International Journal of Pharmaceutics, 56 (1989) 269–271
Elsevier

IJP 01932

Effect of sodium taurodeoxycholate on distribution and elimination of amaranth in rats

Chang-Koo Shim, Sang-Kwon Yun, Min-Hwa Lee and Shin-Keun Kim

College of Pharmacy, Seoul National University, Seoul (Korea)

(Received 7 October 1988)
(Revised versions received 16 March and 19 May 1989)
(Accepted 26 June 1989)

Key words: Amaranth; Distribution volume; Ionic drug interaction; Systemic clearance; Taurodeoxycholate

Summary

The effect of a bile acid, taurodeoxycholate (TDC) on the distribution and elimination of amaranth (AM), an anionic model drug, was studied in rats. Plasma concentration data of AM were analyzed for systemic clearance (CL_s) and distribution volume at steady-state (Vd_{ss}) after i.v. injection to the rats being infused with various concentrations of TDC. CL_s and Vd_{ss} were found to decrease in proportion to the TDC concentration of the infusate. This is in contrast to the effect of TDC on the pharmacokinetics of methylene blue (MB), an organic cation. It was suggested that ionic interaction between ionic drugs and endogenous ionic substances might affect the pharmacokinetics of the drugs substantially.

Some cationic drugs, e.g. tetrabutylammonium bromide, isopropamide iodide and methylene blue (MB) were reported to form ion-pair complexes with sodium taurodeoxycholate (TDC), a representative bile salt (Shim et al., 1981; Shim, 1983). These drugs are known to be excreted into bile, but some cationic drugs like tetraethylammonium bromide do not form ion-pair complexes (Shim et al., 1981; Shim, 1983) and are not excreted into bile. TDC infused intravenously at a constant rate increased the distribution volume (Vd) of MB (Shim, 1986). The increase in lipophilicity of MB due to ion-pair complexation seemed to be the major cause of Vd increase.

Organic anions that are excreted into bile were classified into two groups; one group are anions of which biliary excretion is highly dependent (cholestatic) on the output of bile salts, while the other group is independent (choleretic) on the output of bile salts (Gregus et al., 1980). A different effect of TDC on the biliary excretion of sulfobromophthalein (BSP) and *p*-aminohippurate (PAH) was reported (Rollins et al., 1980). BSP was cholestatic but PAH was choleretic. They suggested that the incorporation of BSP into mixed micelles increases in the presence of TDC, but that PAH does not undergo such an interaction with TDC.

In this study, the effect of TDC on the plasma disposition of amaranth (AM; 3-hydroxy-4-[(4-

Correspondence to: C.K. Shim, College of Pharmacy, Seoul National University, San 56-1, Shinlim-Dong, Kwanak-Ku, Seoul 151-742, Korea.

sulfo-1-naphthalenylazo)]-2,7-naphthalenedisulfonic acid trisodium salt) was examined and compared with its effect on MB (Shim, 1986), an organic cation, in rats.

Under halothane anesthesia, the femoral vein and artery of male Wistar rats (200–350 g) were cannulated with polyethylene tubing (PE-50, Intramedic, Clay Adams, U.S.A.) for drug administration and blood sampling, respectively. The bile duct was cannulated with PE-10 polyethylene tubing. The rats were kept at the supine position and the body temperature was kept about 37 °C using a heating lamp during the surgery and experiment. After complete recovery from the anesthesia, 3% (w/v) mannitol–saline solution containing TDC (5.8, 11.6, 16.3 mM) was infused at a constant rate of 1.55 ml/h to the rats of the test group. To the rats of the control group, 3% (w/v) mannitol–saline solution without TDC was infused in the same manner. AM was injected intravenously at a dose of 50 μmol/kg (about 0.4 ml/rat) through the catheter 30 min after the infusion was started and then the catheter was reconnected to the infusion pump. Blood samples (0.22 ml) were taken at 5, 10, 20, 40, 60, 90 and 120 min from the femoral artery through the catheter. Blood samples were centrifuged at 6000 × *g* for 10 min and 0.1 ml samples of plasma were obtained. The plasma samples were diluted with saline and their absorbance values at 527 nm were measured spectrophotometrically (Takahashi et al., 1985).

As a result, plasma disappearance of AM was retarded as the TDC concentration of the infusate increased (Fig. 1). Some pharmacokinetic parameters obtained by a conventional 2-compartment model (Gibaldi and Perrier, 1975) with the aid of MULTI program (Yamaoka et al., 1981) were also affected by TDC infusion. The correlation between pharmacokinetic parameters and TDC concentration are listed in Table 1. AUC, CL_s, Vp, Vd_{ss}, K_{10} and $t_{(1/2)\beta}$ were inversely proportional to the TDC concentration of the infusate, but K_{21} increased proportionally. This means that the distribution and elimination of AM are related directly to TDC concentration. This is in contrast to the facilitated biliary excretion of MB, an organic cation, by TDC infusion through lipophilic ion-pair formation with TDC (Shim, 1986) , but consistent with our previous study (Shim and Chung, 1986).

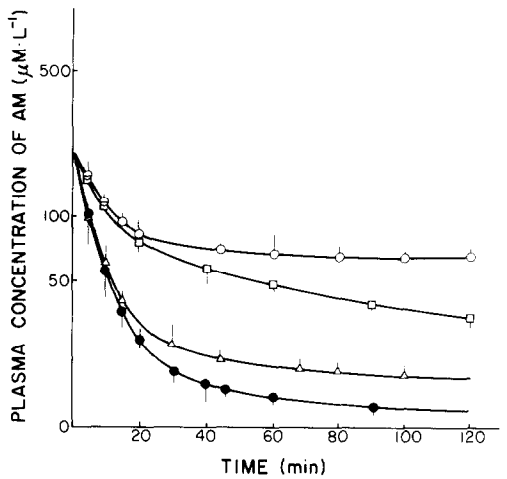

Fig. 1. Plasma disappearance of AM administered intravenously at a dose of 50 μmol/kg to rats infused intravenously (1.55 ml/h) with TDC of various concentrations ($n = 3$, mean ± S.E.M.). Solid curves were obtained by fitting the data to a 2-compartment model by the aid of MULTI program (Yamaoka et al., 1981).

Key: ● = control; △ = TDC 5.8 mM; □ = TDC 11.6 mM; ○ = TDC 16.3 mM.

A cholestatic or choleretic effect of TDC observed by Rollins et al. on some anionic drugs

TABLE 1

Correlation between TDC concentration in the infusate and some pharmacokinetic parameters of AM in rats [a]

Parameters	Correlation coefficient (r)	Significance level (P)
AUC (μM min)	+0.831	< 0.2
CL_s (ml/min/kg)	−1.000	< 0.001
Vd_{ss} (l/kg)	−0.947	< 0.02
V_p (l/kg)	−0.947	< 0.02
V_c (l/kg)	−0.858	< 0.1
K_{21} (1/min)	+0.982	< 0.01
K_{10} (1/kg)	−0.934	< 0.05
K_{12} (1/min)	+0.622	< 0.4
$t_{(1/2)\beta}$ (min)	−0.942	< 0.02

[a] AUC (area under the plasma concentration-time curve from time 0 to infinity), CL_s, Vd_{ss}, V_p (distribution volume of peripheral compartment), V_c (distribution volume of central compartment), K_{21} (distribution rate constant out of peripheral compartment), K_{10} (elimination rate constant from central compartment), K_{12} (distribution rate constant out of central compartment) and $t_{(1/2)\beta}$ were defined and calculated according to Gibaldi and Perrier (1975).

(Rollins et al., 1980) might be simply the reflection of the changed biliary or systemic clearance and distribution of the drugs induced by the ionic interaction of the drugs with the endogenous anion, TDC, in the body. Competition with TDC in the process of distribution and elimination (either biotransformation or excretion) was suggested as one of the possible mechanisms of decreased Vd_{ss} and CL_s of AM by TDC infusion. The exact mechanism of the different effect of TDC on AM (anion) and MB (cation) needs further study.

References

Gibaldi, M. and Perrier, D., Chap. 1, 2, 5 and Appendix 4. In *Pharmacokinetics*, Marcel Dekker, New York, 1975.

Gregus, Z., Fischer, E. and Varga, F., Effect of cholestyramine induced bile acid depletion on the hepatobiliary transport of cholephilic organic anions into liver cells and bile. *Arch. Int. Pharmacodyn. Ther.*, 245 (1980) 311–322.

Rollins, D.E., Freston, J.W. and Woodbury, D.M., Transport of organic anions into liver cells and bile. *Biochem. Pharmacol.*, 29 (1980) 1023–1028.

Shim, C.K., Effect of true partition coefficient on the determination of extraction coefficient of ion-pair complexes. *Yakhak Hoeji*, 27 (1983) 125–131.

Shim, C.K., Effect of ion-pair complexation with bile acids on the biliary excretion and systemic distribution of organic cationic drugs. *Arch. Pharm. Res.*, 9 (1986) 49–54.

Shim, C.K. and Chung, S.J., Effect of sodium taurodeoxycholate on biliary excretion of amaranth as an anionic model drug in rats. *J. Kor. Pharm. Sci.*, 16 (1986) 110–117.

Shim, C.K., Nishigaki, R., Iga, T. and Hanano, M., Determination of extraction constant, true partition coefficient and formation constant of ion-pair complexes of quarternary ammonium salts, tetrabutylammonium bromide and isopropamide iodide, with some organic anions by a solvent extraction technique. *Int. J. Pharm.*, 8 (1981) 143–151.

Takahashi, K., Wada, T., Higeshi, Y. and Yata, N., Pharmacokinetics in hepatic transport of amaranth in rats intoxicated with carbon tetrachloride and naphthylisothiocyanate. *Chem. Pharm. Bull.*, 83 (1985) 4973–4980.

Yamaoka, K., Tanigawara, Y., Nakagawa, T. and Uno, T., A pharmacokinetic analysis program (MULTI) for microcomputer. *J. Pharm. Dyn.*, 4 (1981) 879–885.