Comparative effect of cimetidine and ranitidine on prolactin secretion

*G. F. Nelis M.D.  J. G. C. van de Meene Ph.D.

Departments of *Medicine, and Chemical Pathology, Sophia Ziekenhuis, 8000 GK Zwolle, The Netherlands

Summary
Cimetidine has been shown to stimulate prolactin secretion after intravenous administration. Cimetidine 200 mg and ranitidine 50 mg was given i.v. in a randomly allocated order to 22 volunteers on consecutive days; these doses can be regarded as equivalent as far as inhibition of gastric acid output is concerned. Plasma prolactin was estimated at regular intervals. The prolactin stimulating effect of cimetidine was confirmed while ranitidine did not influence plasma prolactin levels.

Although cimetidine and ranitidine seem to be equally effective in reducing gastric acid output, the effect of the drugs are not the same on their entire spectrum of action since ranitidine does not influence plasma prolactin.

It still has to be established in clinical trials which drug is the best choice in clinical medicine.

Introduction
Intravenous administration of cimetidine stimulates prolactin secretion (Burland et al., 1979; Carlson and Ippoliti, 1977) whereas oral cimetidine treatment in conventional doses does not influence the basal or releasing hormone-stimulated values of prolactin, thyroid-stimulating hormone and luteinizing hormone (Nelis and van de Meene, 1980).

A newly synthesized histamine H2-receptor antagonist ranitidine (Glaxo AH 19065) has recently been entered into controlled clinical trials at the Sophia Ziekenhuis.

Peden, Saunders and Wormsley (1979) demonstrated a dose-dependent reduction in nocturnal and pentagastrin-stimulated acid output after intra-duodenal instillation of ranitidine. The reduction in acid output after 80 mg ranitidine was comparable to the effect of 400 mg cimetidine. Domschke, Lux and Domschke (1979) showed a comparable effect after i.v. infusion of ranitidine; in this study ranitidine was 4 times more effective than cimetidine on a molar base. A dose of 50 mg ranitidine and 200 mg cimetidine was therefore used in this trial.

Materials and methods
The investigation was conducted in 22 volunteers: Group I consisted of 8 males (aged 20 to 76 years, mean 43·4±19·4 s.e. mean); Group II consisted of 8 pre-menopausal females (aged 17 to 23 years, mean 20·4±2·2 s.e. mean) and Group III consisted of 6 post-menopausal females (aged 61 to 89 years, mean 74·2±9·5 s.e. mean). Reasons for exclusion were pregnancy, lactation, use of oral contraceptives, hormonal disorders, previous cimetidine treatment and the use of drugs known to influence plasma prolactin (Lamberts, Klijn and Birkenhager, 1978).

The volunteers were randomly allocated to receive an i.v. bolus injection of 200 mg cimetidine on day one and 50 mg ranitidine the following day, or the reverse. These doses have an equal effect in reducing gastric acid output. All tests started at 9 a.m.; blood samples for prolactin were taken at 0, 15, 30, 60 and 90 min after administration of either drug.

In pre-menopausal women, the phase of the menstrual cycle was determined by history, plasma progesterone and plasma oestradiol. The women were presumed to be in the luteal phase if plasma progesterone exceeded 17 nmol/l and plasma oestradiol exceeded 330 pmol/l. Sera were separated and stored at −20°C. All samples were assayed together. The hormones were estimated by radioimmunoassay using CEA-IRE-SORIN (CIS) kits (Fleurus, Belgium) for prolactin (MRC standard 71/222) and commercial kits from Behringwerke-Hoechst (Frankfurt, Germany) for progesterone and oestradiol. Ranitidine was kindly supplied by the Medical Department of Glaxo Allenburys Research (Ware) Ltd (batch 8 CTR/6853).

The matched Student's t-test for paired observations was used for statistical analysis, each subject serving as his/her own control.

All volunteers gave informed consent and the study was conducted according to the Declaration of Helsinki.

Results
Table 1 shows the average plasma prolactin values in response to cimetidine and to ranitidine in the
Prolactin secretion

Table 1. Plasma prolactin values (µu./ml) in response to cimetidine and to ranitidine i.v. in 22 volunteers

<table>
<thead>
<tr>
<th>Drug (s.e. mean)</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(s.e. mean)</td>
<td>305</td>
<td>672</td>
<td>504</td>
<td>361</td>
<td>306</td>
</tr>
<tr>
<td>(34)</td>
<td>(73)</td>
<td>(67)</td>
<td>(60)</td>
<td>(52)</td>
<td></td>
</tr>
<tr>
<td>Ranitidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(s.e. mean)</td>
<td>302</td>
<td>297</td>
<td>281</td>
<td>290</td>
<td>273</td>
</tr>
<tr>
<td>(36)</td>
<td>(39)</td>
<td>(38)</td>
<td>(46)</td>
<td>(42)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>&gt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

Table 2. Plasma prolactin values (µu./ml) and s.e. mean in response to cimetidine and to ranitidine i.v. in males (n=8, Group I), pre-menopausal females (n=8, Group II) and post-menopausal females (n=6, Group III)

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>15</th>
<th>30</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimetidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>300</td>
<td>649</td>
<td>429</td>
<td>328</td>
<td>306</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>88</td>
<td>61</td>
<td>84</td>
<td>68</td>
</tr>
<tr>
<td>II</td>
<td>291</td>
<td>676</td>
<td>508</td>
<td>315</td>
<td>242</td>
</tr>
<tr>
<td></td>
<td>58</td>
<td>110</td>
<td>73</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>III</td>
<td>329</td>
<td>698</td>
<td>597</td>
<td>466</td>
<td>391</td>
</tr>
<tr>
<td></td>
<td>55</td>
<td>88</td>
<td>64</td>
<td>91</td>
<td>70</td>
</tr>
<tr>
<td>Ranitidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>304</td>
<td>298</td>
<td>259</td>
<td>291</td>
<td>271</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>47</td>
<td>46</td>
<td>63</td>
<td>45</td>
</tr>
<tr>
<td>II</td>
<td>255</td>
<td>251</td>
<td>247</td>
<td>246</td>
<td>214</td>
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<tr>
<td></td>
<td>26</td>
<td>33</td>
<td>17</td>
<td>27</td>
<td>30</td>
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<tr>
<td>III</td>
<td>362</td>
<td>358</td>
<td>357</td>
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<td>59</td>
<td>55</td>
<td>57</td>
<td>55</td>
<td>50</td>
</tr>
</tbody>
</table>

Group as a whole, while the figures for the groups taken separately are given in Table 2.

The plasma prolactin stimulating effect of cimetidine is evident at 15, 30 and 60 min after injection (P<0.01) while ranitidine does not influence plasma prolactin values at 15, 30, 60 and 90 min after injection (P>0.05). The differences between the plasma prolactin values after cimetidine and ranitidine are statistically significant at 15, 30 and 60 min (P<0.01) for the group as a whole. For the sub-groups the difference is statistically significant (P<0.01) at 15, 30 and 60 min in the post-menopausal women but only at 15 and 30 min after injection in pre-menopausal women and males.

Plasma prolactin values on the first day of testing are not different from those on the second day (331.4 µu./ml v. 319.8 µu./ml) irrespective of whether cimetidine or ranitidine was given on the first day. Basal values before cimetidine administration were no different from those before ranitidine administration, neither in the group as a whole (304.6 µu./ml ± 44 s.e. mean v. 302.0 µu./ml ± 36 s.e. mean) nor in the sub-groups taken separately.

Table 3 shows the percentage maximal increase in plasma prolactin in relation to the phase of the menstrual cycle in pre-menopausal women; no influence on either cimetidine response nor ranitidine response could be established.

Table 3. Maximal increase in plasma prolactin levels in response to cimetidine and to ranitidine regarding phase of menstrual cycle in pre-menopausal women

<table>
<thead>
<tr>
<th></th>
<th>Cimetidine</th>
<th>Ranitidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>239</td>
<td>102</td>
</tr>
<tr>
<td>Luteal</td>
<td>254</td>
<td>89</td>
</tr>
</tbody>
</table>

Discussion

Cimetidine is an effective drug in lowering gastric acid output and is therefore useful in the treatment of peptic ulcer, peptic oesophagitis and the Zollinger-Ellison syndrome.

Recently its usefulness in the symptomatic treatment of carcinoid tumours has been claimed (Roberts, Marney and Oates, 1979). Up to now, no major side effects of clinical importance have been established although interference with some biochemical parameters have been described as well as
several other often ill-defined and only occasional clinical events (Flind, Rowley-Jones and Backhouse, 1980). The prolactin-secreting effect of i.v. administered cimetidine is widely proved whereas its mechanism of action is still unclear. Direct action on brain histamine receptors, depletion of hypothalamic dopamine stores and dopamine antagonism at the pituitary receptor site have all been proposed (Arakelian and Libertun, 1977; Burland et al., 1979).

This study showed that ranitidine in equivalent doses to those of cimetidine as regards reduction of gastric acid output failed to stimulate prolactin secretion, so the effect on gastric acid output does not parallel the effect on prolactin-secretion. This could mean that ranitidine does not penetrate into the pituitary as cimetidine does (Cross, 1977) or the prolactin secreting effect is specifically related to the structure of the cimetidine molecule. A more speculative suggestion from these data could be the existence of a sub-classification of H₂ receptors with cimetidine acting as a less selective antagonist than ranitidine.

The authors’ observations are not influenced by the phase of the menstrual cycle as this did not influence the results obtained and as all tests were done on consecutive days which excludes cycle variations in a given person. There is no bias due to a priming or inhibiting effect of either drug as the volunteers were randomly allocated to receive either cimetidine or ranitidine on the first day.

Prolactin secretion is strongly stimulated by stress; the fact that the basal plasma prolactin values on the first day of testing were similar to those on the second day excludes a serious stress situation in the volunteers.

The only difference between the groups is a slightly prolonged rise in plasma prolactin after cimetidine in post-menopausal women (Group III) which could be a result of a diminished prolactin or cimetidine clearance due to ageing.

In conclusion, the authors observed a significant difference between the 2 histamine H₂-receptor antagonists, cimetidine and ranitidine, as regards the stimulation of prolactin secretion. Further investigation into the possibility of a subdivision of histamine H₂ receptors is necessary.

References


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