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Perspective - Minireview

Effects of Lipopolysaccharide on Pharmacokinetics of Drugs

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Lipopolysaccharide (LPS) endotoxin is an active component in the outer membrane of Gram-negative bacteria. LPS is usually used as an inflammatory animal model. During the inflammation, diarrhea and changes in plasma proteins, in hepatic and/or intestinal microsomal cytochrome P450 (CYP) isozymes, and in the renal and/or biliary excretion of drugs have been reported. Thus, in rats pretreated with lipopolysaccharide endotoxin isolated from *Klebsiella pneumoniae* (KPLPS rats), the absorption, distribution, metabolism, and excretion of drugs could be expected to be altered. Interestingly time-dependent effects on the hepatic CYP isozymes have been reported in KPLPS rats. Thus, in KPLPS rats, the pharmacokinetics of drugs which are mainly metabolized via CYP isozymes could be expected to be time-dependent. In this review, an attempt to explain changes in pharmacokinetics of drug reported in the literature was made in terms of CYP isozyme changes or urinary and/or biliary excretion changes in KPLPS rats.

Key words: Pharmacokinetics, KPLPS rats, Hepatic CYP isozymes, Biliary and/or urinary excretion, Rats.

INTRODUCTION

Lipopolysaccharide (LPS) endotoxin is an active component in the outer membrane (cell wall) of Gram-negative bacteria. It indirectly secretes various inflammatory cytokines (e.g., platelet activating factor, tumor necrosis factor-α, interleukin-1β and -6, and interferons) (Cassatella *et al.*, 1993; Evans *et al.*, 1993; Crawford *et al.*, 1997) from activated Kupffer cells (Freudenberg *et al.*, 1986; Bertini *et al.*, 1989). The LPS consists of the O-antigenic polysaccharide, which is linked to the core digosaccharide (R-core), which in turn is linked to lipid A (Westphal *et al.*, 1983; Rietschel *et al.*, 1993). Three kinds of LPS isolated from *Klebsiella pneumoniae* (KPLPS), *Escherichia coli* (ECLPS), and *Pseudomonas aeruginosa* (PALPS) are usually used to find the effects of LPS on the pharmacokinetics of drugs in animals (Ueyama *et al.*, 2005). It has been reported that KPLPS has potent adjuvant (Ohta *et al.*, 1982; Kato *et al.*, 1985; Kido *et al.*, 1985) and antitumor activities (Miyamoto *et al.*, 1984; Hasegawa *et al.*, 1985).

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Pharmacokinetic process of drugs could be altered by KPLPS. For example, absorption of drugs from the gastrointestinal tract could be altered by diarrhea. It has been reported that septic conditions are clinically manifested by a spectrum of symptoms, including hypotension, fever, diarrhea, and widespread clotting in various organs (Liu *et al.*, 1995; Remick *et al.*, 1995; Llewelyn and Cohen, 2001). Distribution of drugs could also be altered by increase or decrease in plasma proteins. It has been reported that during the acute phase response to infection or inflammation, the synthesis of hepatic 'positive acute phase proteins' (such as α_2-macroglobulin and transferin) increases, while the synthesis of 'negative acute phase proteins' (such as albumin and α_{2u}-globulin) decreases (Kushner, 1982). Hepatic metabolism of drugs could be also altered due to the changes in CYP isozymes in the liver and intestine. For example, after the intravenous administration of 0.5-mg/kg KPLPS to male Wistar rats, the expression of hepatic CYP2C11 and CYP 3A2 significantly decreased (60.2% and 50.2% decrease, respectively) at 24 h (24-h KPLPS rats) than that in control rats (Ueyama *et al.*, 2005). After the intravenous administration of 1-mg/kg KPLPS to male Wistar rats, time-dependent effects on hepatic CYP isozymes have been observed (Nadai *et al.*, 1998). The aminopyrine N-demethylase (CYP1A1, 1A2, 2B1, 2B2,

2C6, 2C11, and 3A markers) activity significantly decreased at 24 h and 96 h (24-h and 96-h KPLPS rats) (48.6% and 65.7% decrease, respectively), but was not altered at 2 h (2-h KPLPS rats) compared to that in control rats (Nadai *et al.*, 1998). The aniline hydroxylase (a CYP2E1 marker) activity significantly decreased at 24 h (52.6% decrease), but was not altered at 2 h and 96 h compared to that in the control rats (Nadai *et al.*, 1998). The benzphetamine N-demethylase (CYP2B1, 2C6, 2C11, and 3A markers) activity significantly decreased at 24 h and 96 h (54.9% and 21.4% decrease, respectively), but not altered at 2 h compared to that in the control rats (Nadai *et al.*, 1998). After the tail vein injection of 0.5-mg/kg KPLPS to male Sprague-Dawley (SD) rats, time-dependent effects on hepatic CYP isozymes have also been observed (Yang *et al.*, 2007). The expression of hepatic CYP1A, 2B1/2, and 3A decreased (77.3%, 47.2%, and 59.1%, respectively) in 24-h KPLPS rats, but returned to that in the control rats in 96-h KPLPS rats (Yang *et al.*, 2007). However, the expression of intestinal CYP3A was not altered after 24 h and 96 h (Lee *et al.*, 2007a). Renal and/or biliary excretion of drugs would be also altered by decrease in the glomerular filtration rate (GFR) and renal plasma flow rate (Hinshaw *et al.*, 1959; Gilbert, 1960; Cavanagh *et al.*, 1970; Kikeri *et al.*, 1986; Churchill *et al.*, 1987; Hewett and Roth, 1993) and decrease in the biliary excretion of the organic anionic drug (Haghgoo *et al.*, 1995). Thus, the pharmacokinetics and hence the pharmacodynamics of drugs could be altered by KPLPS.

The changes in the hepatic CYP isozymes in PALPS rats (Ueyama *et al.*, 2005) and in ECLPS rats (Gorodischer *et al.*, 1976; Morgan, 1989, 1993, Wright and Morgan, 1990; Monshouwer *et al.*, 1996, Sewer *et al.*, 1996; Roe *et al.*, 1998; Sewer and Morgan, 1998; Ferrari *et al.*, 2001; Morgan *et al.*, 2002; Cheng *et al.*, 2003; Sachdeva *et al.*, 2003; Kalitsky-Szirtes *et al.*, 2004; Ueyama *et al.*, 2005) have also been reported. Although, the changes in hepatic CYP isozymes have been reported in rat models of KPLPS, ECLPS, and PALPS, the pharmacokinetic changes of drugs in the rat model of KPLPS were only reviewed. In this review, the total area under the plasma concentration-time curve from time zero to time infinity (AUC) of metabolite was compared with respect to CYP isozyme changes in the rat model of KPLPS, if CYP isozymes were known to be involved in the formation of the metabolite(s). Otherwise, the AUC, or time-averaged total body (Cl) or nonrenal (Cl_{nr}) clearance of the parent drug were compared. Therefore, the changes in such parameters did not always correlate with the changes in CYP isozymes. For drugs which are primarily excreted via the bile (feces) and/or urine, the changes in the pharmacokinetic parameters of drugs by KPLPS have also been reviewed. The changes of drugs in other animal models of KPLPS were also reviewed for purposes of comparison, if these changes of drugs have been reported in rats.

A homology (%) of proteins between human and rat CYP isozymes has been reported (Lewis, 1996). Drug metabolism with respect to CYP isozymes and the information on CYP isozymes in humans and animals have been reviewed (Lewis, 1996; Levy *et al.*, 2000; Ortiz de Montellano, 2005).

DRUGS

Drugs mainly metabolized via hepatic CYP isozymes. Changes in the hepatic CYP isozymes in KPLPS rats (Nadai *et al.*, 1998; Ueyama *et al.*, 2005; Yang *et al.*, 2007) are related to changes in the *in vitro* hepatic intrinsic clearance (Cl_{int}) for the disappearance of drugs in the hepatic microsomal fractions. For low hepatic extraction ratio drugs, their hepatic clearance (when the Cl_{nr} of drugs could represent their hepatic metabolic clearance of drugs) depends more on the Cl_{int} for the disappearance of drugs (hepatic CYP isozyme changes) rather than on the hepatic blood flow rate (Wilkinson and Shand, 1975). Thus, the Cl_{int} changes could mainly determine the hepatic (metabolic) clearance changes of the drugs. For intermediate hepatic extraction ratio drugs, their hepatic clearance depends on the Cl_{int} for the disappearance of the drugs, the free (unbound to plasma protein) fraction of the drugs in plasma, and the hepatic blood flow rate (Wilkinson and Shand, 1975). Thus, the magnitude of changes in the above three factors could determine the hepatic clearance of the drugs. For high hepatic extraction ratio drugs, their hepatic clearance depends more on the hepatic blood flow rate and the free fraction of the drug in plasma rather than on the Cl_{int} for the disappearance of the drugs (Wilkinson and Shand, 1975). Thus, the magnitude of changes in the above two factors could determine the hepatic clearance of the drugs. Similar concept could also be applied to the intestine (Lee *et al.*, 2007a) if the hepatic clearance concept (Wilkinson and Shand, 1975) would be applied to the intestine. Thus, the metabolism of drugs in this category is related to hepatic CYP isozymes if the drugs are essentially metabolized via hepatic CYP isozymes with low or intermediate hepatic extraction ratio drugs. The hepatic extraction ratios (the hepatic first-pass effects) of drugs were directly obtained by difference in the AUC values following intravenous and intraportal administration of drugs. Otherwise, the ratios were indirectly estimated by

Table 1. Main hepatic CYP isozyme(s) involved for the metabolism of each drug and the corresponding pharmacokinetic observations in KPLPS rats

No.	Drug	CYP isozyme	Pharmacokinetic observation	Reference
1	Theophylline	CYP1A1/2 (possibly 3A1/2) for the formation of 1,3-DMU	Significantly smaller AUC of 1,3-DMU at 24 h	Yang *et al.*, 2007
			Return to the controls (AUC of 1,3-DMU) at 96 h	Yang *et al.*, 2007
			Comparable 1,3-DMU in 24-h urine (% of dose) at 2 h	Wang *et al.*, 1993
		CYP1A1/2, 2B1/2, and 3A1/2 for the metabolism of theophylline	Significantly slower Cl_{nr} of theophylline at 24 h	Yang *et al.*, 2007
			Return to the controls (Cl_{nr} of theophylline) at 96 h	Yang *et al.*, 2007
			Comparable Cl and Cl_r at 2 h	Wang *et al.*, 1993
2	1-Methyl-3-propylxanthine (MPX)	CYP1A1/2 for the metabolism of MPX	Significantly faster Cl of MPX at 2 h	Wang *et al.*, 1993
3	Antipyrine	CYP2B, 2C6, 2C11, and 3A for the metabolism of antipyrine	Significantly slower Cl of antipyrine at 24 h	Ueyama *et al.*, 2005; Nadai *et al.*, 1998
			Not altered (Cl of antipyrine) at 2 and 96 h	Nadai *et al.*, 1998
4	Metformin	CYP2C11, 2D1, and 3A1/2 for the metabolism of metformin	Significantly slower Cl_{nr} of metformin at 2 h	Choi *et al.*, 2007a
5	DA-8159	CYP3A1/2 for the metabolism of DA-8159 and for the formation of DA-8164	Not altered Cl_{nr} and AUC of DA-8159 at 2 h	Lee *et al.*, 2007b
			Not altered AUC of DA-8164 at 2 h	Lee *et al.*, 2007b
6	Telithromycin	CYP3A1/2 for the metabolism of telithromycin	Significantly slower Cl_{nr} of telithromycin at 24 h	Lee *et al.*, 2007a
			Returned to the controls at 96 h	Lee and Lee, 2007a

dividing the Cl_{nr} of drugs (assuming that the Cl_{nr} of drugs are equal to their hepatic clearance of drugs) following intravenous administration by the hepatic plasma flow rate (Lee and Chiou, 1983). The hepatic plasma flow rate was estimated by multiplying the hepatic blood flow rate, 55.2 ml/min/kg (Davis and Morris, 1993), by the hematocrit, approximately 0.45 (45%) (Mitruka and Rawnsley, 1981), in rats. Thus, the estimated hepatic extraction ratios represent the maximum ability for the metabolism of the drugs in the liver (Lee and Chiou, 1983). The CYP isozyme(s) involved in the metabolism of each drug and the corresponding pharmacokinetic observations of each drug in this category are listed in Table 1.

Theophylline: Human liver microsomal inhibition studies and the use of recombinant CYP isozymes have demonstrated that CYP1A2 is responsible for the formation of 3-methylxanthine and 1-methylxanthine from theophylline, a bronchodilator (Minors and McKinnon, 2000). The CYP1A2 is also the major catalyst for 1,3-dimethyluric acid (1,3-DMU) formation, with contribution from CYP2E1 and possibly from CYP3A4 (Williams *et al.*, 1979). Recently, Yang *et al.* (2008) reported that the formation of 1,3-DMU was primarily mediated via CYP1A1/2 and possibly via 3A1/2 (not via CYP2B1/2, 2C11, 2D1, and 2E1) in male SD rats. The expression of CYP1A and 3A decreased in 24-h KPLPS rats but returned to that in the control rats in 96-h KPLPS rats (Yang *et al.*, 2007). Thus, it could be expected that in 24-h KPLPS rats, the formation of 1,3-DMU would be significantly smaller than that in the control rats but in 96-h KPLPS rats, it could return to that in the control rats. As expected, after the intravenous administration of 5-mg/kg theophylline to male SD rats 24 h and 96 h after tail vein injection of 0.5-mg/kg KPLPS, the AUC of 1,3-DMU was significantly smaller (36.3% decrease) in 24-h KPLPS rats but returned to that in the control rats in 96-h KPLPS rats (Yang *et al.*, 2007). This could be supported by the significantly slower (60.6% decrease) Cl_{int} values for the formation of 1,3-DMU in 24-h KPLPS rats, but returned to that in the control rats in the 96-h KPLPS rats (Yang *et al.*, 2007). Similar results have also been obtained after the oral administration of 5-mg/kg theophylline; the AUC of 1,3-DMU was significantly smaller (21.6% decrease) in 24-h KPLPS rats but returned to that in the control rats in 96-h KPLPS rats (Yang *et al.*, 2007). The liver and kidney function was not seriously impaired by administration of 0.5-mg/kg KPLPS based on the plasma chemistry, creatinine clearance, and tissue histology (Yang *et al.*, 2007).

Yang *et al.* (2007) also reported that theophylline was mainly metabolized via hepatic CYP1A1/2, 2B1/2, and 3A1/2 (not via CYP2C11, 2D6, and 2E1) in male SD rats. The expression of CYP1A and 3A decreased (77.3% and 59.1%, respectively) in 24-h KPLPS rats, but returned to that in the control rats in 96-h KPLPS

rats (Yang *et al.*, 2007). Thus, it could be expected that the Cl_{nr} and AUC of theophylline could be slower and greater, respectively, in 24-h KPLPS rats, but returned to that in the control rats in 96-h KPLPS rats. As expected, after the intravenous administration of 5-mg/kg theophylline to male SD rats 24 h and 96 h after tail vein injection of 0.5-mg/kg KPLPS, the AUC and Cl_{nr} of theophylline was significantly greater (46.5% increase) and slower (41.9% decrease), respectively, in 24-h KPLPS rats, but returned to that in the control rats in 96-h KPLPS rats (Yang *et al.*, 2007). This could be supported by the significantly slower Cl_{int} (37.1% decrease) for the disappearance of theophylline in 24-h KPLPS rats, but returned to that in the control rats in 96-h KPLPS rats (Yang *et al.*, 2007), because theophylline is a low hepatic extraction ratio drug in rats. The 24-h urinary excretion values of unchanged theophylline were 39.4%, 43.1%, and 40.2% of the intravenous dose for the control, 24-h KPLPS, and 96-h KPLPS rats, respectively (Yang *et al.*, 2007). After the oral administration of 5-mg/kg theophylline to rats, the AUC of theophylline was also significantly greater (34.0% increase) in 24-h KPLPS rats, but returned to that in the control rats in 96-h KPLPS rats (Yang *et al.*, 2007). However, after the intravenous administration of 10-mg/kg theophylline to male Wistar rats 2 h after 20~30 min intravenous infusion of 0.25-mg/kg KPLPS, the recovery of 1,3-DMU in the 24-h urine (as expressed in terms of percentage of the intravenous dose of theophylline) were comparable to that in the control rats (Wang *et al.*, 1993). This could have been due to the fact that the expression of CYP1A1/2 and/or 3A1/2 was not seemingly considerably altered 2 h after KPLPS administration.

1-Methyl-3-propylxanthine (MPX): No studies on the CYP isozymes responsible for the metabolism of MPX, a xanthine, in humans have yet been reported. However, Nadai *et al.* (2007) reported that MPX is primarily metabolized via hepatic CYP1A2 in rats. The expression of CYP1A decreased in 24-h KPLPS rats but returned to that in the control rats in 96-h KPLPS rats (Yang *et al.*, 2007). However, the data on 2-h KPLPS rats are not available. After the intravenous administration of 2.5-mg/kg MPX to male Wistar rats 2 h after 20~30 min intravenous infusion of 0.25-mg/kg of KPLPS, the Cl of MPX was significantly faster (15.4% increase) than that in the control rats (Wang *et al.*, 1993). These data suggest that the expression of CYP1A2 seemed to be increased in 2-h KPLPS rats because MPX is a low hepatic extraction ratio drug [estimated to be 15.4% in male Wistar rats (Wang *et al.*, 1993) in rats; the ratio was estimated using the Cl of MPX instead of the Cl_{nr} of MPX because the 24-h urinary excretion of unchanged MPX was about 1% of the intravenous dose of MPX]. The authors explained the faster Cl of MPX by the significant decrease in the binding capacity and number of binding sites on the albumin molecule in 2-h KPLPS rats (Wang *et al.*, 1993). Thus, the apparent volume of distribution at steady state (V_{ss}) in 2-h KPLPS rats was significantly larger (27.6% increase) than that in the control rats (Wang *et al.*, 1993).

Antipyrine: Antipyrine, a pyrazoline derivative that has an analgesic-antipyretic and anti-inflammatory activity, is frequently used as an index of the rate of hepatic microsomal oxidative drug metabolism (a general probe of CYP isozyme activities), because it is completely metabolized in the liver. The studies on CYP isozymes responsible for antipyrine biotransformation indicate that CYP1A2, 2A6, 2C8, 2C9, 2C19, 2E1, and 3A4 all participate to some extent, but they implicate CYP1A2 and 2C9 in the formation of 3-hydroxyantipyrine, CYP1A2 and 3A4 in the formation of 4-hydroxyantipyrine, and predominantly CYP2C9 and 1A2 in the formation of norantipyrine in humans (Leclercq *et al.*, 1989; Engel *et al.*, 1996). Based on the microsomes of uninduced rat livers, the formation of the three major metabolites of antipyrine (norantipyrine, 3-hydroxymethylantipyrine, and 4-hydroxyantipyrine) is extensively mediated by CYP2C6/C11 (Szakacs *et al.*, 2001). Based on the microsomes of induced rat liver, CYP2B and 3A subfamilies may contribute to both the N-demethylation and 4-hydroxylation of antipyrine (Szakacs *et al.*, 2001). In 24-h KPLPS rats, the expression of hepatic CYP2B1/2 and 3A (Yang *et al.*, 2007) and 2C11 and 3A2 (Nadai *et al.*, 1998) decreased than that in the control rats. Thus, it could be expected that the Cl of antipyrine would be slower in 24-h KPLPS rats. As expected, after the intravenous administration of 20-mg/kg antipyrine to male Wistar rats 24 h after intravenous administration of 0.5-mg/kg KPLPS, the Cl of antipyrine was significantly slower (49.8% decrease) than that in the control rats (Ueyama *et al.*, 2005). This could have been due to the slower Cl_{int} for the disappearance of antipyrine in 24-h KPLPS rats, because antipyrine is a low hepatic extraction ratio drug in rats.

After the intravenous administration of 20-mg/kg antipyrine to male Wistar rats 2 h, 24 h, and 96 h after intraperitoneal administration of 1-mg/kg KPLPS, the Cl of antipyrine was significantly slower in 24-h KPLPS rats (30.0% decrease), but was not altered in 2-h and 96-h KPLPS rats (Nadai *et al.*, 1998). This suggests that the CYP isozymes responsible for the metabolism of antipyrine decreased in 24-h KPLPS rats as shown in other studies (Ueyama *et al.*, 2005), but not consider-

ably altered in 2-h and 96-h KPLPS rats. The Cl of antipyrine correlated significantly with CYP content and aminopyrine N-demethylase activity (CYP1A1, 1A2, 2B1, 2B2, 2C, 2C, and 3A markers) (Nadai *et al.*, 1998). After the intravenous administration of 1.0-mg/kg KPLPS to rats, moderate hypertrophy of Kupffer cells was observed with no evidence of severe liver-tissue damage (Nadai *et al.*, 1998).

Metformin: Although metformin, a biguanide antihyperglycemic agent, is primarily excreted in the 24-h urine (64.4% of the intravenous dose of metformin) in male SD rats (Choi *et al.*, 2007b), this drug was included in this category, because it has been reported that metformin is primarily metabolized via CYP2C11, 2D1, and 3A1/2 (not via CYP1A2, 2B1/2, and 2E1) in male SD rats (Choi and Lee, 2006). No studies on the CYP isozymes responsible for the metabolism of metformin in humans have yet been published. The studies on the changes of the expression of CYP2C11, 2D1, and 3A1/2 in 2-h KPLPS rats did not seem to be reported. Following the intravenous administration of 100-mg/kg metformin to the male SD rats 2 h after 30-min infusion of 250-μg/kg KPLPS, the Cl_{nr} of metformin was significantly slower (18.1% decrease) than that in the control rats (Choi *et al.*, 2007a). This could have been due to significantly slower *in vitro* Cl_{int} for the disappearance of metformin (39.9% decrease) than that in the control rats (Choi *et al.*, 2007a), because metformin is a low hepatic extraction ratio drug [27.1% (Choi *et al.*, 2006)] in rats. The Cl_{nr} of metformin could represent the hepatic metabolic clearance of the drug in rats (Choi *et al.*, 2006). The above data suggest that the CYP isozymes responsible for the metabolism of metformin decreased in 2-h KPLPS rats. The liver and kidney function was not seriously impaired at 250-μg/kg KPLPS based on the plasma chemistry data, creatinine clearance, and tissue histology (Choi *et al.*, 2007a).

DA-8159: DA-8159 (Udenafil) is recently marketed in South Korea as an oral agent to treat male erectile dysfunction under the brand name of Zydena®. Based on the human liver microsome study, CYP3A4 was the major enzyme for the formation of DA-8164 (Ji *et al.*, 2004). However, no studies on the CYP isozymes responsible for the metabolism of DA-8159 in humans *in vitro* have yet been reported. Kim *et al.* (2005a) reported that metabolism of DA-8159 and formation of DA-8164 were primarily mediated via CYP3A1/2 (not via CYP2B1/2, 2E1, and 1A1/2) in the male SD rats. The CYP3A based on the enzyme activity test [aminopyrine N-demethylase (CYP1A1, 1A2, 2B1, 2B2, 2C6, 2C11, and 3A markers) and benzphetamine N-demethylase (CYP2B1, 2C11, and 3A markers) (Nadai *et al.*, 1998)] was not altered in 2-h KPLPS rats. Thus, it could be expected that the AUC and Cl_{nr} of DA-8159, and AUC of DA-8164 would be comparable between two groups of rats. As expected, after the intravenous administration of 30-mg/kg DA-8159 to the male SD rats 2 h after 30-min infusion of 250-μg/kg KPLPS, the Cl_{nr} and AUC of DA-8159 and AUC of DA-8164 were almost similar to those in the control rats (Lee *et al.*, 2007b). This could have been due to comparable Cl_{int} for the disappearance of DA-8159 and for the formation of DA-8164 in 2-h KPLPS rats (Lee *et al.*, 2007b), because DA-8159 is a low hepatic extraction ratio drug (23.0%) in rats (Shim *et al.*, 2003). The 24-h urinary excretion values of unchanged DA-8159 were 5.43% and 3.51% for the control and KPLPS rats, respectively (Lee *et al.*, 2007b). After the oral administration of 50-mg/kg DA-8159 to 2-h KPLPS rats, the AUC values of both DA-8159 and DA-8164 were also comparable to those in the control rats (Lee *et al.*, 2007b). The mechanism, pharmacological actions, pharmacokinetics and metabolism, toxicity, and clinical studies on DA-8159 have been reviewed (Kim *et al.*, 2005b).

Telithromycin: Telithromycin, a ketolide antibiotic, was primarily metabolized via hepatic CYP3A4 in humans (Shi *et al.*, 2005) and CYP3A1/2 in rats (Lee and Lee, 2007a). The expression of hepatic CYP3A decreased in 24-h KPLPS rats, but returned to that in the control rats in 96-h KPLPS rats (Yang *et al.*, 2007). Thus, it could be expected that the Cl_{nr} of telithromycin would be slower in 24-h KPLPS rats but returned to that in the control rats in 96-h KPLPS rats. As expected, after the intravenous administration of 50-mg/kg telithromycin to male SD rats 24 h and 96 h after the intravenous administration of 0.5-mg/kg KPLPS, the Cl_{nr} of telithromycin was significantly slower (45.7% decrease) in 24-h KPLPS rats, but returned to that in the control rats in 96-h KPLPS rats (Lee *et al.*, 2007a). This could be supported by the significantly slower Cl_{int} for the disappearance of telithromycin (13.1% decrease) in 24-h KPLPS rats, but returned to that in the control rats in 96-h KPLPS rats, because telithromycin is a low hepatic extraction ratio drug in rats (Lee and Lee, 2007b). After the oral administration of 50-mg/kg telithromycin to 24-h and 96-h KPLPS rats, the AUC of telithromycin was significantly greater (88.7% increase) in 24-h KPLPS rats, but returned to that in the control rats in 96-h KPLPS rats (Lee *et al.*, 2007a). This could have been due to the same reasons explained in the intravenous study, but not due to changes in the intestinal metabolism of the drug; the Cl_{int} for the disappearance of telithromycin in the intestine was comparable among three groups of rats (Lee *et al.*, 2007a).

Table 2. Pharmacokinetic observations of drugs primarily excreted via the kidney and/or bile (feces) in KPLPS rats

No.	Drug	Pharmacokinetic observation	Results	References
1	Metformin	Urine (64.4% of the intravenous dose)	Significantly slower Cl_r of metformin at 2 h	Choi *et al.*, 2007a
2	DA-7867	Feces (64.0% of the intravenous dose) and urine (17.0% of the intravenous dose)	Significantly greater AUC of DA-7867 at 2 h due to significantly smaller fecal recovery of DA-7867 at 2 h	Bae *et al.*, 2004.
3	Enprofylline	Urine (more than 85% of the intravenous dose)	Significantly slower Cl and significantly greater AUC of enprofylline at 2 h	Nadai *et al.*, 1993a
			Significantly slower Cl of enprofylline at 2 h and 10 h	Nadai *et al.*, 1995
			Return to controls (Cl of enprofylline) at 24 h	Nadai *et al.*, 1995
4	Famotidine	Urine (64.9% of the intravenous dose)	Significantly slower Cl and Cl_r of famotidine at 2 h	Hasegawa *et al.*, 1994a
5	Tobramycin	Urine (>75% of the intravenous dose)	Significantly slower Cl on tobramycin at 250-mg/kg and 500-μg/kg KPLPS at 2 h	Nadai *et al.*, 1993b
6	Gentamicin	Urine (93% of the intravenous dose)	Significantly slower Cl of gentamicin at 2 h	Hasegawa *et al.*, 1994b
7	Rhodamine-123	Urine and bile	Significantly slower biliary, renal, and tubular secretory clearance of rhodamine-123 at 6 h but return to the controls at 24 h	Ando *et al.*, 2001
8	Cefazoliln	Renal (87.9% of the intravenous dose)	Significantly slower Cl and Cl_r of cefazolin at 2 h	Nadai *et al.*, 1993c
9	Cefoperazone	Bile (81.7% of the intravenous dose) and urine (20.4% of the intravenous dose)	Significantly slower $Cl_{biliary}$, Cl_r, and Cl of cefoperazone at 2 h	Haghgoo *et al.*, 1995
10	Sparfloxacin	Bile (4.00% and 30.2% of the intravenous dose for sparfloxacin and its glucuronide, repectively)	Significantly slower Cl of sparfloxacin and biliary clearance of sparfloxacin and its glucuronide	Nadai *et al.*, 2001
11	ρ-Nitrophenyl glucuronide	Urine (75.2% of the intravenous dose)	Significantly slower Cl, Cl_r and biliary clearance of ñ-nitrophenyl glucuronide	Nadai *et al.*, 2001

Drugs mainly excreted via the kidney and/or bile (feces). Contribution of hepatic CYP isozymes to the metabolism of drugs in this category seemed almost negligible. Pharmacokinetic observations of drugs in this category are listed in Table 2.

Metformin: Following the intravenous administration of 100-mg/kg metformin to male SD rats 2 h after 30-min infusion of 250-μg/kg KPLPS, the time-averaged renal clearance (Cl_r) of metformin was significantly slower (16.7% decrease) than that in the control rats (Choi *et al.*, 2007a). This could have been due to the changes in the renal organic cation transporter, OCT2, in KPLPS rats, although the changes did not seem to be published yet. The percentages of the intravenous dose of metformin excreted in the urine were 78.9~99.9% in humans (Scheen, 1996), but 64.4% in male SD rats (Choi *et al.*, 2006).

DA-7867: After the intravenous administration of 10-mg/kg DA-7867, a new oxazolidinone antibiotic, to male SD rats, the metabolism of the drug became minimal, whereas approximately 85.0% of the intravenous dose was recovered as unchanged drug in the rats' urine (17.0% of the dose) and feces (64.0% of the dose), and rinsings form metabolic cage for up to 14 days (Bae *et al.*, 2005). Thus, the AUC of DA-7867 could have mainly been affected by its gastrointestinal excretion (Bae *et al.*, 2005). Following the intravenous administration of 10-mg/kg DA-7867 to male SD rats, 2 h after 30-min infusion of 250-μg/kg KPLPS, the AUC of DA-7867 was significantly greater (43.7% increase) due to significantly smaller (30.1% decrease) fecal recovery for up to 14 days (Bae *et al.*, 2004). The 14-day urinary excretion values of unchanged DA-7867 were 18.0% and 17.1% for the control and KPLPS rats, respectively (Bae *et al.*, 2004). The kidney and liver function was not seriously impaired by 250-μg/kg KPLPS based on the plasma chemistry data, creatinine clearance, and tissue histology (Bae *et al.*, 2004).

Enprofylline: Enprofylline (3-propylxanthine), a xanthine derivative having much greater bronchodilatory effects than theophylline (Miyamoto *et al.*, 1989; Ogawa *et al.*, 1989), is mainly excreted in the urine (more than 85% of the intravenous dose of enprofylline) through active tubular secretion mechanism (Nadai *et al.*, 1993a). After the intravenous administration of 20-mg/kg enprofylline to male Wistar rats 2 h after 20~30 min intravenous infusion of 250-μg/kg KPLPS, the timed-interval (every 10- or 20-min urine collection for up to 200 min) renal clearance values of enprofylline as free fraction of the drug were slower for up to 12-μg/ml plasma concentration of enprofylline than those in the controls rats (Nadai *et al.*, 1993a). This could have been due to decrease in both the ability and capacity of the tubular transport system and in turns decrease in the tubular secretary intrinsic clearance of enprofylline by KPLPS (Nadai *et al.*, 1993a). There were no histological changes in the kidney of KPLPS rats (Nadai *et al.*, 1993a).

After the intravenous administration of 2.5-mg/kg enprofylline to male Wistar rats 2 h and 24 h after 5-min intravenous infusion of 250-μg/kg KPLPS, the timed-interval (every 15-min urine collection for up to 120 min) renal clearance values were slower in 2-h KPLPS rats than those in the control rats, but in 24-h KPLPS rats, the renal clearance was returned to that in the control rats, suggesting that the time-dependent reductions in the GFR and renal secretion ability by KPLPS are transient events (Nadai *et al.*, 1995). KPLPS at a dose of 250-μg/kg, at least, does not induce renal cytotoxicity (Nadai *et al.*, 1995).

After the intravenous administration of 2.5-mg/kg enprofylline to male ddY strain mouse 2-h after 5-min intravenous infusion of 1-mg/kg KPLPS, the Cl was significantly slower (53.3% decrease) than that in the control rats and the renal uptake rate of enprofylline decreased compared to that in the control rats (Nadai *et al.*, 1996). These results indicate that KPLPS decreased the renal tubular secretion of enprofylline by inducing a decrease in the renal uptake ability. The time-averaged renal clearance was not measured in this study (Nadai *et al.*, 1996).

Famotidine: After the intravenous administration of 20-mg/kg famotidine (a H_2-receptor antagonist) and 100-mg/kg inulin (a RPFR marker) to male Wistar rats 2 h after 20-min intravenous infusion of 250-μg/kg KPLPS, the Cl and Cl_r were significantly slower (25.6% and 27.3% decrease, respectively), but Cl_{nr} and 24-h urinary recovery of famotidine were comparable to those in the control rats (Hasegawa *et al.*, 1994a). The Cl_r/glomerular filtration rate (GFR) ratios were 64.9% and 63.4% for the control and KPLPS rats, respectively (Hasegawa *et al.*, 1994). The slower Cl_r could have been due to decreased GFR (estimated as creatinine clearance), but not the net tubular secretion (Hasegawa *et al.*, 1994a). In 2-h KPLPS rats, the V_{ss} was significantly smaller (36.4% decrease) than that in the control rats, and this was unlikely due to any changes in plasma protein binding of famotidine (Hasegawa *et al.*, 1994a).

Tobramycin: After the intravenous administration of 2-mg/kg tobramycin (an aminoglycoside antibiotic) and 100-mg/kg inulin to male Wistar rats 2 h after 20~30 min intravenous infusion of 50-, 250-, or 500-μg/kg KPLPS, the Cl was significantly slower at 250-μg/kg and 500-μg/kg KPLPS (38.4% and 36.8% decrease, respectively), but fraction of urinary recovery of unchanged drug was not significantly different among all groups of rats (Nadai *et al.*, 1993b). The GFR was significantly slower (20%) in 250-μg/kg KPLPS and KPLPS increased the tubular reabsorption of tobramycin (Nadai *et al.*, 1993b). The 24-h urinary excretion of unchanged tobramycin was > 75 % (Nadai *et al.*, 1993b).

Gentamicin: After the intravenous administration of 10-mg/kg gentamicin (an aminoglycoside antibiotic) and 100-mg/kg inulin to male Wistar rats 2 h after 20~30 min intravenous infusion of 250-μg/kg KPLPS or lipid A (dose correspond to KPLPS), and active component of endotoxin, the Cl was significantly slower (26.0% and 24.0% decrease for KPLPS and lipid A, respectively) (Hasegawa *et al.*, 1994b). But the 60-min urinary excretion of gentamicin was not changed among three groups of rats. Both LPS and lipid A induced significant decrease in the GFR (by 30%). There were no significant differences among three groups of rats in the renal tubular reabsorption or intrarenal accumulation of gentamicin (Hasegawa *et al.*, 1994b).

Rhodamine-123: Rhodamine-123, an innovative agent for the treatment of prostate cancer, is primarily excreted into the bile and urine as unchanged form (Kunihara *et al.*, 1998). After the intravenous bolus injection of 85-μg/kg rhodamine-123 and 10-mg/kg inulin to male Wistar rats 6 (6-h KPLPS rats) or 24 h after the intraperitoneal injection of 1-mg/kg of KPLPS, the biliary and renal clearances and net tubular secretion rate of rhodamine-123 were significantly slower (61.1%, 60.0%, and 65.6% decrease, respectively) and the GFR (measured as inulin clearance) was also significantly slower (35.2% decrease) in 6-h KPLPS rats, but returned to that in the control rats in 24-h KPLPS rats (Ando *et al.*, 2001). The above data suggest that the endotoxin-induced decrease in p-glycoprotein-mediated biliary excretion and renal handling of rhodamine-123

were probably due to impairment of p-glycoprotein-mediated transport ability (Ando *et al.*, 2001).

Cefazolin: After the intravenous administration of 20-mg/kg of cefazolin, a β-lactam antibiotic, 2 h after 20~30 min intravenous infusion of 250-μg/kg KPLPS to male Wistar rats, the Cl and Cl_r were significantly slower (24.2% and 26.9% decrease, respectively) than those in the control rats (Nadai *et al.*, 1993c). This could have been due to changes in renal handling and plasma protein binding of cefazolin by KPLPS (Nadai *et al.*, 1993c). The Cl_r/Cl ratios were 89.7% and 86.5% for the control and KPLPS rats, respectively; they were not significantly different (Nadai *et al.*, 1993c).

Cefoperazone: After the intravenous administration of 20-mg/kg cefoperazone to male Wistar rats 2-h after 20~30 min intravenous infusion of 250-μg/kg KPLPS, the Cl, biliary clearance, and Cl_r were significantly slower (51.4%, 56.4%, and 34.7% decrease, respectively) than those in the control rats (Haghgoo *et al.*, 1995). The slower biliary clearance could have been due to an inhibition of the anion transport system across the sinusoidal and/or bile canalicular membrane (Haghgoo *et al.*, 1995). The Cl_r/Cl and $Cl_{biliary}$/Cl ratios were 20.4% and 81.7%, respectively, in control rats (Haghgoo *et al.*, 1995).

Sparfloxacin: Sparfloxacin, a new quinolone antibiotic, is a typical group of drug excreted in the bile (Matsunaga *et al.*, 1991; Akiyama *et al.*, 1995). After the intravenous bolus administration of 10-mg/kg sparfloxacin to male Wistar rats 24 h after intraperitoneal injection of 1-mg/kg KPLPS, the Cl and biliary clearances of sparfloxacin and its glucuronide were significantly slower (35.4%, 50.0%, and 56.1% decrease, respectively) than those in the control rats (Nadai *et al.*, 2001). The above data suggest that KPLPS decreases the biliary excretion of sparfloxacin and its glucuronide probably due to impairment of their hepatobiliary transport system and renal handling (Nadia *et al.*, 2001). The biliary clearance/Cl ratio of sparfloxacin was smaller than that in KPLPS rats (22.6% decrease) (Nadai *et al.*, 2001).

ρ-Nitrophenyl glucuronide: After the intravenous bolus administration of 8-mg/kg ρ-nitrophenyl glucuronide to male Wistar rats 24 h after the intraperi`toneal injection of 1-mg/kg KPLPS, the Cl, Cl_r, and biliary clearances of ρ-nitrophenyl glucuronide were significantly slower (32.1%, 42.9%, and 32.9% decrease, respectively) than those in the control rats (Nadai *et al.*, 2001). The above data suggest that KPLPS decreases the renal and biliary excretion of ρ-nitrophenyl glucuronide probably due to impairment of their hepatobiliary transport system and renal handling (Nadia *et al.*, 2001). The Cl_r/Cl and biliary clearance/Cl ratios were 75.2% and 6.42%, respectively, in control rats (Nadia *et al.*, 2001).

CONCLUSION

In KPLPS rats, the time-dependent effects on some hepatic CYP isozymes have been reported (Nadai *et al.*, 1998; Ueyama *et al.*, 2005; Yang *et al.*, 2007). However, the studies on CYP isozymes changes in KPLPS rats were much less than those in ECLPS rats (Gorodischer *et al.*, 1976; Morgan, 1989, 1993, 2002; Wright and Morgan, 1990; Monshouwer *et al.*, 1996, Sewer *et al.*, 1996; Roe *et al.*, 1998; Sewer and Morgan, 1998; Ferrari *et al.*, 2001; Cheng *et al.*, 2003; Sachdeva *et al.*, 2003; Kalitsky-Szirtes *et al.*, 2004; Ueyama *et al.*, 2005). Furthermore, the studies on the pharmacokinetic changes of drugs in KPLPS rats were also less than those in ECLPS rats. Although, the pharmacokinetic changes of drugs in KPLPS rats have been studied (Tables 1 and 2), the studies on humans are scarce. Thus, the extrapolation of the present rats data to humans is hard to have conclusion. For drugs in group B, the urinary excretion of drugs decreased compared to those in the controls rats (Table 2).

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