PHARMACOKINETICS OF 4′epi-ADRIAMYCIN AFTER MORNING AND AFTERNON INTRAVENOUS ADMINISTRATION

STAFFAN EKSBORG,* ULF STENDAHL† and KAIJA ANTILA*
*Karolinska Pharmacy, P.O. Box 60024, S-104 01 Stockholm; †Dept of Gynecological Oncology, University Hospital, Umeå, Sweden

(Received 5 May 1988; accepted 13 September 1988)

The chronopharmacokinetics of 4′epi-adriamycin (Epi) have been studied in ten patients with gynecological malignancies. The drug (45 mg m⁻²) was administered as a short time (5.0 min) intravenous infusion at 7 a.m. and 7 p.m., in a randomized cross-over design. The pharmacokinetics of Epi were evaluated according to the statistical moment theory.

Morning and afternoon dosing of Epi was not bioequivalent. The area under the plasma concentration-time curve (AUC), the maximum plasma concentration (Cₘₐₓ), mean residence time (MRT) and the terminal half-life time (tₑ) could differ by more than 35% after morning and afternoon dosing. The inter-individual variation of AUC and Cₘₐₓ were larger after morning dosing than after afternoon dosing (P < 0.04).

The morning dose of Epi resulted in higher values of AUC in seven of the ten treated patients as compared to the afternoon dose. The terminal half-life times were shorter in eight of the patients after the morning dose.

Key words: 4′epi-Adriamycin, Anthraquinone glycosides, Pharmacokinetics, Chronopharmacology, Bioequivalence.

INTRODUCTION

4′-epi-Adriamycin (Farmorubicin™) is a promising new anthracycline derivative. In early clinical studies it has been suggested to have a considerably higher therapeutic index than adriamycin, one of the most important antineoplastic drugs currently used.¹-³ The pharmacokinetic properties of 4′epi-adriamycin (Epi) and adriamycin are very similar.⁴ Significant daily variation of the pharmacokinetics has been observed for a number of drugs, mainly after their oral administration.⁵-⁸ The importance of the dosing time on the pharmacokinetics and pharmacodynamics has only recently been considered as a tool for optimizing therapy with antineoplastic drugs.⁹-¹¹

Large intra- and inter-individual circadian-varying plasma pharmacokinetics of adriamycin have recently been reported during continuous infusion.¹² No chronopharmacokinetic study of Epi has so far been published, neither during continuous nor after short period infusions.

In the present study the chronopharmacokinetics of Epi have been studied in a randomized cross-over design in ten patients with ovarian carcinoma. The drug was administered intravenously as short time (5.0 min) infusions at 7 a.m. and 7 p.m., respectively.

MATERIAL AND METHODS

Patients

Eight patients with ovarian carcinoma (clinical stage IB–III, FIGO), and two with sarcoma of the uterine body (clinical stage I and IV, FIGO) participated in the study. Their median age was 60 yr (range 45–76 yr). All patients had a Karnofsky performance of ≥ 90%. None of the patients had liver metastases, but one had slightly elevated alkaline phosphatase and transaminase levels. None of the patients was clinically jaundiced. All patients had previously been treated with Epi and cis-platinum.

Treatment schedule

4′epi-adriamycin (Farmorubicin™) was dissolved in physiological saline (drug concentration: 2 mg ml⁻¹) and administered intravenously over a 5.0 min period.

All patients received their Epi dose (45 mg m⁻²) at 7 a.m. (treatment I) and the same dose at 7 p.m. (treatment II) in a randomized cross-over design. Patients in group A started with the afternoon treatment, while patients in group B started with the morning treatment. The time interval between the treatments was 4 weeks (26–30 days).
Blood samples (5-7 ml) were collected in glass test tubes (Vacutainer™) containing 250 IU heparin (freeze-dried). The blood samples were immediately centrifuged for 10 min to separate the plasma fractions, which was removed and stored at -80°C until analysis. Blood samples were collected 5, 15, 30, 45 min and 1, 2, 3, 6, 12, 18 and 24 h after the end of administration.

Analytical procedure

Plasma concentrations of Epi and its active metabolite 4'-epi-adriamycinol were assayed by an analytical method based on extraction and reversed-phase liquid chromatography with photometric detection at 500 nm.13 One millilitre of plasma was used for the analysis. All plasma concentration data used for the pharmacokinetic evaluation are the means of duplicate analysis.

Pharmacokinetic evaluation

The areas under the zero and first moment curves (AUC and AUMC, respectively) were estimated by the logarithmic trapezoidal rule.14 The mean residence time, MRT, was calculated as:

\[
MRT = \frac{\text{AUMC}}{\text{AUC}}
\]  (1)

The maximum plasma concentration, \(C_{\text{max}}\), was estimated by extrapolation of plasma concentration data to zero time (i.e. to the end of the drug administration).

RESULTS AND DISCUSSION

Evaluated pharmacokinetic parameters of Epi after morning and afternoon dosing are presented in Table 1. The very low concentration of 4'-epi-adriamycinol (≤ 5 ng/ml in all samples) did not permit a useful evaluation of its pharmacokinetics.

Morning and afternoon dosings of Epi were not bioequivalent, as outlined by the Westlake modification of the ANOVA-based confidence interval15 and the non-parametric confidence interval. The 95% confidence interval of the morning/afternoon ratio within the range 0.8-1.2 was considered as bioequivalent.

Parametric and non-parametric analysis of variance17,18 were used for evaluation of systematic changes of the pharmacokinetic parameters with dosing time.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Group</th>
<th>Dose mg m⁻²</th>
<th>Morning dose AUC μg.min ml⁻¹</th>
<th>(C_{\text{max}}) μg ml⁻¹</th>
<th>MRT min</th>
<th>(t_{1/2}) h</th>
<th>Afternoon dose AUC μg.min ml⁻¹</th>
<th>(C_{\text{max}}) μg ml⁻¹</th>
<th>MRT min</th>
<th>(t_{1/2}) h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 B</td>
<td>43.3</td>
<td>37.6</td>
<td>5.79</td>
<td>182</td>
<td>8.60</td>
<td>37.0</td>
<td>2.44</td>
<td>726</td>
<td>18.3</td>
<td></td>
</tr>
<tr>
<td>2 B</td>
<td>47.3</td>
<td>41.3</td>
<td>2.08</td>
<td>357</td>
<td>9.35</td>
<td>49.0</td>
<td>4.90</td>
<td>348</td>
<td>11.0</td>
<td></td>
</tr>
<tr>
<td>3 B</td>
<td>44.6</td>
<td>23.3</td>
<td>0.52</td>
<td>460</td>
<td>7.37</td>
<td>70.7</td>
<td>8.45</td>
<td>259</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>4 A</td>
<td>47.2</td>
<td>47.9</td>
<td>3.77</td>
<td>346</td>
<td>8.89</td>
<td>44.5</td>
<td>5.43</td>
<td>223</td>
<td>9.17</td>
<td></td>
</tr>
<tr>
<td>5 A</td>
<td>39.8</td>
<td>63.9</td>
<td>7.33</td>
<td>264</td>
<td>10.8</td>
<td>35.3</td>
<td>4.69</td>
<td>365</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>6 B</td>
<td>47.8</td>
<td>50.7</td>
<td>4.19</td>
<td>352</td>
<td>10.9</td>
<td>43.7</td>
<td>3.06</td>
<td>615</td>
<td>14.4</td>
<td></td>
</tr>
<tr>
<td>7 B</td>
<td>48.2</td>
<td>129</td>
<td>17.6</td>
<td>115</td>
<td>8.70</td>
<td>84.5</td>
<td>6.27</td>
<td>322</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>8 A</td>
<td>47.0</td>
<td>43.6</td>
<td>3.20</td>
<td>330</td>
<td>12.2</td>
<td>37.0</td>
<td>5.76</td>
<td>470</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>9 A</td>
<td>42.4</td>
<td>30.6</td>
<td>2.05</td>
<td>310</td>
<td>5.92</td>
<td>67.8</td>
<td>8.47</td>
<td>120</td>
<td>7.70</td>
<td></td>
</tr>
<tr>
<td>10 A</td>
<td>50.4</td>
<td>85.8</td>
<td>8.18</td>
<td>381</td>
<td>18.3</td>
<td>63.9</td>
<td>6.31</td>
<td>362</td>
<td>13.3</td>
<td></td>
</tr>
</tbody>
</table>

Median values: 47.1 47.9 4.69 322 9.73 51.6 5.58 362 11.8