P-0280 HD-6277 is a selective GPR40 agonist with no drug-induced liver injury compare with TAK-875

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Background

TAK-875, a selective G-protein-coupled receptor 40 (GPR40) agonist, improves glucose tolerance hyperglycemia. However, TAK-875 was withdrawn from phase 3 clinical trials due to drug-induced liver injury (DILI). They asuured the cause of DILI by TAK-875 was to change the homeostasis of bile acid.

AIM

We should consider whether DILI by TAK-875 is associated with GPR40. The hepatotoxicity of TAK-875 is not a class effect of the GPR40 agonist, and HD-6277 is safety.

Material and methods

In this study, HD-6277 (a novel selective GPR40 agonist) was evaluated DILI with TAK-875 in vitro/vivo study. HD-6277 was assessed phospholipidosis in HepG2 cell. We examined the inhibitory effects on hepatobiliary transporters to explore the mechanisms underlying its hepatotoxicity. To evaluate the potential liver toxicity of HD-6277 and TAK-875 administered to Beagle dogs once daily orally by capsule in Beagle Dogs for a period of 2-weeks. And ALT levels were investigated in diet-induced obesity rats induced by ethanol-induced liver injury, following each drug’s administration for 2 weeks.

Results

HD-6277 was not induced phospholipidosis in HepG2 cell by 100 uM, but TAK-875 was. In hepatobiliary transporter inhibitory assay, HD-6277 showed safer value in influx and efflux transporters (NTCP; Na+/taurocholate cotransporting polypeptide, OATPs; organic anion transporter polypeptides, BSEP; human bile salt export pump, MRP2; multidrug resistance-associated protein 2) than TAK-875. TAK-875 induced liver changes consisting of multifocal bile duct proliferation(hyperplasia/hypertrophy). BUT HD-6277 did not. Moreover, in alcoholic fatty liver model, TAK-875 enhanced ALT level.

Fig.1 Pharmacological comparison of HD-6277 and TAK-875

Compou nds	Hyundai Pharm.		Toxicological Sciences, 157(1), 50-61, 2017.	
	TAK- 875	HD-627 7	TAK-875	TAK-875 -Glu
Bile acid Transporters				
MRP2	N.D.	81.0	N.T.	9.0
MRP3	39.0	N.D.	14.7	3.4
MRP4	N.T.	N.T.	11.7	6.7
NTCP	2.5	6.0	2.0	2.4
hOATP1B1	0.2	1.6	2.4	N.T.
hOATP1B3	0.4	1.8	11.6	N.T.
hBSEP	7.6	28.9*	14.3	41.6

N.T.: Not Treated;
N.D.: Not Determined;
*: expected value in solubility of
30 μM; TAK-875-Glu
(TAK-875-glucuronide):
metabolite of TAK-875;
h: human;
r: rat;
d: dog

Table.1 Hepatobiliary Transporter IC50 values

Conclusion

These findings suggest that HD-6277 and TAK-875 showed different inhibitory effects on hepatobiliary transporters. Probably, HD-6277 may be less effects to DILI than TAK-875. It was reported that TAK-875 induced liver toxicity may not related to a class effect of the GPR40 agonist.

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