Comparative Studies of the Effect of Certain Drugs upon the Liver Functions

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While various kinds of drugs have been used for the treatment of liver diseases, many fundamental problems still remain to be studied in the field of pharmacotherapy of liver diseases. An attempt was made in this paper to make a comparative study of the effect of certain drugs upon the liver functions. The liver function studied here was examined from the rate of bile excretion, the rate of biliary excretion of phenolsulfonphthalein (PSP), and the rate of sulfathiazole acetylation of the liver.

Materials and Methods

1) Methods of bile collection and measurement of PSP excretion:

Rabbits were nephrectomized bilaterally and the common bile duct was canulated with a plastic tube to collect bile. Prior to operation the drug to be examined was injected intravenously. Exactly 30 minutes thereafter, 1 ml. per Kg. body weight of 0.6 per cent aqueous solution of PSP was injected intravenosly.

Bile was collected at 15 minutes intervals for 2 hours. The volume of the bile and PSP concentration of the bile was measured[1].

2) Technique of the isolated liver perfusion:

The technique used was essentially the same as that described by Ohishi[2].

The perfusate consisted of 30 ml. of the defibrinated rabbit blood, 60 ml. of normal saline and 10 mg. of sulfathiazole; a definite amout of the drug to be examined was also contained in this solution. The perfusion was carried out under the condition of 90 pulsation per minute and 15 ± 5 mmHg. pressure. The perfusate at 30 minutes intervals for 2 hours was assayed for free and acetylated sulfathiazole concentration according to the method of Tsuda[3], and percentage of the acetylation was calculated.

3) Pre-treatment of rabbits for the liver-perfusion experiment:

We know that when the bile is lost through a biliary fistula for several hours the liver function is decreased and this is useful for distinguishing the medicamental effects on the liver function[4]. The same procedure was used in this experiment. Namely, 5 hours before an isolation of the liver, a bile fistula and an intestinal fistula were made, and bile was continually diminishing; two doses of 20ml. each of normal

saline were administered intraintestinally at the 3 rd. and 4 th. hour, consecutively. The durgs examined were also injected intravenously at the 3 rd. and 4 th. hour.

4) The substances tested were as follows: sodium tioctate (TA), thiamine-8-(methyl-6-acetyl-dihydrothioctate)-disulfide hydrochloride (TATD), magnecium and pottacium-aspartate (ASP), 4-amino-5-imidazole carboxamide (AICA), orotic acid (OTA), adenine hydrochlorate (ADN), sodium adenosine triphosphate (ATP), sodium α-(1-hydroxy-cyclohexyl)-butylate (OHBA), para-hydroxy-phenyl-salicilamide (PHPS), sodium dehydrocholate (DHC), sodium ursodesoxycholate (U-DHC), reducted sodium dehydrocholate (R-DHC), and sodium taurodesoxy-cholate (T-DHC).

Dosage of the durugs is shown in Table I.

5) All the data were represented as the averrage value of 5 experiments.

Table I The Drugs Used in This Report

Abbreviation	The Name of Drugs	Dosage mg./Kg.
Control	Physiolosical saline	
OHBA	Sodium α-(1-hydroxy-cyclohexyl) butyrate	200
PHPS	Para-hydroxy-phenylsalicilamide	200
DHC	Sodium dehydrocholate	300
R-DHC	Reducted sodium dehydrocholate	300
U-DHC	Sodium ursodesoxycholate	20
T-DHC	Sodium taurodesoxycholate	25
TA	Sodium tioctate	10
TATD	Thiamine-8-(methy-6-acetyl-dihydrothioctate)-disulfide hydrochloride	14.2
ASP	Magnecium-aspartate and pottacium-aspartate	200
AICA	4-Amino-5-imidazole carboxamide	20
OTA	Orotic acid	10
ADN	Adenine hydrochlorate	10
ATP	Sodium adenosine triphosphate	10

Results

1) Bile output

As indicated in Table II. bile volume of the control group was 13.3 ml. for two hours, and it decreased gradually with the lapse of time. The bile volume was increased with all the drugs especially with DHC and R-DHC, except for AICA.

In the control group the bile output in the first thirty minutes was 4.0 ml. and it decreased with the lapse of time. This tendency was also revealed in all other groups except for the two groups of T-DHC and TATD. The higher the bile output during the first thirty minutes, the more the subsequent bile output was decreased. This phenomenon might be considered as a consequence of exhaustion of

Table II

Drugs	Bile Volume				
	30 min. (ml.)	60 min. (ml.)	90 min. (ml.)	120min. (ml.)	Total (ml.)
Control	4.0	3.4	3.1	2.8	13.3
OHBA	6.7	6.5	3.3	4.0	20.5
PHPS	5.0	4.2	4.0	2.6	15.8
DHC	7.5	7.2	4.9	4.4	24.0
R-DHC	11.3	7.8	6.0	4.7	29.8
U-DHC	4.4	3.5	3.9	3.5	15.3
T-DHC	3.5	4.6	4.0	3.9	16.0
TA	5.1	3.2	3.1	2.8	14.2
TATD	3.3	4.1	4.1	2.0	13.5
ASP	4.5	3.8	3.7	3.3	15.3
AICA	3.4	2.8	2.2	2.0	10.4
OTA	6.0	4.2	3.8	2.6	16.6
ADN	5.2	5.1	5.1	4.4	19.8
ATP	4.7	4.4	4.2	3.7	17.0

the liver or dehydration of the animal. Treatment with R-DHC and DHC revealed a marked choleretic activity to the degree of about two-times that of the control group.

2) Biliary excretion of PSP

The date on the biliary excretion of PSP are indicated in Table III. In the control group, 22.3 per cent of the injected PSP was excreted into the bile in a period of

Table III

Drugs	Biliary Excretion Rate of PSP				
	30 min. (%)	60 min. (%)	90 min. (%)	120 min. (%)	Total (%)
Control	7.2	5.7	5.0	4.4	22.3
OHBA	10.8	9.0	6.3	5.1	31.2
PHPS	13.3	10.2	7.4	5.6	36.5
DHC	2.2	2.8	2.5	2.3	9.8
R-DHC	4.1	3.3	3.4	3.0	13.8
U-DHC	8.3	5.0	3.8	3.4	20.5
T-DHC	6.0	3.1	2.6	1.8	13.5
TA	13.2	8.7	8.2	7.1	37.2
TATD	11.5	11.1	10.0	5.1	37.7
ASP	11.8	10.3	7.1	4.2	33.4
AICA	10.5	2.8	2.4	1.4	17.1
OTA	16.5	10.3	6.3	3.7	36.8
ADN	16.2	16.0	9.2	6.3	47.7
ATP	20·4	15.2	8.8	6.9	51.3

two hours. The PSP excretion was increased with the administration of all the drugs especially with that of ATP and ADN, except for U-DHC, AICA, T-DHC and DHC.

3) Acetylation activity of an isolated liver

The data on the sulfathiazole acetylation of an isolated rabbit liver are indicated in Table IV. The acetylation rate was increased moderately with the administration

Table IV

Drugs	Sulfathiazole Acetylation Rate of Liver			
	30 min. (%)	60 min. (%)	90 min. (%)	120 min. (%)
Normal	67.3	85.3	88.5	89.3
Control	48.6	60.6	63.1	65.8
OHBA	52.1	79.3	81.4	83.8
PHPS	46.3	74.0	77.6	79.5
DHC	16.0	26.8	43.4	56.5
R-DHC	29.5	56.2	64.2	74.0
U-DHC	37.5	63.2	73.5	75.5
T-DHC	17.5	30.8	46.2	52.5
TA	9.5	26.1	33.8	38.2
TATD	16.9	28.4	30.7	31.6
ASP	56.9	77.5	78.0	86.8
AICA	25.1	36.0	40.0	42.5
OTA	59.1	71.0	72.5	75.5
ADN	64.8	85.2	87.9	89.2
ATP	65.8	84.5	87.9	87.2

of PHPS, U-DHC, OTA and R-DHC, and increased markedly with that of ADN, ASP, ATP and OHBA. It was decreased moderately with the administration of TATD, TA and AICA, and decreased markedly with that of T-DHC and DHC.

DISCUSSION

The data described above are summarized in Fig. 1, in which the data is indicated as the decreasing or increasing percentage in comparison with the control group.

The administration of DHC and R-DHC resulted in a prominent rise in choleretic activity but biliary excretion of PSP was decreased respectively.

The administration of R-DHC resulted in a slight increase in acetylation ability of liver, while that of DHC showed a tendency to decrease. On a clinical application of choleretica, R-DHC might be better than DHC because the acetylation ability, which was considered as one of the detoxication abilities of the liver, was not reduced by the administration of R-DHC.

The administration of OHBA or PHPS did not result in a marked choleretic acti-

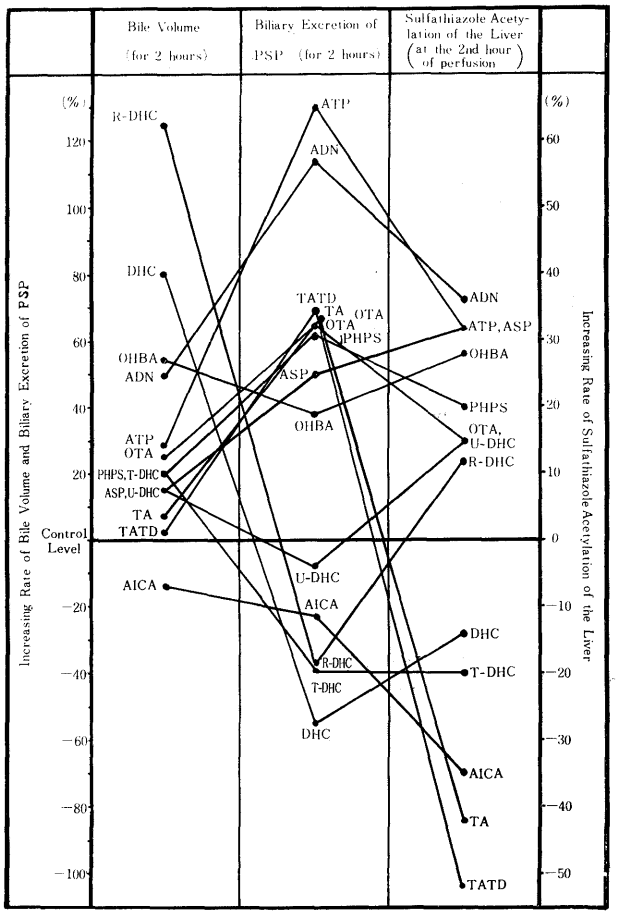

Fig. I. Incrasing Rate of the Bile Volume, Biliary Excretion of PSP and Acetylation Activity of the Liver

vity on rabbits, whereas they revealed a moderate choleresis in the experiments on rats, dogs and human beings.[5)6)7)]

Administration of ADN revealed a moderate choleretic activity and a marked increase in the acetylation ability of the liver and biliary excretion of PSP.

The administration of ATP and ASP revealed the most remarkable biliary excretion of PSP and acetylation ability of the liver, but no choleretic activity was resulted. It suggested that these drugs might be used as the hepatotonica (drugs which have a tonic effects on the liver function except for bile excretion) rather than the choleretica. However the effects of OTA on the liver did not equal that of ATP and ASP.

U-DHC had no effect on the liver function. T-DHC had no choleretic activity, while it revealed a decrease of biliary excretion of PSP as well as acetylation ability

of the liver.

These results suggested that these two drugs were not applicable to clinical use.

TA and TATD elevated the biliary excretion of PSP moderately but not the biliary output, while they decreased the choleretic actvity as well as the acetylation ability of the liver. Thus, the clinical application of such drugs as TA and TATD should not be considered.

The administration of AICA resulted in a decrease of biliary excretion of PSP and acetylation ability of the liver. The possibility of using AICA as a clinical application did not remain on the grounds of this data.

Summary

Thirteen drugs have been tested for their choleretic activity, biliary excretion of PSP and sulfathiazole acetylation ability of the liver.

Sodium dehydrocholate (DHC) and reduced sodium dehydrocholate (R-DHC) had a prominent choleretic action, while they had no ability to increase the biliary excretion of PSP and acetylation ability of the liver.

Adenine hydrochloride (ADN), sodium adenosine triphosphate (ATP), sodium α-(1-hydroxy-cyclohexyl)-butylate (OHBA), para-hydroxy-phenylsalicilamide (PHPS), orotic acid (OTA) and magnecium and potassium aspartate (ASP) had an ability to increase biliary excretion of PSP and sulfathiazole acetylation ability of the liver as well as bile excretion, but the degree of the increasing rate of the liver functions was variable.

Sodium ursodesoxycholate (U-DHC), sodium taurodesoxycholate (T-DHC) and 4-amino-5-imidazole carboxamide (AICA) decreased the sulfathiazole acetylation ability of the liver as well as biliary excretion of PSP.

Sodium tioctate (TA) and thiamine-8-(methyl-6-dihydrothioctate)-disulfide hydrochloride (TATD) increased the biliary excretion of PSP and decreased the sulfathiazole acetylation of the liver and the bile excretion.

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