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LETTER TO THE EDITORS

Nathalie Perdaems · Nathalie Caunes
Pierre Canal · Etienne Chatelut

Possible excretion of etoposide via the intestinal mucosa

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Numerous pharmacokinetics studies of etoposide have been performed during the last decade (see Joel [1] for review). However, the respective parts played by metabolism and biliary secretion in the nonrenal elimination pathways are not yet clear.

A 75-year-old woman with a pancreatic neuroendocrine carcinoma and an extrahepatic biliary obstruction was treated with cisplatin (80 mg/m^2 given on day 1) and etoposide (100 and 50 mg given i.v. on days 1 and 2, respectively). She had a percutaneous biliary catheter placed 8 days before the treatment to enable a decrease in the total bilirubin level (conjugated level) from 380 μ*M* (358 μ*M*) to 154 μ*M* (131 μ*M*). Bile and urine were collected over a period of up to 72 h after the beginning of the first 1-h etoposide infusion. The biliary flow was 0.98 l/day. Seven blood samples were collected. Plasma, bile, and urine concentrations were determined by high-performance liquid chromatography (HPLC) [2]. For quantification of both glucuronide and sulfate conjugates of etoposide, 500 μl of each sample and 1 ml of acetate buffer (pH 4.5) were pretreated overnight at 37 °C with 5000 Sigma units of β-glucuronidase (*Helix pomatia*, type H-1) and 400 Sigma units of sulfatase (Sigma Chemical, St. Louis, USA).

The unbound plasma fraction of etoposide (determined by equilibrium dialysis) was 16.8%. The total body clearance of etoposide was 27.8 ml/min. The plasma etoposide concentration was below the limit of detection (i.e., 0.05 mg/l) at 72 h after the first infusion. The plasma area under the curve (AUC) of conjugated etoposide represented 12% of the total (conjugated plus unchanged etoposide) AUC. Table 1 shows the percentages of the delivered dose recovered in bile and urine.

The observed clearance of this patient coincides with the mean value previously reported (30.2 ml/min [2]). The plasma unbound fraction was twice that of the mean value observed in cancer patients (8.4% [2]). This was due more likely to her low plasma albumin level (i.e., 27 g/l) than to the high bilirubin level, since the bilirubin was mainly conjugated and does not bind to albumin in this form. The percentages recovered in the urine of this patient are consistent with those previously reported by D'Incalci et al. [3] in patients with normal renal and hepatic function: 40.8% for etoposide and 49.2% for unchanged plus glucuronide etoposide. We observed a limited biliary excretion as had Arbuck et al. [4] previously in three patients. They showed that the cumulative biliary excretion of unchanged etoposide was less than 3% of the delivered dose; small amounts of glucuronide and sulfate conjugates were identified but increased the percentage of recovery of total etoposide by only <1% [4]. By contrast, Joel et al. [5] reported the recovery of radioactivity in the urine and feces of patients receiving ^{14}C-labeled etoposide; 56 ± 7% of the radioactivity was recovered in the urine and 44 ± 13%, in the feces, and most of the fecally excreted dose of radioactivity was recovered as etoposide [5].

A probable explanation for this discrepancy is the existence of a substantial excretion of etoposide via the intestinal mucosa. The intestinal P-glycoprotein (P-gp) is likely to contribute to this direct elimination from the systemic circulation. This mechanism of direct intestinal excretion has been demonstrated for digoxin [6] and several cationic drugs [7] in mice with a disrupted *mdr1a* P-gp gene. In human subjects, high levels of the MDR1 P-gp are found in the apical membrane of the intestinal epithelium [8] such that its transport direction is polarized from the systemic circulation into the intestinal lumen.

N. Perdaems · N. Caunes · P. Canal · E. Chatelut (✉)
Institut Claudius-Regaud, F-31052 Toulouse, France
e-mail: chatelut@icr.fnclcc.fr,
Tel.: 33-5-61-42-42-71, Fax: 33-5-61-42-74

Table 1 Biliary and urinary excretion of etoposide, expressed as a percentage of the delivered dose

Sample	Unchanged etoposide	Conjugated etoposide	Total etoposide
Bile	5.6%	0.8%	6.4%
Urine	32.9%	5.5%	38.5%
Total	38.5%	6.3%	44.9%

Moreover, it is now well established that etoposide's oral bioavailability is partly limited because the drug is exsorbed by P-gp after its absorption in the small intestine [9]; the poor solubility of etoposide is another factor that is likely to result in both incomplete absorption and decreasing bioavailability with increasing oral dose [10].

According to our results, direct intestinal excretion may account largely for the elimination of etoposide and other cytotoxics known as substrates for P-gp. We recognize our lack of discernment in a previous discussion of the incomplete recovery of irinotecan [11] and paclitaxel [12] that we observed in patients with biliary catheters; it is probable that the same mechanism of direct intestinal excretion is involved in the pharmacokinetics of these two drugs. Considering the large number of coadministered compounds that are effective reversal agents of P-gp, this excretion phenomenon should be regarded with special attention. Finally, the factors of inter- and intra-individual variability in the expression and activity of intestinal P-gp should be identified.

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