Arch Pharm Res Vol 27, No 7, 693-712, 2004

Archives of Pharmacal Research
http://apr.psk.or.kr

Pharmacokinetic Changes in Drugs during Protein-Calorie Malnutrition: Correlation between Drug Metabolism and Hepatic Microsomal Cytochrome P450 Isozymes

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(Received June 25, 2004)

The rats with protein-calorie malnutrition (PCM, 5% casein diet for a period of 4-week) were reported to exhibit 60 and 80% suppression in the hepatic microsomal cytochrome P450 (CYP) 1A2 and CYP2C11 levels, respectively, and 40-50% decreases in CYP2E1 and CYP3A1/2 levels compared to control (23% casein diet for a period of 4-week) based on Western blot analysis. In addition, Northern blot analysis showed that CYP1A2, CYP2E1, CYP2C11, and CYP3A1/2 mRNAs decreased in the state of PCM as well. Hence, pharmacokinetic changes of the drugs in rats with PCM [especially the area under the plasma concentration-time curve from time zero to time infinity (AUC) changes of metabolite(s)] reported from literatures were tried to explain in terms of CYP isozyme changes in the rats. Otherwise, the time-averaged nonrenal clearance (CL_{NR}) of parent drug was compared. Pharmacokinetic changes of the drugs in other types of malnutritional state, such as kwashiorkor and marasmus, in both human and animal models were also compared. The drugs reviewed are as follows: diuretics, antibiotics, anticancer agents, antiepileptics, antiarrythmics, analgesics, xanthines, antimalarials, and miscellaneous.

Key words: Pharmacokinetics, CYP isozymes, PCM, Kwashiorkor, Marasmus

INTRODUCTION

Protein-calorie malnutrition (PCM) is considered to be a global problem, especially for vulnerable children, infants, and institutional elderly who can be afflicted with PCM (Denke and Wilson, 1998). A number of diseases including cancer, digestive disorders, and acquired immunodeficiency syndrome (AIDS) are also associated with PCM (Bistrian *et al.*, 1974, 1976; Woodward and Filteau, 1990; Wykes *et al.*, 1996; Denke and Wilson, 1998).

Effects of dietary protein on body weight gain, food intakes, and certain laboratory values in male Sprague-Dawley rats have been reported (Kim *et al.*, 2001b). For example, protein deprivation for 4 weeks (PCM, 5% casein diet for a period of 4-week) caused a significant decrease in body weight gain and food consumption. Rats with PCM consumed approximately 53% less food than control rats (23% casein diet for a period of 4-week), despite *ad libitum* supply of food. As a result, their protein and calorie intakes decreased significantly by 90 and 53%, respectively, in rats with PCM. Body weight gain also decreased significantly in rats with PCM. In addition, significant decreases in plasma levels of total proteins (21%), globulin (23%), and urea nitrogen (51%), hepatic microsomal proteins (26%), and hepatic microsomal cytochrome P450 (CYP) based on g liver (42%) were also observed in rats with PCM.

Based on Western blot analysis, male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week) exhibited a marked suppression in CYP1A2 (60% decrease), CYP2C11 (85% decrease), CYP2E1 (5060% decrease), and CYP3A1/2 (slight decrease) levels than control rats (23% casein diet for a period of 4-week) (Cho *et al.*, 1999). Northern blot analysis also showed that CYP1A2 (90% decrease), CYP2C11 (70% decrease),

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and CYP3A1/2 (slight decrease) mRNAs were decreased in the state of PCM (Cho *et al.*, 1999). Human CYP3A4 and rat CYP3A23 (CYP3A1) proteins have 73% homology, and human CYP2C9 and male rat CYP2C11 proteins have 77% homology (Lewis, 1996b). Interestingly, after oral administration of cysteine for one week (250 mg/kg twice daily starting from the fourth week) to rats with PCM (rats with PCMC), the altered CYP isozymes mentioned above returned to control values (Cho *et al.*, 1999).

Effects of PCM (5% casein diet for a period of 4-week) on other enzymes have been reported. Hepatic microsomal epoxide hydrolase was 4-fold induced with 20-fold increase in the mRNA level in male Sprague-Dawley rats during PCM (Cho *et al.*, 2001). Also, hepatic glutathion *S*-transferase (GST) subunit changes in male Sprague-Dawley rats with PCM were reported (Cho *et al.*, 2000). PCM did not cause changes in γGSTA1/2 subunit. In contrast, γGSTA3/5 subunit was 2.4-fold induced during PCM, while the levels for γGSTM1 and γGSTM2 subunits were 30 and 70% suppressed, respectively. Additionally, the fibrinogen B β chain, BTG1, and THRP genes were up-regulated by PCM (Lee *et al.*, 2002).

After starvation for 72-h in male Sprague-Dawley rats, induction of nasal CYP2E1 and CYP1A2 was significant, but the nasal CYP1A1, CYP2B, CYP3A, CYP2C, CYP2G1, and CYP2A levels did not change (Longo *et al.*, 2000). Starvation may induce hepatic CYP2E1 partly from production of ketone bodies such as acetone in young (body weight, 45-55 g) male Sprague-Dawley rats (Tu *et al.*, 1983; Lieber, 1997). It has been reported that starvation for 3 days alone did not induce hepatic CYP2E1 and that the induction of CYP2E1 was greatly affected by coprophagy in starving male Sprague-Dawley rats (Chung *et al.*, 2001). Starvation has been demonstrated to induce hepatic CYP2E1 activity (assayed as chlorzoxazone 6-hydroxylase activity) in male Sprague-Dawley rat kidney (Ronis *et al.*, 1998).

Based on liver and kidney microscopy, the liver function did not seem to be impaired in male Sprague-Dawley rat with PCM (5% casein diet for a period of 4-week) (Choi *et al.*, 1991b), and the kidney function was relatively resistant to PCM (Krishnaswamy, 1978; Kim *et al.*, 1993). The changes in pharmacokinetics of drugs, especially metabolism of drugs, may be dependent on duration and types of malnutrition in humans, such as marasmus (malnutrition as a result of calorie deprivation over months or years), kwashiorkor (malnutrition as a result of a protein deficit over a short period of time), and PCM. The changes may also be dependent on duration and food composition in animal model of PCM.

As mentioned above, the CYP enzyme changes have been reported mainly in rat model of PCM, 5% casein diet for a period of 4-week (Cho *et al.*, 1999). In rats with PCM, the area under the plasma concentration-time curve from time zero to time infinity (AUC) of metabolite(s) was compared with respect to CYP isozyme changes if CYP isozyme was known to be involved in the formation of metabolite(s). If not, the AUC, time-averaged total body (CL), renal (CL_R), and nonrenal (CL_{NR}) clearances, half-life ($t_{1/2}$), and/or plasma concentrations of parent drugs were compared. Therefore, the changes in such parameters did not always correlate with CYP isozyme changes. Pharmacokinetic parameters of drugs in other animal models of PCM were also compared. Even when the metabolism of drugs was not affected considerably by CYP isozymes, such as metabolism *via* conjugations (sulfate, glucuronide, and/or acetylation conjugates) and/or excretion of drugs exclusively in urine, changes in pharmacokinetic parameter of drugs were also reported. Disease states other than PCM, such as marasmus, kwashiorkor, and other types of malnutrition, the pharmacokinetic parameter changes of drugs were also reported. Pharmacokinetic and/or pharmacodynamic changes of drugs in humans with malnutrition have been reviewed in detail (Buchanan, 1978; Krishnaswamy, 1978). The drug metabolism with respect to CYP isozymes and information on CYP isozymes are reviewed in detail elsewhere (Levy *et al.*, 2000; Ortiz de Montellano, 1995; Lewis, 1996a).

DIURETICS

Azosemide

In humans, only azosemide glucuronide was excreted in urine (0.33% of oral dose) and bile (0.19% of oral dose) as a metabolite of azosemide (Schuchmann *et al.*, 1992). No other metabolites were detected. However, eleven metabolites of azosemide including M1 [5-(2-amino-4-chloro-5-sulfamoylphenyl)-tetrazole] and glucuronides of both azosemide and M1 were found in rat urine and bile (Asano *et al.*, 1984). Based on *in vitro* rat hepatic microsomal preparations, azosemide was changed (chemically and/or enzymatically) to M1, thiophenemethanol, and thiophenecarboxylic acid and its glycine conjugate (Schuchmann *et al.*, 1992). Pharmacokinetics and pharmacodynamics of azosemide in humans and animals have been reviewed (Suh *et al.*, 2003).

After intravenous administration of azosemide to male Sprague-Dawley rats pretreated with 3-methylcholanthrene, a main inducer of CYP1A1/2 in rats (Correia, 1995; Spatzenegger *et al.*, 2000), the CL_{NR} of azosemide was significantly faster (102% increase) suggesting that azosemide seemed to be primarily metabolized *via* CYP1A1/2 in rats (Lee and Lee, 1997). However, metabolite of azosemide was not analyzed after pretreatment with 3-methylcholanthrene (Lee and Lee, 1997). In the published

data, neither the type(s) of CYP isozyme(s) catalyzing the formation of metabolite(s) of azosemide in humans and animals nor the types of metabolites being formed as a result of catalysis were identified. Azosemide was mainly metabolized in rats; after intravenous administration at a dose of 10 mg/kg to control male Sprague-Dawley rats, 36.5% of intravenous dose was excreted in urine (Kim *et al.*, 2001b). Azosemide is also mainly metabolized in humans; after intravenous administration, 19.7-37.3% of azosemide were excreted in urine (Brater *et al.*, 1983; Beermann and Grind, 1987; Tsuchiya *et al.*, 1990; Lee *et al.*, 1997). Contribution of intestinal (including biliary) excretion to CL_{NR} of azosemide was almost negligible in male Sprague-Dawley rats (Asano *et al.*, 1984; Lee and Lee, 1996; Kim *et al.*, 2001b). Hence, the CL_{NR} of azosemide could represent metabolic clearance of azosemide in rats, although none of the metabolites except M1 were analyzed (Asano *et al.*, 1984; Lee and Lee, 1996; Kim *et al.*, 2001b). As expected, after intravenous administration of azosemide at a dose of 10 mg/kg to male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week), the CL_{NR} of azosemide was significantly slower (39.7% decrease) and the percentage of intravenous dose of azosemide excreted in 8-h urine as unchanged diuretic was significantly greater than those in control (23% casein diet for a period of 4-week) male Sprague-Dawley rats (Kim *et al.*, 2001b). This could be due to marked suppression of CYP1A2 in male Sprague-Dawley rats with PCM (Cho *et al.*, 1999). However, the AUC values of M1 were not significantly different between two groups of rats (Kim *et al.*, 2001b). Interestingly, by pretreating with cystein in rats with PCM (in rats with PCMC), the CL_{NR} of azosemide returned to the value in control rats (Kim *et al.*, 2001b).

Although the 8-h urinary excretion of unchanged azosemide was significantly greater in rats with PCM, 8-h urine output after intravenous administration was not significantly different between control rats and rats with PCM (Kim *et al.*, 2001b). This could be due to the fact that urine output seemed to reach an upper plateau at an intravenous dose of 10 mg/kg in rats (Greven and Heidenreich, 1981; Lee and Lee, 1996; Kim *et al.*, 2001b).

Furosemide

In humans, only furosemide glucuronide was detected as a metabolite of furosemide (Smith *et al.*, 1980). However, in animals, CSA (4-chloro-5-sulfamoyl anthranilic acid) and glucuronides of both furosemide and CSA were formed (Lee *et al.*, 1997). Neither the type(s) of CYP isozyme(s) catalyzing the formation of metabolite(s) of furosemide in humans and animals nor the types of metabolites being formed as a result of catalysis were identified. The CL_{NR} of furosemide was faster in humans with cigarette smoking (Lambert *et al.*, 1983). The CL_{NR} of furosemide was significantly faster (34.9% increase) (Choi *et al.*, 1991a) in male Sprague-Dawley rats pretreated with phenobarbital, a main inducer of CYP2B1/2 in rats (Correia, 1995; Kawamura *et al.*, 1999). Furosemide was metabolized considerably in rats; after intravenous administration at a dose of 10 mg/kg to control male Sprague-Dawley rats, 39.4% of intravenous dose was excreted in urine (Kim *et al.*, 1993). Contribution of gastrointestinal (including biliary) excretion to CL_{NR} of furosemide after intravenous administration seemed to be minor (Kim *et al.*, 1993). Thus, the CL_{NR} of furosemide could represent metabolic clearance in rats. After intravenous administration of furosemide at a dose of 10 mg/kg to male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week), the CL_{NR} was significantly slower (35.0% decrease) than that in control rats (23% casein diet for a period of 4-week) (Kim *et al.*, 1993). Although the metabolites of furosemide were not analyzed in plasma, this may be due to decrease mainly in CYP2B1/2 in rats with PCM.

After intravenous administration of furosemide at a dose of 10 mg/kg to male Sprague-Dawley rats with PCM, 8-h urinary excretion of unchanged furosemide was significantly greater. However, 8-h urinary output was not significantly different between two groups of rats (Kim *et al.*, 1993). This could be due to the urinary excretion rate of furosemide in rats with PCM causing maximal diuretic effect for a longer period of time (Kim *et al.*, 1993).

Bumetanide

Bumetanide was metabolized to 2'-, 3'-, and 4'-alcohol, 3'-acid, and 3-amino-4-phenoxy-5-sulfamoylbenzoic acid (desbutylbumetanide) *via* phase I pathway and to its glucuronide conjugates *via* the phase II pathway (Halladay *et al.*, 1977). However, neither the type(s) of CYP isozyme(s) catalyzing the formation of metabolite(s) of bumetanide in humans and animals nor the types of metabolites being formed as a result of catalysis were identified. The CL_{NR} of bumetanide was significantly faster (53.4% increase) (Choi *et al.*, 1991b) in male Sprague-Dawley rats pretreated with phenobarbital. Bumetanide was mainly metabolized in rats; after intravenous administration at a dose of 10 mg/kg to control rats, 13.6% of intravenous dose was excreted in urine (Kim and Lee, 1993). Contribution of gastrointestinal (including biliary) excretion to CL_{NR} of bumetanide after intravenous administration of bumetanide seemed to be minor (Choi *et al.*, 1991b; Lee, 1991). Similar results have also been reported (Kolis *et al.*, 1976) with feces; feces contained 61% of the radioactivity with 2% present as unchanged bumetanide, when the feces were collected daily until the excretion of radioactivity was minimal after intravenous administration

of [^{14}C]-bumetanide (5 mg/kg) to rats (n = 2). Moreover, the amount of bumetanide excreted in both oral and nasal mucosa was under the detection limit, when both they were collected at 8-h after intravenous administration of bumetanide (8 mg/kg) to 5 rats (Lee and Lee, 1996). Thus, the CL_{NR} of bumetanide could represent metabolic clearance of bumetanide in rats. After intravenous administration at a dose of 1 mg/100 g body weight to male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week), the CL_{NR} was significantly slower (27.8% decrease) than that in control rats (23% casein diet for a period of 4-week) (Kim and Lee, 1993). Although the metabolite of bumetanide was not analyzed in plasma, this may be due to decrease mainly in CYP2A1/2 in rats with PCM (Cho *et al.*, 1999). In humans, bumetanide was mainly excreted in urine; 62 ± 20% was excreted in urine as unchanged diuretic (Cook *et al.*, 1988).

After intravenous administration of bumetanide at a dose of 10 mg/kg to male Sprague-Dawley rats with PCM, the 8-h urine output was not significantly different between two groups of rats, although the amount of bumetanide excreted in the 8-urine was significantly greater in rats with PCM (Kim and Lee, 1993). This result could be because the dose of bumetanide used in the present study resulted in a urinary excretion rate of bumetanide at the plateau of the concentrationeffect relationship (Kim and Lee, 1993).

Torasemide

Only three torasemide metabolites, M1 (resulting from hydroxylation of the methyl group), M3 (resulting from *p*-hydroxylation), and M5 (the major metabolite, formed by oxidation of M1 at the carboxylic acid group), are formed in humans (Friedel and Buckley, 1991). M1 and M3 are both biologically active and likely to contribute to the diuretic effect of torasemide (Neugebauer *et al.*, 1988). Human CYP2C9 catalyzes the rate-limiting pathway (tolylmethyl hydroxylation, the major biotransformation pathway) of torasemide (Miners *et al.*, 1995). Recently it has been reported that torasemide was metabolized in male rats *via* CYP2C11 (Bae *et al.*, 2004a and our unpublished data). In rats pretreated with phenobarbital and dexamethasone (main inducers of CYP1A1/2 [Spatzenegger *et al.*, 2000] and CYP3A1/2 [Halpert *et al.*, 1988] in rats, respectively), AUC values of torasemide were significantly smaller (28.9 and 18.9% decrease, respectively) than those in respective control rats. Significantly smaller AUC values in rats pretreated with phenobarbital and dexamethasone seemed to be due to increased induction of CYP2C11 by the both drugs (our unpublished data). However, AUC values of torasemide were not significantly different between rats pretreated with 3-methylcholanthrene and isoniazid (main inducers of CYP1A1/2 [Spatzenegger *et al.*, 2000] and CYP2E1 [Correia, 1995] in rats) and quinine and troleandomycin (inhibitors of CYP2D1 [Tomkins *et al.*, 1997; Tyndale *et al.*, 1999] and CYP3A1/2 [Wrighton *et al.*, 1985] in rats). In rats pretreated with sulfaphenazole (an inhibitor of CYP2C9 in rats, [Ogiso *et al.*, 1999]), AUC of torasemide was significantly greater (85.4% increase) than that in control rats.

Torasemide was mainly metabolized in rats; after intravenous administration at a dose of 2 mg/kg to control male Sprague-Dawley rats, 6.20% of intravenous dose was excreted in urine (Bae *et al.*, 2004a). Torasemide was also mainly metabolized in humans; after intravenous administration, only 20% of the parent drug was recovered unchanged in the urine (Knauf and Mutschler, 1998). Contribution of gastrointestinal (including biliary) excretion to CL_{NR} of torasemide was almost negligible after intravenous administration at a dose of 10 mg/kg to control male Sprague-Dawley rats (Kim and Lee, 2003). The above data suggested that the CL_{NR} of torasemide could represent metabolic clearance in rats. After intravenous administration at a dose of 2 mg/kg to male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week), the CL_{NR} of torasemide was significantly slower (56.7% decrease) than that in control rats (23% casein diet for a period of 4-week) (Bae *et al.*, 2004a). Although the metabolites of torasemide were not analyzed, this could be due to decrease in CYP2C11 in male rats with PCM (Cho *et al.*, 1999). Interestingly, the CL_{NR} of torasemide in rats with PCMC returned to that in control rats (Bae *et al.*, 2004a).

The total amount of unchanged torasemide excreted in 8-h urine was comparable between control rats and rats with PCM; hence, the 8-h urine output and 8-h urinary excretion of sodium were not significantly different between control rats and rats with PCM (Bae *et al.*, 2004a).

Chlorothiazide

Chlorothiazide is eliminated by renal excretion in humans. Similar results have also been reported in male Sprague-Dawley rats; the mean 48-h urinary recovery of chlorothiazide was essentially complete following intravenous administration of chlorothiazide at a dose of 10 mg/kg to control male Sprague-Dawley rats (23% protein diet for a period of 4-week) and was not significantly different from that in rats with PCM (5% protein diet for a period of 4-week) (Jung *et al.*, 1990). Hence, pharmacokinetic changes in rats with PCM could not be due to CYP isozyme changes in the rats. After intravenous administration of chlorothiazide in rats with PCM, CL was significantly slower (28.3% decrease) and $t_{1/2}$ was longer (26.4% increase) than those in control rats (Jung *et al.*, 1990). Based on the finding that chlorothiazide

is secreted actively by the kidney, the slower clearance and longer $t_{1/2}$ in rats with PCM could be due to decreased glomerular filtration rate and/or the active renal secretion (Jung *et al.*, 1990).

ANTIBIOTICS

Clarithromycin

The CYP3A4 is involved in the metabolism of clarithromycin to form several metabolites, including 14-hydroxyclarithromycin (the major active metabolite of clarithromycin) in humans (Rodvold, 1999). This could be supported by the following results. Both rifampin and rifabutin induce the clearance of clarithromycin (Wallace *et al.*, 1995), whereas ritonavir, the potent CYP3A inhibitor, markedly increases plasma concentration of clarithromycin and decreases plasma concentration of 14-hydroxyclarithromycin in humans (Ouellet *et al.*, 1998). Recently it has been reported from our laboratories that clarithromycin was metabolized *via* CYP3A1/2 in rats (Lee *et al.*, 2004). The AUC values of clarithromycin were significantly smaller (39.2% decrease) in rats pretreated with dexamethasone, an inducer of CYP3A1/2 in rats (Halpert *et al.*, 1988) and significantly greater (143% increase) in rats pretreated with troleandomycin, an inhibitor of CYP3A1/2 (Wrighton *et al.*, 1985; Lee *et al.*, 2004).

Clarithromycin was mainly metabolized in rats; after intravenous administration at a dose of 20 mg/kg to control male Sprague-Dawley rats, 38.8% of intravenous dose was excreted in urine (Ahn *et al.*, 2003). In humans, approximately 35% of oral dose was excreted in urine as unchanged drug and the extent of absolute oral bioavailability (F) was 52-55% (Rodvold, 1999). As expected, after intravenous administration at a dose of 20 mg/kg to male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week), the CL_{NR} was significantly slower (28.6% decrease) than that in control rats (23% casein diet for a period of 4-week) (Ahn *et al.*, 2003). Although the plasma concentrations of 14-hydroxyclarithromycin were not analyzed, this could be due to marked inhibition of CYP3A1(23) in male Sprague-Dawley rats with PCM (Cho *et al.*, 1999). Interestingly, by pretreating rats with PCM with cystein (in rats with PCMC), the CL_{NR} of clarithromycin returned to that in control rats (Ahn *et al.*, 2003).

Itraconazole

As with clarithromycin, the CYP3A4 is also involved in the metabolism of itraconazole to form several metabolites, including 7-hydroxyitraconazole (the major active metabolite of itraconazole) in humans (Penzak *et al.*, 1999; Janssen Pharmaceutica and Research Foundation, 2001). The CYP3A1/2 could be involved in the metabolism of itraconazole in rats (Lee *et al.*, 2003). Itraconazole was mainly metabolized in rats; after intravenous administration at a dose of 20 mg/kg to control male Sprague-Dawley rats, 8.0% of intravenous dose was excreted in urine (Lee *et al.*, 2003). Itraconazole was also mainly metabolized in humans (Meuldermans *et al.*, 1986; Heykants *et al.*, 1987, 1989). The contribution of intestinal (including biliary) excretion to CL_{NR} of itraconazole seemed to be negligible in male Sprague-Dawley rats (Lee *et al.*, 2003). The above data suggested that the CL_{NR} of itraconazole could represent metabolic clearance in rats. As expected, after intravenous administration at a dose of 20 mg/kg to male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week), the CL_{NR} of itraconazole was significantly slower (26.0% decrease) than that in control rats (23% casein diet for a period of 4-week) (Lee *et al.*, 2003). Although the plasma concentrations of 7-hydroxyitraconazole were not analyzed (Lee *et al.*, 2003), this could be due to decrease in CYP3A23 in rats with PCM (Cho *et al.*, 1999). However, the CL_{NR} of itraconazole in rats with PCMC was not significantly different from those in control rats and rats with PCM (Lee *et al.*, 2003). Note that pharmacokinetics of itraconazole are dose-dependent and oral absorption of itraconazole depends on grapefruit juice (Penzak *et al.*, 1999), food (Zimmermann *et al.*, 1994a,b), and cola beverage (Lange *et al.*, 1997).

Sulfonamides

Sulfadiazine is metabolized to its acetylated metabolite and 55% of the dose was excreted in urine as its acetylated compound in humans (Bergan *et al.*, 1986). Hence, acetylation is related to cytosolic *N*-acetyltransferase activity and not CYP isozyme activities. There are two acetylation phenotypes; fast and slow acetylators. The elimination rate constant and/or clearance rate constant of sulfadiazine were significantly slower in young rhesus monkeys with PCM [25 mg/kg (Nehru *et al.*, 1988)] and malnourished children [25 mg/kg (Mehta *et al.*, 1982)]. After single oral administration of sulfadiazine at a dose of 25 mg/kg to 6 children with PCM, terminal half-life was significantly longer (49.4% increase), AUC was significantly greater (more than double), and urinary excretion of sulfadiazine was significantly smaller (29.5% decrease) than those in 5 control children (Mehta *et al.*, 1980). However, metabolic clearance rate of a single dose of sulfadiazine given either orally at a dose of 80 mg/kg or intravenously at a dose of 20 mg/kg was faster in undernourished subjects (Arunkumar and Krishnaswamy, 1979).

The major metabolic derivative of sulfamethoxazole is the N^4-acetylated sulfonamide. After oral administration of cotrimoxazole suspension (20 mg trimethoprim and 100 mg sulfamethoxazole in 5 mL) to seven malnourished

(marasmic) infants for treatment of urinary tract infection, terminal half-life of sulfamethoxazole was longer (95.9% increase) and AUC of sulfamethoxazole was greater (74.7% increase) than those in nutritionally normal infant, hospitalized for first and second degree burns, receiving cotrimoxazole for treatment of bronchitis (Bravo *et al.*, 1984).

Chloramphenicol

Chloramphenicol was mainly metabolized to its glucuronide conjugate and 75-85% of the drug excreted in urine was its glucuronide conjugate in children (Mehta *et al.*, 1975). Hence, the role of CYP isozyme is almost negligible in the pharmacokinetics of chloramphenicol. The chloramphenicol-specific uridine diphosphate glucuronosyltranferase (UDPGT) activity decreased (34.0% decrease) in young male rhesus monkeys with PCM (Sharma *et al.*, 1986). Biotransformation of chloramphenicol in liver was slower, half-life was longer, and/or CL was significantly slower in 10 infants with PCM [after oral administration at a dose of 25 mg/kg chloramphenicol palmitate in a fine suspension; 35-55% was excreted in urine as conjugated form while the comparative value was 75-85% in 4 normal infants (Mehta *et al.*, 1975)], Ethiopian children with kwashiorkor [after intravenous and oral administration at a dose of 25 mg/kg (Eriksson *et al.*, 1983)], 10 Ethiopian children with severely malnourished having kwashiorkor [after a single intravenous administration of chloramphenicol sodium monosuccinate at a dose of 25 mg/kg as chloramphenicol than under-weighed (n = 14) and marasmus (n = 10) children (Ashton *et al.*, 1993a)], young male rhesus monkeys with PCM (17.9% protein diet for a period of 10~12-week, at a dose of 40 mg/kg), there was a decrease in the activity of chloramphenicol-specific UDP-glucuronosyltransferase (Sharma *et al.*, 1986) and malnourished children [25 mg/kg (Mehta *et al.*, 1982)]. Interestingly, the above mentioned pharmacokinetic parameters were reversible following nutritional rehabilitation (Mehta *et al.*, 1975; Sharma *et al.*, 1986).

Isoniazid

Isoniazid is mainly metabolized to its acetylated metabolite. Hence, the role of CYP isozyme is almost negligible in the pharmacokinetics of isoniazid. After oral administration of isoniazid to humans, 7 ± 2 and 29 ± 5% of dose were excreted in urine for fast and slow acetylator, respectively (Petri, 2001a). Isoniazid plasma half-life and clearance rates were studied in children with kwashiorkor before and after nutritional rehabilitation (Buchanan *et al.*, 1979c); isoniazid half-life was shorter and clearance rate was faster with nutritional rehabilitation. After oral administration at a dose of 20 mg/kg to 13 children with protein-energy malnutrition, hospitalized for the treatment of tuberculosis meningitis, the pharmacokinetic parameters were evaluated on two occasions 6 months apart. There were no significant differences in pharmacokinetic parameters during this period (Seifart *et al.*, 1995).

Tetracyclines (tetracycline and minocycline)

The primary route of elimination for tetracyclines is the kidney *via* glomerular filtration except for doxycycline. Hence, the role of CYP isozyme is almost negligible in the pharmacokinetics of tetracycline. Approximately 58 ± 8% of the dose of tetracycline is excreted in human urine (Chambers, 2001). After oral administration of tetracycline hydrochloride at a dose of 40 mg/kg to male Wistar rats with protein deficiency (9% protein diet *ad libitum* for a period of 12-week), terminal half-life was shorter than that in control rats (20% protein diet in a restricted quantity for a period of 12-week) (Raghuram *et al.*, 1982). After oral administration of conventional dose of tetracycline hydrochloride, 250 mg at 6 h intervals, the relative bioavailability and C_{min} levels of tetracycline were comparable between well-nourished and under-nourished subjects (Raghuram and Krishnaswamy, 1977). However, after intravenous administration of tetracycline hydrochloride at a dose of 10 mg/kg to patients with nutritional edema, AUC was significantly greater than that in normal subjects (Raghuram and Krishnaswamy, 1982).

After intravenous administration of minocycline at a dose of 2.2 mg/kg as minocycline hydrochloride to male and female sheeps, CL was not significantly different between before and after blood was collected to induce hypoproteinemia (Wilson and Green, 1986).

Aminoglycosides (gentamicin, amikacin, and streptomycin)

Aminoglycosides are excreted almost completely by the glomerular filtration; hence, pharmacokinetics of aminoglycosides are dependent on kidney function. After intravenous administration of gentamicin at a dose of 2.4 mg/kg to 6 children with kwashiorkor, terminal half-life of gentamicin was longer (28.3% increase) than that in normal subjects due to diminished glomerular filtration rate and renal plasma flow rate seen in the acute phase of kwashiorkor (Buchanan *et al.*, 1979a).

After intravenous administration of amikacin at a dose of 5.5 mg/kg to children between the ages of 1 and 4 years with kwashiorkor, CL and $t_{1/2}$ remained close to the reference values for adults (not compared with those in children) (Hendricks *et al.*, 1995).

After intramuscular administration of streptomycin at a dose of 20-30 mg/kg to fifty-six malnourished Ethiopian children with tuberculosis, $t_{1/2}$ was prolonged only in those with kwashiorkor because of decreases in plasma protein binding and CL_R due to a decrease in glomerular filtration

rate (Bolme *et al.*, 1988).

Penicillins (penicillin G)

Penicillin is rapidly eliminated from the body, mainly by the kidney (active renal secretion), small part in the bile and by other routes, and the remainder is metabolized to penicilloic acid in humans (Petri, 2001b). Hence, pharmacokinetics of penicillin are mainly dependent on kidney function. After intravenous administration of penicillin G at a dose of 25000 units/kg to eight children with kwashiorkor on admission to hospital and when rehabilitated (Buchanan *et al.*, 1979d), a 75% faster in CL was observed with recovery, associated with a fall in $t_{1/2}$ probably due to an improvement of both renal blood flow rate and tubular function. After intravenous, intramuscular, or oral administration of penicillin to 104 children with different nutritional status (normal, underweight, marasmus, and kwashiorkor), CL was significantly slower in all malnourished groups compared to the normal weight age group (Bolme *et al.*, 1995).

Metronidazole

The liver is the main site of metabolism for metronidazole, accounting for over 50% of the systemic clearance of metronidazole; the two metabolites result from oxidation of side chains, a hydroxy derivative and an acid (Lamp *et al.*, 1999). Based on the clearance data (10 malnourished and 10 patients undergoing nutritional rehabilitation), daily maintenance doses for pediatric patients with severe malnutrition should be 12.0 mg/kg/day, corresponding to a 60% reduction of the common dose calculated to achieve and maintain a plasma concentration of 6.0 μg/mL of metronidazole (Lares-Asseff *et al.*, 1993), suggesting slower CL. After oral administration of metronidazole at a dose of 30 mg/kg to 10 severely malnourished children (aged 4 to 43 months), $t_{1/2}$ was significantly larger (101% increase) and CL was significantly slower (53.6% decrease) than those in 10 nutritionally rehabilitated children (aged 3 to 25 months) (Lares-Asseff *et al.*, 1992).

DA-7867, a new oxazolidinone

After intravenous administration of DA-7867 at a dose of 10 mg/kg to rats, metabolism of DA-7867 was negligible, while renal and gastrointestinal (including biliary) excretion was considerable; approximately 85.0% of intravenous dose was recovered from urine (17.0% of intravenous dose for up to 3 days), feces (64.0% of intravenous dose for up to 9 days), gastrointestinal tract (0.421% of intravenous dose at 14 days), and rinsings of metabolic cage (3.16% of intravenous dose at 14 days) when collected for up to 14 days (Bae *et al.*, 2004b). Hence, the role of CYP isozyme is almost negligible in the pharmacokinetics of DA-7867. After intravenous administration of DA-7867 at a dose of 10 mg/kg to rats with PCM, AUC was significantly smaller (35.3% decrease) than that in control rats and this could be due to significantly faster CL (54.8% increase) (Bae *et al.*, 2004c). The faster CL could be due to significantly faster CL_{NR} (65.1% increase) due to significantly greater gastrointestinal (including biliary) excretion; the amount of unchanged DA-7867 recovered from the entire gastrointestinal tract at 24 h was significantly greater than that in control rats (260% increase). After oral administration to rats with PCM, AUC was also significantly smaller than that in control rats (45.4% decrease) (Bae *et al.*, 2004c)

ANTICANCER AGENTS

Anthracyclines [adriamycin (doxorubicin) and DA-125]

Two enzyme systems for the metabolism of adriamycin have been identified based on *in vitro* mammalian tissue homogenates or rat liver microsome studies; adriamycin was reduced to adriamycinol by cytoplasmic aldo-keto reductase and to their deglycosylated metabolites (7-deoxyaglycones) by deglycosylation *via* CYP system (Buchanan, 1978; Lovless *et al.*, 1978). It has also been reported (Lee and Lee, 1999) that the formation of M3 and M4 (aglycone metabolites of adriamycin and adriamycinol, respectively) was increased in male Sprague-Dawley rats by pretreating with dexamethasone [an inducer of CYP3A1/2 in rats (Halpert, 1988)], but not by pretreating with phenobarbital, 3-methylcholanthrene, or isoniazid and decreased by pretreating with SKF 525-A.

Although they were not significantly different, $AUC_{0\text{-}12\ h}$ of adriamycin in male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week) tended to be greater (42.3% increase) than that in control rats (23% casein diet for a period of 4-week) after intravenous administration of adriamycin at a dose of 16 mg/kg (Kim *et al.*, 2000). However, the serum concentrations of adriamycin at 0.5, 1, 2, 24, and 48 h after intravenous administration of adriamycin at a dose of 5.0 mg/kg to male Sprague-Dawley rats with protein-free diet (0% protein diet for a period of 10-day) were significantly lower than those in control rats (24.5% protein diet for a period of 10-day) (Kapelanski *et al.*, 1981). The reason for differences between two studies (Kapelanski *et al.*, 1981; Kim *et al.*, 2000) are not clear; however, it could be due to differences in protein contents of the diet, duration of feeding, and/or assay method of adriamycin [HPLC (Kim *et al.*, 2000) or spectrofluorometric (Kapelanski *et al.*, 1981) method]. Adriamycin was mainly metabolized in rats; after intravenous administration of adriamycin at a dose of 16 mg/kg to control male Sprague-Dawley rats, 2.69% of intravenous dose was excreted in urine (Kim *et al.*, 2000). Adriamycin

is also mainly metabolized in humans; after intravenous administration, only 6.9% of adriamycin and its metabolite is recovered in the urine (Mross *et al.*, 1998).

After intravenous administration of adriamycin at a dose of 16 mg/kg to male Sprague-Dawley rats with PCM, total amount of urinary excretion of M3, M4, plus their conjugates (glucuronide and/or sulfate conjugates) tended to be smaller (45.4% decrease) than that in control rats (Kim *et al.*, 2000). This suggested that CYP3A1/2 was not induced considerably in rats with PCM. Interestingly, in rats with PCMC, the M3, M4, plus their conjugates were significantly greater than those in control rats (Kim *et al.*, 2000).

Adriamycin at a dose of 5 mg/kg was intravenously administrated to rabbits with normal-protein (15% protein diet for a period of 8-12 weeks) and low-protein (5% protein diet for a period of 8-12 weeks) diets (Cusack *et al.*, 1992). Although M3 and M4 were not analyzed, CL of adriamycin was significantly slower (18.6% decrease) and terminal half-life of adriamycin was significantly longer (27.3% increase), and terminal half-life of adriamycinol was significantly longer (30.0% increase) in rabbits with low-protein diet than those in control rabbits (Cusack *et al.*, 1992).

DA-125 ((8*S*,10*S*)-8-(3-Aminopropanoyloxyacetyl)-10-[(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione) is a new adriamycin analogue containing fluorine. DA-125, a water soluble prodrug of M1 ((8s,10s)-8-hydroxyacetyl-10-[(2,6-dideoxy-2-fluoro-α-L-talopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12-naphthacenedione), is a β-alanine derivative of M1. M1 was metabolized to its alcohol derivative, M2, and both M1 and M2 were further metabolized to their aglycones, M3 and M4, respectively, in mice (Yoon *et al.*, 1996), rats (Yoon *et al.*, 1996; Shim *et al.*, 1994), dogs (Yoon *et al.*, 1994), and humans (Roh *et al.*, 1998). After intravenous administration of DA-125 at a dose of 10 mg/kg to male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week), AUC_{0-t} of M3 (under detection limit vs. 5.41 ± 2.75 μg min/mL) and M4 (28.2% decrease) were significantly smaller than that in control rats (23% casein diet for a period of 4-week) (Kim *et al.*, 1996). DA-125 is currently being evaluated in phase II clinical trial as an anticancer agent.

Methotrexate

Methotrexate was metabolized to 7-hydroxymethotrexate by hepatic mixed function oxidase system, APA (DAMPA) by intestinal flora, and polyglutamate by intracellular folypolyglutamate synthetase (Crom and Evans, 1992). After intraperitoneal administration of methotrexate at a dose of 10 mg/kg to female Lewis rats with protein-depleted diet (0.03% protein diet for a period of 35-day), $AUC_{0\text{-}3\,h}$ was greater (176% increase) than that in control rats (22.0% protein diet for a period of 35-day) (Charland *et al.*, 1994). After intraperitoneal administration of methotrexate at a dose of 20 mg/kg to protein-free diet for 10 days to Sprague-Dawley rats, the plasma concentrations of methotrexate was significantly higher than those in rats with regular diet (Mihranian *et al.*, 1984).

5-Fluorouracil

5-Fluorouracil is inactivated by reduction of the pyrimidine ring; this inactivation is carried out by dihydropyrimidine dehydrogenase (DPD), which is formed in liver, intestinal mucosa, tumor cells, and other tissues. After intraperitoneal injection of 5-fluorouracil at a dose of 100 mg/kg to rats with PCM (2.5% protein diet for a period of 25-day), CL of 5-fluorouracil was significantly slower. This could be due to significantly reduced hepatic DPD activity in the rats compared to that in control rats (21.5% protein diet for a period of 25-day) (Davis *et al.*, 1993).

2-(Allylthio)pyrazine

The AUC of 2-(allylthio)pyrazine, a new chemopreventive agent, was significantly smaller (Bu *et al.*, 2000) after intravenous administration at a dose of 50 mg/kg to male Sprague-Dawley rats pretreated with dexamethasone, phenobarbital, and 3-methylcholanthrene. Therefore, it could be expected that the plasma concentrations of 2-(allylthio)pyrazine could be higher and the resultant AUC could be significantly greater in rats with PCM than those in control rats. However, the results were opposite; the metabolism of 2-(allylthio)pyrazine rather increased in rats with PCM (5% casein diet for a period of 4-week) compared to that in control male Sprague-Dawley rats (23% casein diet for a period of 4-week). In order to find the reason for the unexpected result, the amount of metabolites excreted in 24-h urine were analyzed (Kim *et al.*, 2003). The amount of M4 [2-(S-methylthio)-α-hydroxypyrazine] was significantly greater (128% increase) in rats with PCM than that in control rats (Kim *et al.*, 2003a). M4 seemed to be one of the main metabolites of 2-(allylthio)pyrazine in rats (Kim *et al.*, 2003). This could be due to increased expression of *S*-methyltransferase in rats with PCM (Kim *et al.*, 2003). After pretreatment with SKF 525-A to rats, AUC of 2-(allylthio)pyrazine was significantly greater than that in control rats (Bu *et al.*, 2000). SKF 525-A was used as an inhibitor of potent cytosolic thiopurine methyltransferase and microsomal thiol methyltransferase (Otterness *et al.*, 1986). Therefore, the effect of SKF 525-A could be at least partially due to decrease in the S-methyltransferase activities to form M4 from 2-(allylthio)pyrazine. Interestingly in rats with PCMC, AUC of 2-(allylthio)pyrazine was significantly greater than that in control rats (Kim *et al.*, 2003). 2-(Allylthio)pyrazine is no longer being studied as a new chemopreventive agent.

ANTIEPILEPTICS

Phenytoin

It has been reported (Giancarlo *et al.*, 2001) that formation of HPPH (5-[4-hydroxyphenyl]-5-phenylhydantoin) was mediated exclusively *via* CYP2C9 and CYP2C19, with CYP2C9 playing the major role, based on *in vitro* human liver microsomes. CYP2C19, CYP2C9, and CYP3A4 catalyzed 3',-4'-dihydroxy product (Komatsu et al., 2000) with the most effective catalyst being CYP2C19 based on *in vitro* human liver microsomes (Cuttle *et al.*, 2000). Phenytoin was mainly metabolized in rats; after intravenous administration at a dose of 25 mg/kg to control male Sprague-Dawley rats, 0.067 and 54.7% of intravenous dose were excreted in urine as phenytoin and HPPH (expressed in terms of phenytoin), respectively (Kim *et al.*, 2001a). After intravenous administration at a dose of 25 mg/kg to male Sprague-Dawley rats with PCM (5% protein diet for a period of 4-week), AUC of HPPH was not significantly different between control rats and rats with PCM (Kim *et al.*, 2001a). The above data suggested that the CYP2C11 enzymes which catalyze the formation of HPPH from phenytoin was not reduced considerably in male rats with PCM. Note that phenytoin follows Michaelis-Menten type elimination kinetics.

Phenobarbital

The formation of *p*-hydroxyphenobarbital represents a major elimination pathway of phenobarbital, accounting for 10 to 35% of the administered dose (Dodson and Rust, 1995). The enzymes responsible for the metabolic clearance have not been completely elucidated; however, *in vitro* studies in human liver microsomes or expressed enzymes suggest that CYP2C9 and CYP2C19 contribute substantially to the formation of *p*-hydroxyphenobarbital (Hargreaves *et al.*, 1996). After oral administration of phenobarbital at a dose of approximately 7.0 mg/kg to malnourished children, terminal $t_{1/2}$ of phenobarbital was longer (95.4% increase) than that in healthy children (Syed *et al.*, 1986). Although *p*-hydroxyphenobarbital was not analyzed, the longer terminal $t_{1/2}$ of phenobarbital in malnourished children (Syed *et al.*, 1986) could be at least partly due to decrease in CYP2C9 and/or CYP2C19 (Dodson and Rust, 1995).

Carbamazepine

Carbamazepine is metabolized by CYP3A4 to its epoxide (Stafstrom *et al.*, 1995). After oral administration of carbamazepine at a single dose of 10 mg/kg to 6 children with protein-energy malnutrition, the plasma peak levels were lower and systemic availability was reduced than those in 6 healthy children (Bano *et al.*, 1986).

ANTIARRYTHMICS

Procainamide

Between 50 and 70% of procainamide is eliminated unchanged in human urine (Siddoway *et al.*, 1985). The major metabolite of procainamide in plasma and urine is the pharmacologically active *N*-acetylprocainamide by the polymorphic *N*-acetyltransferase. Recent *in vitro* study has shown that formation of metabolite of procainamide (*N*-hydroxyprocainamide) is primarily catalyzed by CYP2D6 (Lessard *et al.*, 1997). After intravenous administration of procainamide at a dose of 50 mg/kg to male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week), CL of procainamide was significantly slower (46% decrease), urinary excretion of *N*-acetylprocainamide was significantly smaller (38.3% decrease), and metabolic clearance to *N*-acetylprocainamide was significantly slower (65.8% decrease) than those in control rats (23% casein diet for a period of 4-week) (Jung *et al.*, 1985).

Digoxin

Digoxin is mainly excreted by glomerular filtration without being metabolized in humans (Koren, 1988). After intraarterial administration of digoxin at a dose of 1 mg/kg to protein-deficient male albino guinea pigs (5% protein diet for a period of 4-week), the pharmacokinetics of digoxin were not significantly different compared with control pigs (21% protein diet for a period of 4-week) (Varma, 1980b).

ANALGESICS

Acetaminophen

Glucuronidation and sulfation, the major pathways of elimination of acetaminophen in all animals, account for approximately 50 and 30%, respectively, of therapeutic doses of the drug. Hence, the role of CYP isozyme is almost negligible in the pharmacokinetics of acetaminophen. Acetaminophen is oxidized to *N*-acetyl-*p*-benzoquinoneimine (NAPQI) *via* CYP1A2 and CYP3A4 at therapeutic concentrations, CYP1A1, CYP1A2, and CYP2E1 at moderately high concentrations (0.5-2 mM), and CYP2A6 and CYP2D6 at high concentrations (more than 2 mM) (Raucy *et al.*, 1989; Patten *et al.*, 1993; Thummel *et al.*, 1993; Chen *et al.*, 1998). NAPQI is normally detoxified by conjugation with glutathione and glutathione conjugate is further hydrolyzed to cysteine and mercaptoric conjugates. Even on induction, neither CYP1A1 nor CYP1A2 appears to play a significant role in the metabolism of acetaminophen in humans (Anderson *et al.*, 1983; Miners *et al.*, 1984; Sarich *et al.*, 1997). Hence, pharmacokinetics of acetaminophene depends on the formation of sulfate and glucuronide conjugates. After

intravenous administration of acetaminophen at a dose of 100 mg/kg to rats with PCM (5% casein diet for a period of 4-week), CL of acetaminophen was significantly slower (36.2% decrease) than that in control male Sprague-Dawley rats (23% casein diet for a period of 4-week) (Jung, 1985a). This could be due to slower partial metabolic clearance of sulfate conjugate (9.6 versus 3.6 ml/min/kg) and faster partial metabolic clearance of glucuronide conjugate (1.6 versus 3.1 mL/min/kg) in the rats (Jung, 1985a). Glutathione, cysteine, and mercaptoric conjugates of acetaminophen were not analyzed in the study (Jung, 1985a). Note that the pharmacokinetics of acetaminophen are very complex as a result of the capacity-limited formation of the glucuronide (high-capacity biotransformation) and sulfate (low-capacity than glucuronide conjugation) conjugates and the depletion of endogenous sulfate which is utilized in the formation of acetaminophen sulfate (Galinsky and Levy, 1981).

Phenylbutazone

Phenylbutazone is metabolized to oxyphenbutazone *via* CYP2B subfamily (Peterson *et al.*, 1987). Phenylbutazone at a dose of 50 mg/kg was administered intravenously to male Sprague-Dawley rats feeding on 5% (rats with dietary protein deficiency) and 21% (control rats) protein diet for a period of 3-week (Varma, 1980a). Based on 9000 *g* liver supernatant fraction, 5% protein diet decreased the conversion of phenylbutazone into oxyphenbutazone (Varma, 1980a). Also dietary protein deficiency was associated with a decrease in the urinary excretion of various metabolites of phenylbutazone (Varma, 1980a). Phenylbutazone at a dose of 10 mg/kg was administered intravenously to male Sprague-Dawley rats feeding on 5 and 21% protein diet for a period of 3-week (Varma, 1979). In protein-deficient rats (5% diet), the $t_{1/2}$ of phenylbutazone was longer and CL of phenylbutazone was slower (Varma, 1979). However, after oral administration of phenylbutazone at a dose of 6 mg/kg in adult male subjects with differing nutritional status, the terminal $t_{1/2}$ was significantly shorter and clearance was faster in undernourished patients who had significant deficit and low serum albumin level (Krishnaswamy *et al.*, 1981). Although oxyphenbutazone was not analyzed, this could be due to decrease in CYP2B subfamily in the undernourished patients.

Antipyrine

Based on *in vitro* rat hepatic microsomal studies, the formation of the 3 major metabolites of antipyrine, 3-methylhydroxylated, *N*-demethylated, and 4-hydroxylated metabolites, is extensively mediated by CYP2C11/C6 (Szakacs *et al.*, 2001). In microsomes from induced animal liver, CYP2B and CYP3A may contribute to both *N*-demethylation and 4-hydroxylation of antipyrine (Szakacs *et al.*, 2001). The hepatic enzyme aminopyrine *N*-demethylase (which is metabolized by CYP2E1) activity was estimated in young rhesus monkey with protein-energy malnutrition (Sharma *et al.*, 1985); the $t_{1/2}$ was longer and the clearance rate was slower in the malnourished monkeys, which correlated with a corresponding decrease in aminopyrine N-demethylase activity. The metabolic clearance rate and CL of antipyrine in patients with global PCM (ages between 16-77 years) were significantly slower than those in patients with energy malnutrition and subjects with good nutritional status (control groups); the values were comparable between energy malnourished and control groups (intravenous administration at a dose of 15 mg/kg; Tranvouez *et al.*, 1985). The plasma concentrations were higher, plasma $t_{1/2}$ was longer, and/or metabolic clearance rate was significantly slower in 10 infants and young children between ages of 6 months to 5 years suffering from severe degree of PCM (intravenous administration at a dose of 16 mg/kg; Narang *et al.*, 1977), 8 Sudanese malnourished children ages between 9 and 12.5 years (oral administration at a dose of 600 mg; Homeida *et al.*, 1979), malnourished children (intravenous administration at a dose of 16 mg/kg; Mehta *et al.*, 1982), and 15 children with kwashiorkor (oral administration at a dose of 18 mg/kg; Buchanan *et al.*, 1979b). However, no effect was observed after oral administration (at a dose of 1 g) of very low calorie diet to 11 otherwise healthy obese subjects (Sonne *et al.*, 1989). Interestingly, after nutritional rehabilitation, the above mentioned pharmacokinetic parameters were similar to their respective controls or before nutritional rehabilitation values (Narang *et al.*, 1977; Buchanan *et al.*, 1979b; Mehta *et al.*, 1982; Pantuck *et al.*, 1985; Tranvouez *et al.*, 1985). After rehabilitation (improvement in nutritional state), the $t_{1/2}$ was shorter and clearance was faster than those in malnourished 8 Sudanese children before rehabilitation (Homeida *et al.*, 1979).

Salicylates

Salicylic acid can undergo cytochrome P450-mediated hydroxylation to form gentisic acid (only 1-2% of dose) (Ingelman-Sundberg *et al.*, 1991). Salicylic acid and gentisic acid form salicylurate and gentiurate, respectively, *via* glycine conjugate in the mitochondria (Forman *et al.*, 1971). Glucuronidation of the phenolic (salicyl phenolic glucuronide) and carboxylic (salicylacyl glucuronide) acid moieties (the major metabolic pathways) are catalyzed by uridine diphosphoric-glucuronosyltransferase (Smith, 1960). Acetylsalicylic acid forms salicylic acid by nonenzymatic or esterase hydrolysis. After intravenous and intraperitoneal administration of sodium salicylate at a dose of 62 μmol/kg to male and female Sprague-Dawley rats (with different

age groups) with PCM (5% protein diet for a period of 3-week), PCM decreased $t_{1/2}$ of salicylate and increased CL of salicylate (Varma and Yue, 1984a). Pharmacokinetic parameters of salicylates were dose-dependent. For example, after intravenous administration of sodium salicylate at a dose of 2 mg/kg, the CL and $t_{1/2}$ were not significantly different between male Sprague-Dawley rats with PCM (5% protein diet for a period of 3-week) and control rats (21% protein diet for a period of 3-week) (Yue and Varma, 1982). However, at a dose of 10 and 100 mg/kg to rats with PCM, $t_{1/2}$ of salicylate was shorter and CL was faster (Yue and Varma, 1982). Salicylurate formation increased by kidney mitochondrial preparations and urinary excretion of salicylurate was also increased in rats with PCM (Yue and Varma, 1982). After single oral administration of sodium salicylates at a dose of either 12.5 or 25 mg/kg to 57 malnourished Ethiopian children, AUC of salicylate based on unbound drug was greater in children with kwashoirkor due to lower hepatocellular metabolic activity in the patients (Ashton *et al.*, 1993b). Aspirin at a dose of 12 mg/kg was administered orally to African children with normal nutrition and malnutrition; nutritional status seemed to have no prominent effect on plasma concentrations of salicylic acid (Treluyer *et al.*, 1991).

XANTHINES

Theophylline

In humans, theophylline is almost entirely (90%) metabolized in the liver by the hepatic mixed-function oxidase system (Ogilvie, 1978) to form 3-methylxanthine *via* CYP1A2, 1-methylxanthine *via* CYP1A2, and 1,3-dimethyluric acid *via* CYP1A2 and CYP2E1. Similar results were also reported in mutant Nagase analbuminemic rats (Kim *et al.*, 2003b), in rats with acute renal failure induced by uranyl-nitrate (Yu *et al.*, 2002), in rats pretreated with 2-(allylthio)pyrazine (Han and Lee, 1999), and rats with diabetes mellitus induced by alloxan or streptozotocin (our unpublished data). 1-Methylxanthine undergoes further oxidation by xanthine oxidase to form 1-methyluric acid. Theophylline was also mainly metabolized in rats; after intravenous administration of theophylline at a dose of 10 mg/kg to control male Sprague-Dawley rats, 27.8% of intravenous dose was excreted in urine (Jung, 1985b). Although the metabolites of theophylline were not measured after intravenous administration of aminophylline at a dose of 10 mg/kg as theophylline to rats with PCM (5% casein diet for a period of 4-week), CL was significantly slower (39% decrease) than that in control male Sprague-Dawley rats (23% casein diet for a period of 4-week) (Jung, 1985b). After intravenous administration of aminophylline at a dose of 10 mg/kg as theophylline to rats with PCM (5% casein diet for 4-week feeding), CL was significantly slower in both 2 and 14 months old male Fischer 344 virgin rats (23% casein diet for a period of 4-week) (Jung and Nanavaty, 1990). This could be due to decrease in CYP1A2 and CYP2E1 in rats with PCM (Cho *et al.*, 1999). After intravenous administration of aminophylline at a dose of 5 mg/kg as theophylline, the $AUC_{0-2\,h}$ of 1,3-dimethyluric acid (37.9% decrease) and the percentages of intravenous dose of theophylline excreted in 24-h urine as 1,3-dimethyluric acid (40.4% decrease) decreased significantly in 2-(allylthio)pyrazine-pretreated male Sprague-Dawley rats (Han and Lee, 1999). 2-(Allylthio)pyrazine considerably suppressed CYP2E1 and tended to suppress CYP1A2 in rats (Kim *et al.*, 1997). After oral administration of uncoated theophylline tablet at a dose of approximately 5 mg/kg to 12 undernourished and 12 well-nourished asthmatic patients, CL in undernourished asthmatic patients was significantly slower (Raj *et al.*, 1998).

Caffeine

N^1-Demethylation to form theobromine, N^3-demethylation to form paraxanthine, and N^7-demethylation to form theophylline account, on average, for 80, 11, and 4% of caffeine metabolism in humans, respectively (Lelo *et al.*, 1986). Once formed, the above three metabolites are subject to extensive metabolism. Evidence supporting the involvement of hepatic CYP1A2 in the conversion of caffeine to the above three metabolites is overwhelming (Butler *et al.*, 1989; Tassaneeyakul *et al.*, 1992, 1994). After intravenous administration of caffeine at a dose of 5 mg/kg to 10 Holstein-Friesian calves after 4 days of starvation, CL was significantly slower (20% decrease) than that in control calves (Janus *et al.*, 2001). The above data supported that 4-day starvation could cause decrease in CYP1A2 in calves (Janus *et al.*, 2001). After nasogastric intubation of caffeine at a dose of 3.6-5.6 mg/kg to seven children with kwashiorkor, the $t_{1/2}$ of caffeine was significantly longer (254% increase) than that in 5-healthy children (Akinyinka *et al.*, 2000). In children with kwashiorkor, the maximum plasma concentration (C_{max}) of paraxanthine was significantly lower (76.9% decrease) and CYP1A2 activity was significantly lower than those in healthy children (Akinyinka *et al.*, 2000).

ANTIMALARIALS

Chloroquine

In humans, chloroquine is metabolized to one major metabolite, *N*-desethylchloroquine (Projean *et al.*, 2003). At therapeutically relevant concentrations (approximately 100 μM chloroquine in the liver), CYP2C8, CYP3A4, and to a much lesser extent, CYP2D6 are expected to account for most of *N*-desethylchloroquine based on human liver

microsomes and recombinant human cytochrome P450 (Projean *et al.*, 2003). After intraperitoneal administration of chloroquine at a dose of 10 mg/kg to malnourished white rats of the Wistar strains (kwashiorkorigenic diet, 20% protein diet for a peroid of 74-day), $t_{1/2}$ was significantly longer (47.9% increase) and elimination rate constant was significantly slower (34.6% decrease) than those in control rats (21% protein diet for a period of 74-day) (Adelusi and Salako, 1982). Although *N*-desethylchloroquine was not analyzed, longer $t_{1/2}$ and slower elimination rate constant in malnourished rats could be due to decrease in CYP2C8, CYP3A4, and/or CYP2D6 in the rats. Interestingly, when malnourished rats were allowed to recover from their state of malnutrition (2.0% protein diet for a period of 24-day followed by 21.0% protein diet for a period of 50-day), $t_{1/2}$ and elimination rate constant of chloroquine were no longer differed from those of animals that had never been malnourished (Adelusi and Salako, 1982).

Quinine

CYP3A4 is involved in the metabolism of quinine to form several metabolites, including hydroxyquinine (the major metabolite of quinine) in rats (Mirghani *et al.*, 2002). After oral administration of quinine HCl at a dose of 10 mg/kg to 6 African children suffering from kwashiorkor, quinine was eliminated more slowly and terminal $t_{1/2}$ was significantly longer than those in 7 normal African children (Salako *et al.*, 1989). When compared to control children, malaria and malnutrition increased plasma concentrations of quinine and slowered CL after intravenous injection of 8 mg/kg of a combination solution of cinchonic alkaloids (corresponding to 4.7 mg/kg as quinine base) containing 96.1% quinine, 2.5% quinidine, 0.68% cinchonine, and 0.67% cinchonidine (Pussard *et al.*, 1999). After intramuscular administration of Quinimar® (quinine resorcine HCl) at a dose of 16 mg/kg as quinine base at 0 and 12 h and at a dose of 8 mg/kg to children with global malnutrition, CL/*F* (*F*; the extent of bioavailability) was significantly faster (91.3% increase) and $t_{1/2}$ was significantly shorter (37.6% decrease) than those in children with normal nutrition (Treluyer *et al.*, 1996). In malnourished children, $AUC_{hydroxyquinine}/AUC_{quinine}$ ratio was significantly increased indicating that metabolism of quinine increased in children with global malnutrition (Treluyer *et al.*, 1996).

MISCELLANEOUS

Chlorzoxazone

It is well known that chlorzoxazone primarily undergoes hydroxylation to form 6-hydroxychlorzoxazone catalyzed mainly by CYP2E1 in humans (Peter et al., 1990; Conney and Burns, 1960). Chlorzoxazone has been used as a noninvasive chemical probe to assess the activity of CYP2E1 *in vitro* and *in vivo* due to the good correlation between the formation rate of 6-hydroxychlorzoxazone and CYP2E1 activity in male Sprague-Dawley rats (Rockich and Blouin, 1999) and humans (Lucas *et al.*, 1999). Chlorzoxazone was mainly metabolized in rats; after intravenous administration at a dose of 25 mg/kg to control male Sprague-Dawley rats, 0.166% of intravenous dose of chlorzoxazone was excreted in 8-h urine (Kim *et al.*, 2002). As expected, after intravenous administration of chlorzoxazone at a dose of 25 mg/kg to male Sprague-Dawley rats with PCM (5% casein diet for a period of 4-week), plasma levels of 6-hydroxychlorzoxazone were lower than that in control rats (23% casein diet for a period of 4-week) (Kim *et al.*, 2002). This resulted in a significantly smaller AUC of 6-hydroxychlorzoxazone in rats with PCM (55.1% decrease) than that in control rats (Kim *et al.*, 2002), possibly due to decreased CYP2E1 in rats with PCM (Cho *et al.*, 1999). However, AUC of 6-hydroxychlorzoxazone in rats with PCMC was not significantly different compared to those in control rats and rats with PCM (Kim *et al.*, 2002). Chlorzoxazone at a dose of 250 mg was administered orally to 6 healthy white men, first after an overnight fast and after a 38-h fast on a separate occasion. Prolonged fasting produced a decrease in plasma concentration of 6-hydroxychlorzoxazone (O'Shea *et al.*, 1994). Chlorozoxazone is no longer used in clinic as a muscle relaxant.

Dexamethasone

Dexamethasone is extensively metabolized to 6-hydroxydexamethasone *via* CYP3A4 (Tomlinson *et al.*, 1997a,b) and side chain cleaved metabolites *via* CYP17 (Tomlinson *et al.*, 1997a) in human liver both *in vitro* and *in vivo* (Tomlinson *et al.*, 1997b). After intravenous administration at a dose of 1, 2, and 3 mg/kg to male Sprague-Dawley rats with PCM (5% protein diet for a period of 4-week), the $t_{1/2}$, CL, and apparent volume of distribution were not significantly different between two groups of rats (Varma, 1980). The above data suggested that the CYP isozymes which catalyze the formation of 6-hydroxydexamethasone from dexamethasone seemed not to be reduced considerably in rats. After intravenous administration of dexamethasone at a dose of 4 μmol/kg to virgin Sprague-Dawley female rats with PCM (5% casein diet for 20-day feeding), the $t_{1/2}$ was longer and volume of distribution was larger in pregnant but not in nonpregnant rats (Varma, 1984b).

Apomorphine

After intravenous administration of apomorphine at a dose of 2 mg/kg to low-protein diet male Sprague-Dawley rats (0.5% protein diet for a period of 6-7 weeks) to produce prekwashoirkor, there was an almost twofold

decrease in the plasma clearance in the malnourished rats compared with control rats (commercial food pellets for a period of 6-7 weeks) (Bredberg and Paalzow, 1990).

Ouabain

After intravenous administration of ouabain at a dose of 1 μg/kg/min to protein-deficient male albino guinea pigs (5% protein diet for a period of 4-week), the pharmacokinetics of ouabain were not significantly different compared with control pigs (21% protein diet for a period of 4-week) (Varma, 1980b).

Oxazepam

Oxazepam is biotansformed mainly by glucuronide conjugation mediated by one or more glucuronosyl transferases (Greenblatt *et al.*, 1976; Greenblatt, 1981; Locniskar and Greenblatt, 1990). After oral administration of oxazepam at a dose of 30 mg to eleven otherwise healthy obese subjects before and after feeding a very low calorie diet (Pordic) for 14 days (daily intake of protein was 52.7 g and carbohydrate was 25.7 g, corresponding to 360 kcal), CL was slower (0.88-fold) after the diet and $t_{1/2}$ increased to 1.22-times the control value (Sonne *et al.*, 1989).

DA-8159

DA-8159 (5-[2-propyloxy-5-(1-methyl-2-pyrollidinylethylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-d)pyrimidine-7-one), a new inhibitor of cyclic guanosine monophosphate (cGMP)-specific phophodiesterase type V, was metabolized to DA-8164 (5-[2-propyloxy-5-(aminosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazoleo(4,3-d) pyrimidine-7-one) *via* CYP3A1/2 in rats (our unpublished data). After intravenous (46.3% decrease) and oral (54.9% decrease) administration of DA-8159 to rats with PCM (5% casein diet for a period of 4-week), AUC values were significantly smaller than those in control rats (23% casein diet for a period of 4-week) (our unpublished data). This could be due to suppressed CYP3A1/2 in rats with PCM (Cho *et al.*, 1999). DA-8159 is being evaluated in phase II clinical trial to treat male erectile dysfunction.

Oltipraz

Oltipraz was mainly metabolized *via* hepatic CYP1A1/2, CYP2B1/2, CYP2C11, CYP3A1/2, and CYP2D1 in rats (our unpublished data). After intravenous administration of oltipraz at a dose of 10 mg/kg to rats with PCM, AUC was significantly greater (138% increase), and $t_{1/2}$(63% increase) and MRT (101% increase) were significantly longer than those in control rats (our unpublished data). Interestingly, in rats with PCMC, the above mentioned parameters were returned to those in control rats (our unpublished data). The slower values of CL, CL_{NR}, and intrinsic oltipraz disappearance clearance (CL_{int}) in rats with PCM were partially returned to control levels in rats with PCMC.

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