Pharmacokinetic and Preliminary Metabolic Fate of Navelbine in Humans as Determined by High Performance Liquid Chromatography

François Jehl, Elisabeth Quoix, Dominique Leveque, Gabrielle Pauli, Fabienne Breillout, Anais Krikorian, and Henri Monteil


ABSTRACT

The pharmacokinetics and metabolism of Navelbine (NVB) were investigated in 20 patients by a high performance liquid chromatographic methodology allowing the monitoring of NVB, deacetyl-NVB, and N-oxide NVB. After the i.v. (15 min) administration of 30 mg/m² of drug, blood and urine samples were collected for, respectively, 144 and 48 h. NVB is characterized by a three compartmental kinetics, with a $C_{\text{max}}$ of 1130 ± 139 (SEM) ng/ml. The total body clearance and apparent volume of distribution, as defined by high performance liquid chromatography, are 1.26 ± 0.09 liter/h/kg (48.6 ± 4.1 liters/h/m²) and 75.6 ± 9.2 liters/kg (2918.4 ± 307.2 liters/m²). No metabolite could be detected in serum; the urinary excretion of NVB represented 11% of the administered dose. Deacetyl-NVB could be identified as a minor urinary metabolite when no N-oxide NVB appeared in the urine samples. Two additional peaks appeared in most of urinary chromatograms as trace amounts. Thus, the major pathway of NVB, as for other Vinca alkaloids, should-be hepatic clearance, as biliary elimination and/or hepatic biotransformation.

INTRODUCTION

Navelbine (5'-noranhydrovinblastine) is a new semisynthetic Vinca alkaloid developed by Mangeney et al. (1, 2) who demonstrated its pharmacological property, i.e., a potent inhibition of tubulin polymerization and a weak induction of tubulin spirilization. Experimental models, such as L1210, P388 leukemia, and B16 melanoma as numerous human tumors grafted on nude mice, were used to demonstrate its important antitumor activity (3). Moreover, this new drug is also characterized by a low cross-resistance with other Vinca alkaloids (4). Navelbine has proved to be very effective in at least three cancer types: non-small cell lung cancer; breast cancer; and Hodgkin's disease. Some data also indicate that Navelbine has significant activity as a single agent in second or third line treatment of patients with advanced ovarian epithelial cancer (5).

The up to now published data on the pharmacokinetic behavior of Navelbine result either from RIA2 measurement or from direct radioactive determinations after injection of [3H]Navelbine into cancer patients (6-9). Because there is evidence for the existence of an important metabolism of this drug, there was a need for a specific, reliable methodology for the measurement of Navelbine in biological fluids. This is why we recently developed a high performance liquid chromatographic (HPLC) method for the determination of Navelbine and two of its potential metabolites, deacetylNavelbine and N-oxide Navelbine, in biological fluids (10). We present here the first pharmacokinetic data of the new anticancer drug Navelbine, determined in 20 patients, by a parent drug as well as metabolite specific HPLC methodology.

MATERIALS AND METHODS

Patients. Twenty patients (19 men and 1 woman) with non-small cell lung cancer were included in this pharmacokinetic study after written informed consent. Their ages ranged from 41 to 74 years (58.5 ± 8.4 (SEM)) and their weights from 49 to 97 kg (69.1 ± 13.3). All had normal liver and renal functions.

Protocol. All of the patients were undergoing a single agent Navelbine therapy. The drug, at a dose of 30 mg/m², was infused over a 15-min period. Blood samples were drawn before infusion and then 0.25, 0.5, 1, 2, 4, 12, 24, 48, 72, 96, 120, and 144 h after the beginning of infusion. They were centrifuged at 4000 rpm for 10 min and then the serum were frozen at -80°C until analysis.

Urine samples were collected during the following intervals: 0-4 h; 4-8 h; 8-12 h; 12-24 h; and 24-48 h. Each volume was measured and an aliquot was frozen for analysis.

Blood and urine samples were obtained during the first cycle of treatment.

Analytical Method. Navelbine (as the ditartrate salt), deacetylNavelbine and N-oxide Navelbine were kindly provided by Pierre Fabre Medicament Company as pure powders. The concentrations of these compounds in biological fluids were measured by high performance liquid chromatography as described previously (10).

The extraction recoveries of the drugs ranged from 66.8 ± 0.9 to 88.1 ± 1.7%. The limits of detection, respectively, were 0.5 and 1.0 ng/ml in serum and urine samples.

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Pharmacokinetic Parameters. AUCs were evaluated using the trapezoidal rules, including all experimental data points. The pharmacokinetic parameters were estimated using a three compartment linear model suggested by the triphasic serum concentrations decay. All the parameters were calculated according to the method of Gibaldi and Perrier (11):
where \( D \) is the administered amount and \( Cl_i \) is total clearance,

\[
\frac{t_{1/2\gamma}}{\gamma} = 0.693
\]

where \( \gamma \) is the slope of the \( \gamma \) phase (last elimination phase) of the serum concentration-time curve and \( t_{1/2\gamma} \) is the half-life of elimination

\[
AVD = Cl_i / \gamma
\]

\[
Cl_i = Cl_r \times f
\]

where \( f \) represents the percentage of total dose eliminated in the urines as unchanged form and \( Cl_r \) is renal clearance.

RESULTS

As shown in Fig. 2, a curve stripping on the semilog plot of the serum concentrations versus time data revealed that the kinetics of NVB best fits a three compartment model. The equation of the triphasic decay is

\[
C(\text{ng/ml}) = 3073 \times e^{-0.17t} + 56.2 \times e^{-0.247t} + 5.09 \times e^{-0.0168t}
\]

The mean serum concentrations obtained in 20 patients are summarized in Table 1. The 2 first hours are characterized by a rapid decrease from a \( C_{max} \) value of 1130 ± 139 ng/ml. After the 24th h, concentrations declined very slowly. The calculated elimination half-life was 42.1 ± 4.7 h. The half-lives of the \( \alpha \) and \( \beta \) phases, respectively, were 0.14 ± 0.02 and 2.80 ± 0.35 h. All the pharmacokinetic parameters are reported in Table 2.

The urinary excretion of NVB, measured up to 48 h, amounted to 10.9 ± 0.7% of the administered dose, with about 8% being eliminated in the 0–8-h interval. When no deacetyl-NVB could be detected in serum, 0.24 ± 0.07% of the admin-

![Fig. 1. Chromatograms of (a) human blank urine supplemented with vinblastine (internal standard), deacetylnavelbine, N-oxide navelbine, and Navelbine and (b) human urine sampled from a treated patient 4 h after the i.v. administration of 30 mg/m² of Navelbine.](Image12x5_to_600x787)
istered dose of NVB was eliminated in the urine as deacetyl-
NVB. No N-oxide NVB was found in serum or in urine samples.
Furthermore, 2 minor peaks (UP, and UP2) appeared on
most urinary chromatograms of patients as trace amounts.

DISCUSSION

Some experimental data obtained either in vitro or in vivo in
animals (12) revealed the existence of 1 to 3 metabolites of
Navelbine.
Furthermore, investigations carried out in two patients by
Bore et al. (9) revealed that the AUC determined by RIA were
23 and 31% of that measured by radioactivity.
Taking into account these evidences for Navelbine metabo-
lisim, we developed a specific HPLC method assay that can
discriminate between the parental drug and two potential me-
tabolites namely deacetyl-NVB and N-oxide NVB (10). This
specific methodology was then used to redefine the pharma-
kogetic parameters of this new anticancer drug in a large pop-
ulation of 20 patients.

The chromatographically measured serum concentrations are
specific from parent drug and thus are lower than those result-
ing from RIA especially after the 12th h after administration.
The most direct consequences of this fact concern the area
under the serum concentrations versus time curve that are lower
in our study (Table 3): 701.2 ± 54.4 ng/h/ml (0–144 h) versus
779 ± 162.5 ng/h/ml (0–72 h) or 1782.5 ± 3.5 ng/h/ml (0–
240 h) for the same dosage. Consequently, AUC-derived param-
eters (in term of data reduction), such as Cl, or AVD, are
characterized by equivalent discrepancies: our total body clear-
ance is the highest ever published for Navelbine (1.26 liters/h/
kg) and the AVD is from 1.5 to 3 times higher than those result-
ing from RIA.

The biological half-life is not significantly affected by the
analytical method used (Table 3).

As for other Vinca alkaloids (13–16), Navelbine is poorly
excreted in the urine, both as unchanged form and as metabo-
lites. The mean urinary recovery obtained in this study was
11% (range, 6.4–15.8%). This value is to be compared with the
4% recovery (RIA; 11 patients) published by Rahmani et al. (8)
and with the 18.5–24.5% recovery (RA-RIA; 2 patients) pub-
lished by Bore et al. (9). A radiochromatogram performed on
one urine sample by these authors revealed the existence of
metabolite, and thus interferences with RIA of Navelbine were
significant importance in the NVB metabolism schedule as they
were present as trace amounts.

The formation of conjugates of Navelbine, essentially glu-
curo- and sulfo-conjugates, remains to be investigated, and
work in this area is currently underway using urine from pa-
tients. The high hepatic clearance of this drug also calls for the
quantitation of elimination of NVB and the research of deace-
ty-NVB and N-oxide NVB in human bile.

In conclusion pharmacokinetic properties of NVB are similar
to those of other Vinca alkaloids (13–16); they all are best
described by a three compartment model and characterized by
a low urinary excretion, indicating a predominant hepatic clear-
ance. Among these drugs, NVB is characterized by a much
more increased body clearance and a wider volume of distribu-
tion than what was previously shown by Rahmani et al. (7).
These findings may, in part, explain its lower toxicity and raise
the potential interest in this new anticancer drug for the treat-
ment of solid tumors.

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injection of Navelbine and related alkaloids to cancer patients and rats.

Table 3 Comparison of the pharmacokinetic parameters of NVB as determined
by RIA or HPLC after i.v. administration of 30 mg/m²

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Assay</th>
<th>t½ (h)</th>
<th>Clᵣ (liters/h/kg)</th>
<th>AVD (liters/kg)</th>
<th>AUC (ng/h/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahmani</td>
<td>7</td>
<td>RIA</td>
<td>31.2</td>
<td>0.92</td>
<td>51.4</td>
<td>780*</td>
</tr>
<tr>
<td>Bore</td>
<td>9</td>
<td>RIA</td>
<td>62–97</td>
<td>23.5</td>
<td>25.0</td>
<td>1782²</td>
</tr>
<tr>
<td>Rahmani</td>
<td>8</td>
<td>RIA</td>
<td>38</td>
<td>0.66</td>
<td>27.2</td>
<td>75.6</td>
</tr>
<tr>
<td>Our study</td>
<td>20</td>
<td>HPLC</td>
<td>42.1</td>
<td>1.26</td>
<td>75.6</td>
<td>701*</td>
</tr>
</tbody>
</table>

* AUC₀–72h
² Litters/h
³ AUC₀–240h
⁴ AUC₀–120h
PHARMACOKINETICS AND METABOLISM OF NAVERLINE

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