Letter to the Editor


Clinical trials of 4-HPR in several organ sites are ongoing, and the paper by Follen et al. (1) reports the results of a trial in patients with high-grade squamous intraepithelial lesions of the cervix. 4-HPR, administered for 6 months at 200 mg/day with a 3-day/month drug holiday was not active compared with placebo. I appreciated the decision of the authors to monitor the drug plasma levels, and I read with interest their hypothesis that the lack of activity was attributable to low drug serum levels. As pointed out in the discussion section, the 4-HPR concentrations effective in suppressing the in vitro growth of tumor cells range from 1 to 10 µM, which correspond to 400–4000 ng/ml, whereas the mean serum levels of 4-HPR in the participants in the trial were 34.8 ng/ml. We found, in patients participating in a breast prevention trial and treated with 4-HPR at the same dose and with the same schedule, 4-HPR plasma levels of 350 ng/ml (2,3), which are concentrations 10 times higher.

To understand the reasons for such differences and to provide information for 4-HPR monitoring in future trials, we reviewed the published data on similar analyses. Table 1 reports the levels of 4-HPR and of its metabolite 4-MPR found in plasma or serum of subjects participating in six different clinical trials in which the drug was administered at 200 mg/day with a 3-day/month drug holiday and in which blood samples for drug measurement were collected at a single point. Table 1 also reports the results of a study by Doose et al. (4) on 4-HPR bioavailability that clearly showed the influence of meals and meal composition on 4-HPR plasma levels. In the study, at variance with the clinical trials, the dose of 4-HPR was 300 mg, and drug levels were measured at different intervals after a single drug administration. Doose et al. showed that administration of 4-HPR after a high-fat breakfast increased 4-HPR peak levels three times (from 198 to 596 ng/ml) compared with administration of the same dose in the fasting state. They also showed that a high-fat meal caused the highest increase in 4-HPR absorption compared with high-protein and high-carbohydrate meals.

Among the six clinical trials with monitoring of 4-HPR levels, two were performed in Italy (2,5) and four in the United States (1,6–8). In a prevention trial run in Italy, in women operated on for early breast cancer, 4-HPR was taken after dinner, and blood samples were collected 12 h after drug intake (2). In these subjects, we found mean 4-HPR and 4-MPR plasma levels of 363 and 369 ng/ml, respectively. Similar levels were found in other subjects participating in the same trial whose blood was collected at different times after the beginning of treatment starting from 5 months up to 5 years (3). In another trial run in Italy, patients with bladder cancer who took the drug after dinner had 4-HPR plasma levels similar to those found in our study (297 ng/ml; Ref 5). However, the coefficient of variation was higher, possibly because of the wide range of the interval between drug intake and blood sampling (18 ± 11 h). The 4-HPR levels found in the four trials carried out in the United States were much lower. In the trial run by Thaller et al. (6), Conley et al. (7), and Kurie et al. (8), they were three times lower, whereas in the trial by Follen et al. (1) they were 10 times lower. No information was provided on the modality of drug administration or on the interval between drug intake and blood sampling in the paper by Kurie et al. (8) and by Follen et al. (1). In the trial by Thaller et al. (6) the drug was taken after dinner, similarly to the two trials run in Italy (2,5), whereas in the trial by Conley et al. (7) it was taken after breakfast. The interval between drug intake and blood sampling was ~24 h in both studies. The longer interval than in the two studies run in Italy might in part account for the lower drug levels. The coefficient of variation of drug levels in the four studies was high (≥0.6), suggesting high variability in the drug intake-blood sampling interval. It might also reflect high variability in meal composition as a consequence of the different demographic origins of the trial participants. In the Doose et al. study (4), subjects received tests meals of which the composition was well defined. In our study (2), all of the participants lived in the northern part of Italy, where alimentary habits are rather uniform and where olive oil, which might account for higher 4-HPR bioavailability, is a constant component of the meals.

In conclusion, from the analysis of the results on 4-HPR levels measured in different clinical trials, we suggest that the observed differences might be attributable to differences in meal composition and in the interval between drug intake and blood sampling. Therefore, we draw attention to the importance of the modalities of drug administration and of meal composition in 4-HPR bioavailability, and of the interval from drug intake in monitoring drug levels. From this analysis we also conclude that the highest 4-HPR plasma concentrations achieved with the 200-mg daily dose are ~1 µM, i.e., the least effective in suppressing tumor cell growth in vitro. For this reason we agree with the conclusion of the authors that higher doses should be tested in future clinical trials. The suggestion seems reasonable taking into account that 4-HPR was not toxic at 200 mg/day and is supported by the fact that high-dose 4-HPR was more effective than low dose in preventing mammary tumors in rats (9).

Franca Formelli
Department of Experimental Oncology
Istituto Nazionale Tumori
Via Venezian 1
20133 Milan, Italy

Received 12/19/01; accepted 2/1/02.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 Supported in part by a grant from the Associazione Italiana Ricerca sul Cancro, Milan, Italy.

2 The abbreviations used are: 4-HPR, N-(4-hydroxyphenyl)retinamide; 4-MPR, N-(4-methoxyphenyl)retinamide.

Downloaded from clincancersres.aacrjournals.org on October 15, 2017. © 2002 American Association for Cancer Research.
<table>
<thead>
<tr>
<th>Dose (mg/day)</th>
<th>No. of subjects</th>
<th>Sex</th>
<th>Age range (yr)</th>
<th>Drug administration modality</th>
<th>Length of treatment</th>
<th>Interval from last drug intake</th>
<th>4-HPR (C.V.)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>4-MPR (C.V.)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Ref/Kind of subjects/In plasma (P) or serum (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300</td>
<td>13</td>
<td>M</td>
<td>(19–50)</td>
<td>While fasting</td>
<td>1 day</td>
<td>at peak&lt;sup&gt;b&lt;/sup&gt;</td>
<td>198 ± 75 (0.38)</td>
<td>91 ± 31 (0.34)</td>
<td>Healthy subjects (P)</td>
</tr>
<tr>
<td>15</td>
<td>M (18–43)</td>
<td></td>
<td></td>
<td>After HF&lt;sup&gt;c&lt;/sup&gt; breakfast</td>
<td>1 day</td>
<td>at peak&lt;sup&gt;b&lt;/sup&gt;</td>
<td>596 ± 265 (0.44)</td>
<td>211 ± 94 (0.44)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>After HF meal</td>
<td>1 day</td>
<td>at peak&lt;sup&gt;b&lt;/sup&gt;</td>
<td>669 ± 178 (0.27)</td>
<td>217 ± 49 (0.22)</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>10</td>
<td>F</td>
<td>(35–65)</td>
<td>After dinner</td>
<td>5 months</td>
<td>12 h</td>
<td>363 ± 140 (0.38)</td>
<td>369 ± 193 (0.53)</td>
<td>Early breast cancer patients (P)</td>
</tr>
<tr>
<td>7</td>
<td>F (35–65)</td>
<td></td>
<td></td>
<td>After dinner</td>
<td>5 months</td>
<td>14 ± 2 h</td>
<td>348 ± 133 (0.38)</td>
<td>349 ± 173 (0.49)</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>31</td>
<td>M/F</td>
<td>(46–81)</td>
<td>After dinner</td>
<td>12 months</td>
<td>18 ± 11 h</td>
<td>297 ± 200 (0.67)</td>
<td>339 ± 194 (0.57)</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>14</td>
<td>M</td>
<td>(46–70)</td>
<td>After dinner</td>
<td>28 days</td>
<td>≤24 h</td>
<td>127 ± 107 (0.84)</td>
<td>141 ± 87 (0.62)</td>
<td>Bladder cancer patients (P)</td>
</tr>
<tr>
<td>200</td>
<td>32</td>
<td>F</td>
<td>(36–74)</td>
<td>After breakfast</td>
<td>25 days</td>
<td>20–24 h</td>
<td>132 ± 82 (0.62)</td>
<td>113 ± 85 (0.75)</td>
<td>Prostate cancer patients (S)</td>
</tr>
<tr>
<td>200</td>
<td>34</td>
<td>M/F</td>
<td>(31–67)</td>
<td>n.d.&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2–6 months</td>
<td>n.d.</td>
<td>104 ± 64 (0.61)</td>
<td>201 ± 136 (0.68)</td>
<td>High risk subjects for breast cancer (P)</td>
</tr>
<tr>
<td>200</td>
<td>20</td>
<td>F</td>
<td>(18–42)</td>
<td>n.d.</td>
<td>6 months</td>
<td>n.d.</td>
<td>35 ± 27&lt;sup&gt;e&lt;/sup&gt; (0.77)</td>
<td>53 ± 33 (0.63)</td>
<td>Smokers with bronchial squamous metaplasia and/or dysplasia (S)</td>
</tr>
</tbody>
</table>

<sup>a</sup>C.V. = coefficient of variation.

<sup>b</sup>At peak: corresponding to 3–4 h for 4-HPR and 6–12 h for 4-MPR.

<sup>c</sup>HF, high-fat; HP, high-protein; HC, high-carbohydrate.

<sup>d</sup>n.d., not described.

<sup>e</sup>The SD was calculated from the results of the authors, assuming that all assessable patients in the 4-HPR group (i.e. 20) had serum drug measurement.

<sup>f</sup>Cervical intraepithelial neoplasia.
Acknowledgments

We thank Dr. Carmen Pollini for useful discussion about the letter and Elena Cavadini for excellent technical help in all my studies on 4-HPR plasma levels.

References


Franca Formelli