Lack of influence of the antidopaminergic drug domperidone on basal and TRH-stimulated TSH-serum levels after oral administration

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Abstract. Since antidopaminergic drugs are known to elevate basal and TRH-stimulated TSH-serum levels and since this effect was also shown after iv administration of the novel dopamine antagonistic agent domperidone, it was investigated, whether this antiemetic drug could interfere after oral intake with the evaluation of thyroid function. Oral domperidone caused a marked TSH-enhancement of TRH-induced TSH increments in 6 out of 14 euthyroid subjects, with no statistical significance, however. The difference between oral and parenteral influence as well as inter-individual changes are probably due to the varying first pass effect of the drug after oral absorption.

It is known that the dominant inhibitory control of thyrotrophin (TSH) release is mediated by the central neurotransmitter dopamine and that antidopaminergic drugs, such as metoclopramide and sulpiride are capable of enhancing TSH-secretion in both normal and, particularly, hypothyroid subjects (Delitala 1977; Healy & Burger 1977; Scanlon et al. 1977; Massara et al. 1978; Zanoboni et al. 1979). Metoclopramide increases TSH-levels in serum of normal subjects after iv (Scanlon et al. 1980a; Staub et al. 1980) as well as after oral administration (Healy & Burger 1977; Scanlon et al. 1980b), thus effecting the accuracy of thyroid function tests (Wenzel 1981). It was even proposed to use the enhancing effect on TSH-secretion of metoclopramide as a diagnostic tool for the recognition of subclinical hypothyroidism (Scanlon et al. 1979) or preclinical hyperthyroidism (Birkhäuser et al. 1980; Staub et al. 1980).

Recently the new dopamine antagonist domperidone has been developed which unlike metoclopramide does obviously not penetrate the blood-brain barrier (Laduron & Leysen 1978; Reytiens et al. 1978; Costal et al. 1979; Cocchi et al. 1980). There is convincing evidence that this compound is capable of increasing TSH levels even more than metoclopramide in euthyroid and hypothyroid subjects; all investigations, however, were performed either by im injections (Delitala et al. 1980) or by iv application (Pourmand et al. 1980; Scanlon et al. 1981; Massara et al. 1981; Kamijo et al. 1981). Hitherto, no publications about the oral influence of domperidone on TSH concentrations exist. Since this drug has been developed because of its antiemetic potential in the absence of central side effects, it may be assumed that the consumption of domperidone may rise in a short time.

Therefore the purpose of this study was to investigate the influence of such a presumably abundant remedy like domperidone on the serum concentrations of basal and TRH-mediated TSH. Especially in consideration of the importance (Wenzel 1979) of the TRH-test (stimulation of the pituitary with thyrotrophin releasing hormone) such an interference would hamper the frequently used thyroid function tests.

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Fig. 1.
Comparison of basal TSH values ± SD in males (a) and females (b) before (—) and after (---) oral intake of domperidone.

Materials and Methods

Seven healthy male (19–39 years) and 7 healthy female (18–38 years) volunteers were studied. All subjects were clinically and biochemically euthyroid (TSH < 4.5 μU/ml, normal serum T3 and T4 levels) and neither history nor previous laboratory investigations had given any signs of liver disease. The body weights differed between 71 and 80 kg for the males and 54 and 63 kg for the females. All test persons gave informed consent. The investigation was approved by the local Ethical Committee. Three of the female subjects were taking oral contraceptives, the others did not. Tests were carried out in one week intervals at the same time of day i.e. 14.00–18.00 for the TSH-levels and 18.00–19.00 for TRH-tests. While the probands remained in the recumbent position after a 4 h fast, blood samples were taken via forearm venous puncture kept patent by a slow infusion of saline.

For basal tests, blood was sampled for TSH estimation every 30 min during 4 h and the TRH-test was performed at −15, 0, 20, 30, 40 and 60 min after iv injection of 400 μg TRH (HENNING, Berlin). In order to allow an adequate absorption, blood samplings for the TSH estimation or the TRH-test were started 1 h after intake of 20 mg domperidone (Janssen Pharmazeutika, Düsseldorf). Finally, the TRH-test was repeated after the subjects had taken 3 × 20 mg domperidone daily during 3 entire weeks.

Fig. 2.
Comparison of TRH-tests ± SD in males (a) and females (b) before (—) and after (---) domperidone and after 3 weeks medication (---) of domperidone.
Serum was stored at −20°C until assayed. TSH was measured by specific radioimmunoassay (TSH-RIA-HENNING). All samples from each subject were measured in the same assay. Statistical analysis was performed using Student’s t-test for paired comparisons and the Wilcoxon rank test.

Results

Domperidone administration was followed by a slight increase of basal TSH-levels which, however, did not reach statistical significance by both statistical tests at any time after intake (Fig. 1). Six subjects (4 males, 2 females, body weights 72, 74, 81, 80, 51 and 60 kg) showed markedly higher TSH increments in the TRH-test; this effect could be repeated after 3 weeks’ intake of domperidone (Table 1). However, the average values were not significantly different from basal test values, neither in the whole group nor in the female or in the male group (Fig. 2). Three weeks’ intake of domperidone did not induce a significant increase of basal TRH-stimulated TSH levels in any group.

Table 1.

Serum values of TSH (μU/ml) in the TRH test of 6 subjects in a control test, after domperidone (D) (20 mg per os), and after domperidone (20 mg per os) following 3 weeks pre-medication with 3 × 20 mg domperidone per day.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>−15 min</th>
<th>0 min</th>
<th>20 min</th>
<th>30 min</th>
<th>40 min</th>
<th>60 min</th>
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<tbody>
<tr>
<td>1 (male)</td>
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<td>1.6</td>
<td>11.6</td>
<td>9.5</td>
<td>8.3</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>20 mg D 3.1</td>
<td>2.1</td>
<td>12.5</td>
<td>16.0</td>
<td>15.8</td>
<td>10.6</td>
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<tr>
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<td>5 weeks D 2.0</td>
<td>1.8</td>
<td>13.1</td>
<td>15.5</td>
<td>13.0</td>
<td>9.6</td>
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<tr>
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<tr>
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<td></td>
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<td>12.1</td>
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<tr>
<td></td>
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<td>18.5</td>
<td>14.9</td>
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</tr>
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<td>2.4</td>
<td>1.4</td>
<td>1.3</td>
</tr>
<tr>
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<td>2.9</td>
<td>3.1</td>
<td>2.2</td>
<td>1.7</td>
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<td>2.9</td>
<td>2.2</td>
<td>1.8</td>
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<td>12.7</td>
<td>13.4</td>
<td>11.8</td>
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<td>19.2</td>
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<td>17.1</td>
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<td>16.1</td>
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</tr>
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<td>6 (female)</td>
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<td>18.6</td>
<td>16.1</td>
<td>10.4</td>
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Discussion

It was reported that administration of dopamine (Besses et al. 1975; Burrow et al. 1977) and L-Dopa (Spaulding et al. 1972; Lamberg et al. 1977) lowered basal and TRH-stimulated TSH levels in man. On the other hand dopamine antagonists, such as metoclopramide (Delitala 1977; Healy & Burger 1977; Scanlon et al. 1977, 1979; Feek et al. 1980; Staub et al. 1980) or sulpiride (Massara et al. 1978; Zanoboni et al. 1979) induced a significant rise of TSH serum levels in controls or hypothyroid patients and of TSH increments after TRH-stimulation. Recently, the novel agent domperidone, which combines the properties of specific dopamine receptor blockade and inability to cross the blood-brain barrier, was also shown to provoke marked elevations of basal and TRH-stimulated TSH (Delitala et al. 1980; Pourmand et al. 1980; Scanlon et al. 1981; Massara et al. 1981; Kamiyo et al. 1981). Furthermore, in vitro experiments with pituitary tissue cultures gave evidence that domperidone is
capable of stimulating TSH secretion directly, too (Powell et al. 1981). Since TSH elevations after domperidone seem to be more pronounced than by metoclopramide and since oral administration of metoclopramide easily induced TSH increments, it was to be expected that oral domperidone would also increase basal and TRH-mediated TSH serum concentrations. Because of the frequent use of these thyroid tests, the implication of such an interference would have been obvious.

Unexpectedly, there was no significant increase of TSH serum concentrations after oral domperidone application. A marked TSH elevation was found in only 6 out of 14 subjects. Since the conditions (fasting, position, time of day) were the same for every subject and since the body weights gave no explanation for differences, the reason for the different behaviour after parenteral or oral administration and in different subjects could be due to the passage of domperidone from the gut to the circulation. This view is supported by pharmacological investigations done by the manufacturer with radioimmunological determinations as well as radioactive labelling of domperidone. In dogs, plasma levels of domperidone were markedly lower after oral than after iv dosing (Meuldermans et al. 1977), and in human volunteers only 14% of the radioactivity present in the plasma after oral intake of labelled domperidone was due to the unchanged drug while only 0.4% of the oral dose was excreted unchanged, indicating that domperidone was extensively metabolized in the liver before reaching central circulation (Heykants et al. 1977). Moreover, the inter-individual amount of unchanged drug in the plasma differed by a factor up to 2.4 (Heykants et al. 1977). These data indicate that the 'first pass effect' of domperidone is responsible for the lacking TSH increase and for the inter-individual differences in this study. Retrospectively, it is conspicuous that 5 out of 7 publications dealing with the effect of metoclopramide on TSH levels were done with oral administration, whereas all of the 5 existing studies with domperidone were done by parenteral application.

In conclusion, it can be derived from these results that oral medication of the antiemetic drug domperidone does not exhibit major interferences with TSH serum concentrations or with the TRH test. One should be aware, however, that in some individuals TSH elevations could result and that the diagnosis of subclinical hypothyroidism should be re-evaluated after cessation of the drug.

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References


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