Preclinical Prediction of Factors Influencing the Elimination of 5,6-Dimethylxanthenone-4-acetic Acid, a New Anticancer Drug

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ABSTRACT

The glucuronidation of 5,6-dimethylxanthenone-4-acetic acid (DMXAA), a newly developed anticancer drug, was investigated in vitro to determine factors likely to affect the elimination of this compound in patients. Human liver microsomal DMXAA glucuronidation followed Michaelis-Menten kinetics, with a mean apparent $K_m$ of approximately 100 $\mu$M. Two cDNA-expressed UGT isoforms, UGT1*02 and UGT2B7, had the capacity to glucuronidate DMXAA, although comparative kinetic and inhibitor studies were more consistent with a greater contribution of UGT2B7 to the human hepatic reaction. Microsomal DMXAA glucuronide formation was screened for inhibition by drugs known to be eliminated by glucuronidation. Of the drugs screened, significant inhibition was observed with diclofenac, efavirenz, indomethacin, R,S-ketoprofen, lorazepam, S-naproxen, oxazepam, and temazepam; apparent $K_i$ values ranged from 9.5–318 $\mu$M. These values are substantially above unbound concentrations of the individual drugs achieved in vivo. DMXAA glucuronide was found to be unstable at physiological pH values, and the rate of degradation was marginally increased in the presence of albumin. Taken together, these data indicate that the kinetics of DMXAA glucuronidation in vivo are likely to be linear and unaffected by the coadministration of most glucuronidated drugs, but plasma DMXAA clearance may be decreased in patients with renal dysfunction. This study illustrates the utility of in vitro techniques for the prediction of potential drug interactions and other dispositional characteristics of newly developed anticancer drugs before their administration to patients.

INTRODUCTION

In comparison to most other drug classes, pharmacokinetic optimization of therapy is difficult with anticancer agents. Anticancer drugs tend to have a narrow therapeutic index and exhibit wide interindividual variability in pharmacokinetics (1). Hepatic (and possibly nonhepatic) metabolism is the dominant elimination pathway for most anticancer drugs, and for these compounds, genetic, physiological, and environmental factors potentially contribute to the interindividual variability in pharmacokinetics (2). In particular, the contribution of metabolic drug interactions to the pharmacokinetic and pharmacodynamic variability associated with this class of compounds is probably underestimated given the need for multiple-drug therapy in cancer treatment (2). For these reasons, the application of in vitro techniques to identify the enzyme(s) involved in the metabolism of individual anticancer drugs is of special relevance because it provides a means of rationalizing and ultimately predicting factors likely to influence elimination in defined patient groups (3, 4). Indeed, recent studies have utilized in vitro procedures to characterize the CYP3A4 isoforms responsible for the oxidative metabolism of a number of established anticancer drugs (2). However, such approaches have not been applied to anticancer drugs in the early stages of clinical development or to anticancer drugs eliminated in humans by enzymes other than CYP.

DMXAA (Fig. 1) is a newly developed anticancer agent currently undergoing Phase I clinical trial. Although structurally related to flavone-8-acetic acid, DMXAA possesses superior antitumor properties. DMXAA has been shown to be curative in 80% of mice bearing colon 38 tumors and 12 times more potent than flavone-8-acetic acid, which can only produce delays in tumor growth (5). Disposition data in the mouse in vivo and in the isolated perfused rat liver indicate that DMXAA and related compounds are more extensively metabolized than flavone-8-acetic acid (6–8). In both species, glucuronidation of the acetic acid side chain of DMXAA is the dominant metabolic pathway and is rate-limiting in DMXAA elimination (6, 8).

Based on the animal disposition data, it is highly likely that glucuronidation will represent the major route of DMXAA hepatic metabolism in humans. Studies with human liver microsomes and cDNA-expressed UGT isoforms were therefore undertaken to characterize DMXAA acyl glucuronidation in vitro and to identify the individual enzyme(s) that contribute to this pathway. Moreover, potential interactions between DMXAA and other drugs eliminated by glucuronidation were investigated. The results of these studies allow prediction of certain factors likely to influence DMXAA pharmacokinetics and hence response before its administration to patients in efficacy studies.

MATERIALS AND METHODS

Chemicals and Reagents. DMXAA was synthesized according to the method of Newcastle et al. (5). DMXAA glucuronide was isolated from the bile of isolated rat livers perfused with DMXAA, as described previously (8). Xenobiotics investigated as inhibitors of DMXAA metabolism in vitro (and their sources) were as follows: acetaminophen, amitriptyline, cyclizine, cyclobenzaprine, indomethacin, propranolol, salicylic acid, and valproic acid (Sigma Chemical Co., St. Louis, MO); codeine (Ph Faulding, Adelaide, Australia); diclofenac (Ciba-Geigy Australia, Sydney, Australia); eptubulin (Pharmacia Upjohn, Sydney, Australia); R,S-ketoprofen (Rhone-Poulenc Rorer Australia, Melbourne, Australia); lamotrigine and zidovudine (Wellcome Australia, Sydney, Australia); lorazepam, oxazepam, and temazepam (Wyeth Australia, Sydney, Australia); morphine (Glaxo Australia, Melbourne, Australia); S-naproxen (Syntex Australia, Sydney, Australia). UDPGal was purchased from Sigma Chemical Co. All other reagents and solvents were of analytical reagent grade.

Human Liver Samples and cDNAs. Human liver samples were obtained from renal transplant donors with the approval of the next of kin and the Flinders Medical Centre Committee on Clinical Investigation. Relevant details of the donors of the six livers used in the present study (i.e. H7–10, H12, and H13) have been reported previously (9). Under the conditions of storage, activities toward glucuronidated substrates have been shown to be stable for at least 6 years. Hepatic microsomes were prepared by differential centrifugation (10), suspended in 0.1 M phosphate buffer (pH 7.4), aliquoted, and stored at −70°C until use.

UGT1*02, UGT1*6, UGT2B7, UGT2B10, and UGT2B11 cDNAs were

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2 To whom requests for reprints should be addressed.

3 The abbreviations used are: CYP, cytochrome P450; DMXAA, 5,6-dimethylxanthenone-4-acetic acid; UDPGA, UDP-glucuronic acid.

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cell lysate protein concentrations were determined by the method of Lowry et al. (15) using BSA as the standard.

**Assay for DMXAA Glucuronidation.** Standard 0.3-ml incubations contained human liver microsomal (0.075 mg) or COS cell lysate (0.25 mg) protein, UDPGA (20 mM), MgCl2 (5 mM), and DMXAA (5—300 μM) in phosphate buffer (0.1 M, pH 6.8). Reaction tubes were protected from light with aluminium foil to avoid degradation of DMXAA, which is known to be light-sensitive. When appropriate, microsomes were detergent-activated by preincubation with Brij 58 for 45 min on ice; maximal activation of DMXAA glucuronidation was shown to occur when the Brij 58: microsomal protein ratio was 0.15:1 (w/w; data not shown). Reactions were initiated by the addition of UDPGA and carried out in air at 37°C in a shaking water bath. Incubations were terminated after 10 min by the addition of 11.6 M perchloric acid (9 μl) and cooling on ice. Within 5 min of the termination of incubations, 0.5 M KOH (12 μl) was added to reaction mixtures to raise the pH value to approximately 5.0. Mixtures were centrifuged (1500 X g for 10 min) to pellet microsomal/COS cell protein. An aliquot (0.05—0.1 ml) of the supernatant fraction was injected directly onto the high-performance liquid chromatograph for measurement of DMXAA glucuronide formation.

The high-performance liquid chromatography system utilized comprised a Beckman Gold (Beckman Instruments, San Ramon, CA) dual-solvent delivery system, an ICI LC1250 fluorescence detector (ICI Instruments, Melbourne, Australia), and a dual-pen chart recorder (BBC SE20; Brown-Boveri, Vienna, Austria). The excitation and emission wavelengths of the detector were 346 and 408 nm, the respective excitation and emission wavelengths for DMXAA and DMXAA glucuronide in the mobile phase. The chromatograph was fitted with a Beckman Ultrasphere octadecylsilane column (25 X 4.6 mm i.d.; 5 μM particle size; Beckman Instruments) that was eluted with 20 mM phosphate buffer (pH 5.2):acetonitrile (76:24) at a flow rate of 1.5 ml/min for 11 mm. After this time, the acetonitrile content of the mobile phase was increased to 80% for 1 min. Under the chromatographic conditions used, retention times for DMXAA glucuronide and DMXAA were 5.0 and 9.0 min, respectively (Fig. 2). Given the limited availability of DMXAA glucuronide, standard curves were constructed with DMXAA over the concentration range 0.5—10 μM. Concentrations calculated from the DMXAA standard curve were multiplied by 12.2 to correct for differences in fluorescence between DMXAA and its glucuronide (data not shown).

Under the reaction conditions used, rates of reaction were shown to be linear with protein concentration to at least 1.0 mg/ml and with time to 60 min. Within-day assay precision for the formation of DMXAA glucuronide, determined from the calculation of metabolite formation in 10 separate incubations of the same batch of microsomes, was 5.2 and 2.3% at substrate concentrations of 10 and 100 μM, respectively.

**Kinetic and Inhibitor Studies.** DMXAA glucuronidation by human liver microsomes and by cDNA-expressed UGT2B7 was measured over the substrate concentration range 10—300 μM. The substrate concentration range used for the measurement of DMXAA glucuronidation by cDNA-expressed UGT1*02 was 10—80 μM. DMXAA was added to incubation mixtures as a solution in phosphate buffer (0.1 M, pH 6.8). A number of drugs known to be glucuronidated in humans (16) were screened as potential inhibitors of DMXAA glucuronidation. Drugs screened and concentrations used are listed in Tables 2 and 3. When inhibition suggestive of a therapeutically relevant K\textsubscript{i} value was observed, kinetic studies were undertaken to identify the mechanism of inhibition and the apparent K\textsubscript{i} value. The potential inhibitors were dissolved in DMSO such that the final concentration of solvent in incubations was 1.0% (v/v). Control incubations contained the same volume of DMSO, which was shown to have a negligible effect on DMXAA glucuronidation.

**Data Analysis.** All results are presented as mean ± SD. Initial estimates of apparent K\textsubscript{m} and V\textsubscript{max} and apparent K\textsubscript{i} values were obtained by linear regression analysis of Eadie-Hofstee and Dixon plots, respectively. These values were then used as the first estimates for MK model, an extended least-squares modeling program. The significance of differences between kinetic constants of native and detergent-activated human liver microsomes was assessed using Student’s paired t test.

**RESULTS**

**Stability of DMXAA Glucuronide.** DMXAA glucuronide was unstable in aqueous solutions at pH 7.4 (Fig. 3). The degradation half-life of this compound at pH 7.4 was approximately 45 min. In contrast, DMXAA glucuronide was relatively stable at pH 6.8, with <20% degradation occurring over 1 h. The presence of human liver microsomes (1.0 mg/ml) did not markedly alter the rate of DMXAA glucuronide degradation at pH 7.4, but the degradation half-life was
reduced marginally (to approximately 40 min) in the presence of human serum albumin (600 μM; Fig. 3). To minimize the problems of metabolite instability, microsomal incubations were conducted over 10 min at pH 6.8.

Human Liver Microsomal DMXAA Metabolism. The conversion of DMXAA to its glucuronide conjugate by both native and detergent-activated human liver microsomes followed Michaelis-Menten kinetics (Fig. 4), although kinetic behavior characteristic of substrate inhibition tended to occur at DMXAA concentrations exceeding V_max (data not shown). The mean apparent K_m and V_max values for DMXAA glucuronidation by native microsomes were 114 ± 26 μM and 0.34 ± 0.09 nmol/min/mg, respectively (Table 1). Detergent activation had no significant effect on apparent K_m (mean 103 ± 22 μM), but V_max increased almost 3-fold (P < 0.01). An approximate 2.5-fold range of V_max values was observed for the six livers studied (Table 1). Incubations performed with NADPH generating system (rather than UDPGA) over 30 min did not lead to the formation of fluorescent products detectable under the chromatographic conditions used here. This suggests that CYP-mediated oxidation is unlikely to be important in DMXAA elimination.

Inhibition of Human Liver Microsomal DMXAA Glucuronidation by Drugs. A number of drugs known to be glucuronidated in humans were screened for inhibitory effects on human liver microsomal DMXAA glucuronidation (Table 2). Acetaminophen, amitriptyline, codeine, cyclizine, cyclobenzaprine, lamotrigine, morphine, phenylbutazone, probenecid, salicylic acid, tripteryline, valproic acid, and

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**Table 1** Derived kinetic constants for human liver microsomal DMXAA glucuronidation

<table>
<thead>
<tr>
<th>Human liver microsomes</th>
<th>Apparent K_m (μM)</th>
<th>V_max (nmol/min/mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Native</td>
<td>114 ± 26 (78–149)</td>
<td>0.34 ± 0.09 (0.22–0.52)</td>
</tr>
<tr>
<td>Detergent-activated</td>
<td>103 ± 22 (81–143)</td>
<td>0.95 ± 0.22 (0.66–1.79)</td>
</tr>
</tbody>
</table>

*Parameters shown as mean (±SD) of values from six human livers. Values in parentheses give the range for each parameter.*
and zidovudine each inhibited DMXAA glucuronidation to a relatively minor extent (<40%) at an added concentration of 500 μM. From the substrate concentration used in these experiments (i.e. 100 μM), it can be estimated that the apparent $K_i$ of compounds causing <40% of DMXAA glucuronidation is in excess of 500 μM, which is of little or no therapeutic relevance. In contrast, diclofenac, epirubicin, indomethacin, R,S-ketoprofen, lorazepam, S-naproxen, oxazepam, and temazepam inhibited DMXAA glucuronidation by ≥30% and >65% at added concentrations of 100 and 500 μM, respectively. Additional kinetic studies were undertaken with this latter group of compounds to calculate apparent $K_i$ values and to determine the mechanism of inhibition. Apparent $K_i$ values ranged from 9.5 μM for diclofenac to 318 μM for S-naproxen (Table 2). The mechanism of inhibition was competitive in all cases. Representative Dixon plots for diclofenac and S-naproxen (the most and least potent inhibitors, respectively) are shown in Fig. 5.

**DMXAA Glucuronidation by cDNA-expressed UGT Isoforms.** The ability of a number of UGT gene family 1 and 2 isoforms (expressed in COS-7 cells) to glucuronidate DMXAA was investigated. UGT1*02 and UGT2B7 glucuronidated DMXAA, whereas UGT1*6, UGT2B10, and UGT2B11 exhibited no activity towards DMXAA. Apparent $K_m$ values for DMXAA glucuronidation by UGT1*02 and UGT2B7 were 33 and 95 μM, respectively (Fig. 4). Close similarities were apparent in the inhibition profile of human liver microsomal and UGT2B7-catalyzed DMXAA glucuronidation by diclofenac, indomethacin, lorazepam, S-naproxen, and oxazepam (Tables 2 and 3). However, these drugs generally inhibited UGT1*02-catalyzed DMXAA glucuronidation to a lesser extent (Tables 2 and 3). Notably, S-naproxen, which inhibited human liver microsomal and UGT2B7-catalyzed DMXAA glucuronidation by 40–50% was without effect on the UGT1*02-mediated reaction, and diclofenac was a considerably less potent inhibitor of this enzyme.

**DISCUSSION**

Metabolic drug interactions have been proposed as a significant contributor to the variability in pharmacokinetics and response observed with anticancer drugs (2). Thus, the present study sought to identify potential drug-drug interactions involving DMXAA at an early stage of clinical development. Because acyl glucuronidation is likely to be the rate-limiting step in DMXAA elimination, a range of glucuronidated drugs not uncommonly used in cancer patients and other model glucuronidated xenobiotics were screened for the ability to inhibit human liver microsomal DMXAA glucuronidation.

Acetaminophen, amitriptyline, codeine, cyclizine, lamotrigine, morphine, phenylbutazone, probenecid, salicylic acid, valproic acid, and zidovudine inhibited DMXAA glucuronidation in vitro to a negligible or relatively minor effect. Indeed, apparent $K_i$ values in excess of 500 μM would be expected for all of these compounds. In contrast, diclofenac, epirubicin, indomethacin, ketoprofen, lorazepam, naproxen, oxazepam, and temazepam all inhibited DMXAA glucuronidation by more than 65% at an added concentration of 500 μM. Kinetic studies demonstrated apparent $K_i$ values ranging from 9.5–318

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**Table 2 Inhibition of Human Liver Microsomal DMXAA Glucuronidation**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage of remaining activity at inhibitor concentrations of</th>
<th>Apparent $K_i$ (μM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 μM</td>
<td>500 μM</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>92 ± 6</td>
<td>93 ± 3</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>93 ± 7</td>
<td>64 ± 6</td>
</tr>
<tr>
<td>Codeine</td>
<td>94 ± 8</td>
<td>75 ± 4</td>
</tr>
<tr>
<td>Cyclizine</td>
<td>76 ± 5</td>
<td>66 ± 4</td>
</tr>
<tr>
<td>Cyclobenzapine</td>
<td>100 ± 7</td>
<td>74 ± 7</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>15 ± 6</td>
<td>9 ± 7</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>70 ± 7</td>
<td>34 ± 8</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>57 ± 4</td>
<td>27 ± 10</td>
</tr>
<tr>
<td>R,S-Ketoprofen</td>
<td>60 ± 8</td>
<td>31 ± 4</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>90 ± 7</td>
<td>79 ± 5</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>46 ± 4</td>
<td>17 ± 9</td>
</tr>
<tr>
<td>Morphine</td>
<td>91 ± 4</td>
<td>83 ± 5</td>
</tr>
<tr>
<td>S-Naproxen</td>
<td>64 ± 9</td>
<td>34 ± 7</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>40 ± 4</td>
<td>24 ± 11</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>85 ± 3</td>
<td>65 ± 10</td>
</tr>
<tr>
<td>Probencid</td>
<td>77 ± 9</td>
<td>66 ± 8</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>89 ± 3</td>
<td>85 ± 2</td>
</tr>
<tr>
<td>Temazepam</td>
<td>54 ± 9</td>
<td>20 ± 12</td>
</tr>
<tr>
<td>Triptelamine</td>
<td>89 ± 4</td>
<td>81 ± 10</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>87 ± 9</td>
<td>68 ± 2</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>96 ± 11</td>
<td>72 ± 7</td>
</tr>
</tbody>
</table>

*Mean (±SD) of percentage of remaining activity in detergent-activated microsomes from 3 human livers (H8, H9, and H12) at added drug concentrations of 100 and 500 μM. The substrate concentration was 100 μM, the apparent approximate $K_m$ for DMXAA glucuronidation in human liver microsomes. Apparent $K_i$ values were determined using detergent-activated microsomes from a single liver (H8). ND, not determined.

**Fig. 5.** Dixon plots for the inhibition of human liver microsomal (liver H8) DMXAA glucuronidation by diclofenac and S-naproxen. Concentrations of DMXAA are shown alongside individual plots.
µM for these compounds. Diclofenac was the most potent inhibitor of DMXAA glucuronidation. With the exception of epirubicin, a key feature of all of the compounds shown to inhibit DMXAA glucuronidation is their extensive plasma protein binding in vivo; unbound fractions range from 0.05 to <0.01 (17–20). Consequently, unbound concentrations of diclofenac, indomethacin, ketoprofen, lorazepam, naproxen, oxazepam, and temazepam observed during normal therapeutic use are low and certainly well below the apparent Ki values for inhibition of DMXAA glucuronidation calculated here. Major inhibitory interactions between DMXAA these drugs are therefore highly unlikely. Epirubicin, the only anticancer drug in current clinical use that is glucuronidated to any extent, inhibited DMXAA glucuronidation with an apparent Ki of 255 µM. Again, this value is substantially greater than peak plasma concentrations observed during treatment (21). However, epirubicin may accumulate in the liver (21), and intracellular concentrations approaching the apparent Ki cannot be discounted (but are considered unlikely). Numerous other drugs undergo glucuronidation to a variable extent (16), but the use of most of these is limited in cancer patients. Moreover, most are from similar therapeutic classes (particularly nonsteroidal anti-inflammatory drugs) and are frequently structural analogues of the drugs screened here. The extent of any interaction occurring with such compounds would therefore be expected to be no greater than for those drugs identified as inhibitors here. Inhibition of DMXAA glucuronidation by nonglucuronidated drugs cannot be discounted but is considered improbable.

Data presented here also allow other important predictions concerning DMXAA elimination in humans. The apparent Km for DMXAA glucuronidation in both native and detergent-activated microsomes was approximately 100 µM. Preliminary data ex vivo (8) indicate that DMXAA is highly bound to human plasma proteins (fraction unbound, <0.01) and invariably over a wide concentration range. It is inconceivable that unbound concentrations in vivo will approach the estimated apparent Km even if a protein binding displacement interaction was to occur. Thus, the plasma clearance of DMXAA would not be expected to be dose-dependent under clinically relevant conditions. DMXAA glucuronidation intrinsic clearances (Vmax/Km) for the six livers studies here varied only 2.7-fold. Even given the limited number of livers studied, this degree of interindividual variability is low for a metabolized drug. Interestingly, the donor of the liver (H8) exhibiting the highest intrinsic clearance and Vmax (0.52 and 1.79 nmol/min/mg in native and detergent-activated microsomes, respectively) was a cigarette smoker. Acyl glucuronides are potentially reactive metabolites capable of undergoing hydrolysis, rearrangement, and covalent binding with small nucleophiles and proteins (22). In patients with renal dysfunction, who have impaired ability to excrete glucuronides, hydrolysis of acyl glucuronides in vivo leads to regeneration of the parent drug and hence decreased plasma drug clearance with accumulation (23). At physiological pH values, DMXAA glucuronide was unstable, with a degradation half-life of approximately 45 min. In the presence of human serum albumin, a known catalyst of acyl glucuronide hydrolysis, the degradation half-life of DMXAA glucuronide was reduced marginally. These data suggest that DMXAA plasma clearance will be reduced in the elderly and in patients with renal dysfunction, probably necessitating lower DMXAA doses in these groups. Should DMXAA glucuronide bind covalently to protein in vivo, a not uncommon occurrence with acyl glucuronides, there is a possibility that the adduct(s) may provoke an immune response (22).

Studies were undertaken to identify the UGT isofrom(s) responsible for DMXAA glucuronidation because once isoform regulation is understood, this allows prediction of those genetic, environmental, and physiological factors likely to alter drug clearance in vivo. Of the five UGT cDNA-expressed isoforms investigated here, UGT1*02 and UGT2B7 glucuronidated DMXAA. Although the affinity of UGT1*02 was higher than that for UGT2B7, the apparent Km for DMXAA glucuronidation by UGT2B7 closely matched the mean apparent Km observed for human liver microsomal DMXAA glucuronidation. Moreover, close similarities in the extent of drug inhibition of the human liver microsomal and UGT2B7-catalyzed reactions were observed, whereas differences were apparent with UGT1*02. Taken together, these data suggest that UGT1*02 is expressed minimally in liver, and hence UGT2B7 contributes to human hepatic DMXAA glucuronidation to a larger extent than UGT1*02. It is noteworthy that UGT2B7 and UGT1*02 are the only UGT isofroms characterized to date that have the capacity to glucuronidate xenobiotic aliphatic carboxylic acids (11, 24). At this stage, factors affecting UGT2B7 expression are not well understood. As they become known, however, greater predictability of DMXAA clearance in specific patient populations will become possible. Of some interest is the observation that both UGT1*02 and UGT2B7 are expressed in the kidney (25, 26), indicating the possibility of extrhepatic DMXAA glucuronidation.

In summary, the present study has illustrated the utility of in vitro techniques for the prediction of the likelihood of potential drug interactions and other disposition characteristics of newly developed anticancer drugs before their administration to patients in efficacy studies. The work has further demonstrated that in vitro approaches may be applied effectively to drugs metabolized by enzymes other than CYP. Specifically, it has been shown that DMXAA glucuronidation kinetics are likely to be linear at therapeutically relevant concentrations in vivo and unaffected by the coadministration of a range of glucuronidated drugs. However, due to the instability of the acyl glucuronide formed, plasma DMXAA clearance may be decreased in the elderly and in other patients with renal dysfunction.

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