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SHORT COMMUNICATION

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Phenytoin-induced alteration in the *N*-dechloroethylation of ifosfamide stereoisomers

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Abstract *Case*: A suspected alteration in ifosfamide (IFF) metabolism and pharmacokinetics was observed in a pediatric patient receiving phenytoin. *Methods*: Sequential plasma samples were obtained and analyzed for the concentrations of the enantiomers of IFF and their *N*-dechloroethylated metabolites (DCE-IFF) using a validated enantioselective gas chromatographic-mass spectrometric method. *Results*: In the phenytoin-treated patient, the metabolic formation of IFF enantiomers was increased and the metabolic pattern of the *N*-dechloroethylation altered from non-phenytoin-treated patients: (*R*)-3-DCE IFF≫(*S*)-3-DCE-IFF = (*S*)-2-DCE-IFF > (*R*)-2-DCE-IFF (control) vs (*S*)-3-DCE-IFF = (*S*)-2-DCE-IFF > (*R*)-3-DCE-IFF≫(*R*)-2-DCE-IFF (patient). *Conclusions*: Previous studies have attributed the production of the (*S*)-2-DCE-IFF and (*S*)-3-DCE-IFF metabolites to the activity of CYP2B6 and (*R*)-2-DCE-IFF and (*R*)-3-DCE-IFF to the activity of CYP3A4. The results suggest that phenytoin induced the activity of CYP2B6 to a greater extent than CYP3A4. In addition, the patient, who was at least partially refractory to several other treatments, went into remission after IFF treatment suggesting that phenytoin pretreatment might increase IFF therapeutic efficacy.

Key words CYP2B6 · Ifosfamide · Phenytoin · Metabolic induction

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Introduction

Ifosfamide (IFF) is a chiral oxazaphosphorine alkylating agent which is administered as a racemic mixture of (*R*)-IFF and (*S*)-IFF. IFF is extensively metabolized by cytochrome P450 enzymes. One pathway involves *N*-dechloroethylation (DCE) which produces four DCE-IFF metabolites, (*R*)-2-DCE-IFF, (*R*)-3-DCE-IFF, (*S*)-2-DCE-IFF and (*S*)-3-DCE-IFF. In vitro studies have demonstrated that human cytochrome P450 isoform 2B6 (CYP2B6) is responsible for the formation of (*S*)-2-DCE-IFF and (*S*)-3-DCE-IFF while CYP3A is the source of (*R*)-2-DCE-IFF and (*R*)-3-DCE-IFF [3].

The *N*-dechloroethylation of IFF has been linked to treatment-limiting neurotoxicities [6]. Thus, any alteration in the enzymatic activity of CYP2B6 and/or CYP3A4 could have direct clinical consequences. This is illustrated by an alteration in the metabolism of IFF in a patient who also received phenytoin (PHE).

Materials and methods

Patient

The patient was an 8-year-old Cree girl with acute lymphoblastic leukemia. Standard three-drug induction therapy with vincristine, prednisone and L-asparaginase was administered but was unsuccessful. The induction was complicated by severe disability, nutritional problems, one episode of transient coma requiring ventilatory support following the last dose of L-asparaginase, and a potentially epileptic condition. The patient was begun on PHE. Subsequent induction attempts up to the treatment described below yielded only partial remission.

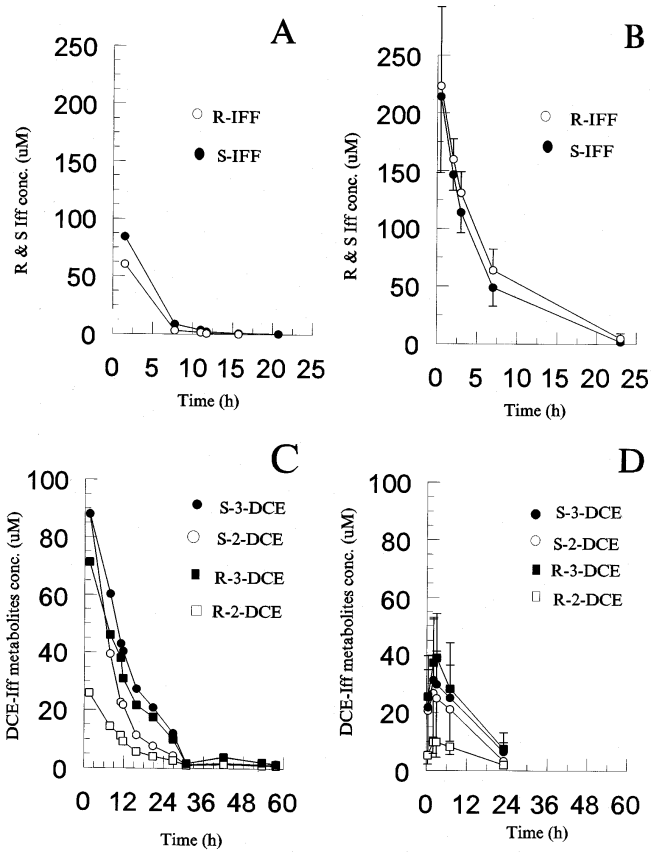

Fig. 1 **A** (*R*)- and (*S*)-ifosfamide (R-and S-IFF) observed concentrations versus time in a patient treated with phenytoin (PHE) after receiving a 2.8 g/m² dose of (*R*,*S*)-IFF. **B** Average (*R*)- and (*S*)-IFF concentrations versus time observed after five daily doses of (*R*,*S*)-IFF (2.8 g/m²) in 14 pediatric patients not receiving PHE. **C** Observed concentrations of *N*-dechloroethylated IFF metabolites (2- and 3-DCE) versus time in a patient receiving PHE after a 2.8 g/m² dose of (*R*,*S*)-IFF. **D** Average concentrations of 2- and 3-DCE metabolites versus time observed after five daily doses of (*R*,*S*)-IFF 2.8 g/m² in 14 pediatric patients not receiving PHE

Three months after initiation of PHE, she received 3 days of etoposide 100 mg/m² over 1 h, followed by IFF 2.8 g/m² over 1 h. On day 3, confusion was noted at 1.5 h following IFF administration, which progressed to obtundation at 5 h and a generalized tonic-clonic seizure at 11 h. Intermittent abnormal movements lasted until 30 h. By day 3 post-dose her neurological status had returned to normal.

Plasma samples and analysis

Plasma samples were obtained from 1.5 h until 59 h after the end of the infusion. Concentrations of (*R*)- and (*S*)-IFF and their corresponding *N*-DCE metabolites were determined in duplicate by enantioselective gas chromatography [6]. Inter- and intraday coefficients of variation of the analytical method were less than 7% and the limit of detection was 1.0 μ*M*.

Results and discussion

The results of the plasma analyses are presented in Fig. 1A, C. The corresponding average IFF and DCE-IFF concentrations from 14 pediatric patients who had received IFF at similar doses with concomitant etoposide for five consecutive days without PHE pretreatment are presented in Fig. 1B, D. This population was chosen to correct for any autoinduction of IFF metabolism.

In all patients who had not received PHE, peak plasma concentrations of the DCE-IFF metabolites were in the order (*R*)-3-DCE-IFF≫(*S*)-3-DCE-IFF = (*S*)-2-DCE-IFF > (*R*)-2-DCE-IFF (Fig. 1D). This is consistent with previously reported results from adult patients who had received (*R*,*S*)-IFF [2]. The metabolic patterns of the patient were dramatically different: (*S*)-3-DCE-IFF = (*S*)-2-DCE-IFF > (*R*)-3-DCE-IFF≫(*R*)-2-DCE-IFF (Fig. 1C). Among our control population, concentrations 2 h after the end of infusion ranged from 144 to 188 μ*M* for (*R*)-IFF, 3.6 to 16.8 μ*M* for (*R*)-2-DCE-IFF, 10.2 to 54.5 μ*M* for (*S*)-3-DCE-IFF, 128 to 162 μ*M* for (*S*)-IFF, 14 to 56 μ*M* for (*R*)-3-DCE-IFF, and from 12 to 59.8 μ*M* for (*S*)-2-DCE-IFF. In contrast our patient exhibited peaks 1.5 h after the end of infusion of 85, 26, 88, 60, 71 and 88 μ*M* for (*R*)-IFF, (*R*)-2-DCE-IFF, (*S*)-3-DCE-IFF, (*S*)-IFF, (*R*)-3-DCE-IFF, and (*S*)-2-DCE-IFF, respectively. Therefore, our patient had much lower concentrations of (*R*)-IFF and (*S*)-IFF (two to three times lower than average), while having at the same time higher peak plasma concentrations of (*S*)-3-DCE-IFF and (*S*)-2-DCE-IFF (four times higher than average), and of (*R*)-3-DCE-IFF and (*R*)-2-DCE-IFF (two times higher than average).

The highest concentrations of the metabolites cannot be attributed to a smaller volume of distribution as (*R*)- and (*S*)-IFF concentrations were much lower than expected. Although we did not possess baseline metabolism for the patient, these results suggest a significant in vivo induction of CYP2B6 activity by PHE with an accompanying lesser effect on CYP3A activity.

In humans, PHE increases the metabolism of CYP3A and CYP1A2 substrates [1] and in rats, induces CYP3A and CYP2B1 [5]. CYP2B1 is 76% homologous to the human CYP2B6 [4]. However, induction of CYP2B6 activity has not been reported. This is the first report suggesting the induction of CYP2B6 activity in a patient after chronic administration of PHE.

An interesting aspect is that the patient, who was at least partially refractory to several other treatments, went into remission after IFF therapy. The results presented are consistent with substantial induction of CYP2B6 activity by PHE and also suggest that PHE pretreatment might increase therapeutic efficacy. Preclinical studies in tumor-bearing animals have been initiated.

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