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PHARMACOKINETICS AND ACETYLCHOLINESTERASE(ACHE) INHIBITORY EFFECTS OF DISTIGMINE IN STREPTOZOTOCIN-INDUCED DIABETIC RAT.

Hypothesis / aims of study

Distigmine bromide (distigmine) is a long-acting acetylcholinesterase (AChE) inhibitor that has been used in the treatment of detrusor underactivity (DU) in Japan and other several contories [1] Distigmine inhibits AChE in the urinary bladder and thereby indirectly enhances and prolongs the physiological effect of parasympathetic acetylcholine (ACh). This results in the increased stimulation of muscarinic receptors and enhances the contractile force of bladder smooth muscle. On the other hand, distigmine is associated with a serious adverse reaction, cholinergic crisis, due to a marked decrease in AChE activity. Since distigmine is eliminated through the renal excretion route, renal dysfunction is considered to be one of the risk factors for cholinergic crisis by this agent. Because diabetic nephropathy is the common cause of renal dysfunction, we used streptozotocin (STZ)–induced diabetic rat model to examine whether diabetic nephropathy affects to the pharmacokinetics and pharmacodynamics of distigmine.

Study design, materials and methods

Diabetic rats were induced by peritoneal injection of streptozotocin (STZ) at 50 mg/kg body weight in sodium citrate buffer. STZ-induced diabetic rats are associated with nephropathy as judged by HE staining, serum creatinine (SCre) and blood urea nitrogen (BUN). Blood samples were drawn through the needle placed in the tail vain at 0, 5, 15 and 30 min and 1, 1.5, 2.5, 4 and 6 h after oral administration of distigmine (0.1, 0.3 and 1.0 mg/kg). Plasma distigmine concentrations were measured by LC/MS/MS, as previously described [2]. Inhibitory effect of distigmine on AChE activity were measured by DTNB methods.

Results

Level of SCre in the STZ rats was significantly increased by 1.7 fold compared with that in the control rats. The level of BUN in STZ rats was about 3.6 times higher than that in the control rat. Histopathological studies in STZ-treated rats showed mild dilatation of urinary tubule and vacuolization in distal tubules. The plasma concentrations of distigmine in control and STZ-treated rats peaked 0.5 h after the oral administration and the inhibitory effect of distigmine on AChE activity in both rats blood peaked 1-2.2 h after the maximum plasma concentration of distigmine (fig. 1). The maximum concentration (C_{max}) of STZ-treated rats at 0.1, 0.3 and 1.0 mg/kg were 1.5, 1.2 and 1.8 times higher, respectively, than that in control rats at same doses (table 1). In addition, the AUC_{0-6} in STZ-treated rats (0.1, 0.3 and 1.0 mg/kg) were 1.4, 1.6 and 2.5 times higher, respectively, than control rat value (table 1). The inhibitory effect of distigmine on AChE activity reached a maximum of 1.5-2.7 h after the administration. In STZ-treated rats, maximum inhibitory effect values (I_{max}) of AChE at the dose of 0.3 mg/kg distigmine was significantly 1.6 times higher than that in control rats at the same dose.

Interpretation of results

From results of SCre, BUN and HE staining, renal function remained lower in our STZ-treated diabetic model rats. The C_{max} of plasma distigmine in STZ-treated rats was about 1.5 times higher than that of control rats. The AUC_{0-6} in STZ-treated rats increased by approximately 1.4-2.5 fold compared with the control values. I_{max} at dose of 0.3 mg/kg in STZ-treated rats significantly enhanced by 1.6-fold compared with control rat value at same dose, ensuing high plasma concentration of distigmine.These data have suggested that renal dysfunction influences significantly the pharmacokinetics of distigmine, since plasma distigmine is eliminated by renal excretion.

Concluding message

The current study has shown that plasma distigmine concentration was increased and AChE inhibitory effect was enhanced in STZ-treated rats compared with control rats. Therefore diabetes is one of the risk factors for cholinergic crisis by distigmine.

Table. Pharmacokinetic parameters of distigmine in the plasma of control and streptozocine (STZ)-treated rats after oral administration at 0.1, 0.3 and 1.0 mg/kg.

	Distigmine (mg/kg p.o.)					
	0.1		0.3		1.0	
	control	STZ	control	STZ	control	STZ
T_{max} (h)	0.73 ± 0.08	0.73 ± 0.30	0.38 ± 0.07	0.54 ± 0.06	0.42 ± 0.13	1.16 ± 0.79
C_{max} (ng/mL)	1.34 ± 0.53	1.85 ± 0.36	3.55 ± 0.22	4.35 ± 1.25	12.9 ± 3.0	23.1 ± 8.5
AUC_{0-6} (h ng/mL)	3.52 ± 1.23	4.75 ± 0.40	10.0 ± 1.2	16.1 ± 5.6	37.5 ± 3.8	94.4 ± 49

T_{max}: time to reach maximum plasma concentration, C_{max}: maximum plasma concentration, AUC_{0-6}: area under the plasma concentration versus time curve. Values are the mean ± S.E. of 3-7 rats.

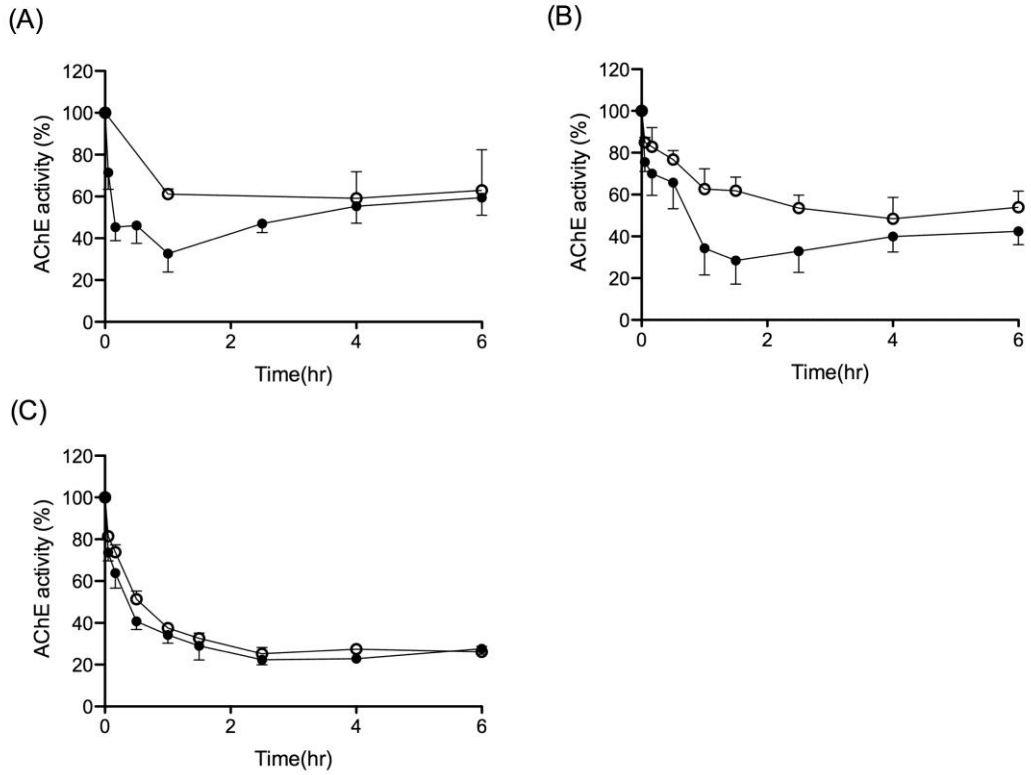

Fig. 1. Whole blood AChE activity-time profiles after the oral administration of distigmine at doses of 0.1 (A), 0.3 (B), 1.0 (C) mg/kg in control (●) or streptozocine (STZ)-treated (○) rats. Rats received distigmine (0.1—1.0 mg/kg) orally and then blood samples were taken from the tail vain. Each point represents the mean ± S.E. for 4—7 rats.

References
1. Biol Pharm Bull, 33: 653-658 (2010)
2. Drug Metab Pharmacokinet, 25: 254-261 (2010)

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