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Review

Pharmacokinetics of drugs in rats with diabetes mellitus induced by alloxan or streptozocin: comparison with those in patients with type I diabetes mellitus

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Abstract

Objectives In rats with diabetes mellitus induced by alloxan (DMIA) or streptozocin (DMIS), changes in the cytochrome P450 (CYP) isozymes in the liver, lung, kidney, intestine, brain, and testis have been reported based on Western blot analysis, Northern blot analysis, and various enzyme activities. Changes in phase II enzyme activities have been reported also. Hence, in this review, changes in the pharmacokinetics of drugs that were mainly conjugated and metabolized via CYPs or phase II isozymes in rats with DMIA or DMIS, as reported in various literature, have been explained. The changes in the pharmacokinetics of drugs that were mainly conjugated and mainly metabolized in the kidney, and that were excreted mainly via the kidney or bile in DMIA or DMIS rats were reviewed also. For drugs mainly metabolized via hepatic CYP isozymes, the changes in the total area under the plasma concentration–time curve from time zero to time infinity (AUC) of metabolites, $AUC_{metabolite}$/$AUC_{parent\ drug}$ ratios, or the time-averaged nonrenal and total body clearances (CL_{NR} and CL, respectively) of parent drugs as reported in the literature have been compared.

Key findings After intravenous administration of drugs that were mainly metabolized via hepatic CYP isozymes, their hepatic clearances were found to be dependent on the in-vitro hepatic intrinsic clearance (CL_{int}) for the disappearance of the parent drug (or in the formation of the metabolite), the free fractions of the drugs in the plasma, or the hepatic blood flow rate depending on their hepatic extraction ratios. The changes in the pharmacokinetics of drugs that were mainly conjugated and mainly metabolized via the kidney in DMIA or DMIS rats were dependent on the drugs. However, the biliary or renal CL values of drugs that were mainly excreted via the kidney or bile in DMIA or DMIS rats were faster.

Summary Pharmacokinetic studies of drugs in patients with type I diabetes mellitus were scarce. Moreover, similar and different results for drug pharmacokinetics were obtained between diabetic rats and patients with type I diabetes mellitus. Thus, present experimental rat data should be extrapolated carefully in humans.

Keywords alloxan; cytochrome P450 isozymes; diabetes mellitus; pharmacokinetics; streptozocin

Introduction

Animal models of insulin-dependent (type I) diabetes mellitus induced by the administration of several chemicals, principally alloxan or streptozocin, have been reported.[1,2] There are major differences between the diabetogenic effects of diabetes mellitus induced by alloxan (DMIA) and streptozocin (DMIS).[2] For example, it is known that structural alterations in pancreatic beta cells (total degranulation) occur within 48 h after the administration of streptozocin and last for up to four months. Alloxan causes a decrease in hepatic glycogen within 24–72 h, which insulin can partially reverse. Alloxan generally produces greater cytotoxicity due to its conversion to anionic radicals. Streptozocin is more commonly used because of its greater stability and relative lack of extrapancreatic toxicity.[3]

In male Sprague-Dawley DMIS rats, a return to the pre-injection bile acid levels and bile flow rates occurred on the 15th day after streptozocin administration.[4] This result

suggested that streptozocin-induced hepatotoxicity might have contributed to the results of the biliary excretion studies performed less than two weeks after streptozocin administration. Complications from any toxic effect of streptozocin were minimized by carrying out the experiments four to five weeks after the initial streptozocin injection.[4] Streptozocin has direct effects (streptozocin itself) on the pharmacokinetic parameters of drugs due to its hepatotoxicity as well as indirect effects (produced by changes in the cytochrome P450 (CYP) isozyme expression pattern).[3] Approaches have been proposed for ensuring that observed pharmacokinetic effects in DMIS rats are due to the indirect effect of streptozocin (diabetes-related changes in CYP isozyme patterns) and not streptozocin itself.[3] Considering the very short half-life of streptozocin (approximately 15 min), it is unlikely that its direct effects could be sustained for seven or twenty-nine days after administration of streptozocin. Moreover, the decreased total area under the plasma–concentration time curve from time zero to infinity AUC and faster nonrenal clearance (CL_{NR}) of intravenous metformin in DMIS rats were comparable on days seven and twenty-nine.[5] Streptozocin had no effect on the metabolism of model substrates *in vitro*, and analogues of streptozocin, devoid of diabetogenic activity, failed to influence the metabolism of various substrates.[6,7] Furthermore, insulin reversed the streptozocin-induced changes in CYP isozyme expression, and the AUC of ciclosporin in DMIS rats was comparable with that of controls after NPH insulin (isophane insulin).[8] Similar results have been reported from metformin in DMIA rats.[9] The above data suggested that the effect of streptozocin on day seven or twenty-nine occurred through its indirect, and not direct, mechanism.

Changes in the CYP isozymes in the liver, intestine, lung, and kidney of DMIA or DMIS rats based on Western or Northern blot analysis are listed in Table 1.[10–23] Changes in the CYP isozymes in the liver, lung, kidney, intestine, brain, and testis in the various enzyme activity tests and phase II enzyme activities in the liver, kidney, testis, and brain of DMIA and DMIS rats are listed in Tables 2 and 3, respectively.[7,11–15,17–19,22,24–32] In rats with diabetes mellitus, changes in the glutathione (GSH) contents, and in the glutathione S-transferase (GST) and uridine diphosphate glucuronosyltransferase (UDPGT) activity have been reviewed.[2,33] Note that there have been gender differences in enzyme activity in the liver, lung, and intestine in DMIA and DMIS rats (Table 2).[7,11,13–15,17–19,22,24–26,28] However, the changes in the CYP isozymes in patients with type I diabetes mellitus were scarce. For example, an increase in CYP2E1 in peripheral blood mononuclear cells and CYP1A2 activity in patients with type I diabetes mellitus has been reported.[34,35] It has been reported that in insulin-dependent adults with untreated type I diabetes mellitus, the antipyrine metabolism (markers of CYP1A2, 2B6, 2C, and 3A) clearly increased.[36] Approximately 3, 3, 4, 8, 11, 16, 19, and 36% of all marked drugs were metabolized via CYP2A6, 2B6, 2E1, 2C19, 1A1/2, 2C8/9, 2D6, and 3A4/5, respectively.[37]

The following results have been reported after insulin treatment of rats with diabetes mellitus. First, the hepatic CYP2C11 increased two times, CYP1A2 and 3A2 returned to the levels of the controls, CYP2B1 decreased, but CYP2B2 did not change in male Sprague-Dawley DMIA or DMIS rats.[13] Second, the increase in the hepatic CYP1A2, 1B1, 2B1, and 2E1 and the decrease in CYP2C11 were partially or completely ameliorated in male Sprague-Dawley DMIS rats.[22] Third, the activity of amidopyrine demethylase and aniline hydroxylase partially or fully returned to their levels in the control male and female Sprague-Dawley DMIS rats.[7] Fourth, the increase in the amounts of hepatic CYP2A1, 2C6, 2C7, 2E1, 3A2, 4A2, and 4A3 and the decrease in CYP2C11 returned to their levels as much as the control in male and female Sprague-Dawley DMIS rats.[17]

Diabetes mellitus can alter the pharmacokinetic processes of drugs. For example, the drug absorption from the gastrointestinal tract could be altered by a delayed gastrointestinal transit time due to hyperglycaemia in male Sprague-Dawley DMIS rats and gastroparesis in male Wistar DMIA rats.[38,39] Gastroparesis develops early in DMIS rats, and it involves a ferment with diarrhoea.[38] In DMIA or DMIS rats, the gastrointestinal absorption of furosemide was decreased, but that of chlorzoxazone, theophylline, telithromycin, clarithromycin, DA-8159, phenytoin, and metformin was not changed by alloxan or streptozocin.[5,9,21,40–45] The drug distribution could also be altered by reductions in the plasma protein-binding of drugs because of elevated plasma fatty acid levels (especially for acidic drugs) or glycosylation of plasma proteins.[46] Additionally, intracellular dehydration was observed in male Sprague-Dawley DMIS rats.[47] The time-averaged total body clearance (CL) is calculated by multiplying the terminal phase elimination rate constant (k_{last}) by apparent post-pseudodistribution volume of distribution (Vd_{area}). The CL, k_{last}, and Vd_{area} are independent parameters. Therefore, the CL and Vd_{area} have a direct relationship only when the k_{last} is not changed. The metabolism of drugs could increase if the volume of distribution of drugs in the metabolizing organs (such as liver) increased in diabetes mellitus. The drug metabolism could also be altered by changes in the CYP isozymes in the liver, intestine, lung, and kidney (Table 1), by the various enzyme activities in the tissues (Table 2), and by changes in the phase II enzyme activity in the tissues (Table 3). The hepatic plasma flow rate was significantly faster in male Wistar DMIS rats on day 14 after streptozocin administration.[48] Thus, the hepatic metabolism of a drug with a high or an intermediate hepatic extraction ratio could be increased by increasing the hepatic blood flow rate of DMIS rats or the free (unbound to plasma proteins) fractions of the drugs in the plasma.[49] The blood flow rates in the duodenum, jejunum, and ileum were also significantly faster in DMIS rats.[50] In male Sprague-Dawley DMIS rats, the cardiac index increased, and the blood flow rate to the diaphragm, abdominal wall, and small intestine increased, but that to the skin and some skeletal muscles decreased.[50] In male Carworth Farms E (CFE) DMIA or DMIS rats, the blood flow rate to the kidney, fat, and gastrointestinal tract increased.[51] The renal excretion of drugs with a timed-interval renal clearance that was dependent on the urine flow rate (the more urine is evacuated, the more drug is excreted in the urine) could increase due to the increase in the urine output of rats with diabetes mellitus.[52] The changes in urinary pH, possibly due to the ketones in uncontrolled

Table 1 Cytochrome P450 isozyme changes in various tissues from rats with induced diabetes mellitus based on Western or Northern blot analysis

CYP isozyme	Liver	Intestine	Lung	Kidney
CYP1A	↑ [a]			
CYP1A1	↑ [b,c]			
CYP1A2	↑ [d†,e,f], ↔ [d‡,g‡]			
CYP1A1/2		↑ [*]		
CYP1B1	↑ [f]			
CYP2A1	↑ [c,g†,h,i]			
CYP2A2	↓ [c,g†]			
CYP2B	↑ [a]			
CYP2B1	↑ [c,d,f]			
CYP2B2	↔ [d]			
CYP2B1/2	↑ [e]	↔ [*]		
CYP2C		↓ [*]		
CYP2C6	↑ [h], ↓ [i]			
CYP2C7	↑ [h], ↔ [j]			
CYP2C11	↓ [d,e,f,h,i], ↔ [j]			
CYP2C12	↑ [g†], ↓ [i], ↔ [g‡]			
CYP2C13	↓ [c,g†]			
CYP2D	↔ [k]	↓ [*]		
CYP2D1	↔ [j]			
CYP2D6	↑ [l], ↓ [i]		↑ [l]	↑ [l]
CYP2E	↑ [a]			
CYP2E1	↑ [b,c,e,f,g†,g‡,h,i,l,m]	↔ [*]	↑ [l]	↑ [h,l], ↓ [b]
CYP3A		↔ [*]		
CYP3A1	↑ [e], ↓ [i], ↔ [d]			
CYP3A2	↑ [g,h], ↔ [d]			
CYP3A1/2	↑ [g‡], ↔ [10]	↔ [*]		
CYP3A4	↑ [c], ↔ [b]			↔ [b]
CYP4A	↑ [a]			
CYP4A1	↑ [b,n], ↔ [h]			↑ [b], ↔ [h]
CYP4A2	↑ [c,h]			↑ [h]
CYP4A3	↑ [h]			
CYPK2				↑ [h]
CYPK4				↔ [h]

Diabetes mellitus was induced in rats by administration of alloxan (DMIA) or streptozocin (DMIS). The tissues tested were the liver, intestine, lung, and kidney. Cytochrome P450, CYP. [*]In DMIS rats at seventh day (our unpublished data). ↑, increased; ↓, decreased; ↔, not changed. [a]Western blot analysis in male and female Wistar albino DMIS rats.[15] [b]Western blot analysis (for liver and kidney) in male Wistar DMIS rats.[19] [c]Western blot analysis in male CD rats with DMIS.[18] [d]Western blot analysis (Northern blot analysis only for CYP2C11) in male Sprague-Dawley DMIA[†] and DMIS[‡] rats.[13] [e]Western and Northern blot analyses in male Sprague-Dawley DMIA and DMIS rats.[21] [f]Western blot analysis in male Sprague-Dawley DMIS rats.[22] [g]Western blot analysis in male[†] and female[‡] CD DMIS rats.[16] [h]Western blot analysis in male Sprague-Dawley DMIS rats.[17] [i]Western blot analysis in male Sprague-Dawley DMIS rats.[12] [j]Western blot analysis in male Sprague-Dawley DMIS rats.[20] [k]Western blot analysis in male Sprague-Dawley DMIS rats.[23] [l]Western and Northern blot analyses in male Sprague-Dawley DMIS rats.[10] [m]Western blot analysis in male Sprague-Dawley DMIA and DMIS rats.[11] [n]Western blot analysis in male Wistar albino DMIS rats.[14]

diabetes mellitus, could also change the urinary excretion of drugs in diabetes mellitus.[53] However, the urinary pH was not changed 35 weeks after administration of streptozocin.[54] The renal excretion of drugs could decrease in DMIS rats, however, due to an impaired kidney function.[55,56] The kidney function of DMIA rats in two studies was also impaired based on the plasma and urine chemistry data and the kidney histology.[40,57] It has been reported that 'The kidney is perhaps next in importance to the pancreas as a site of lesions in alloxan diabetes; the severest damage occurs in the convoluted tubules and appears to be generally proportional to the size of the dose'.[58] It has been reported, however, that in contrast to alloxan, streptozocin (60 mg/kg) caused no detectable renal injury in rats.[59] Additionally, a decrease in the bile flow rate, altered bile compositions, and hepatotoxicity have been reported in DMIS rats.[4,55]

It has been reported that the renal and hepatic expression of organic anion and cation transporters (Oats/Octs), multidrug resistance (MDR)-associated proteins (Mrps) and P-glycoprotein (P-gp), ABC-transporters in the liver, and P-gp in the blood–brain barrier and the liver were altered in diabetes mellitus (streptozocin-treated) rats.[60–64] Drug treatment in MDR in diabetes mellitus associated with function of ABC-transporters has been reviewed.[64] Thus the above mentioned changes could affect the pharmacokinetics of drugs in diabetes mellitus.

Many diabetic patients develop serious complications during the course of the disease, including cardiovascular disease, nephropathy, neuropathy, or retinopathy.[65] Pharmacokinetic changes of drugs in patients with diabetes mellitus have been reviewed.[65,66] The pharmacokinetic and pharmacodynamic changes in drugs in patients with diabetes

Table 2 Enzyme activity changes in various tissues from rats with induced diabetes mellitus

Enzyme activity	Liver	Lung	Kidney	Intestine	Brain	Testis
Aminopyrene N-demethylase (APD) activity	M: ↓ [a,b]		M: ↑ [b]		M: ↓ [b]	M: ↔ [b]
Amidopyrine N-demethylase activity	M: ↓ [c,d] F: ↑ [d]					
Aniline dehydroxylase activity	M: ↑ [e]					
Aniline *p*-hydroxylase (AH) activity	M: ↑ [a,b,d,f] F: ↑ [g]		M: ↑ [b]			
Aryl hydrocarbon hydroxylase (AHH) activity	M: ↓ [g,h] F: ↑ [g,h]	M: ↓ [g,h] F: ↓ [g,h]		M: ↓ [g] M: ↑ [g]		
Benzphetamine demethylase activity	M: ↓ [i]					
Biphenyl 4-hydroxylase activity	F: ↑ [d]					
Erythromycin demethylase activity	M: ↓ [i], ↑ [j]					
7-Ethoxycoumarin-O-deethylase (ECOD) activity	M: ↑ [b,f,h], ↓ [a] F: ↑ [h]	M: ↑ [h] M: ↑ [d]	M: ↑ [b]		M: ↑ [b]	M: ↔ [b]
7-Ethoxyresorufin O-deethylase (EROD) activity	M: ↑ [a,c,g,k,l] F: ↑ [g,k]	M: ↓ [g] F: ↓ [g]		M: ↑ [g] F: ↑ [g]		
Ethylmorphine N-demethylase activity	M: ↑ [j,k] F: ↔ [k]					
Lauric acid ω-hydroxylase activity	M: ↑ [b,j,k] F: ↑ [k]		M: ↑ [b]		M: ↑ [b]	
p-Nitroanisole demethylase activity	M: ↓ [i]					
N-Nitrosodimethylamine (NDMA) activity	M: ↑ [i]					
p-Nitrophenol hydroxylase activity	M: ↑ [k], ↔ [c] F: ↑ [k]					
N-Nitrosodimethylamine demethylase (NDMAD) activity	M: ↑ [m†] F: ↑ [m‡]					
7-Pentoxyresorufin O-dependentylase (PROD) activity	M: ↑ [k] F: ↑ [k]					
Testosterone 2α-hydroxylase activity	M: ↓ [f,n,o†,o‡] F: ↓ [n]					
Testosterone 2β-hydroxylase activity	M: ↑ [f,n] F: ↔ [n]					
Testosterone 6β-hydroxylase activity	M: ↑ [f], ↓ [c,o†] ↔ [n,o†] F: ↔ [n]					
Testosterone 7α-hydroxylase activity	M: ↑ [f,o‡] F: ↔ [n,o†]					
Testosterone 15α-hydroxylase activity	M: ↔ [n] F: ↔ [n]					
Testosterone 15β-hydroxylase activity	M: ↔ [n] F: ↔ [n]					
Testosterone 16α-hydroxylase activity	M: ↓ [n] F: ↓ [n]					
Testosterone 16β-hydroxylase activity	M: ↑ [f,n] F: ↑ [n]					
Testosterone 17-hydroxylase activity	M: ↔ [n] F: ↔ [n]					

Diabetes mellitus was induced in rats by administration of alloxan (DMIA) or streptozocin (DMIS). The tissues tested were liver, lung, kidney, intestine, brain, and testis. M, male rats; F, female rats; ↑, increased; ↓, decreased; ↔, not changed. [a]Wistar DMIS rats.[18] [b]Wistar DMIS rats.[19] [c]Male Sprague-Dawley DMIS rats.[28] [d]Male and female Sprague-Dawley DMIS rats.[7] [e]Sprague-Dawley DMIA rats.[27] [f]Sprague-Dawley DMIS rats.[17] [g]Male and female Sprague-Dawley DMIS rats.[24] [h]Male and female Sprague-Dawley DMIS rats.[25] [i]Sprague-Dawley DMIS rats.[12] [j]Male Wistar albino DMIS rats.[14] [k]Wistar DMIS rats.[15] [l]Male Sprague-Dawley DMIS rats.[22] [m]Male Sprague-Dawley DMIA[†] or DMIS[‡] rats.[11] [n]Male Sprague-Dawley DMIA[a] or DMIS[b] rats.[13] [o]Wistar DMIA[†] or DMIS[‡] rats.[26]

mellitus may depend on the disease types (insulin-dependent or noninsulin-dependent diabetes mellitus), whether the disease is controlled, the severity and duration of the disease, the severity of the impairment of the liver and kidney functions, and the coadministration of other drugs.[65,66]

In this study, the AUC or AUC_{0-t} (area under the curve up to the last measured time, t, in the plasma) of metabolites were compared after the intravenous or oral administration of drugs to DMIA or DMIS rats, with known CYP isozyme/metabolite pairs, with respect to changes in their hepatic (and intestinal) CYP isozymes. The $AUC_{metabolite}/AUC_{parent\ drug}$ ratio was also compared. Otherwise, the AUC (or AUC_{0-t}), CL, and CL_{NR} of parent drug were also compared, although these changes were not always correlated with CYP isozyme

Table 3 Phase II enzyme changes in various tissues from rats with induced diabetes mellitus

	Liver	Kidney	Testis	Brain
Cytosolic or microsomal glutathione S-transferase (GST) activity	↓ [a,b,c]			
Most forms of cytosolic or microsomal uridine diphosphate glucuronosyltransferase (UDPGT) activity	↓ [b]			
Cytosolic GST activity	↑ [d]	↓ [a,c,e]		
Glutathione (GSH) contents and GST activity	↓ [d,f]	↓ (GST)[f] ↑ (GSH) [f]	↔ [f]	↑ [d]
GSTα	↑ [d]			
GSTμ	↓ [d]			
GSTπ	↑ [d,f]			

Diabetes mellitus was induced in rats by administration of alloxan (DMIA) or streptozocin (DMIS). The tissues tested were liver, kidney, testis, and brain. ↑, increased; ↓, decreased; ↔, not changed. [a]Male albino DMIA rats.[30] [b]Male albino DMIA rats.[29] [c]Male albino DMIA rats.[32] [d]Male CD DMIS rats.[18] [e]Male albino DMIA rats.[31] [f]Male Wistar DMIS rats.[19]

changes. The pharmacokinetic changes of drugs were also measured even when their metabolism would have been relatively unaffected by changes in the hepatic CYP isozymes, such as with respect to drugs primarily metabolized in the kidney via renal dehydropeptidase-I (DHP-I), or drugs mainly excreted via the kidney.[67–69] It was predicted that a drug which is hardly excreted in the urine and that has a significant hepatic CYP metabolism would be influenced by the hepatic CYP isozyme changes in a drug with a low or an intermediate hepatic extraction ratio. A drug with a significant timed-interval renal clearance would be greatly influenced by urine output and an impaired kidney function.[52,55–57] As mentioned above, changes in CYP isozymes in the liver, intestine, and other tissues (Tables 1 and 2) and in the activity of GST and UDPGT (Table 3) have been extensively studied in DMIA and DMIS rats. Thus, in this study, only the pharmacokinetic and pharmacodynamic changes in drugs in DMIA and DMIS rats have been reviewed. The changes of drugs in patients with type I diabetes mellitus were reviewed if these changes were reported in rats with diabetes mellitus.

The human and rat CYP isozymes showed homology, and similar functions, target drugs, and regulations as reviewed.[70–73]

Group A. Drugs that are Mainly Metabolized

Drugs that are mainly metabolized via hepatic CYP isozymes

In rats, diabetes mellitus induces changes in CYP isozymes in the liver (Tables 1 and 2) that are related to changes in the in-vitro hepatic intrinsic clearance (CL_{int}: the maximum velocity (V_{max}) divided by the apparent Michaelis–Menten constant (K_m)) for the disappearance of the drugs. For a drug with a low hepatic extraction ratio (<30%), its hepatic clearance (when the CL_{NR} of the drug could have represented its hepatic metabolic clearance) depends more on the hepatic CL_{int} (the hepatic CYP isozyme changes) than on the hepatic blood flow rate.[49] Changes in the free (unbound to plasma proteins) fractions of a drug in the plasma could also affect the hepatic CL_{int} of a drug with a low hepatic extraction ratio, if the protein binding value of the drug in the control rat is extensive (thus, the free fractions of a drug in diabetes mellitus rats is considerably greater compared with that in the controls). Hence, the hepatic CL_{int} changes influence the hepatic (metabolic) clearance changes of a drug with a low hepatic extraction ratio. For a drug with an intermediate hepatic extraction ratio (30–70%), its hepatic clearance depends on the hepatic blood flow rate, the free fractions of the drug in the plasma, and the hepatic CL_{int} of the drug.[43] For a drug with a high hepatic extraction ratio (>70%), its hepatic clearance depends more on the hepatic blood flow rate and the free fractions of the drug in the plasma than on the hepatic CL_{int}.[43] Thus, changes in hepatic CYP isozymes would have the most profound influence on drug targets with a low or an intermediate extraction ratio. The hepatic extraction ratio (the hepatic first-pass effect) of a drug was 'directly' measured by comparing the AUC values following the intravenous and intraportal administration of a drug. Otherwise, the ratios were 'indirectly' estimated by dividing the CL_{NR} of a drug after its intravenous administration by the hepatic plasma flow rate.[74] The hepatic plasma flow rate was estimated by multiplying the hepatic blood flow rate of 55.2 ml/min per kg by the (1 – haematocrit), in which the haematocrit in rats was approximately 0.45 (45%).[75,76] Thus, this 'indirect' estimate represented the maximum ability to metabolize a drug in the liver.[74] Note that just because a drug is mainly metabolized in the liver does not always mean that it has an intermediate or a high hepatic extraction ratio. For example, theophylline and antipyrine are almost completely metabolized in the liver, but are classified as drugs with low hepatic extraction ratios. After the intravenous administration of 8 mg/kg methotrexate, which was not metabolized via hepatic CYP isozymes, to male Sprague-Dawley DMIS rats on the seventh day after administration of alloxan, the values for AUC and CL_{NR} of methotrexate became comparable with those of the controls.[55,77] The hepatic CYP enzymes involved in the metabolism of each drug and the corresponding pharmacokinetic and pharmacodynamic observations of each drug in this category have been listed in Table 4.

Amidopyrine

In rats, it was noted from the breath test, which is a well established quantitative and sensitive test of the microsomal liver function, that amidopyrine (aminopyrine) was mainly

Table 4 Drugs mainly metabolized via hepatic cytochrome P450 isozymes and corresponding pharmacokinetic and pharmacodynamic observations in rats with induced diabetes mellitus and patients with type I diabetes mellitus

No.	Drug	CYP isozyme	Pharmacokinetic observations
1	Amidopyrine	CYP1A1/2, 2B1/2, 2C6/11, and 3A subfamily to form desmethylaminopyrine in rats	Significantly faster and slower intraperitoneal CL values of amidopyrine in female DMIS rats and male DMIA and DMIS rats, respectively[81,82,84]
2	Chlorzoxazone (CZX)	CYP2E1 to form 6-OHCZX in rats and humans	Greater intravenous and oral $AUC_{6\text{-}OHCZX}/AUC_{CZX}$ ratios in DMIA and DMIS rats[41] Comparable oral AUC value of 6-OHCZX in DMIA rats[27] Significantly smaller oral AUC value of chlorzoxazone in male DMIA and DMIS rats[41] and in patients with type I diabetes mellitus[34,41]
3	Theophylline	CYP1A1 and 1A2 (less via CYP3A1 and 3A2) in rats, and CYP1A2, 2E1, and 3A4 in humans to form 1,3-DMU	Greater intravenous and oral $AUC_{1,3\text{-}DMU}/AUC_{theophylline}$ ratios in DMIA and DMIS rats[21] In patients with type I diabetes mellitus, the pharmacokinetic parameters of intravenous theophylline were comparable with controls[96] Significantly faster oral CL of theophylline in poorly controlled type I diabetes mellitus patients[97]
4	Lidocaine	CYP3A2 or 2B1 to form MEGX in rats	Significantly greater intravenous AUC value of MEGX in DMIS rats[99]
5	Oxycodone	CYP3A1/2 to form noroxycodone in rats	Greater subcutaneous $AUC_{noroxycodone}/AUC_{oxycodone}$ ratio in DMIS rats[100]
6	Telithromycin	CYP3A1/2 in rats	Significantly faster intravenous CL_{NR} values of telithromycin in DMIA and DMIS rats[42]
7	Clarithromycin	CYP3A1 in rats	Significantly faster (smaller) intravenous CL_{NR} values (AUCs) of clarithromycin in DMIA and DMIS rats[43]
8	Furosemide	CYP2C11, 2E1, 3A1, and 3A2 in rats	Comparable intravenous CL_{NR} value of furosemide in DMIA rats[40] Significantly smaller 8-h urine output after intravenous administration to DMIA rats[40]
9	Torasemide	CYP2C11 in rats	Significantly slower and comparable intravenous CL_{NR} values of torasemide in DMIA and DMIS rats, respectively[111] Significantly larger 8-h urine output after the intravenous administration to DMIA and DMIS rats[111]
10	Azosemide	CYP1A1/2 in rats	Comparable intravenous CL_{NR} of azosemide in DMIA rats[116] Comparable 8-h urine output after intravenous administration to DMIA rats[116]
11	Omeprazole	CYP1A1/2, 2D1, and 3A1/2 in rats	Significantly faster intravenous CL_{NR} values of omeprazole in DMIA and DMIS rats[121]
12	Oltipraz	CYP1A1/2, 2B1/2, 2C11, 3A1/2, and 2D1 in rats	Significantly faster (smaller) intravenous CL values (AUCs) of oltipraz in DMIA and DMIS rats[23,126]
13	DA-8159	CYP3A1/2 in rats	Comparable intravenous CL_{NR} of DA-8159 in DMIS rats[44]
14	Ipriflavone	CYP1A1/2 and 2C11 in rats	Significantly faster intravenous CL_{NR} of ipriflavone in DMIS rats[132]
15	Phenytoin	CYP2C6 (less via 2C11) to form 4′-HPPH in rats, and CYP2C9 in humans	Comparable intravenous AUC and oral $AUC_{0-12\ h}$ values of phenytoin and 4′-HPPH in DMIA and DMIS rats[45] Significantly lower steady-state plasma concentrations of phenytoin after 200 and 300 mg/day to patients with type I diabetes mellitus[138]
16	Diclofenac	CYP2C11 in rats	Significantly slower intravenous CL_{NR} values of diclofenac in DMIA and DMIS rats[140]
17	Digoxin	CYP3A subfamily in rats	Significantly faster intravenous CL and biliary clearance values of digoxin in DMIS rats[4]
18	Propofol	CYP2B1 and 2C11 in rats	Comparable intravenous CL and AUC values of propofol in DMIS rats[147] Significantly lower dose (or less infusion time) was required to reach the same pharmadynamical effect after the intravenous administration to DMIS rats[147]
19	Doxorubicin	CYP2B1/2 and 3A1/2 to form both M3 and M4 from doxorubicin and doxorubicinol, respectively, in rats	Comparable intravenous $AUC_{0-12\ h}$ of doxorubicin in DMIS rats[153]
20	Ciclosporin	CYP3A1/2 in rats	Significantly smaller, unchanged, and significantly greater intravenous AUC values of ciclosporin in DMIS rats[8,157,158]
21	Fluorouracil	CYP1A1/2 in rats	Significantly faster intravenous CL_{NR} of fluorouracil in DMIS rats[159]
22	DA-125	CYP1A1/2 and 2B1/2 to form M3 and CYP2B1/2 to form M4 from M1 and M2, respectively, in rats	Significantly smaller intravenous $AUC_{0-90\ min}$ of M4 in DMIA rats[162]
23	Itraconazole	CYP3A1/2 in rats	Comparable values for intravenous and oral $AUC_{0-24\ h}$ of both itraconazole and hydroxyitraconazole in DMIS rats (our unpublished data)

(Continued)

Table 4 *(Continued)*

No.	Drug	CYP isozyme	Pharmacokinetic observations
24	Metformin	CYP2C11, 2D1, and 3A1/2 in rats	Significantly slower intravenous CL_{NR} values of metformin in short-term and long-term DMIS and DMIA rats[5,9]
25	Mirodenafil	CYP1A1/2, 2B1/2, 2D subfamily, and 3A1/2 in rats	Faster intravenous CL_{NR} of mirodenafil in DMIS rats (our unpublished data).
26	Diazepam	CYP3A subfamily in rats	Slower intravenous CL of total radioactivity in DMIS rats[173]
27	Hexobarbital	CYP2C6 and 2C11 in female rats	Significantly longer sleeping time after the intravenous administration to DMIS rats[6]
28	Nelfinavir	No data available in rats	Significantly faster and slower CL values of nelfinavir based on total and unbound fractions, respectively, in DMIS rats[176]
29	Hydroxychloroquine	No data available in rats	Significantly faster intravenous CL_{NR} values of *R*- and *S*-hydroxychloroquine in DMIS rats[177]
30	YJA 20379-8	No data available in rats	Significantly slower intravenous CL of YJA 20379-8 in DMIS rats[178]
31	Losartan	No data available in rats	Comparable intravenous CL_{NR} values of losartan and EXP3174[179]
32	Insulin	Various tissues in rats	Significantly faster intravenous CL of insulin in DMIS rats[180]

Diabetes mellitus was induced in rats by administration of alloxan (DMIA) or streptozocin (DMIS). CYP, cytochrome P450; MEGX, monoethylglycinexylidide; 1,3-DMU, 1,3-dimethyluric acid; 4′-HPPH, (*S*)-5-(4-hydroxyphenyl)-5-phenylhydantoin. For DA-125: M1, active compound of DA-125; M2, alcohol resulting from M1 being reduced; M3 and M4, aglycones resulting from when M2 is reduced further. For doxorubicin: M3 and M4 are the deglycosylated aglycones of doxorubicin and doxorubicinol, respectively. AUC, area under the curve; CL, total body clearance; CL_{int}, hepatic intrinsic clearance; CL_{NR}, nonrenal clearance.

metabolized via hepatic CYP2B1/2 to form desmethylaminopyrine.[78] Desmethylaminopyrine was further metabolized to form formic acid and CO_2. In male and female Sprague-Dawley rats, the hepatic CYP1A1/2, 2C6/11, and 3A subfamily also mediated in the formation of desmethylaminopyrine.[79] In Sprague-Dawley rats, gender-different hepatic extraction ratios of amidopyrine have been reported.[80] For example, in male Sprague-Dawley rats, amidopyrine was a drug with a high hepatic extraction ratio, with values of 81 ± 16 and 78 ± 6% found in in-vivo and liver perfusion studies, respectively. Thus, the contribution of hepatic CYP isozyme (CL_{int}) changes to the CL value of amidopyrine did not seem to be considerable in male rats. After the intraperitoneal administration of 50 mg/kg amidopyrine to male Wistar DMIA rats on the third day after the administration of alloxan and to male Wistar DMIS rats on the seventh day after the administration of streptozocin, the CL values of amidopyrine became significantly slower (by 55.7 and 50.8%, respectively) than those of the controls.[81] Similar results were reported from other studies; after the intraperitoneal administration of 100 mg/kg amidopyrine to male Fischer DMIA rats on the fourth day and to male Fischer DMIS rats on the second day, the CL values of amidopyrine became significantly slower (by 23.5 and 24.4%, respectively) than those of the controls.[82] The exact reason for this was not clear. This was because the hepatic blood flow rate was rather faster in DMIS rats, and plasma protein binding of amidopyrine was small (not measured). The plasma protein binding of amidopyrine in humans was approximately 15%.[48,83]

On the other hand, in female Sprague-Dawley rats, amidopyrine is a drug with an intermediate hepatic extraction ratio of 41 ± 6 and 41 ± 8% in in-vivo and liver perfusion studies, respectively.[80] The protein expression and mRNA levels of the hepatic CYP1A1 and 2B1 increased in female Wistar albino DMIS rats, but in female CD DMIS rats, CYP3A1/2 increased and CYP2C11 was not detected.[15] After the intraperitoneal injection of 40 μCi/kg [^{14}C] amidopyrine (0.7 mg/kg) to female Sprague-Dawley DMIS rats on the 10th day, the CL value of amidopyrine became significantly faster (by 129%) than that of the controls.[84] Although the protein expression and mRNA levels of hepatic CYP1A1, 2B1, and 3A1/2 increased in the female rats, as mentioned above, the hepatic V_{max} and K_m values of the controls and the DMIS rats became comparable.[84] The significantly faster CL value of amidopyrine could have at least been partly due to the faster hepatic blood flow rate of the diabetes mellitus rats.[48] The free fractions of amidopyrine were not measured. Note that the CL value of amidopyrine in the DMIS rats was restored to that of the controls via insulin treatment.[84]

Gender-different CO_2 formation in DMIS rats has also been reported. For example, after the intravenous administration of 40 μCi/kg [^{14}C]amidopyrine to male and female Sprague-Dawley DMIS rats on the 10th day, the AUC values of CO_2-exhalation decreased in the male rats, but increased in female rats.[80] After the intravenous administration of 1 μCi/kg [^{14}C]amidopyrine to male and female Sprague-Dawley DMIS rats on the 10th day, the CO_2 elimination rate constants showed a strong gender-dependency, but the CO_2 elimination rate constants of the male controls were significantly faster (by 66.7%) than those of the females.[80] Note that CO_2 is formed from desmethylaminopyrine. Hence, the increase in the formation of CO_2 was not always correlated to the hepatic CYP isozymes in the metabolism of amidopyrine.

Chlorzoxazone

Chlorzoxazone, once used as a skeletal muscle relaxant for the treatment of painful muscle spasms, primarily undergoes hydroxylation to form 6-hydroxychlorzoxazone (6-OHCZX), which is mainly catalysed by hepatic CYP2E1 in humans and rats.[85–91] 6-OHCZX has been used as a chemical probe to assess the activity of hepatic CYP2E1 *in vitro* and *in vivo* due to the good correlation between the formation rate of

6-OHCZX and CYP2E1 activity in humans and rats.[87,92] The protein expression and mRNA level of hepatic CYP2E1 increased in male DMIA and DMIS rats[10–12,16–19,21,22] (Table 1), which should increase 6-OHCZX formation. In fact, after the intravenous administration of 20 mg/kg chlorzoxazone to male Sprague-Dawley DMIA rats on the fourth day and to male Sprague-Dawley DMIS rats on the seventh day, their $AUC_{6\text{-}OHCZX}/AUC_{CZX}$ ratios became significantly greater (by 204 and 225%, respectively) than those of the controls.[41] This was supported by a significantly faster (by 75.9 and 129% in DMIA and DMIS rats, respectively) in-vitro hepatic CL_{int} value for the formation of 6-OHCZX.[41] The pharmacokinetic parameters of 6-OHCZX were comparable (not significantly different) between DMIA and DMIS rats.[41]

After the oral administration of 50 mg/kg chlorzoxazone to both DMIA and DMIS rats, their $AUC_{6\text{-}OHCZX}/AUC_{CZX}$ ratios also became greater (by 180 and 172%, respectively) than those of the controls.[41] The 180 and 172% increase were smaller than the 204 and 225% increase, respectively, after intravenous administration.[41] This suggested that the formation of 6-OHCZX in the intestine did not seem to be considerable in DMIA and DMIS rats, possibly due to the unaltered expression of intestinal CYP2E1 in the male DMIS rats and the controls (Table 1). The greater AUC values of 6-OHCZX, however, after the oral administration of chlorzoxazone to the DMIA and DMIS rats were unlikely to have been due to the increase in the gastrointestinal absorption of chlorzoxazone, as more than 97% of the oral dose of chlorzoxazone was absorbed for up to 24 h by all the groups of rats using the reported equation.[41,74] The pharmacokinetic parameters of 6-OHCZX were comparable also between the DMIA and DMIS rats. Different results have been reported, however, in other studies.[27] Although the exact reason for this is unclear, the AUC value of 6-OHCZX was comparable with that of the controls after the oral administration of 50 mg/kg chlorzoxazone to male Sprague-Dawley DMIA rats on the seventh day.[27]

After the oral administration of 50 mg/kg chlorzoxazone, the AUC values of chlorzoxazone became significantly smaller (by 44.5 and 37.2%, respectively) in the DMIA and DMIS rats compared with that of the controls.[41] Similar results have been reported in type I diabetes mellitus patients; after the oral administration of 500 mg chlorzoxazone, the AUC value of chlorzoxazone was reduced by 25% compared with controls.[34] This was supported by the increase in the mRNA level of CYP2E1 in peripheral blood mononuclear cells in patients with type I diabetes mellitus compared with that of the controls.[34]

Theophylline

Based on human liver microsomes, CYP1A2 was the major catalyst of the formation of 1,3-dimethyluric acid (1,3-DMU) from theophylline, a bronchodilator, with the contribution of CYP2E1 and, possibly, CYP3A4.[93] In male Sprague-Dawley rats, the formation of 1,3-DMU was primarily mediated via hepatic CYP1A1 and 1A2 and less via CYP3A1 and 3A2 (not via CYP2B1/2, 2C11, 2D1, and CYP2E1).[94,95] The protein expression and mRNA levels of hepatic CYP1A1, 1A2, 3A1, and 3A2 increased in male DMIA and DMIS rats (Table 1), which should have increased the formation of 1,3-DMU.[13,16–19,21,22] In fact, after the intravenous administration of 5 mg/kg theophylline to male Sprague-Dawley DMIA rats on the fourth day and DMIS rats on the seventh day, their $AUC_{1,3\text{-}DMU}/AUC_{theophylline}$ ratios became greater (by 184 and 111%, respectively) than those of the controls.[21] This was supported by the significantly faster in-vitro hepatic CL_{int} value for the formation of 1,3-DMU (by 110 and 30.7% for DMIA and DMIS rats, respectively).[21] Although the exact reason for this was not clear, different results have been reported in patients with type I diabetes mellitus; after the intravenous administration of 5 mg/kg theophylline, the pharmacokinetic parameters of theophylline were comparable with controls.[96] The CYP1A2 activity increased in patients with type I diabetes mellitus.[35] The pharmacokinetic parameters of 1,3-DMU in DMIA and DMIS rats were comparable.[21]

After the oral administration of 5 mg/kg theophylline to DMIA and DMIS rats, their $AUC_{1,3\text{-}DMU}/AUC_{theophylline}$ ratios also became greater (by 85.2 and 72.8%, respectively) than those of the controls.[21] The greater AUC values of 1,3-DMU, however, were not likely due to the increase in the gastrointestinal absorption of theophylline compared with that of the controls, since theophylline was almost completely absorbed in the controls. The pharmacokinetic parameters of 1,3-DMU in both DMIA and DMIS rats were comparable.[21]

After the oral administration of 5 mg/kg theophylline to DMIA and DMIS rats, the AUC values of theophylline became significantly smaller (by 21.5 and 24.7%, respectively) than those of the controls.[21] Similar results have also been reported in patients with type I diabetes mellitus.[97] After the oral administration of 200 mg theophylline to patients with poorly controlled type I diabetes mellitus, the CL ($dose_{oral}/AUC_{oral}$) of the patients became significantly faster (by 144%) than that of the controls.[97]

Lidocaine

In male Sprague-Dawley rats, the formation of monoethylglycinexylidide (MEGX) from lidocaine, a widely used anaesthetic and antiarrhythmic drug, depends on the levels of hepatic CYP3A2 or 2B1.[98] The protein expression of hepatic CYP3A2 and 2B1 increased in male DMIS rats (Table 1), which should increase the formation of MEGX.[13,16–18,22] In fact, after the intravenous administration of 5 mg/kg lidocaine to male Wistar DMIS rats on the 10th day, the AUC values of lidocaine and MEGX became significantly smaller (by 48%) and greater (by 94.8%), respectively, than that of the controls.[99]

Oxycodone

In male Sprague-Dawley rats, the formation of noroxicodone from oxycodone, an opioid analgesic, was mediated via hepatic CYP3A1/2.[100] The protein expression and mRNA levels of hepatic CYP3A1, 3A2, and 3A1/2 increased in male DMIS rats (Table 1), which should have increased the AUC ratio of noroxycodone to oxycodone.[16,17,21] In fact, after the subcutaneous administration of 2 mg/kg oxycodone to male

Sprague-Dawley DMIS rats on the 22nd day, the ratio became greater (by 122%) than that of the controls.[100]

Telithromycin

In male Sprague-Dawley rats, hepatic CYP3A1/2 was involved in the metabolism of telithromycin, a ketolide antibiotic.[101] After the intravenous administration of 50 mg/kg telithromycin to male Sprague-Dawley DMIA rats on the fourth day and to male Sprague-Dawley DMIS rats on the seventh day, the values of CL_{NR} (which could have represented metabolic clearance of telithromycin) became significantly faster (by 32.3 and 53.1%, respectively) and the AUC values became significantly smaller (by 25.0 and 33.8%, respectively) than those of the controls.[42,102] This was supported by the significantly faster hepatic CL_{int} for the disappearance of telithromycin (by 22.2 and 20.2% in the DMIA and DMIS rats, respectively) than that of the controls.[42] Telithromycin is a drug with a low hepatic extraction ratio in rats (its 'direct' hepatic first-pass effect was found to be almost negligible).[102] The faster hepatic CL_{int} could have been due to the increase in the protein expression or mRNA levels of CYP3A1, 3A2, and 3A1/2 in the male DMIA and DMIS rats (Table 1).[16,17,21] The pharmacokinetic parameters of telithromycin in the DMIA and DMIS rats were comparable.[42]

Clarithromycin

In male Sprague-Dawley rats, clarithromycin, a macrolide antibiotic, was metabolized via hepatic CYP3A1.[103,104] Although the protein expression and mRNA level of CYP3A1 increased in DMIA and DMIS rats (Table 1), the contribution of this factor to the CL_{NR} of clarithromycin seemed to have been almost negligible.[21] This was because clarithromycin is a drug with a high hepatic extraction ratio in rats (its 'indirect' hepatic first-pass effect was found to be 87.3–104%).[43] After the intravenous administration of 20 mg/kg clarithromycin to male Sprague-Dawley DMIA rats on the fourth day and DMIS rats on the seventh day, their CL_{NR} values became significantly faster (by 43.8 and 34.0%, respectively) and their AUC values became significantly smaller (by 26.1 and 24.5%, respectively) than those of the controls.[43] This was due to the faster hepatic blood flow rate of DMIS rats and the greater (by 19.7%) free fractions of clarithromycin in the plasma of DMIS rats.[43,48] The CL_{NR} of clarithromycin in the DMIS rats became significantly slower (by 21.6%) than that in the DMIA rats.[43] Although the exact reason for this was unclear, this could have been due to the differences in the diabetogenic effects of alloxan (DMIA) and streptozocin (DMIS).[2]

Furosemide

In male Sprague-Dawley rats, 4-chloro-5-sulfamoyl anthranilic acid and the glucuronides of both furosemide and 4-chloro-5-sulfamoyl anthranilic acid were formed from furosemide, a loop diuretic.[105] In humans, however, only furosemide glucuronide was formed; the formation of 4-chloro-5-sulfamoyl anthranilic acid was an artefact due to the acid treatment for the sample preparation.[106] In male Sprague-Dawley rats, furosemide was primarily metabolized via hepatic CYP2C11, 2E1, 3A1, and 3A2 (not CYP1A1/2, 2B1/2, 2C6, and 2D).[107] After the intravenous administration of 6 mg furosemide to male Sprague-Dawley DMIA rats on the fourth day, the CL_{NR} of furosemide (which could have represented its metabolic clearance) was comparable with that of the controls.[40] This could have been due to the opposite results of the hepatic CYP isozymes; the protein expression and mRNA levels of hepatic CYP2C11 decreased, but that of 2E1, 3A1, and 3A2 increased, in DMIA rats (Table 1).[10–13,16–18,,21,22] Although the plasma protein-binding value of furosemide in the controls was extensive, the value was comparable with DMIA rats.[40] This was because furosemide is a drug with a low hepatic extraction ratio in rats (its 'direct' hepatic first-pass effect was found to be 11.7%).[108] The metabolism of furosemide in the controls and in the DMIA rats after its incubation in the 9000*g* (S9) supernatant fraction of the liver were comparable.[40]

After the intravenous administration of furosemide to DMIA rats, their 8-h urine output became significantly smaller (by 59.2%) than that of the controls, due to the significantly smaller 8-h urinary excretion of unchanged furosemide (by 39.3%) as a consequence of impaired kidney function in the DMIA rats.[40,57]

Torasemide

In male Sprague-Dawley rats, torasemide, a loop diuretic, was primarily metabolized via hepatic CYP2C11 (not via CYP1A1/2, 2B1/2, and 2E1).[109,110] After the intravenous administration of 2 mg/kg torasemide to male Sprague-Dawley DMIA rats on the fourth day, the CL_{NR} (which could have represented their metabolic clearance) became significantly slower (by 27.2%) than that of the controls.[111] This could have been at least partly due to the significantly smaller free fractions of torasemide in the plasma from DMIA rats (3.56 vs 9.57%).[111] The hepatic CL_{int} for the disappearance of torasemide was not measured because torasemide is a drug with a low hepatic extraction ratio in rats (its 'direct' hepatic first-pass effect was found to be 3–4%).[111,112] However, the CL_{NR} values of torasemide in the controls and the DMIS rats on the seventh day were comparable.[111]

After the intravenous administration of 2 mg/kg torasemide to DMIA and DMIS rats, their 8-h urine outputs became significantly larger (by 41.2 and 69.9%, respectively) than those of the controls.[111] This was due to the greater 8-h urinary excretion of torasemide by the DMIA and DMIS rats (by 196 and 191%, respectively) because of the urine flow rate-dependent timed-interval renal clearance of torasemide in rats.[111]

Azosemide

In the urine and bile of male Wistar rats, 11 metabolites of azosemide, a loop diuretic, including 5-(2-amino-4-chloro-5-sulfamoylphenyl)-tetrazole (M1) and the glucuronides of both azosemide and M1, were found.[113] In humans, however, only azosemide glucuronide was excreted in urine and bile.[114] In male Sprague-Dawley rats, azosemide was metabolized via hepatic CYP1A1/2 (not via CYP2B1/2 and 2E1).[115] After the intravenous administration of 10 mg/kg azosemide to DMIA rats on the fourth day, the CL_{NR} of

azosemide became comparable with that of the controls.[116] This could possibly have been due to the increase in the free fractions of azosemide in the plasma of the DMIA rats (not measured), since the protein expression and mRNA level of hepatic CYP1A1, and 1A2 increased in the DMIA rats (Table 1).[13,18,19,21,22] This was because azosemide is a drug with a low hepatic extraction ratio in rats (its 'direct' hepatic first-pass effect was found to be 20%).[117]

After the intravenous administration of 10 mg/kg azosemide to male Sprague-Dawley DMIA rats, their 8-h urine output became comparable with that of the controls, due to the comparable 8-h urinary excretion of azosemide.[116] The pharmacokinetics and pharmacodynamics of azosemide in humans and animals have been reviewed.[118]

Omeprazole

In male Sprague-Dawley rats, omeprazole, a histamine H_2-receptor antagonist, was metabolized via hepatic CYP1A1/2, 2D1, and 3A1/2 (not via CYP2B1/2, 2C11 or 2E1).[119] After the intravenous administration of 20 mg/kg omeprazole to DMIA rats on the fourth day and DMIS rats on the seventh day, their CL_{NR} values (which could have represented their hepatic metabolic clearance in rats) became significantly faster (by 27.1 and 34.8%, respectively) than those of the controls.[119–121] This was due to the significantly faster hepatic CL_{int} for the disappearance of omeprazole (by 30.3 and 23.5% for the DMIA and DMIS rats, respectively), the significantly greater (by 141%) free fractions in the plasma of the DMIA rats, and the faster hepatic blood flow rate of the DMIS rats.[48] This was because omeprazole is a drug with an intermediate hepatic extraction ratio in rats (its 'direct' hepatic first-pass effect was found to be 59%).[119] The faster hepatic CL_{int} could have been due to the increase in the protein expression or mRNA levels of CYP1A1, 1A2, 3A1, 3A2, and 3A1/2 in the DMIA and DMIS rats (Table 1).[13,16–19,21,22]

Oltipraz

In male Sprague-Dawley rats, oltipraz, a new liver antifibrotic agent, was metabolized via hepatic CYP1A1/2, 2B1/2, 2C11, 3A1/2, and 2D1 (not via CYP2E1).[122] Thirteen metabolites of oltipraz were formed in rats.[123] After the intravenous administration of 10 mg/kg oltipraz to DMIS rats on the seventh day, their CL (the renal excretion of oltipraz was almost negligible, thus, the CL could have represented its hepatic metabolic clearance in rats) and AUC became significantly faster (by 60.0%) and smaller (by 36.9%), respectively, than those of the controls.[23,124] This was due to the significantly faster hepatic CL_{int} for the disappearance of oltipraz (by 35.9%) and the faster hepatic blood flow rate of DMIS rats, since their plasma protein-binding value was comparable with that of the controls.[23,48] This was because oltipraz is a drug with an intermediate hepatic extraction ratio in rats (its 'direct' hepatic extraction ratio was found to be 40%).[125] The faster hepatic CL_{int} could have been due to the increase in the protein expression or mRNA levels of CYP1A1, 1A2, 2B1,[22] 3A1, and 3A2 in DMIS rats (Table 1).[13,16–19,21,22] Similar results have been reported in DMIA and DMIS rats.[126] Based on the hepatoprotective effect of oltipraz in liver cirrhotic rats induced by *N*-dimethylnitrosamine, oltipraz is being evaluated in a phase II clinical study in South Korea to assess its effectiveness and safety in patients with liver fibrosis and cirrhosis caused by types B and C chronic hepatitis.[127,128]

DA-8159

In male Sprague-Dawley rats, DA-8159, an inhibitor of phosphodiesterase 5 (PDE5), was metabolized via hepatic CYP3A1/2 (not via CYP1A1/2, 2B1/2, or 2E1).[129] After the intravenous administration of 30 mg/kg DA-8159 to male Sprague-Dawley DMIS rats on the seventh day, their CL_{NR} became comparable with that of the controls.[44] This was supported by the comparable values of the hepatic CL_{int} for the disappearance of DA-8159 and the comparable plasma protein-binding values of the controls and the DMIS rats.[44] This was because DA-8159 is a drug with a low hepatic extraction ratio in rats (its 'direct' hepatic first-pass effect was found to be 23%).[130] DA-8159 (udenafil) is marketed in South Korea as an oral treatment for male erectile dysfunction under the brand name of Zydena.

Ipriflavone

In male Sprague-Dawley rats, ipriflavone, an agent for osteoporosis, was metabolized via hepatic CYP1A1/2 and 2C11 (not via CYP2D1, 2B1/2, 2E1, or 3A1/2).[131] After the intravenous administration of 20 mg/kg ipriflavone to male Sprague-Dawley DMIS rats on the seventh day, their CL_{NR} (which could have represented their metabolic clearance) became significantly faster (by 64.5%) than that of the controls.[131,132] This was supported by the significantly faster hepatic CL_{int} (by 25.5%) and the faster hepatic blood flow rate of DMIS rats, since the protein-binding values of the two groups of rats were not significantly different.[48,132] This was because ipriflavone is a drug with a low hepatic extraction ratio drug in rats (its 'direct' hepatic first-pass effect was found to be 29.4%).[133] The faster hepatic CL_{int} could have been due to the increase in the protein expression or mRNA levels of hepatic CYP1A1 and 1A2 in DMIS rats (Table 1).[13,18,19,21,22]

Phenytoin

In humans, phenytoin (diphenylhydantoin), an anticonvulsant, was mainly metabolized to (*S*)-5-(4-hydroxyphenyl)-5-phenylhydantoin (4′-HPPH) via hepatic CYP2C9.[134] Studies on liver microsomes of male Wistar rats have shown that phenytoin was mainly metabolized via CYP2D6 and less via CYP2C11 (not via CYP1A1/2, 2A1, 2E1, or 3A1/2) to form 4′-HPPH (a main metabolite of phenytoin).[135] In male Sprague-Dawley rats, 4′-HPPH was primarily formed via CYP2C6 and 2C11.[45] After the intravenous administration of 25 mg/kg phenytoin to male Sprague-Dawley DMIA rats on the fourth day and to male DMIS rats on the seventh day, the AUC values of phenytoin and 4′-HPPH became comparable with those of the controls.[45] This could possibly have been due to the slower hepatic CL_{int} (not measured) because of decrease in the protein expression or mRNA level of CYP2C11 (Table 1), since the protein expression of CYP2C6 increased (Table 1) and the hepatic blood flow rate became faster in DMIA and DMIS rats, but the free fractions of phenytoin in the plasma

of the DMIA and DMIS rats and the controls became comparable.[12,13,17,21,22,45,48] This was because phenytoin is a drug with an intermediate hepatic extraction ratio in rats (its hepatic extraction ratio in the isolated perfused rat liver was 53%).[136]

After the oral administration of 25 mg/kg phenytoin to DMIA and DMIS rats, the values of $AUC_{0-12\ h}$ of phenytoin and 4′-HPPH became comparable with those of the controls.[45] However, different results were obtained from patients with type I diabetes.[137,138] After a single oral administration of 300 mg phenytoin to undernourished male patients with poorly controlled type I diabetes mellitus, their phenytoin plasma concentrations became significantly lower than those of the controls.[137] After the oral administration of phenytoin at doses of 200 and 300 mg per day to patients with type I diabetes mellitus ($n = 10$), the steady state concentrations of phenytoin were significantly lower than those of controls.[138] This could have been due to the significant decrease in the protein binding values of phenytoin in the plasma of type I diabetic patients compared with the controls.

Diclofenac

Studies on hepatic microsomes of male Wistar rats have shown that CYP2C11 catalyses the metabolism of diclofenac, an arylacetic non-steroidal anti-inflammatory drug (NSAID).[139] After the intravenous administration of 5 mg/kg diclofenac to DMIA rats on the fourth day and DMIS rats on the seventh day, their CL_{NR} values (which could have represented their metabolic clearances) became significantly slower (by 16.9 and 47.0%, respectively) than those of the controls.[140] This could possibly have been due to the slower hepatic CL_{int} (not measured) resulting from the decrease in the protein expression or mRNA level of hepatic CYP2C11 in the DMIA and DMIS rats (Table 1), since the free fractions of the drug in the plasma were comparable with those of the controls, and the hepatic blood flow rate increased in the DMIS rats.[12,13,17,21,22,48,140] This was because diclofenac is a drug with an intermediate hepatic extraction ratio in rats (its 'indirect' hepatic first-pass effect was found to be 44.8–50.1%).[140] The pharmacokinetic parameters of diclofenac in the DMIA and DMIS rats were comparable.[140]

Digoxin

In humans, digoxin, a cardiotonic agent, was metabolized via the hepatic CYP3A subfamily.[141] Studies on male and female Sprague-Dawley rat liver microsomes have shown that the cleavage of digoxin and one of its metabolites, digoxigenin bisdigitoxoside, was mediated via the CYP3A subfamily.[142] After the intravenous administration of 0.08 mg/kg digoxin to male Sprague-Dawley DMIS rats on the fourth to fifth weeks, their CL and biliary clearance became significantly faster (by 39.3 and 86.0%, respectively) than those of the controls.[4] This could possibly have been due to the faster hepatic CL_{int} (not measured) resulting from the increase in the protein expression and mRNA levels of hepatic CYP3A1 and 3A2 (Table 1), and an increase in the free fractions of digoxin in the plasma (not measured) in the DMIA and DMIS rats and the faster hepatic blood flow rate.[16,17,21,48] This was because digoxin is a drug with an intermediate hepatic extraction ratio in rats (its 'indirect' hepatic first-pass effect was found to be 42.2%).[143] Note that the urinary excretion of digoxin was the main elimination route in patients with normal renal function, but its metabolism was the main elimination route in female Sprague-Dawley rats.[144,145]

Propofol

Studies on six cDNA-expressed male and female Wistar rat hepatic CYP isozymes have shown that hepatic CYP2B1 and 2C11 had high catalytic activity for the metabolism of propofol, a widely used intravenous anaesthetic, for 5 and 25 μM propofol concentrations, respectively.[146] After the intravenous administration of 6 mg/kg per min propofol for 2 min to male Sprague-Dawley DMIS rats on the 29th day, their CL value (and AUC) became comparable with those of the controls.[147] This could possibly have been due to the slower hepatic CL_{int} for the disappearance of propofol (not measured), since the free fractions of the drug in the plasma were significantly greater (by 48.9%) and hepatic blood flow rate was faster in DMIS rats.[48] This was because propofol is a drug with an intermediate hepatic extraction ratio (its 'direct' hepatic first-pass effect was found to be approximately 61%) in rats.[148]

After the intravenous administration of 6 mg/kg per min propofol until the endpoint to DMIS rats, a significantly lower dose (or less infusion time) of the drug was required to reach the same pharmacological effect than that of the controls, due to alterations in the pharmacokinetics, secondary to the pathology.[147]

Doxorubicin

Two enzyme systems for the metabolism of doxorubicin (adriamycin), an anticancer agent, have been identified.[149,150] Doxorubicin was reduced to doxorubicinol (adriamycinol) by the cytoplasmic aldo-keto reductase, and doxorubicin and doxorubicinol were further metabolized to their deglycosylated aglycones, M3 and M4, respectively, by microsomal glycosidases. In male Sprague-Dawley rats, both aglycones were formed via hepatic CYP2B1/2 and 3A1/2.[151,152] After the intravenous administration of 16 mg/kg doxorubicin to male Sprague-Dawley DMIA rats on the fourth day, the value of $AUC_{0-12\ h}$ doxorubicin became comparable with that of the controls.[153] This could possibly have been due to the decrease in the free fractions of doxorubicin (not measured) since the hepatic blood flow rate was faster in the DMIS rats.[48] This was because doxorubicin is a drug with a high hepatic extraction ratio in rats (its 'indirect' hepatic first-pass effect was found to be 229%).[153]

Ciclosporin

In male and female Sprague-Dawley rats, hepatic CYP isozymes except for CYP3A1/2 (a main metabolizing enzyme) were involved in the metabolism of ciclosporin.[154] More than 18 metabolites of ciclosporin have been identified.[155,156] After the intravenous administration of 5 mg/kg per day ciclosporin for 13 days to male CD DMIS rats on the 35th day, their AUC values became significantly smaller (by 31.9%) than that of the controls.[157] This could possibly have been due to the significantly faster in-vitro CL_{int} for the disappearance of ciclosporin (not measured) in

the DMIS rats. This was because ciclosporin is a drug with a low hepatic extraction ratio drug in rats (its 'indirect' hepatic first-pass effect was found to be 14.7%).[157] The faster hepatic CL_{int} could have been due to the increase in the protein expression or mRNA levels of hepatic CYP3A1, 3A2, and 3A1/2 in the DMIS rats (Table 1).[16,17,21] However, different results have been reported. After the intravenous administration of 20 mg/kg ciclosporin to male Sprague-Dawley DMIS rats on the eighth day, their AUC values became significantly greater (by 129%) than that of the controls, due to the decrease in the amidopyrine N-demethylase and aniline *p*-hydroxylase (AH) activity in both male Fischer DMIS rats.[83,158] This was because ciclosporin is demethylated and hydroxylated; the reduction in the activity of these enzymes may partly explain the greater AUC in the DMIS rats.[8] After the intravenous administration of 10 mg/kg ciclosporin to male Wistar DMIS rats on the seventh day, their AUC values became comparable with that of the controls.[8]

Insulin affected the CL value of ciclosporin. For example, after the subcutaneous administration of NPH insulin at a dose of 20 U/kg for five days beginning two days after the induction of diabetes mellitus (in insulin-treated rats with diabetes), the CL value of ciclosporin was partially restored to that of the controls.[155]

Fluorouracil

In male Sprague-Dawley rats, fluorouracil, a pyrimidine analogue antineoplastic agent, was metabolized via hepatic CYP1A1/2.[159] Although the protein expression and mRNA levels of CYP1A1 and 1A2 increased in DMIS rats (Table 1), the contribution of this factor to the value of CL_{NR} of fluorouracil did not seem to be considerable.[13,18,19,21,22] This was because fluorouracil is a drug with a high extraction ratio (its 'direct' hepatic first-pass effect was found to be 94.5%) in rats[159] After the intravenous administration of 30 mg/kg fluorouracil to DMIS rats on the seventh day, their values for CL_{NR} became significantly faster (by 34.1%) than that of the controls, due to the faster hepatic blood flow rate and the significantly greater (by 20.6%) free fractions of fluorouracil in the plasma than those of the controls.[48,159]

DA-125

DA-125, once synthesized as an anthracycline anticancer agent, was almost completely hydrolysed to its active compound (M1), and M1 was reduced to its alcohol (M2). M1 and M2 were further metabolized to their aglycones, M3 and M4, respectively, in male Sprague-Dawley rats.[160] In male Sprague-Dawley rats, M1 was metabolized to M3 via hepatic CYP1A1/2 and 2B1/2, and M2 was metabolized to M4 via CYP2B1/2.[161] After the intravenous administration of 15 mg/kg DA-125 to male Sprague-Dawley DMIA rats on the fourth day, the value of $AUC_{0–90\ min}$ of M4 became smaller than that of the controls, and the value of $AUC_{0–90\ min}$ of M3 went below the detection limit for both groups of rats.[162]

Itraconazole

In male Sprague-Dawley rats, both the metabolism of itraconazole and the formation of 7-hydoxyitraconazole were mediated via hepatic CYP3A1/2 (our unpublished data). After the intravenous and oral administration of 5 mg/kg itraconazole to DMIS rats on the seventh day, the values of $AUC_{0–24\ h}$ for itraconazole and 7-hydroxyitraconazole became comparable with those of the controls (our unpublished data). This could have been due to the comparable hepatic and intestinal CL_{int} values for the disappearance of itraconazole and formation of 7-hydroxyitraconazole, and the comparable free fractions of itraconazole in the plasma of both groups of rats (our unpublished data). Itraconazole is a drug with a low hepatic extraction ratio (a negligible hepatic first-pass effect) in male Sprague-Dawley rats.[163] However, the in-vitro protein binding values of itraconazole in the serum of patients with insulin-dependent and noninsulin-dependent diabetes mellitus were significantly lower than that of the controls.[164]

Metformin

Metabolism of metformin, a biguanide antihyperglycaemic agent, was suggested in humans based on its incomplete recovery in the urine after its intravenous administration and on a further study in which 20% of the dose was not accounted for.[165–167] In male Sprague-Dawley rats, metformin was metabolized via hepatic CYP2C11, 2D1, and 3A1/2 (not via CYP1A1/2, 2B1/2, or 2E1).[168] After the intravenous administration of 100 mg/kg metformin to male Sprague-Dawley short-term DMIS rats on the seventh day and to male Sprague-Dawley long-term DMIS rats on the 29th day, and to DMIA rats on the fourth day, their values for CL_{NR} became significantly slower (by 28.0 and 34.3% in the DMIS rats on the seventh and 29th days, respectively, and by 62.2% in the DMIA rats) than those of the controls.[5,9] This was supported by the significantly slower hepatic CL_{int} for the disappearance of metformin in the seventh- and 29th-day of DMIS rats and in the fourth day of DMIA rats by 21.6, 19.4, and 22.4%, respectively, compared with that of the controls, since the protein binding values of metformin in the diabetes mellitus rats and the controls were comparable.[5,9] This was because metformin is a drug with a low hepatic extraction ratio in rats (its 'direct' hepatic first-pass effect was found to be 27.1%).[169] The slower hepatic CL_{int} values could have been due to the decrease in the protein expression or mRNA level of hepatic CYP2C11 in the DMIS and DMIA rats (Table 1).[12,13,17,21,22] Note that after the intravenous administration of insulin to DMIA rats, the significantly slower CL_{NR} value returned back to the level of the controls.[9] This was due to the restoration of the hepatic CYP enzyme changes in the DMIA rats to that of the controls.[9]

After the oral administration of 100 mg/kg metformin to male DMIS rats on the seventh and 29th day, the values for the AUC of metformin were significantly smaller (by 18.6 and 33.7%, respectively) than that of controls.[5] However, after the oral administration of 100 mg/kg metformin to male DMIA rats, the AUC value for metformin was significantly greater (by 23.2%).[9]

Mirodenafil

In male Sprague-Dawley rats, the metabolism of mirodenafil, a PDE5 inhibitor, was mediated via hepatic CYP1A1/2, 2B1/2, 2D subfamily, and 3A1/2.[170] After the intravenous administration of 20 mg/kg mirodenafil to DMIS rats on the

seventh day, their values for CL_{NR} and AUC became significantly faster (by 51.6%) and smaller (by 28.0%), respectively, than those of the controls (our unpublished data). This could have been due to the faster CL_{int} for the disappearance of mirodenafil (by 36.2%) and faster hepatic blood flow rate in the DMIS rats.[48] This was because mirodenafil is a drug with an intermediate hepatic extraction ratio in rats (its 'direct' hepatic first-pass effect was found to be 49.6%).[169] Mirodenafil is marketed in South Korea as Mvix for the oral treatment of male erectile dysfunction.

Diazepam

Studies on male Sprague-Dawley rat liver microsomes have shown the metabolism of diazepam (a hypnotic, sedative, and minor tranquilizer) was metabolized via the CYP3A subfamily.[171] Although the protein expression and mRNA level of hepatic CYP3A1, 3A2, and 3A1/2 increased in male Sprague-Dawley DMIS rats (Table 1), the contribution of this factor to the CL_{NR} of diazepam in diabetes mellitus rats seems to have been almost negligible.[16,17,21] This was because diazepam is a drug with a high extraction ratio in rats (its 'indirect' hepatic first-pass effect was found to be 710%).[172] After the intravenous administration of 5 mg (2 μCi) [2-^{14}C]diazepam to male Wistar DMIS rats on the second day, the CL value of their total blood radioactivity became slower (by 59%) than that of the controls.[173]

Hexobarbital

Hexobarbital was metabolized via CYP2C6 and 2C12 in female rats.[174] Hexobarbital is a drug with an intermediate hepatic extraction ratio (the hepatic first-pass effect of 64%) in rats.[175] The hexobarbital sleeping times of male Holtzman DMIS rats on the 24th and 48th days became significantly longer (by 74.4 and 65.7%, respectively) 24 and 48 h after their injection with streptozocin than those of the controls.[6] This could have been due to the significant decrease in the expression of CYP2C6 in rats, because the hepatic blood flow rate was significantly faster in diabetes mellitus rats.[15,48] The plasma protein binding was not measured.

Nelfinavir

In in-vitro human liver microsomes, nelfinavir, an HIV protease inhibitor, was primarily metabolized via hepatic CYP3A4, followed by 2C19, 2D6, and possibly 2D9, but no studies have been conducted on rats.[176] After the intravenous administration of 3.46 mg/kg nelfinavir to male Wister DMIS rats on the seventh day, their values for CL (which could have represented their hepatic metabolism clearance) and AUC became significantly faster (by 30.5%) and smaller (by 22.3%), respectively, than those of the controls.[176] This was due to the significantly greater free fractions of the drug in the plasma (4.0 vs 1.5%) and the faster hepatic blood flow rate, since the in-vitro CL_{int} values of the two groups of rats were comparable.[48,176] This was because nelfinavir is a drug with an intermediate hepatic extraction ratio in rats (its 'direct' hepatic first-pass effect was found to be 54.4 and 64.5% for the controls and the DMIS rats, respectively).[176] Interestingly, in the DMIS rats, the values for AUC and CL of nelfinavir as unbound fractions were significantly greater (by 10.8%) and slower (by 51.0%), respectively, than those of the controls.[176]

Hydroxychloroquine

No literature was found on the hepatic CYP isozymes in rats, which are responsible for the metabolism of hydroxychloroquine, a racemic antimalarial agent that is also an effective disease modifying drug against rheumatoid arthritis. After the intravenous administration of 40 mg/kg racemic hydroxychloroquine to male Sprague-Dawley DMIS rats on the 10th day, the values for CL_{NR} (based on the blood data) of *R*- and *S*-hydroxychloroquine became significantly faster (by 100 and 145%, respectively) than those of the controls.[177] This could have been at least partly due to the faster hepatic blood flow rate of the DMIS rats.[48] The hepatic CL_{int} and the plasma protein-binding value of hydroxychloroquine were not measured. This was because hydroxychloroquine is a drug with very close to an intermediate hepatic extraction ratio (its 'indirect' hepatic first-pass effects was found to be 30.3 and 32.1% for the *R*- and *S*-hydroxychloroquine, respectively) in rats.[177]

YJA-20379-8

Although no published literature could be found on the types of hepatic CYP isozymes in rats that are involved in the metabolism of YJA-20379-8, once synthesized as a new proton pump inhibitor, its contribution to the CL of YJA-20379-8 seems to have been almost negligible. This was because YJA-20379-8 is a drug with a high hepatic extraction ratio in rats (its 'indirect' hepatic first-pass effect was found to be 188%).[178] After the intravenous administration of 20 mg/kg YJA-20379-8 to male Sprague-Dawley DMIS rats on the seventh day, the CL value of YJA-20379-8 became significantly slower (by 28.3%) than that of the controls.[178] This could possibly have been due to the decrease in the free fractions of the drug in the DMIS rats (not measured), because the hepatic blood flow rate increased in the DMIS rats.[48,178]

Losartan

No literature could be found on the hepatic CYP isozymes of rats that were involved in the metabolism of losartan, an angiotensin II receptor antagonist. Losartan is a drug with an intermediate hepatic extraction ratio in rats (its 'indirect' hepatic first-pass effect was found to be 54.3%).[179] After the intravenous administration of 5 mg/kg losartan to DMIS rats on the 21st day, the values of the AUC (CL_{NR}) of both losartan and EXP3174 (a metabolite of losartan) did not significantly differ compared with those of the controls.[179]

Insulin

The insulin-degrading enzyme is present in various tissues in rats.[180–182] After the intravenous administration of 10 μCi or 14 mU/kg [^{3}H]insulin to DMIS rats on the 16th day, their CL values became significantly faster (by 44.2%) than that of the controls.[180]

Drugs (or compounds) that mainly form conjugates

The effects of diabetes mellitus on the formation of glutathione, glucuronide, and sulfate conjugations of drugs

Table 5 Drugs that mainly form conjugates and the corresponding pharmacokinetic observations in rats with induced diabetes mellitus

No.	Drug	Main metabolic pathway	Pharmacokinetic observations
1	Bilirubin	Glucuronide conjugation	Comparable intravenous CL and biliary clearance values of bilirubin, and comparable biliary excretions of monoglucuronide, monoglucuronide diester, and diglucuronide conjugates of bilirubin in DMIS rats[4]
2	Paracetamol	Glucuronide and sulfate conjugations	Significantly greater and smaller urinary and biliary excretions of intravenous paracetamol, respectively, and comparable intravenous CL in DMIS rats[4]
			Smaller 2-h biliary excretions of glucuronide and sulfate conjugates of paracetamol in DMIS rats[4]
3	Diflunisal	Ester and ether glucuronide conjugations	Significantly faster metabolic CL values to ester and ether glucuronides of intravenous diflunisal, respectively, and faster intravenous CL in DMIS rats[186]
4	Fenoprofen	Diastereomeric glucuronide conjugations	Significantly faster intravenous CL of *S*-fenoprofen in DMIS rats[187]
5	Liquiritigenin	Glucuronide conjugation	Comparable intravenous CL and AUC values of liquiritigenin in DMIS rats (our unpublished data)

Diabetes mellitus was induced in rats by administration of alloxan (DMIA) or streptozocin (DMIS). AUC, area under the curve; CL, total body clearance.

in rats have been reported.[2,33] Pharmacokinetic observations of each drug in this category are listed in Table 5.

Bilirubin

Bilirubin was excreted via the bile after the formation of glucuronide conjugates. After the intravenous administration of 60 μmol/kg bilirubin to male Sprague-Dawley DMIS rats on the fourth to fifth weeks, the values for CL, biliary clearance, elimination half-life, and Vd_{ss} of bilirubin became comparable with those of controls.[4] The biliary excretions of monoglucuronide, monoglucuronide diester, and diglucuronide conjugates of bilirubin also became comparable with those of the controls.[4] These data suggested that streptozocin did not significantly affect the formation of glucuronide conjugates of bilirubin.

Paracetamol

Glucuronide and sulfate conjugations were the major pathways for the elimination of paracetamol (acetaminophen), a NSAID. After the intravenous administration of 50 mg/kg paracetamol to male Sprague-Dawley DMIS rat on the 28th day, the urinary and biliary excretions of paracetamol became significantly greater (by 280%) and smaller (by 65%), respectively, than those of the controls. The CL value of paracetamol became comparable with that of the controls.[4] In the DMIS rats, the 2-h urinary excretions of glucuronide and the sulfate conjugates became smaller (by 75 and 50%, respectively) than those of the controls.[4] These data suggested that streptozocin affected the formation of glucuronide and sulfate conjugates of paracetamol.

The salivary elimination of paracetamol was studied after the oral administration of 1 g paracetamol to 10 healthy volunteers and to patients with type I diabetes mellitus. In the patients with type I diabetes mellitus ($n = 9$), the half-life and Vd of paracetamol became significantly longer (by 125%) and larger (by 63.4%), respectively, than those of the controls, but the CL value of paracetamol did not change.[183]

Diflunisal

Diflunisal, a fluorinated salicylate with non-steroidal anti-inflammatory properties, was mainly eliminated via conjugation as ester and ether glucuronides. Only a minor fraction of the administered diflunisal was excreted unchanged in rats.[184,185] After the intravenous administration of 10 mg/kg diflunisal to male Sprague-Dawley DMIS rats on the 10th day, the metabolic formation clearances to ester and the ether glucuronides became significantly faster (by 96.5 and 90.4%, respectively) than those of the controls.[186] This suggested an increase in the process of glucuronidation of diflunisal in the diabetic rats.[186] The CL value of diflunisal became significantly faster (by 78.2%) than that of the controls due to the increase in the enzyme activity, and not due to the increase in the free fractions of diflunisal in the plasma.[186]

Fenoprofen

Diastereomeric glucuronide conjugates were major metabolites of fenoprofen, a NSAID, in rats.[187] For the in-vitro procedure, the rates of glucuronide formation were dependent on the substrate (fenoprofen) and the cosubstrate (UDP glucuronic acid, or UDPGA), with the initial rates of glucuronide formation higher for *R*- than for *S*-fenoprofen.[187] Both enantiomers of fenoprofen were substantially acyl-glucuconjugated in the epithelial and muscular layers, and in the intestinal contents of female Sprague-Dawley rats.[188] After the intravenous administration of 10 mg/kg racemic fenoprofen to male Wistar DMIS rats on the 14th day, the CL value of *S*-fenoprofen became significantly faster (by 105%) and its *S*/*R* plasma concentration ratio became significantly greater (by 204%) than those of the controls.[189] This could have been due to the increase in the unidirectional chiral inversion rate of fenoprofen in the *R*- to *S*-sequence and the altered fenoprofen oxidation in the DMIS rats.[189] The glucuronide of fenoprofen was found in rat liver and kidney microsomal fractions and the intestinal mucosa was the main site of the first-pass metabolism after the oral administration of fenoprofen to rats.[189,190]

After the oral administration of 600 mg racemic fenoprofen to patients with type I diabetes mellitus ($n = 7$), the AUC and the oral clearances of (+)-(*S*)-fenoprofen became significantly smaller (by 36.9%) than those of the controls ($n = 13$).[191]

Liquiritigenin

Liquiritigenin (2,3-dihydro-7-hydroxy-2-(4-hydroxyphenyl)-(S)-4*H*-1-benzopyran-4-1) is an aglycone of liquritin, which

is contained in the glycyrrhizae radix. In male Sprague-Dawley rats, liquiritigenin was metabolized mainly to two glucuronide metabolites (M1 and M2).[192] The glucuronide formation of liquiritigenin in rats was greater in the intestines than in the liver.[192] After the intravenous administration of 20 mg/kg liquiritigenin to DMIS rats, the pharmacokinetic parameters of liquiritigenin became comparable with those of the controls (our unpublished data). The reason for this is being evaluated. Liquiritigenin is being evaluated in a preclinical study in South Korea as an agent for the treatment of inflammatory liver disease.

Drugs that are mainly metabolized in the kidney

Hepatic CYP isozymes do not significantly metabolize drugs in this category.

DA-1131

Carbapenem antibiotics are mainly hydrolysed via the renal DHP-I.[69–71] DA-1131, a carbapenem antibiotic, was relatively stable against the hydrolysis from an ICR mouse, a Sprague-Dawley rat, a New Zealand white rabbit, a beagle dog, and a human renal DHP-I compared with imipenem, meropenem, and other carbapenems.[193] After the intravenous administration of 50 mg/kg DA-1131 to male Sprague-Dawley DMIA rats on the fourth day, the CL value of DA-1131 became significantly slower (by 40.4%) than that of the controls due to the significantly slower value for CL_R (by 47.1%; because of the considerable decrease in the glomerular filtration rate) and the significantly slower value for CL_{NR} of DA-1131 (by 37.1%; possibly due to the considerably slower metabolism of DA-1131 in the rat kidney) than those of the controls.[57]

Recombinant human insulin-like growth factor-1

Recombinant human insulin-like growth factor-1 (rhIGF-1) is a single-chain polypeptide of approximately 7.6 kDa with a proinsulin-like structure. It is used for the therapy of Laron dwarfism and insulin-resistant diabetes.[194] The kidney was the main eliminating organ (in the brush border and lysosomal fractions of the tubular cells) of rhIGF-1.[194] After the intravenous administration of 0.32, 1.0, and 3.2 mg/kg rhIGF-1 to male Sprague-Dawley DMIS rats on the 14th day, the CL values of rhIGF-1 became significantly faster (by 13.9, 60.9, and 32.3%, respectively) than those of the controls.[195]

Recombinant rat soluble advanced glycation end-product

Vascular dysfunction in diabetes mellitus patients is related to advanced glycation end-product (AGE) formation. AGEs increase vascular permeability and generate oxidant stress after they bind to the receptor (RAGE) present in the endothelium.[196] [^{125}I]Recombinant rat soluble advanced glycation end-product (rR-RAGE) was extensively reabsorbed at the kidney level, and such peptidic hydrolysis was probably an important source of [^{125}I]rR-RAGE catabolism.[196] After the intravenous and intraperitoneal administration of 250 μg/kg [^{125}I]rR-RAGE to male Wistar DMIS rats on the ninth to 11th weeks, the values for CL, CL_R, and AUC of [^{125}I]rR-RAGE became comparable with those of the controls.[196] The urinary excretion of rR-RAGE was almost negligible; the values were 1.45 and 2.31% for the controls and the DMIS rats, respectively.[196]

Group B. Drugs (or Compounds) that are Mainly Excreted via the Kidney or Bile (Faeces)

The effects of hepatic CYP isozymes on the pharmacokinetic parameters of drugs in this category did not seem to be considerable. Rather, the liver or kidney functions contributed considerably to the pharmacokinetic parameters of drugs in this category. The pharmacokinetic results of the drugs in this category are listed in Table 6.

Cefoperazone

Cefoperazone, a third-generation cephalosporin, was predominantly excreted as an unchanged drug in the bile by the organic anionic transport system of the bile's canalicular membrane for biliary excretion.[197] The 2-h biliary excretions of cefoperazone were 70 ± 3 and 62 ± 11% for the dose administered to the controls and the DMIS rats, respectively.[54] After the intravenous administration of 40 mg/kg cefoperazone to male Sprague-Dawley DMIS rats, after 35 weeks the values for CL and biliary clearance became significantly faster (by 46.1 and 29.7%, respectively, in terms of ml/min) than those of the controls.[54] Different results, however, were obtained from patients with type I diabetes mellitus. After the intravenous administration of 1 g cefoperazone to patients with type I insulin-dependent diabetes mellitus ($n = 12$), the pharmacokinetic parameters of cefoperazone became comparable with those of the controls.[198]

Cefazolin

Cefazolin, a first-generation cephalosporin antibiotic, was not metabolized and was mainly excreted in the urine via glomerular filtration and renal tubular secretion of the transport system for organic anion in male albino Wistar rats.[199] After the intravenous administration of 10–40 mg/kg cefazolin to male Wistar DMIS rats after at least 12 weeks, the values for CL and CL_R of cefazolin became significantly faster (by 79.3 and 88.3%, respectively) than those of the controls due to the 1.9-times increase in the filtration clearance, but the secretion clearance did not change.[46] The V_{max} and K_m of the active renal tubular secretion of cefazolin became significantly slower and lower (by 49.5 and 69.8%, respectively) in the DMIS rats than those of the controls, which indicated that diabetes caused some alterations to the proximal tubular cell functions for the secretion of cefazolin.[46] The free fractions of cefazolin in the plasma also increased by 60% in the DMIS rats due to the increase in the glycosylated protein and the plasma free fatty acids compared with those of the controls.[46]

Cefradine

Cefradine, a first-generation cephalosporin antibiotic, was mainly excreted in the rat urine.[54] The 2-h biliary excretions of cefradine became 16 ± 7 and 9 ± 1% of the intravenous dose for the control and DMIS rats, respectively.[54] Following the intravenous administration of 40 mg/kg cefradine to male Sprague-Dawley DMIS rats after

Table 6 Drugs mainly excreted via the kidney or bile and the corresponding pharmacokinetic observations in rats with induced diabetes mellitus

No.	Drug	Main excretion pathway	Pharmacokinetic observations
1	Cefoperazone	Bile	Significantly faster intravenous CL and biliary clearance values of cefoperazone in DMIS rats[54]
2	Cefazolin	Urine	Significantly faster intravenous CL and CL_R values of cefazolin in DMIS rats[46]
3	Cefradine	Urine	Significantly faster and slower intravenous CL and biliary clearance values of cefradine, respectively, in DMIS rats[54]
4	Cefotaxime	Urine	Significantly smaller value for subcutaneous AUC of cefotaxime in DMIA rats[201]
5	Zopolrestat	Bile	Smaller oral value for AUC of zopolrestat in DMIS rats[204]
6	Atenolol	Urine	Significantly faster intravenous CL and CL_R values of *S*-(−) and *R*-(+) atenolol in DMIS rats[205]
7	Sodium tungstate	Urine	Smaller oral value for AUC of sodium tungstate in DMIS rats[210]
8	DA-7867	Faeces and urine	Significantly faster intravenous CL value and significantly smaller value for oral AUC of DA-7867 in DMIS rats[211]
9	Dexamethasone	Urine	Comparable intravenous CL value of dexamethasone in DMIS rats[213]
10	Ouabain	Bile	Significantly faster intravenous CL and biliary clearance values of ouabain in DMIS rats[214]
11	Taurocholate	Bile	Significantly faster intravenous CL and biliary clearance values of taurocholate in DMIS rats[214]
12	PAEB	Bile	Significantly faster intravenous CL and biliary clearance values of PAEB in DMIS rats[214]
13	Organic anions	Bile	Comparable intravenous CL values of amaranth, BST, DBSP, aeosin, bromocresol green, and indocyanine green, significantly faster intravenous CL values of rose bengal, and significantly faster intravenous CL and biliary clearance values of phenol red in DMIS rats[215]

Diabetes mellitus was induced in rats by administration of alloxan (DMIA) or streptozocin (DMIS). PAEB, procainamide ethobromide; DBSP, phenol-3,6-dibromphthalein disulfonate; BSP, sulfobromophthalein; AUC, area under the curve; CL, total body clearance; CL_R, renal clearance.

35 weeks, the values for CL and biliary clearance of cefradine became significantly faster (by 37.6% based on the ml/min) and slower (by 36.4% based on the ml/min), respectively, than those of the controls.[54] The significantly faster CL in the DMIS rats could have been due to the significantly faster CL_R (not measured), because the biliary clearance was significantly slower in the DMIS rats than that of the controls.[54]

Cefotaxime

More than 80% of cefotaxime, a third-generation cephalosporin, was excreted in the urine.[200] After the subcutaneous administration of 20 mg/kg cefotaxime to male Sprague-Dawley DMIA rats on the 30th day, the AUC of cefotaxime became significantly smaller (by 24.5%) than that of the controls.[201] The 50% protective dose (PD50) of cefotaxime against *S. pneumoniae* did not significantly differ between the two groups of rats.[201]

Zopolrestat

Biliary excretion was a major route of elimination of zopolrestat, a carboxylic acid aldose reductase inhibitor that prevents proteinuria, albuminuria, and cataractogenis, as well as its metabolites in rats.[202] The renal excretion accounted for 0.4% of the oral dose of 50 mg/kg.[203] After the oral administration of 50 mg/kg zopolrestat to male Sprague-Dawley DMIS rats on the seventh day, the value for AUC of zopolrestat became smaller (by 32.8%) than that of the controls.[204]

Atenolol

Atenolol, a cardioselective β-adrenoreceptor blocking agent, was mainly excreted in rat urine.[205] After the intravenous administration of 10 mg/kg racemic atenolol to male Sprague-Dawley DMIS rats on the ninth day, the values for CL of *S*-(–) and *R*-(+) enantiomers became significantly faster (by 55.7 and 55.7%, respectively) than those of the controls due to the significantly faster CL_R values (by 82.4 and 81.6%, respectively) compared with those of the controls. This was because the CL_{NR} values of both enantiomers in the two groups of rats were comparable.[205] The greater CL_R in the DMIS rats compared with the controls could have been due to diabetes-induced kidney hyperfiltration.[205]

Sodium tungstate

Sodium tungstate showed antidiabetic activity and corrected hyperglycaemia in insulin- and noninsulin-dependent diabetes mellitus rats.[206–208] It was mainly excreted via the kidney in rats; its 3-h urinary excretion accounted for approximately 75% of radioactivity.[209] After the oral administration of 36 mg/kg sodium tungstate to male Sprague-Dawley DMIS rats on the eighth day, the value for AUC of sodium tungstate became smaller (by 49.3%) than that of the controls.[210]

DA-7867

After the intravenous administration of 10 mg/kg DA-7867, a new oxazolidinone antibiotic, to male Sprague-Dawley rats, the metabolism became minimal, whereas approximately 85.0% of the intravenous dose was recovered unchanged in the urine (17.0% of the dose), faeces (64.0% of the dose), and rinsings of the metabolic cage for up to 14 days.[211] This suggested that the CL value of DA-7867 was affected mainly by the urinary and gastrointestinal excretions. After the intravenous administration of 10 mg/kg DA-7867 to male Sprague-Dawley short-term DMIS rats on the seventh day and to male Sprague-Dawley long-term DMIS rats on the 29th day, the values for CL of DA-7867 became significantly faster (by 127 and 183%, respectively) than

those of the controls due to the significantly greater 24-h urinary excretion (by 55.6 and 127%, respectively).[212]

After the oral administration of 10 mg/kg DA-7867 to DMIS rats, the values for AUC of DA-7867 became significantly smaller (by 61.3 and 72.6% for the short- and long-term DMIS rats, respectively) than those of the controls due to the significantly greater amount of unchanged DA-7867 excreted in the 24-h urine (by 218 and 364%, respectively).[212] The greater urinary excretion of unchanged DA-7867 was due to its urine flow rate-dependent timed-interval renal clearance in the controls and the diabetic rats before and after insulin administration.[212]

Dexamethasone

After the intravenous administration of 4 μmol/kg dexamethasone, a hormonal anticancer agent, to DMIS rats (Sprague-Dawley nonpregnant and pregnant (day 20 of gestation) rats), the value for CL of dexamethasone became comparable with that of the controls.[213]

Ouabain

Following the intravenous administration of 10 μCi/kg [^{3}H] ouabain octahydrate, a cardiotonic agent, to male Sprague-Dawley DMIS rats after four to five weeks, the values for CL and biliary clearance of ouabain became significantly faster (by 146 and 122%, respectively) than those of the controls.[214] The 3-h biliary excretion of ouabain in the two groups of rats became comparable.[212] The contributions of the biliary clearance to the CL of ouabain were 73.3 and 66.0% for the controls and the DMIS rats, respectively.[214]

Taurocholate

Following the intravenous administration of 10 μmol/kg [^{3}H] taurocholic acid, a cholagogue and cholerectic, to male Sprague-Dawley DMIS rats after four to five weeks, the values for CL and biliary clearance of [^{3}H]taurocholic acid became significantly faster (by 143 and 147%, respectively) than those of the controls.[214] The contributions of the biliary clearance to the CL of taurocholic acid were 101 and 103% of the dose for the controls and the DMIS rats, respectively.[214] The 3-h biliary excretion of taurocholic acid in the two groups of rats became comparable.[214]

Procainamide ethobromide

Following the intravenous administration of 30 μmol/kg procainamide ethobromide (PAEB), an organic cation, to male Sprague-Dawley DMIS rats after four to five weeks, the values for CL and biliary clearance of PAEB became significantly faster (by 143 and 74.9%, respectively) than those of the controls.[214] The contributions of the biliary clearances to the CL values of PAEB were 32.2 and 23.1% for the controls and the DMIS rats, respectively.[214] The 3-h biliary excretion of *N*-acetyl-PAEB was smaller (by 26%) in the DMIS rats.[214]

Organic anions (amaranth, sulfobromophthalein, phenol-3,6-dibromphthalein disulfonate, aeosin, rose bengal, bromocresol green, and indocyanine green)

The biliary excretions of amaranth, phenol-3,6-dibromphthalein disulfonate (DBSP), and aeosin are thought to be bile-acid-independent, and those of bromocresol green, indocyanine green, rose bengal, and sulfobromophthalein (BSP) are thought to be bile-acid-dependent.[215] Following the intravenous administration of amaranth (300 μmol/kg), BST (200 μmol/kg), DBSP (120 μmol/kg), aeosin (120 μmol/kg), rose bengal (600 μmol/kg), bromocresol green (30 μmol/kg), and indocyanine green (30 μmol/kg) to male Sprague-Dawley DMIS rats after four to five weeks, the values for CL became comparable with those of the controls, except for the significantly faster (by 68.0%) CL of rose bengal.[215] Following the intravenous administration of 30 μmol/kg phenol red to male Sprague-Dawley DMIS rats after four to five weeks, the values CL and biliary clearance of phenol red became significantly faster (by 88.5 and 75.6%, respectively) than those of the controls.[215] The contributions of the biliary clearance to the CL of phenol red were 70.1 and 65.3% of the dose for the controls and the DMIS rats, respectively.[215] Although the serum concentrations of phenol red-glucuronic acid increased in the DMIS rats, the 3-h biliary excretion of the conjugates in the two groups of rats became comparable.[215]

Conclusions

We have tried to explain changes in the values for CL_{NR} of drugs that were mainly metabolized via CYP isozymes, reported in the literature in terms of changes in the above mentioned CYP isozymes, the free fractions of the drug in the plasma, and the hepatic blood flow rate, depending on the hepatic extraction ratios of drugs. Similar (chlorzoxazone and theophylline in the patients) and different (theophylline and phenytoin in the patients) results were obtained from the DMIS rats and patients with type I diabetes mellitus as mentioned earlier.[34,96,97,137,138] This possibly could have been due to the disease type, whether the disease was controlled, the severity and duration of the disease, the severity of the impairment of the liver and kidney functions, and the coadministration of other drugs as mentioned earlier. The formation of glucuronide or sulfate conjugates of drugs was dependent on drugs in DMIA and DMIS rats; formation of bilirubin was not altered, paracetamol decreased, but diflunisal and fenoprofen increased compared with controls.[4,186,189] The metabolism of drugs that were mainly metabolized via the kidney was also dependent on drugs in DMIA or DMIS rats; the metabolism of DA-1131 and rR-RAGE was not altered, but rhIGF-1 increased compared with controls.[57,95,196] The values for CL_R of intravenous cefazolin, cefradine, atenolol, and DA-7867 were faster and the values for the AUC of subcutaneous cefotaxime, and oral sodium tungstate and DA-7867 were smaller in DMIA and DMIS rats.[46,54,201,205,210,212] The biliary CL values of intravenous cefoperazone, ouabain, taurocholate, and PAEB were faster and the value for the AUC of oral zopolrestat was smaller in DMIA and DMIS rats.[54,204,214] Pharmacokinetic studies of drugs in patients with type I diabetes mellitus are scarce (chlorzoxazone, theophylline, phenytoin, paracetamol, fenoprofen, and cefoperazone).[34,96,97,137,138,183,191,198] Thus, the present experimental rat data should be extrapolated carefully in humans. More studies are required in patients with type I diabetes mellitus.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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