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Pharmacokinetics of a New Proton-pump Inhibitor, YJA-20379-8, after Intravenous and Oral Administration to Rats with Streptozotocin-induced Diabetes Mellitus

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Abstract

Because physiological changes occurring in diabetes mellitus patients could alter the pharmacokinetics of the drugs used to treat the disease, the pharmacokinetics of a new proton pump inhibitor, YJA-20379-8, were investigated after intravenous and oral administration of the drug ($50\,mg\,kg^{-1}$) to control rats and to rats with streptozotocin-induced diabetes mellitus (SIDM).

After intravenous administration of YJA-20379-8 to SIDM rats, plasma concentrations of the drug were significantly higher and this resulted in a significantly greater AUC (area under the concentration–time curve; 2520 ± 366 compared with $1870 \pm 272\,\mu g\,min\,mL^{-1}$). This was because of significantly slower clearance (CL; $19{\cdot}5 \pm 2{\cdot}88$ compared with $27{\cdot}2 \pm 3{\cdot}93\,mL\,min^{-1}\,kg^{-1}$) in SIDM rats. The significantly slower metabolism of YJA-20379-8 in SIDM rats was confirmed by an in-vitro tissue metabolism study; the amounts of YJA-20379-8 remaining in the liver ($27{\cdot}1 \pm 5{\cdot}19$ compared with $18{\cdot}9 \pm 8{\cdot}24\,\mu g\,(g\,tissue)^{-1}$) were significantly greater after 30-min incubation of the drug ($50\,\mu g$) with supernatant fractions obtained from the tissues by centrifugation at 9000 *g*. After oral administration of YJA-20379-8 to SIDM rats the plasma concentrations of the drug were significantly lower
and this resulted in significantly smaller AUC ($128 \pm 31{\cdot}0$ compared with $219 \pm 45{\cdot}6\,\mu g\,min\,mL^{-1}$). This was because of reduced gastrointestinal absorption of YJA-20379-8 in SIDM rats; the amounts of the oral dose recovered as unchanged drug from the entire gastrointestinal tract after 24 h were significantly greater (32·9 compared with 19·2%) in SIDM rats.

The tissue distribution of YJA-20379-8 was not affected by SIDM.

Many diabetic patients develop serious complications during the course of the disease, including cardiovascular disorders, nephropathy, neuropathy and retinopathy (Gwilt et al 1991). Some physiological changes, for example disorders of the gastrointestinal tract, reductions in protein binding of drugs, possibly because of elevated plasma fatty acid levels, and glycosylation of plasma proteins (Nadai et al 1990), and increases in the levels of rat liver cytochrome P450 (O'Connor & Feely 1978; Gwilt et al 1991) have been reported to occur in diabetes mellitus. Therefore, the rate and extent of absorption of drugs given orally could also be expected to be altered in such patients; disorders of the gastrointestinal tract, such as diarrhoea, constipation and delayed gastric emptying, occur as a result of gastroparesis in as many as 20% of diabetic patients who have had the disease for several years. Animal models of insulin-dependent diabetes mellitus induced by administration of several chemicals, principally alloxan, streptozotocin and zinc chelators, have been reported (Pickup & Williams 1991; Watkins & Sanders 1995). Changes in pharmacokinetics have been reported for para-

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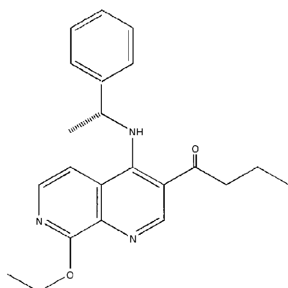

Figure 1. The structure of YJA-20379-8.

cetamol, bilirubin and digoxin (Watkins & Sherman 1992), dexamethasone (Mulay & Varma 1984), cefa drugs (Nadai et al 1990; Nakashima et al 1992), cyclosporin (D'Souza et al 1988), zopolrestat (Inskeep et al 1991), atenolol enantiomers (Mehvar 1991), and methotrexate (Park et al 1996) after administration to rats with streptozotocin-induced diabetes mellitus (SIDM).

In this study the pharmacokinetics of a new proton-pump inhibitor, YJA-20379-8 (3-butyryl-4-[5-*R*-(+)-methylbenzylamino-8-ethoxy-1,7-naphthyridine, Figure 1) have been investigated after intravenous and oral administration of the drug, 50 mg kg^{-1}, to control and SIDM rats.

Materials and Methods

Chemicals

YJA-20379-8 was donated by the Pharmacology and Toxicology Laboratory of Yung Jin Pharmaceutical Company (Hwasung, Korea). Streptozotocin, the reduced form of nicotinamide adenine dinucleotide phosphate, and uridine diphosphoglucuronic acid were from Sigma (St Louis, MO). Cremophor was obtained from BASF (Rhein, Germany). Other chemicals were of reagent- or HPLC-grade and were used without further purification.

Induction of diabetes mellitus in rats by streptozotocin injection

Male Sprague–Dawley rats, 260–305 g, were purchased from Charles River Company (Atsugi, Japan). They were randomly divided into two groups, control and SIDM. Freshly prepared streptozotocin (dissolved in citrate buffer, pH 4·5, final concentration 40 mg mL^{-1}; 45 mg kg^{-1}) was administered once via the tail vein (total injection volume approx. 0·3 mL) to overnight-fasted rats (Watkins & Sherman 1992). On the seventh day after intravenous administration of streptozotocin (SIDM rats) or citrate buffer (control rats), serum glucose levels were measured by the GOD POD enzymatic method with a Glucose-E Kit (Yeong Dong Pharmaceutical, Seoul, Korea) and rats with blood glucose levels > 300 mg dL^{-1} were chosen as SIDM rats. Induction of diabetes mellitus was apparent after single intravenous administration of streptozotocin to rats; the mean ($\pm$ s.d.) plasma glucose levels in SIDM rats were $388 \pm 93{\cdot}8$ and $396 \pm 54{\cdot}7$ mg dL^{-1} for intravenous and oral studies, respectively, and the corresponding values for control rats were $82{\cdot}9 \pm 26{\cdot}4$ and $90{\cdot}9 \pm 8{\cdot}01$ mg dL^{-1}.

Intravenous study

In the early morning on the seventh day after the start of treatment with streptozotocin (SIDM rats) or citrate buffer (control rats), the carotid artery and the jugular vein (for intravenous study only) were catheterized with polyethylene tubing (Clay Adams, Parsippany, NJ) under light ether anaesthesia. Both cannulae were exteriorized to the dorsal side of the neck where each terminated individually in long silastic tube (Dow Corning, Midland, MI). Both silastic tubes were covered with a wire to enable free movement of the rats. Each rat was housed individually in a metabolic cage (Daejong Scientific, Seoul, Korea) and left to recover from the anaesthesia for 4–5 h before drug administration. They were not restrained at any time during the study. Food was withdrawn overnight before the oral study, and food and tap water were withdrawn throughout the entire experimental period for both intravenous and oral studies.

YJA-20379-8 powder was dissolved in dimethylsulphoxide–Cremophor, 5 : 1 (v/v). By means of this solution YJA-20379-8 (50 mg kg^{-1}) was administered by intravenous infusion over a 15-min period via the jugular vein (total injection volume approx. 0·4 mL) of control (n = 7) and SIDM rats (n = 9). Blood samples (0·12 mL) were collected via the carotid artery 15 min before drug infusion (to serve as a control), at −7·5 min and 0 min (at the end of infusion) during infusion, and 1, 5, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, 600 and 720 min after infusion. Heparinized 0·9% NaCl injectable solution (0·25 mL; 20 units mL^{-1}) was used to flush the cannula after each blood sampling to prevent blood clotting. Blood samples were centrifuged immediately and a sample (50 μL) of the plasma was stored in the freezer until high-performance liquid-chromatographic (HPLC) analysis of YJA-20379-8 (Chung 1998). The metabolic cage was rinsed with distilled water (10 mL) 24 h after intravenous injection and the rinsings were combined with 24-h urine. After measurement of the exact volume of the 24-h combined urine two 100-μL volumes of the combined sample were stored in the freezer until HPLC analysis of YJA-

20379-8 (Chung 1998). At the end of the experiment (24 h) the whole kidneys and livers were excised and weighed.

Oral study

YJA-20379-8 powder was suspended in 0·2% carmellose sodium. By means of this suspension YJA-20379-8 (50 mg kg^{-1}) was administered orally by use of a feeding tube to control (n = 9) and SIDM rats (n = 10). Blood samples (0·12 mL) were collected via the carotid artery at time 0 (to serve as a control) and 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 480, 600 and 720 min after oral administration. Urine was collected between 0 and 12 h and between 12 and 24 h. Rats were killed by cervical dislocation 24 h after oral administration and their abdomens were opened. The entire gastrointestinal tract (including contents and faeces) was removed, transferred into a beaker containing methanol (200 mL), and cut into small pieces with scissors. After stirring with a glass rod, two samples (100 μL) of the supernatant were collected from each beaker and stored in the freezer until HPLC analysis of YJA-20379-8 (Chung 1998). Other procedures were similar to those of the intravenous study.

Tissue distribution study

YJA-20379-8 (the solution used in the intravenous study; 20 mg kg^{-1}) was administered intravenously to control (n = 4) and SIDM rats (n = 4). A large volume of blood was collected 30 min after the start of intravenous infusion of the drug and the rats were killed by cervical dislocation. Blood samples were centrifuged immediately and plasma was collected. Brain, heart, lung, stomach, small intestine, large intestine, liver, kidney, mesentery, muscle and spleen (approx. 1 g of each) were excised and washed with cold 0·9% NaCl injectable solution to eliminate blood remaining in the tissues. After blotting with paper tissue the tissues were homogenized separately with 4 vols distilled water by means of a tissue homogenizer (Ultra-Turrax T25; Janke & Kunkel, IKA Labortechnik, Staufen, Germany). After centrifugation two samples (50 μL) of the supernatant were stored in the freezer until HPLC analysis of YJA-20379-8 (Chung 1998). A plasma sample was also diluted with 4 vols distilled water. All procedures were conducted at 4°C on an ice-bath.

In-vitro disappearance of YJA-20379-8 in homogenates of rat tissues

The procedures were similar to the reported method (Litterst et al 1975; Kim et al 1993). The control (n = 4) and SIDM rats (n = 4) were killed after 30 min by cervical dislocation. Small intestine, large intestine, heart, brain, lung, liver, stomach, muscle, kidney and spleen (approx. 1 g) were excised, washed with cold 0·9% NaCl injectable solution, blotted with dry tissue paper, and weighed. All subsequent procedures were conducted at 4°C on an ice-bath. The tissues were minced with scissors and homogenized with 4 vols cold 0·25 M sucrose in a tissue homogenizer (Ultra-Turrax, T25). The homogenate was then centrifuged at 9000 *g* for 20 min, by means of a Beckman (Palo Alto, CA) model J2-21 centrifuge, and the supernatant fraction was collected.

Metabolic activity was initiated by adding the 9000 *g* supernatant (1 mL) from each tissue to a glass test tube containing YJA-20379-8 (50 μg; dissolved in methanol, 25 μL), the reduced form of nicotinamide adenine dinucleotide phosphate (1 mM, 100 μL), Tris-HCl buffer, pH 7·4 (100 mM, 1·9 mL), and uridine diphosphoglucuronic acid (3·3 mM, 25 μL). The mixture was then thoroughly mixed by hand and shaken at 50 oscillations min^{-1} in a water-bath shaker at 37°C. After 30-min incubation NaOH (1 M, 1 mL) was added to terminate enzyme activity. After centrifugation samples (2×100-μL) of the supernatant were collected and stored in the freezer until HPLC analysis of YJA-20379-8 (Chung 1998).

HPLC analysis of YJA-20379-8

Concentrations of YJA-20379-8 in the samples were analysed by reversed-phase HPLC (Chung 1998) on a YMC (Tokyo, Japan) 25 cm $\times$ 4·6 mm i.d., 4-μm particle, C_{18} column. The mobile phase, acetonitrile–water, 5 : 1 (v/v), was delivered at a flow rate of 1·3 mL min^{-1} by means of an Xper Chrom (St Louis, MO) model 400 pump.

A 2·5-fold volume of acetonitrile was added to deproteinate the sample. After vortex mixing for 1 min and centrifugation for 10 min, the supernatant (50 μL) was injected directly on to the column by means of a Rheodyne (Cotati, CA) model 7125 injector. Column effluent was monitored by UV detection at 255 nm (Gilson (Middleton, WI) model 118 UV-Vis detector and Linear (Reno, NV) model 1200 recorder). The retention time of YJA-20379-8 was 5·2 min (approx.). The detection limits of YJA-20379-8 in plasma and urine from man were 50 and 100 ng mL^{-1}, respectively. The intraday and interday coefficients of variation of YJA-20379-8 in plasma and urine from man, and in rat tissue homogenates, were $< 9{\cdot}49\%$.

Pharmacokinetic analysis

The total area under the plasma concentration–time curve from time zero to time infinity (AUC for intravenous study) or to the last measured time,

12 h, in plasma (AUC_{0-12} for oral study) was calculated by the trapezoidal rule-extrapolation method (Kim et al 1993) employing the logarithmic trapezoidal rule (Chiou 1978) for calculation of area during the declining plasma-level phase and the linear trapezoidal rule for the rising plasma-level phase. The area from the last data point to time infinity (AUC for intravenous study) was estimated by dividing the last measured plasma concentration by the terminal rate constant.

Standard methods (Gibaldi & Perrier 1982) were used to calculate the time-averaged total body clearance (CL; equation 1), the area under the first moment of the plasma concentration–time curve (AUMC; equation 2), the mean residence time (MRT; equation 3), and the apparent volume of distribution at steady state (Vd_{SS}; equation 4).

$$CL = Dose/AUC \quad (1)$$

$$AUMC = \int_0^{\infty} tC_p dt \quad (2)$$

$$MRT = AUMC/AUC - T/2 \quad (3)$$

$$Vd_{SS} = CL \times MRT \quad (4)$$

Where C_p is the plasma concentration of YJA-20379-8 at time t and T is the infusion time.

The mean values of Vd_{SS} (Chiou 1979), terminal half-life, $t_{1/2}$ (Eatman et al 1977), and CL (Chiou 1980) were calculated by the harmonic mean method.

Statistical analysis

The statistical significance of differences between two means for unpaired data was assessed by means of the *t*-test. Significant differences were judged as $P < 0·05$. All results are expressed as means ± s.d.

Results and Discussion

The mean arterial plasma concentration–time curves after intravenous administration of YJA-20379-8 to control (n = 7) and SIDM rats (n = 9) are shown in Figure 2; some relevant pharmacokinetic parameters are listed in Table 1. After intravenous administration the plasma levels of YJA-20379-8 declined polyexponentially for both groups of rats with significantly higher levels from 60 min to 6 h in SIDM rats than in control rats (Figure 2); this resulted in a significantly greater AUC for YJA-20379-8 in SIDM rats (2520 compared with 1870 $\mu g\, min\, mL^{-1}$; Table 1). The significantly greater AUC in SIDM rats could be because of the significantly slower clearance of YJA-20379-8 (CL 19·5 compared with 27·2 $mL\, min^{-1}\, kg^{-1}$; Table 1) in SIDM rats. Because YJA-20379-8 concentrations in the urine samples were below the detection limit, the CL of YJA-20379-8 listed in Table 1 could represent non-renal clearance (CL_{NR}) of YJA-20379-8 in rats. The contribution of biliary excretion of YJA-23079-8 to CL_{NR} of the drug was minor; the 24-h biliary excretion of unchanged YJA-20379-8 was less than 0·5%

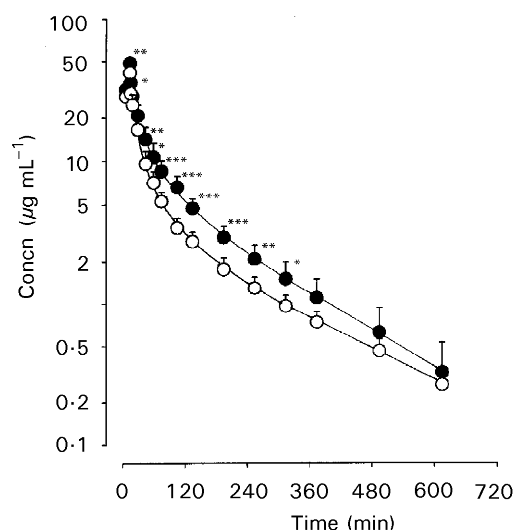

Figure 2. Mean arterial plasma concentration–time curves for YJA-20379-8 after 15-min intravenous infusion of the drug (50 $mg\, kg^{-1}$) to streptozotocin-induced diabetes mellitus rats (●, n = 7) and to control rats (○, n = 9). Bars represent standard deviation. *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$ compared with control.

Table 1. Mean (± s.d.) pharmacokinetic parameters for YJA-20379-8 after 15-min intravenous administration of the drug (50 $mg\, kg^{-1}$) to control and streptozotocin-induced diabetes mellitus rats.

Parameter	Control rats (n = 9)	SIDM rats (n = 7)
Body weight (g)	268 ± 6·95	219 ± 23·9***
Area under the plasma concentration–time curve from time zero to time infinity ($\mu g\, min\, mL^{-1}$)	1870 ± 272	2520 ± 366***
Terminal half-life (min)	209 ± 38·9	116 ± 31·1**
Mean residence time (min)	131 ± 15·9	122 ± 25·8
Time-averaged total body clearance ($mL\, min^{-1}\, kg^{-1}$)	27·2 ± 3·93	19·5 ± 2·88***
Apparent volume of distribution at steady state ($mL\, kg^{-1}$)	3770 ± 625	2400 ± 606**

**$P < 0·01$, ***$P < 0·001$ compared with control.

Table 2. Mean (± s.d.) amounts (μg (g tissue)$^{-1}$) of YJA-20379-8 remaining after 30-min incubation of the drug (50 μg), in the presence of the reduced form of nicotinamide adenine dinucleotide phosphate, with the supernatant obtained by centrifugation (9000 *g*) of tissue homogenates from control and streptozotocin-induced diabetes mellitus rats.

Tissue	Control rats (n = 4)	SIDM rats (n = 4)
Small intestine	16·4 ± 0·98	18·9 ± 3·72
Large intestine	21·0 ± 1·67	24·2 ± 5·10
Heart	21·5 ± 3·81	25·7 ± 3·10
Brain	25·8 ± 3·19	27·4 ± 4·26
Lung	25·9 ± 3·33	29·6 ± 3·41
Liver	18·9 ± 8·24	27·1 ± 5·19
Stomach	19·0 ± 1·18	21·7 ± 4·14
Muscle	24·3 ± 2·87	29·9 ± 7·79
Kidney	22·0 ± 4·97	23·0 ± 2·62
Spleen	18·9 ± 0·67	23·3 ± 2·49*

*$P < 0·05$ compared with control.

Table 3 Mean (± s.d.) amounts of YJA-20379-8 obtained (μg mL^{-1} plasma or μg (g tissue)$^{-1}$) 30 min after 15-min intravenous infusion of the drug (20 mg kg^{-1}) to control and streptozotocin-induced diabetes mellitus rats. The numbers in parentheses are mean (± s.d.) values of tissue-to-plasma ratios.

Tissue	Control rats (n = 4)	SIDM rats (n = 4)
Plasma	2·51 ± 0·892	3·78 ± 0·401
Small intestine	5·01 ± 1·66	6·97 ± 2·58
	(2·07 ± 0·445)	(1·80 ± 0·524)
Large intestine	2·39 ± 1·83	5·40 ± 2·39
	(0·959 ± 0·644)	(1·46 ± 0·757)
Heart	5·47 ± 1·55	9·85 ± 2·73
	(2·23 ± 0·345)	(2·57 ± 0·527)
Brain	3·21 ± 0·737	4·11 ± 1·13
	(1·24 ± 0·112)	(1·07 ± 0·190)
Lung	3·34 ± 0·818	5·36 ± 1·35
	(1·26 ± 0·329)	(1·43 ± 0·393)
Liver	6·17 ± 2·73	12·1 ± 2·71*
	(1·85 ± 0·743)	(3·18 ± 0·509)
Stomach	2·07 ± 0·790	14·2 ± 5·09
	(2·48 ± 1·12)	(3·71 ± 1·02)
Muscle	3·17 ± 1·53	4·27 ± 1·20
	(0·932 ± 0·081)	(1·17 ± 0·240)
Kidney	1·82 ± 0·084	7·05 ± 3·01
	(1·37 ± 0·459)	(1·84 ± 0·728)
Spleen	2·51 ± 0·333	3·18 ± 0·736
	(0·709 ± 0·0660)	(0·84 ± 0·167)

*$P < 0·05$ compared with control.

of intravenous dose when the drug (20 mg kg^{-1}) was administered intravenously to four rats (Chung 1998). These data indicated that the non-renal clearance of YJA-20379-8 could represent the metabolic clearance of the drug, therefore, the slower CL of the drug in SIDM rats indicated slower metabolism of YJA-20379-8. The slower metabolism of YJA-20379-8 in SIDM rats was confirmed by in-vitro tissue metabolism studies in which 50 μg of the drug was incubated for 30 min with the supernatant fraction of rat tissue homogenates after centrifugation at

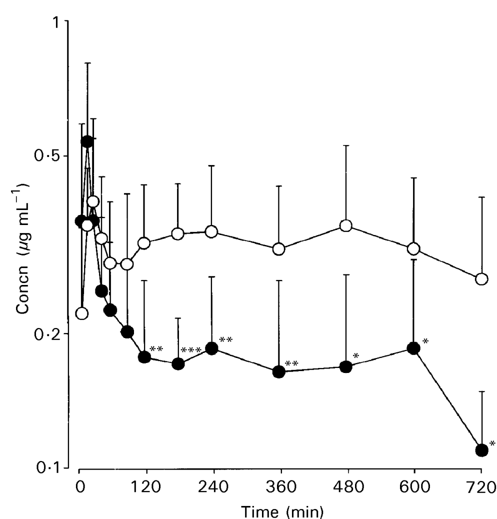

Figure 3. Mean arterial plasma concentration–time curves for YA-20379-8 after oral administration of the drug (50 mg kg^{-1}) to streptozotocin-induced diabetes mellitus rats (●, n = 10) and to control rats (○, n = 9). Bars represent standard deviation. *$P < 0·05$, **$P < 0·01$, ***$P < 0·001$ compared with control.

9000 *g*; the amounts of the drug remaining in liver (27·1 compared with 18·9 μg) and spleen (23·3 compared with 18·9 μg) were significantly greater in SIDM rats (Table 2). It has been reported (Mehvar 1991) that CL and CL_{NR} of atenolol enantiomers were significantly slower in SIDM rats. In SIDM rats, the Vd_{SS} decreased significantly (2400 compared with 3770 mL kg^{-1}) and similar results were also reported for cephradine (Nakashima et al 1992) and paracetamol (Watkins & Sherman 1992). However, the volume of distribution of digoxin (Watkins & Sherman 1992) and dexamethasone in pregnant rats (Mulay & Varma 1984) was reported to increase in SIDM rats. The exact reason for the significant decrease in Vd_{SS} of YJA-20379-8 in SIDM rats is not clear, although it might be because of saturation of tissue binding of YJA-20379-8 in SIDM rats with an increase in the unbound fraction of the drug at higher plasma concentrations (Figure 2). It has also been reported (Lee et al 1994) that tissue binding of bumetanide was saturated after large-dose intravenous administration of the drug to control rats. Pretreatment with streptozotocin caused a significant decrease in body weight gain (mean body weight decreased from 265 g before pretreatment with streptozotocin to 219 g at the seventh day just before drug administration), and a significant increase in liver weight (3·21 ± 0·511 compared with 2·82 ± 0·102% of body weight, $P < 0·001$) and kidney weight (0·886 ± 0·0927 compared with 0·750 ± 0·162% of body weight) after intravenous administration; similar results were obtained after oral administration (data not shown).

The mean arterial plasma concentration–time curves after oral administration of YJA-20379-8 to control rats (n = 9) and SIDM rats (n = 10) are shown in Figure 3. After oral administration, the plasma concentrations of YJA-20379-8 in SIDM rats were significantly lower from 3 to 12 h than those in control rats (Figure 3) and this resulted in a significantly smaller AUC_{0-12} (128 ± 31.0 compared with 219 ± 45.6 μg min mL^{-1}, $P < 0.001$). This could be because of reduced gastrointestinal absorption of YJA-20379-8 in SIDM rats because the AUC of YJA-20379-8 was significantly higher in SIDM rats after intravenous administration than in the control rats (Figure 2 and Table 1). The reduced gastrointestinal absorption of YJA-20379-8 in SIDM rats was proved by the amounts (%) of the oral dose of YJA-20379-8 recovered from the gastrointestinal tract as the unchanged drug after 24 h—the values were 19·2 and 32·9% for control and SIDM rats, respectively. YJA-20379-8 was reported (Chung 1998) to be stable in solutions of pH ranging from 1 to 14 for up to 48-h incubation at 37°C in a water-bath shaker at 50 oscillations min^{-1}. Because the CL of YJA-20379-8 was dose-independent after intravenous administration of the drug (10–50 mg kg^{-1}) to rats (Chung 1998), for purposes of comparison the extent of absolute oral bioavailability (F) was estimated by comparing the AUC (intravenous study) and AUC_{0-12} (oral study) data; the F values were 11·7 and 5·08% for control and SIDM rats, respectively. These data also indicated the reduced absorption of YJA-20379-8 from the gastrointestinal tract in SIDM rats.

The results obtained from the tissue studies are listed in Table 3. In control rats YJA-20379-8 had high affinity for the rat tissues studied; the tissue-to-plasma ratios were greater than unity in all the tissues studied except large intestine, muscle, and spleen (Table 3). The high affinity of YJA-20379-8 for rat tissues was confirmed by the substantial values of Vd_{SS}, 3770 mL kg^{-1}, after intravenous administration of the drug (50 mg kg^{-1}) to rats (Table 1). The tissue distribution and tissue-to-plasma ratios of YJA-20379-8 were no different in SIDM rats; except for the liver, the values for control and SIDM rats were not significantly different (Table 3).

Acknowledgements

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