Single and repeated dose pharmacokinetics of thio-TEPA in patients treated for ovarian carcinoma*

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Summary. Triethylenethiophosphoramide (thio-TEPA) pharmacokinetics were studied in 15 patients being treated for epithelial ovarian carcinoma. Unchanged thio-TEPA was assayed in serum and urine by means of a gas chromatographic procedure.

No accumulation or alteration of the pharmacokinetics occurred during therapy, which was continued for up to 7 months with biweekly administrations of 20 mg, after two initial loading courses with 20 mg daily for 3 consecutive days 2 weeks apart. No significant difference in the pharmacokinetics between i.m. and i.v. administration was demonstrated. However, three patients showed a reduced absorption ability from the i.m. injection site to the systemic circulation and an apparent increase in the elimination half-life (3.86 ± 0.97 h), which could be of clinical relevance.

A first-order elimination process with a short elimination half-life (~1.5 h) was demonstrated for thio-TEPA in all patients after i.v. administration. The apparent volume of distribution averaged 50 l. The renal clearance was below 1% of the total-body clearance, which averaged 412 ml/min. The urinary excretion of unchanged thio-TEPA was complete within 8 h after administration, with an average urinary recovery of 0.14% of the dose. Calculation of the area under the serum concentration vs time curve revealed wide variation between patients (range 517-1480 ng/h ml⁻¹), indicating the need for drug monitoring during therapy.

Introduction

Triethylenethiophosphoramide (thio-TEPA) was introduced into cancer treatment in the early 1950s and is one of the oldest alkylating agents still in clinical use. Besides epithelial ovarian cancer, the drug is used for adjuvant treatment of bladder carcinoma [13], metastatic breast carcinoma [7], and meningeal carcinomatosis [14]. In the treatment of ovarian cancer thio-TEPA is used both as single agent [3, 16] and in combination therapy [1].

Due to acid instability the drug has to be injected; both the i.m. and the i.v. route have been widely used. Thio-

TEPA causes little local irritation in biologic tissue and has also been given by intracavitary administration (abdomen, pleura, subarachnoid space). Alkylating agents, including thio-TEPA, are known to be myelotoxic. Apart from that, the drug is very well tolerated, causing little or no deterioration in the patients’ quality of life.

A close dose–response relationship of thio-TEPA has been found following administration to monolayer cultures of human ovarian cancer cells [16]. The same relationship for thio-TEPA has been demonstrated in studies of in vitro models with human bladder tumor cells [9] and mammary tumors induced in rats [5]. In a study of the dose–response relationship in cancer patients, it was concluded that a direct positive correlation existed [8]. However, in clinical work, the dosing of thio-TEPA has often been based on the development of myelotoxicity. Dosing up to bone marrow depression has been advocated. The scientific basis for this, however, is scanty. In a study of the relation between drug response and toxicity in 144 patients with ovarian cancer no positive correlation was found, and it was concluded that the development of myelotoxicity was not a good indicator for correct dosing of thio-TEPA [15].

A better knowledge of the clinical pharmacology of thio-TEPA is therefore needed. The aim of the present study was to examine the pharmacokinetics of thio-TEPA in ovarian cancer patients.

Materials and methods

Patients. Fifteen patients with epithelial ovarian carcinoma were included in the study. The median age at the start of therapy was 65 years (range 43–75 years). All patients underwent laparotomy for the purpose of surgical tumor clearing and staging of disease prior to chemotherapy. All patients had normal renal and hepatic functions. The patient characteristics are given in Table 1.

Prior to loading and maintenance treatment a hematologic status, with hemoglobin concentration (Hgb), white blood cell count (WBC), and platelet count (PC), was obtained. Limits were: Hgb, 9.5 g/100 ml; WBC, 2.5–10⁹/1, and PC, 100–10⁹/1. Values below these limits were taken to indicate dose reduction.

Treatment. Thio-TEPA (Lederle Laboratories) was dissolved in 0.9% sterile saline to a concentration of 1 mg/ml. Two loading courses of 20 mg thio-TEPA daily for 3 con-
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Age (years)</th>
<th>Body weight (kg)</th>
<th>Stage (FIGO)</th>
<th>Postoperative statusa</th>
<th>Histologic diagnosis</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>70</td>
<td>56</td>
<td>III</td>
<td>C</td>
<td>Papillomatous adenocarcinoma</td>
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<td>C</td>
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<td>3</td>
<td>57</td>
<td>66</td>
<td>III</td>
<td>C</td>
<td>Low differentiation, adenocarcinoma</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>41</td>
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<td>C</td>
<td>Low differentiation, adenocarcinoma</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>50</td>
<td>IA</td>
<td>A</td>
<td>Mucinous cystadenocarcinoma</td>
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<tr>
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<td>C</td>
<td>Mixed adenocarcinoma (serous/endometroid)</td>
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<tr>
<td>7</td>
<td>43</td>
<td>55</td>
<td>III</td>
<td>C</td>
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<td>8</td>
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<td>84</td>
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<td>C</td>
<td>Serous papillomatous adenocarcinoma</td>
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<tr>
<td>9</td>
<td>67</td>
<td>55</td>
<td>IV</td>
<td>C</td>
<td>Low differentiation, adenocarcinoma</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>50</td>
<td>II</td>
<td>B</td>
<td>Mucinous cystadenocarcinoma</td>
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<tr>
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<td>C</td>
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<td>C</td>
<td>Serous papillomatous adenocarcinoma</td>
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<td>65</td>
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<td>A</td>
<td>Mucinous cystadenoma (borderline lesion)</td>
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<tr>
<td>14</td>
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<td>80</td>
<td>IV</td>
<td>A</td>
<td>Low differentiation, adenocarcinoma</td>
</tr>
<tr>
<td>15</td>
<td>62</td>
<td>51</td>
<td>III</td>
<td>C</td>
<td>Serous cystadenocarcinoma</td>
</tr>
</tbody>
</table>

a A, no macroscopic residual tumor; B, residual tumor, diameter ≤ 2 cm; C, residual tumor, diameter > 2 cm

The six patients in the crossover study underwent the sampling procedures after the first and third doses in both loading courses. For the remaining nine patients sampling was performed after the first dose during loading and/or during maintenance therapy.

Drug assay. In a previous article we described a gas chromatographic method for quantitation of thio-TEPA in serum and urine [6]. Thio-TEPA was extracted from 500 μl serum or urine into 300 μl ethylacetate, and 1 μl of the organic layer was injected onto the gas chromatograph.

Diphenylamine was used as internal standard. The retention times for thio-TEPA and diphenylamine were 1.9 and 2.5 min, respectively. The detection limit of thio-TEPA in serum and urine was 5 ng/ml. All analyses were performed in duplicate.

Pharmacokinetic calculations. The following model-independent parameters were calculated. The apparent first-order elimination rate constant (Ke) of thio-TEPA was calculated from the slope of the serum concentration – time curve in the linear phase of the semilogarithmic plot. The slope was computed as the least-square regression line, with equal weight for each point. The correlation (r) between the experimental points and the straight line was always better than 0.980.

The elimination half-life (t½) was derived from the equation:

$$t\frac{1}{2} = \ln 2 / K_e$$

The area under the serum concentration – time curve from zero to infinite time after a single dose (AUC0-∞) and after repeated doses (AUC0-24 h) was calculated by the trapezoid rule:

$$AUC = \sum_{i=0}^{n-1} (t_{i+1} - t_i) \frac{C_{i+1} + C_i}{2} + \frac{C_n}{K_e}$$

where Ci represents the the serum concentration measured at time ti and Cn denotes the last measurable serum concentration on the serum concentration – time curve at time tn. The term Cn/Ke was only used for the determination of AUC0-∞.

For patients receiving thio-TEPA i.v. and i.m. the fraction of the dose entering the systemic circulation (F) was calculated as:

$$F = \frac{AUC_{i.m.}}{AUC_{i.v.}}$$

The apparent volume of distribution (Vd) was obtained from the equation:

$$V_d = \frac{D}{AUC \times K_e}$$

where D is the dose administered i.v.

Total body clearance (Cl) was calculated as:

$$Cl = \frac{V_d}{K_e}$$

and renal clearance (Clr) as:

$$Clr = \frac{X_u}{AUC}$$

where X_u is the total amount of thio-TEPA excreted in the urine after a single dose or the amount excreted during a dosage interval; AUC represents the corresponding area under the serum concentration – time curve.

Six consecutive days were given, with a 2-week period between the two courses followed by maintenance therapy with 20 mg once every 2 weeks. The drug was administered i.m. or by i.v. bolus injection (i.v.). No dose correction based on the body surface area was made.

Six patients received the two loading courses according to a crossover design for the mode of administration. Three were given the first 3-day loading course by i.m. administration and the second 3-day course 2 weeks later by i.v. administration, and for the other three the order was the opposite. The remaining nine patients received most of the treatment by i.m. injection. All patients were given injections of vitamins and anabolic steroids as supportive therapy.

Blood and urine sampling. From a Venflon cannula 5 ml blood was taken before, and 0.5, 1, 1.5, 2, 4, 6, 8, and 24 h after administration of thio-TEPA. The samples were allowed to coagulate at 4 °C. Within 2 h serum was separated by centrifugation (1100 g for 10 min at room temperature) and stored at −20 °C until analysis, which was performed within 1 week. Urine was collected at intervals of 2 h for 8 h after administration of thio-TEPA. An additional urine sample was taken 24 h after administration. Aliquots were immediately placed at 4 °C and within 2 h were moved storage at −20 °C. The urine samples were analyzed within 1 week.