

Anticancer Drugs as Inhibitors of Two Polymorphic Cytochrome P450 Enzymes, Debrisoquin and Mephenytoin Hydroxylase, in Human Liver Microsomes¹

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ABSTRACT

To identify potential substrates for the debrisoquin and mephenytoin hydroxylation polymorphisms, we performed *in vitro* inhibition studies with human liver microsomes and the respective prototype substrates in the absence and presence of several anticancer drugs. (+)-Bufuralol 1'-hydroxylation (as the prototype reaction for the debrisoquin polymorphism) was tested at 5 μM substrate concentration and in the presence of cyclophosphamide (0 to 200 μM), teniposide (0 to 100 μM), vinblastine (0 to 220 μM), etoposide (0 to 200 μM), flavone acetic acid (0 to 1000 μM), or ifosfamide (0 to 200 μM). (*S*)-Mephenytoin 4-hydroxylation was tested at 60 μM substrate concentration and in the presence of the same drugs as above; vincristine was also tested at 0 to 200 μM . Teniposide competitively inhibited the 4-hydroxylation of (*S*)-mephenytoin, with a K_i of 12 μM (K_m of the reaction = 65 μM). Etoposide and flavone acetic acid were weaker inhibitors of this reaction. The only agent to inhibit bufuralol hydroxylation was vinblastine, which did so with a K_i of 90 μM (K_m of the enzyme for the substrate = 12 μM). We conclude that teniposide and high concentrations of flavone acetic acid could spuriously alter mephenytoin phenotype determination in cancer patients, and that teniposide deserves further investigation as a possible substrate for the genetically regulated mephenytoin hydroxylase.

INTRODUCTION

Several studies have recently described a relation between the systemic exposure to antineoplastic agents and either therapeutic outcome or toxicity (1-3). For most of these anticancer drugs, there is a large degree of interpatient variability in their pharmacokinetics, leading to a wide range of systemic drug exposure in patients given exactly the same doses (4, 5). Elucidation of the mechanisms underlying these intersubject differences in antineoplastic drug disposition would therefore be helpful in the design of anticancer dosage regimens.

One source of variability in hepatic clearance of drugs is genetic polymorphism of drug-metabolizing enzymes. At least two independent cytochrome P-450 enzymes, characterized by debrisoquin hydroxylation (6-8) and mephenytoin hydroxylation (9-11), are subject to common genetic polymorphisms. Approximately 5 to 10% and 5% of Caucasians are poor metabolizers for debrisoquin and mephenytoin, respectively; the poor metabolizer trait has been shown to exhibit autosomal recessive inheritance in both cases (8, 10). Poor metabolizers of debrisoquin excrete most of the drug unchanged in the urine, leading to high plasma concentrations of parent compound. The debrisoquin hydroxylase deficiency has been shown to affect over 20 different drugs, so that individuals unable to metabolize debrisoquin are unable to metabolize a host of other drugs also metabolized by the deficient enzyme (8). Toxic drug

effects have been demonstrated in poor metabolizers of debrisoquin and related drugs (6). Recently, the enzyme responsible for this polymorphism has been cloned and expressed (12), and the defect has been shown to be due to a lack of the debrisoquin hydroxylase enzyme in human liver microsomes (13).

Mephenytoin undergoes metabolism by two principal pathways: 4-hydroxylation and *N*-demethylation (10). In extensive metabolizers, 4-hydroxylation predominates and is stereospecific: the enzyme involved has a much higher affinity for the (*S*)- than for the (*R*)-isomer of mephenytoin, whereas the *N*-demethylation of mephenytoin is not stereospecific and independent of the genetic polymorphism. Poor metabolizers of mephenytoin excrete most of the drug as the *N*-demethylated nirvanol and nonstereoselectively metabolize a small percentage of drug to 4-hydroxymephenytoin. These properties have been confirmed *in vitro* with microsomes from extensive and poor metabolizer subjects (14). Mephenytoin hydroxylation cosegregates with mephobarbital hydroxylation (15) and is interesting in that there are large interracial differences in the frequency of the poor metabolizer phenotype; for instance, 20% of Japanese populations are deficient in this metabolic pathway (10).

Several studies have been performed to assess the distribution of drug metabolism phenotypes in patients with cancer. The role of cytochrome P-450 in carcinogenesis and cancer has been recently reviewed (16). Associations between debrisoquin hydroxylation phenotype (metabolic ratio) and lung cancer (17), gastrointestinal/hepatic cancer (18), and aggressive bladder cancer (19) have been described. Nonaggressive bladder cancer was associated with the mephenytoin hydroxylation phenotype in one study (19).

To date, no anticancer drugs are known to be metabolized by a genetically regulated polymorphic enzyme, although several are known to be metabolized by cytochrome P-450 enzymes. Polymorphic metabolism of anticancer drugs could easily go undetected clinically, since comprehensive pharmacokinetic studies are rarely performed in a cancer population large enough to detect the minority that comprise the poor metabolizer phenotype (*i.e.*, 5 to 10% of a population). Because genetic polymorphism of drug metabolism is responsible for dramatic deviations in the pharmacokinetics of affected substrates, and because it is relatively resistant to environmental influences (*i.e.*, family studies show clear autosomal recessive phenotype assignment), the existence of genetic polymorphism for antineoplastic drug metabolism could have important consequences for these agents with such narrow therapeutic ranges.

As an initial step to identify potential substrates for the debrisoquin and mephenytoin hydroxylation polymorphisms, we performed *in vitro* inhibition studies with human liver microsomes and the respective prototype substrates, in the absence and presence of several concentrations of extensively metabolized antineoplastic drugs. Drugs whose metabolism cosegregates with these substrates should competitively inhibit the reactions in question, although not all competitive inhibitors are necessarily substrates for the enzyme. Thus, the lack of inhibition of a test drug is informative in that it indicates that

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the drug is not metabolized by the polymorphic enzyme, while competitive inhibition identifies those drugs which are candidate substrates for future investigation.

MATERIALS AND METHODS

Materials. (+)-Bufuralol and 1'-hydroxybufuralol were gifts from Hoffmann-La Roche, Basel, Switzerland. (S)-Mephenytoin and 4-hydroxymephenytoin were provided by Dr. A. Kupfer and Dr. G. Karlaganis, University of Berne, Switzerland. Teniposide and etoposide were obtained from Bristol Meyers Co., Wallingford, CT. Cyclophosphamide was purchased from Mead Johnson, Syracuse, NY. Ifosphamide and flavone acetic acid were obtained from the National Cancer Institute, NIH, Bethesda, MD. Vincristine and vinblastine were purchased from Sigma.

Human Liver Microsomes. Human liver samples were obtained from kidney transplant donors, frozen in liquid nitrogen, and stored at -80°C prior to use. Microsomes were prepared as previously described (20), frozen in liquid nitrogen, and stored at -80°C . The livers used for this study have been characterized to have kinetic constants consistent with an extensive metabolizer phenotype for both debrisoquin and mephenytoin, when compared with liver microsomes from *in vivo* phenotyped subjects (13, 14). Under the conditions used in this study, both the mephenytoin and bufuralol hydroxylation microsomal assays demonstrated monophasic linear Michaelis-Menten kinetics, suggesting a single binding site for the involved substrates in these assays. The microsomes had an apparent K_m and V_{max} of $12\ \mu\text{M}$ and $2.0\ \text{nmol/mg/min}$ for (+)-bufuralol 1'-hydroxylation, and $64.2\ \mu\text{M}$ and $0.178\ \text{nmol/mg/min}$ for (S)-mephenytoin 4-hydroxylation, respectively.

Incubations and Assays. As the prototype reaction for the debrisoquin polymorphism, the 1'-hydroxylation of (+)-bufuralol was assayed using the peroxygenase function of debrisoquin hydroxylase (13). Incubation mixtures (final volume, 0.15 ml) contained $5\ \mu\text{g}$ of microsomal protein, $5\ \mu\text{M}$ (+)-bufuralol, 100 mM sodium phosphate buffer (pH 7.4), and either the inhibitor or the appropriate control solvent. Reactions were started by the addition of $15\ \mu\text{l}$ of cumene hydroperoxide (1.25 mM), proceeded for 10 min at 25°C , and were stopped with $15\ \mu\text{l}$ of 60% perchloric acid. Fifty μl of the supernatant were assayed for 1'-hydroxybufuralol by HPLC³ fluorescence detection, as previously described (21). Test drugs and their concentrations were: etoposide (10 to 200 μM); teniposide (10 to 100 μM); vinblastine (10 to 220 μM); cyclophosphamide (10 to 200 μM); ifosphamide (50 to 200 μM); and flavone acetic acid (250 to 1000 μM). Each drug was studied at 3 to 6 different concentrations in duplicate incubations. Vincristine was not studied because we previously found it did not inhibit bufuralol hydroxylase (22). In addition, an incubation containing a high concentration (300 μM) of (+)-bufuralol was performed to determine the maximal rate of transformation of the substrate in each set of incubations.

Mephenytoin incubations (final volume, 0.25 ml) contained 100 μg of microsomal protein, 60 μM (S)-mephenytoin, 100 mM potassium phosphate buffer (pH 7.4), and either the inhibitor or control solvent. Reactions were initiated by the addition of an NADPH-regenerating system at final concentrations of 5 mM isocitrate, 1 mM sodium NADP, 5 mM magnesium chloride, and 1 unit/ml of isocitric dehydrogenase; proceeded at 37°C for 60 min; and were stopped by the addition of 100 μl of 2.495 μM sodium phenobarbital (internal standard) in 2% sodium azide. The samples were extracted and assayed for 4-hydroxymephenytoin by an HPLC-UV detection system as previously described (23). Test drugs and concentrations were as above, except that vincristine was also tested at 10 to 200 μM . Incubations were repeated at 200 and 67 μM (S)-mephenytoin and several different concentrations for anticancer drugs showing >50% inhibition, to characterize the type and extent of inhibition.

Data Analysis. For those anticancer drugs showing >50% inhibition of metabolite formation at any concentration, Dixon plots were used to estimate linearity of inhibition and K_i , and Cornish-Bowden plots were done to confirm the nature of inhibition.

³ The abbreviation used is: HPLC, high-pressure liquid chromatography.

RESULTS

Results are summarized in Table 1. None of the drugs (or their products following *in vitro* microsomal incubation) interfered with quantitation of peaks of interest in the two HPLC assays. At concentrations exceeding the K_m of the reaction by at least 10-fold, the only drug to inhibit bufuralol hydroxylation was vinblastine. The Dixon plot (not shown) indicated competitive inhibition with an approximate K_i of 90 μM .

For mephenytoin hydroxylation, with drug concentrations always tested above the K_m for the hydroxylation reaction, three drugs were inhibitors. The Dixon plot depicting inhibition by teniposide (Fig. 1) shows competitive inhibition and an apparent K_i of 12 μM . The Cornish-Bowden plot (not shown) confirmed competitive inhibition. Although inhibition of mephenytoin hydroxylation by etoposide and flavone acetic acid appeared linear, a K_i was not estimated due to the relatively modest degree of inhibition by high concentrations of these compounds. The *Vinca* alkaloids and oxazaphosphorines did not inhibit 4-hydroxylation of mephenytoin.

DISCUSSION

Different compounds that are substrates for the same enzyme should competitively inhibit the metabolism of each other, and this has been demonstrated for metoprolol, sparteine, and desmethylimipramine with debrisoquin hydroxylase (24, 25) and for mephobarbital with mephenytoin hydroxylase (26). Conversely, it is possible for compounds to competitively inhibit a substrate's metabolism without themselves being a substrate, as

Table 1 Inhibition of mephenytoin and bufuralol hydroxylation by anticancer agents

Drug	Highest concentration tested (μM)	Clinically relevant plasma concentration (μM)	% of inhibition of bufuralol hydroxylation (maximum)	% of inhibition of mephenytoin hydroxylation (maximum)
Ifosphamide	200	<250	0	0
Cyclophosphamide	200	<1000	0	0
Flavone acetic acid	1000	<700	0	41 ^a
Teniposide	100	<150	0	83 ^b
Etoposide	200	<340	0	25 ^c
Vinblastine	220	<0.1	58 ^d	0
Vincristine	200	<0.1	0 ^e	0

^a One thousand μM inhibitor, 60 μM (S)-mephenytoin.

^b One hundred μM inhibitor, 67 μM (S)-mephenytoin.

^c Two hundred μM inhibitor, 60 μM (S)-mephenytoin.

^d Two hundred twenty μM inhibitor, 5 μM (+)-bufuralol.

^e Previously reported by Fonné and Meyer (22).

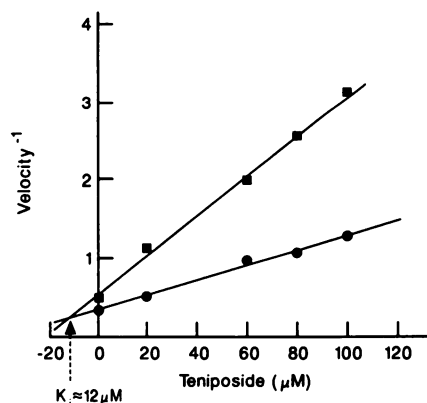


Fig. 1. Dixon plot showing competitive inhibition by teniposide of mephenytoin 4-hydroxylation at 67 μM (■) and 200 μM (●) (S)-mephenytoin.

is the case for quinidine, a potent inhibitor of debrisoquin hydroxylation (24, 27) but not a substrate for the debrisoquin metabolizing enzyme *in vitro* (28) or *in vivo* (29). *In vitro* inhibition studies are thus useful for two major purposes: identification of inhibitors which may merit further investigation as potential substrates; and identification of potent inhibitors which may cause erroneous phenotype assignment by altering the metabolic ratio when given concurrently with a prototype substrate. An important consideration for evaluating the potential clinical relevance of these *in vitro* findings is the magnitude of the K_i of the competitive inhibitor and its relationship to the concentration of inhibitor that is clinically achievable. If the K_i of an inhibitor is much higher than plasma concentrations achieved in patients, such inhibition may occur *in vitro* but not *in vivo*.

We found that teniposide competitively inhibited the polymorphic 4-hydroxylation of (*S*)-mephenytoin with a K_i below the K_m for the substrate (12 versus 65 μM) and at concentrations easily achieved in human plasma with clinically used dosages of teniposide. In fact, teniposide is one of the most potent competitive inhibitors of this reaction described to date (25, 26). Thus, one would predict that concurrent administration of teniposide and mephenytoin to cancer patients in a mephenytoin phenotyping study could spuriously increase the prevalence of the poor metabolizer phenotype. Etoposide, a congener of teniposide, was also an inhibitor of this enzyme, although its K_i was much higher (>300 μM).

Both teniposide and etoposide undergo extensive metabolism, with a smaller percentage of a teniposide dose recovered as unmetabolized drug (5 to 20%) compared to etoposide (30 to 50%) (30). We have recently reported a relationship between steady-state teniposide plasma concentrations in this range (from 4 to 46 μM) and oncolytic response in children with refractory acute lymphocytic leukemia and solid tumors, with a 10-fold intersubject variability in teniposide clearance and plasma concentrations (2). Thus, the polymorphic regulation of teniposide metabolism could have important clinical consequences, for both efficacy and toxicity. We are currently investigating whether teniposide could itself be a substrate for this enzyme in human liver. The exact nature of the hepatic metabolism of epipodophyllotoxins is not well defined. Several teniposide metabolites have been identified, although quantitatively the fate of a large percentage of the administered dose remains unknown. The hydroxy-acid, the *cis*-isomer, and the glucuronide of the aglycone have all been detected in relatively small amounts in patients' urine. It is currently not clear which, if any, of the above teniposide metabolites are formed via hepatic metabolism. Recently, two groups have shown cytochrome P-450-mediated *O*-demethylation of the dimethoxyphenol ring of etoposide and the production of hydroxymetabolites and quinones in mouse and rat liver microsomes (31, 32). These metabolites have toxic effects *in vitro*, causing DNA damage and cytotoxicity to Chinese hamster ovary cells (31). Whether these metabolites are formed in humans is not known.

Flavone acetic acid is an investigational oncolytic in Phase I and II trials for a number of solid tumors. It is apparently extensively metabolized and exhibits nonlinear pharmacokinetics *in vivo* (33). It was a relatively weak inhibitor of mephenytoin hydroxylation, with a K_i which is well above the K_m for mephenytoin. However, flavone acetic acid is administered at very high doses (*i.e.*, 5 to 10 g/m²) which result in plasma concentrations which could exceed this K_i , and thus may have clinical importance as an inhibitor of mephenytoin hydroxylation.

Because of analytical difficulties, little is known about the metabolism of vinblastine and vincristine. Only about 12% of a dose is recovered from a 72-h urine collection (4). Both have desacetylated metabolites, and desacetylvinblastine appears to have some cytotoxic activity. The only inhibitor of bufuralol hydroxylation was vinblastine: it competitively inhibited with a K_i of 90 μM . This K_i is much greater than clinically achievable vinblastine plasma concentrations (<100 nm) (4), so it is not likely to be a clinically important substrate or inhibitor.

Of the other drugs tested, cyclophosphamide and ifosfamide are given as prodrugs and require activation through cytochrome P-450 to 4-hydroxylated derivatives. These metabolites undergo secondary metabolism to phosphoramidate mustard and acrolein. All three metabolites have been proposed to contribute to cytotoxicities (34). The situation is complex, however, in that P-450 enzymes are also responsible for formation of inactive metabolites. Thus, genetic polymorphism of either bioactivating or detoxifying pathways could be clinically important for the oxazaphosphorines. Our results indicate that the primary metabolism of the two parent drugs is unlikely to be regulated by the mephenytoin or debrisoquin polymorphisms.

We conclude that most of these extensively metabolized anticancer drugs are not subject to two well-defined oxidative polymorphisms of drug metabolism, mephenytoin and debrisoquin hydroxylation. Teniposide, however, is a potent competitive inhibitor of (*S*)-mephenytoin 4-hydroxylation at clinically relevant concentrations. It would likely interfere with mephenytoin phenotype determination and could therefore lead to spurious results if coadministered with mephenytoin in a cancer population phenotyping study. Moreover, because of wide interpatient pharmacokinetic variability, a probable relationship between systemic exposure and response, and the potential importance of teniposide metabolites in its mechanism of action, it will be important to determine whether teniposide is a substrate for the genetically regulated polymorphic mephenytoin hydroxylase.

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