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# Clinical Pharmacokinetics of $(NPAz_2)_2NSOAz$: 'SOAz'*

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***Summary.*** *Pharmacokinetic studies of 1,3,3,5,5 pentakis (aziridino)-1λ⁶,2,4,6,3λ⁵,5λ⁵ thiatriazadiphosphorine-1-oxide ('SOAz'), a new antineoplastic agent containing an inorganic ring system and five aziridino groups, were performed in six patients who took part in a phase I clinical trial of the agent. The drug was administered as a rapid IV infusion. Serum decay curves could be fitted to an open two-compartment model of drug disappearance. After a short initial phase with a $t_{1/2}$ (± SD) of 7.8 ± 4.2 min a terminal phase with a dose-independent half-life of 203± 17 min occurred. The coefficient of apparent distribution was 0.71 ± 0.13. The renal clearance was 75 ± 11 ml/min and the total body clearance 162 ± 23 ml/min. A percentage of 46.5 ± 6.6 of the administered drug could be recovered unchanged in the urine within 24 h. It is concluded that in view of concentrations known to be effective in vitro, administration in large single doses may be advantageous. Dose adjustments should be made for patients with impaired renal function.*

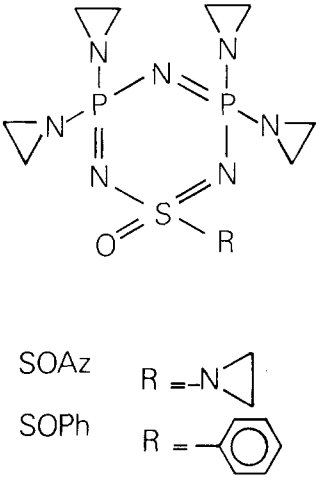


**Fig. 1.** Structure of SOAz and SOPh

## Introduction

Aziridino-substituted inorganic heterocycles constitute a new class of agents with cytotoxic activity [10]. Systematic screening revealed that most of these compounds display antitumor effects in in vitro system [5; H.B. Lamberts et al., 1983, unpublished work]. A limited number of derivatives has been tested in tumor-bearing mice and activity was confirmed. The first of these agents to be evaluated in humans is $(NPAz_2)_2NSOAz$, or 'SOAz' (Fig. 1), which is a 'thiatriazadiphosphorine' as it contains a six-membered ring system consisting of nitrogen, phosphorus and sulfur [1]. SOAz is active in a broad spectrum of experimental tumor systems in vivo and in vitro, including L1210 and P388 leukemias and B16 melanoma [6].

Recently we reported a sensitive assay for the detection of SOAz and other cyclophosphathiazenes in biological fluids [2]. This assay was applied to the determination of pharmacokinetic parameters in six patients who took part in a phase I clinical trial of SOAz.

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* SOAz, 1,3,3,5,5 pentakis (aziridino)-1λ⁶,2,4,6,3λ⁵,5λ⁵ thiatriazadiphosphorine-1-oxide

## Patients, Materials and Methods

*Patients.* Six patients with advanced cancer were studied. Some of their characteristics are shown in Table 1. All took part in a phase I clinical trial of SOAz, and informed consent was obtained according to institutional policy. The study was approved by the local ethical committee. All patients had adequate renal and hepatic function as determined by standard biochemical tests. SOAz was administered by rapid IV infusion over 3–6 min. Serum samples were drawn seven times during the first hour and six times during the next 14 h. Urine was collected at hourly intervals during the first 3 h after administration and at least five times during the next 21 h.

*SOAz.* SOAz was supplied by Otsuka Chemical Co., Tokushima, Japan. The required amount of the drug substance was dissolved in 100 ml 0.9% NaCl solution for injection and sterilized by filtration by the Department of Pharmacy.

*Assay.* The determination of SOAz and other cyclophosphathiazenes is described in detail elsewhere [2]. Briefly, 0.5 ml serum was added to 25 µl sodium hydroxide 4 *M* and 100 µl internal standard solution containing 40 mg $(NPAz_2)_2NSOPh/l$ (a structural analogue of SOAz, supplied and synthesized by

**Table 1.** Patient characteristics and dose of SOAz

| Patient | Age (years) | Sex | Weight (kg) | BSA[a] ($m^2$) | Cr.cl.[b] (ml/min 1.73 $m^2$) | Dose IV (mg) |
|---|---|---|---|---|---|---|
| H. N. | 28 | M | 72 | 1.98 | 125 | 200 |
| V. A. | 63 | M | 69.5 | 1.87 | 103 | 105 |
| V. B. | 28 | M | 66.5 | 1.96 | 95 | 110 |
| J. F. | 43 | M | 73 | 1.96 | 94 | 110 |
| K. B. | 66 | M | 52 | 1.69 | 114 | 95 |
| D. W. | 56 | M | 71 | 1.93 | 109 | 135 |

[a] Body surface area
[b] Creatinine clearance

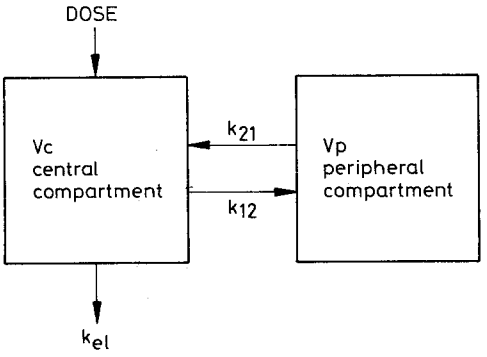


**Fig. 2.** Two-compartment open model of SOAz

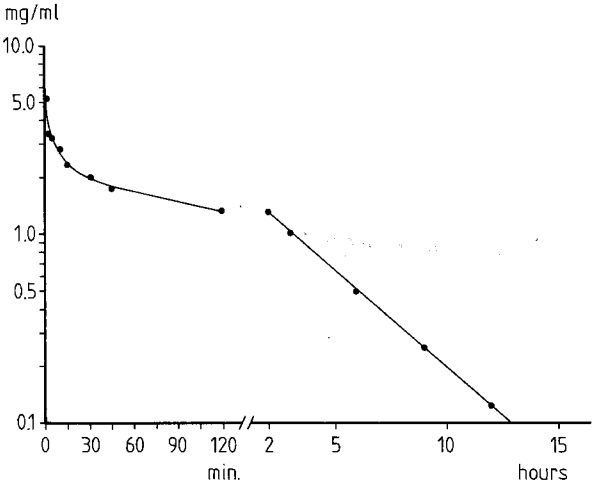


**Fig. 3.** Typical serum concentration curve (pt V.B.): $C^t = 4.15\ e^{-0.139t} + 2.17\ e^{-0.00398t}$

**Table 2.** Pharmacokinetic parameters of SOAz

| Patient | SOAz dose ($mg/m^2$) | $t_{1/2\alpha}$[a] (min) | $t_{1/2\beta}$ (min) | AUC[b] ($mg \cdot min \cdot l^{-1}$) | $k_{12}$ | $k_{21}$ | $k_{el}$ | Apparent total body clearance (ml/min) | Apparent volume of distribution | | $V_c$[c] (l) | $V_p$[d] (l) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | l | % | | |
| H. N. | 101 | 6.7 | 191 | 1,229 | 0.0596 | 0.0361 | 0.0103 | 163 | 44.8 | 62 | 15.8 | 29.0 |
| V. A. | 56 | 7.2 | 211 | 647 | 0.0478 | 0.0448 | 0.0071 | 162 | 49.4 | 71 | 23.0 | 26.4 |
| V. B. | 56 | 5.0 | 174 | 575 | 0.0818 | 0.0504 | 0.0110 | 191 | 48.1 | 72 | 17.4 | 30.7 |
| J. F. | 56 | 6.1 | 214 | 635 | 0.0647 | 0.0433 | 0.0085 | 173 | 53.5 | 73 | 20.4 | 33.0 |
| K. B. | 56 | 16.3 | 208 | 588 | 0.0088 | 0.0328 | 0.0043 | 162 | 48.5 | 93 | 37.3 | 11.1 |
| D. W. | 70 | 5.4 | 221 | 1,103 | 0.0742 | 0.0494 | 0.0082 | 122 | 39.1 | 55 | 15.7 | 23.4 |
| Mean | | 7.8 | 203 | | | | | 162 | 47 | 71 | 21.6 | 25.6 |
| SD | | 4.2 | 17 | | | | | 23 | 5 | 13 | 8.2 | 7.8 |

[a] $t_{1/2\alpha}$, half-life of initial redistribution phase
[b] AUC, area under the curve
[c] $V_c$, volume of the central compartment
[d] $V_p$, volume of the peripheral compartment

the Department of Inorganic Chemistry of Groningen State University, The Netherlands) (Fig. 1). This mixture was extracted with dichloromethane and the organic layer was evaporated under reduced pressure. The residue was dissolved in 200 µl 1,2 dichloroethane. Urine samples were centrifuged and 100 µl of the clear supernatant was diluted with 400 µl demineralized water. Further treatment was as for serum. Separation took place by capillary gas chromatography, using a wall-coated open tubular column, fused silica, 3.3 m × 0.225 mm (inside diameter) (Chrompack B.V., Middelburg, The Netherlands). After detection by a model 18789A N-P-FID thermionic detector (Hewlett Packard Co., Avondale, PA, USA), registration and integration of the chromatograms were performed by a laboratory computer.

The detection limit of SOAz was 0.01 mg/l, the coefficient of variation for the serum determinations was 6%, and that for urine determinations, 1.6%.

*Protein Binding.* To determine the amount of drug bound to plasma proteins, five plasma samples drawn from the same

**Table 3.** Urinary excretion of SOAz

| Patient | Dose IV (mg) | UCD[a] 6 h | | UCD[b] total (mg) | %UCD[c] total (%) | Renal clearance[d] (ml/min) |
|---|---|---|---|---|---|---|
| | | mg | % | | | |
| H. N. | 200 | 78.6 | 39 | 100.9 | 50.5 | 82 |
| V. A. | 105 | 25.6 | 24 | 50.9 | 48.5 | 79 |
| V. B. | 110 | 33.8 | 31 | 45.3 | 41.2 | 79 |
| J. F. | 110 | 26.5 | 24 | 39.5 | 35.9 | 62 |
| K. B. | 95 | 39.8 | 42 | 50.7 | 53.4 | 87 |
| D. W. | 135 | 45.0 | 33 | 66.5 | 49.3 | 60 |
| Mean | | | 32 | | 46.5 | 75 |
| SD | | | 7 | | 6.6 | 11 |

[a] Amount of drug excreted unchanged into urine within 6 h
[b] Total amount of drug excreted unchanged into urine
[c] % of drug excreted unchanged into urine
[d] Defined as %UCD total/AUC

**Table 4.** Concentration of SOAz at various times in plasma samples and in protein-free filtrates of these samples

| Time | SOAz concentration (mg/l) | |
|---|---|---|
| | Plasma | Filtrate |
| 5 min | 2.6 | 2.6 |
| 2 h | 1.1 | 1.2 |
| 6 h | 0.53 | 0.51 |
| 9 h | 0.32 | 0.26 |
| 12 h | 0.14 | 0.14 |

patient (K.B.) at different times were filtered to yield a protein-free solution (Worthington Ultrafree Filter, Millipore Corp., Bedford, Mass., USA). The SOAz concentrations were compared with concentrations in plasma samples drawn at the same times.

*Pharmacological Calculations.* Assuming first-order pharmacokinetics, best-fit models containing up to five phases were calculated utilizing a DEC system 10 computer and a computer program designed by one of us (AHJS). The calculations included a correction for infusion time [7] and a statistical analysis comparing the accuracy of models containing different numbers of phases [3]. The distribution constants (k12 and k21), the elimination constant ($k_{el}$), the total body clearance (C1), the apparent volumes of the central ($V_c$) and the peripheral ($V_p$) compartments, and the volume of distribution were computed by means of equations described elsewhere [4]. The renal clearance (Cren) was computed from the urine data using standard equations [8].

## Results

Postinfusion serum curves were obtained from six patients. All curved could be fitted well to a two-phase linear pharmacokinetic model. In three cases (patients V.B., J.F., and D.W.) a three-phase model offered a good alternative but was not found to be significantly better by computer analysis. Therefore an open two-compartment model of drug disappearance is assumed (Fig. 2) and used as a basis for the calculation of the pharmacokinetic parameters.

In each case the postinfusion serum curve (Fig. 3) was characterized by a short initial phase with a half-life of a few minutes (Table 2), followed by an elimination phase with a half-life of 3–4 h. Serum levels of SOAz in blood samples drawn 24–25 h after administration ranged from 0.01 to 0.02 mg/l in all patients. Since these values are very close to the detection limit of the assay, they cannot be considered as exact as the other determinations. Nevertheless, they are entirely consistent with the pharmacokinetic model adopted. There was no indication of dose-dependency of the half-life times, which confirms first-order kinetics. The apparent volume of distribution ranged from 39.1 to 53.5 l and the apparent total body clearance ranged from 122 to 191 ml/min (Table 2).

Somewhat less than half the amount of SOAz administered was excreted unchanged in the urine, most of this within 6 h (Table 3). The renal clearance ranged from 60 to 87 ml/min.

Determination of SOAz in plasma samples and in protein-free filtrates of these samples yielded the results shown in Table 4. The differences in SOAz concentration between plasma samples and the filtrates were not significant, indicating that protein binding of SOAz is negligible.

## Discussion

The six patients studied took part in phase I clinical studies of SOAz. Patient H.N. received therapy courses each consisting of a single infusion, while the others received 4-day courses and the pharmacokinetic studies were conducted on day 1. It is of interest that all patients except of K.B. experienced mild to moderate toxicity, indicating that the information gathered is relevant for clinically employed doses.

The pharmacokinetic model adopted for SOAz is of the open two-compartment type. The central compartment is rather large and is evidently not confined to the intravascular space. This may be the result of the lack of protein binding, which allows the agent to permeate freely over basement membranes. The relatively high concentrations of SOAz found in ascites fluid and pleural fluid in patients described elsewhere [2] may be ascribed to the same phenomenon.

The pharmacokinetic parameters determined in five of the six patients were rather similar, but one patient (K.B.) showed a central compartment roughly twice the size of the others and

had an initial phase half-life about three times as long as was determined in the other patients. The only respect in which he differed from the other patients was his clearly worse nutritional status. There are, however, insufficient data to support a causal relation.

The only toxicity is myelosuppression, which is delayed and cumulative in subsequent courses and sometimes even irreversible [9]. This pattern of toxicity closely resembles the one seen after administration of mitomycin C or one of the nitrosourea derivatives. This study demonstrates that this delay and cumulation of toxicity are not the result of cumulation of the agent in some body compartment. It is possible, however, that certain active metabolites exist with a considerably longer biological half-life than SOAz itself, a situation known from the chloroethyl and cyclohexyl moieties in the case of methyl-CCNU [11].

The serum levels in the patients studied varied between 6.8 mg/l (median peak level) and 0.86 mg/ml (median serum level after 6 h). In preclinical studies of SOAz the agent was found to inhibit growth of L1210 leukemia cells at a concentration of approximately 4 mg/l, while Ehrlich ascites cells required a concentration approximately three times as high (H. B. Lamberts et al., 1983, unpublished work). Since it must be assumed that the drug concentrations near tumor cells in vivo are considerably lower than the corresponding serum levels, it seems probable that the administration schedule used may not lead to effective drug concentrations at the tumor cell level. Administration of SOAz in large single doses may therefore prove to be advantageous.

The finding that renal excretion is a major route of elimination indicates that dose adjustments should be made for patients with impaired renal function. This assumption is confirmed by the data of two patients in our phase I study [9], who both had a creatinine clearance of 55 ml/min. Both experienced much more severe myelosuppression than other patients treated at the same dose level who had normal renal functions.

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