting basal values) to the administered dose. As shown in Table 2, less than 1% of the ingested DIT appeared in the urine within 2 days, whereas more than 50% of the iodine administered in the form of the DIT carrier compound was already excreted in the urine within the first 24 h.

![Fig. 2.](image-url)

Comparison of mean DIT concentrations in the total serum volume of 10 normal subjects after oral administration of 1.57 µmol of DIT (lower curve) with results of a separate study, in which 10 other normal subjects had received a lower dose of 0.46 µmol DIT iv (Meinhold et al. 1987). The values obtained after iv DIT injection in the cited study were extrapolated to a dose of 1.57 µmol of DIT (upper curve).
Discussion

This study confirms previous in vivo and in vitro investigations showing that DIT and also its analogue 3-monoiodo-L-tyrosine (MIT) are rapidly metabolized with deiodination as the predominant degradation pathway (Albert & Keating 1951; Tong et al. 1954; Stanbury et al. 1956; Stanbury 1960). Oral administration led to rapidly increasing serum DIT levels within the first 60 min, indicating a fast transfer of the iodoamino acid from the gastrointestinal tract into the blood. Very similar observations were made by Nelson & Lewis (1977) after administration of 10 mg of DIT to 3 normal subjects. Comparison of mean serum DIT concentrations found after oral administration in this study (Fig. 2, lower curve) with extrapolated values from a separate kinetic study (Fig. 2, upper curve), in which 10 normal subjects had received a dose of 460 nmol of DIT intravenously (Meinhold et al. 1987), reveals clear differences between the DIT contents of the total serum pools in the two study groups. The clearly lower serum levels after oral administration suggest a significant first-pass effect, i.e. a considerable percentage of orally administered DIT is apparently already metabolized in the gastrointestinal tract before entering the circulation. Chromatographic studies on the fate of MIT and DIT in man (Stanbury et al. 1956) have demonstrated that after administration of radioiodine-labelled DIT, no labelled compound other than DIT and iodide is present in the urine. MIT, the intermediate compound after DIT monodeiodination, was deiodinated so rapidly that it was excreted almost entirely as iodide and conjugation or degradation products scarcely appeared in detectable amounts in the urine. In the present study, less than 1% of the administered dose was found as immunoassayable DIT in the urine within 2 days. This very low percentage of the intact iodoamino acid in the urine, its negligible faecal excretion (Albert & Keating 1951), and the high urinary iodine excretion make it seem likely that the metabolic degradation of exogenous DIT is nearly complete and that it takes place largely by deiodination. The pharmacological properties, i.e. rapid absorption from the gastrointestinal tract combined with rapid and almost complete liberation of iodine, make orally applied DIT seem suitable as an iodine carrier for therapeutic measures.

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References


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