Arch. Toxicol. 39, 219–223 (1978)

Archives of
TOXICOLOGY

The Influence of Unithiol and Spironolactone on the Biliary Excretion of ^{203}Hg in Rat

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Summary. Rats with cannulated bile ducts were intravenously given $^{203}HgCl_2$ in the dose of 120 μg of Hg^{2+} per rat. Intramuscular administration of Unithiol® (sodium 2,3-dimercaptopropanosulphonate) 4 and 7 h after ^{203}Hg injection markedly increased both biliary and urinary excretion of ^{203}Hg.

In rats with Spironolactone (17-Hydroxy-7α-mercapto-3-oxo-17α-pregn-4-ene-21-carboxylic acid, γ-lactone, acetate) pretreatment the effect of Unithiol® on the biliary excretion of ^{203}Hg was enhanced. Urinary excretion of mercury was lowest in comparison with Unithiol treated group.

Key words: Mercury — Spironolactone — Unithiol.

Zusammenfassung. Ratten mit Gallengangsfistel erhielten intravenös $^{203}HgCl_2$ mit 120 μg Hg^{2+}. Die Anwendung von Unithiol® (Natrium-2,3-dimercaptopropanosulfonat) 4 und 7 Stunden nach der ^{203}Hg-Injektion brachte einen bemerkenswerten Anstieg der ^{203}Hg-Ausscheidung mit Galle und Urin. Die Wirkung von Unithiol® auf die Galleausscheidung von ^{203}Hg war nach Vorbehandlung der Tiere mit Spironolacton (3-(3-oxo-7α-thioacetyl-17β-hydroxy-4-androsten-17α-yl)propionsäure-γ-lacton) erhöht. Die Urinausscheidung war dagegen sehr niedrig. Toxische Hg-Wirkungen auf die Niere können vermindert werden, wenn die Ausscheidung überwiegend mit den Faeces erfolgt.

Introduction

Spironolactone (SPL) is a hormonally inactive nontoxic steroide lactone, protective action of which against toxic effects of different pharmacologically active substances, including $HgCl_2$ (Seley, 1970), had been already proved in experimental animals. It was found that mercury excretion in feces was increased in rats pretreated with SPL [Garg et al. (1971) and Haddow and Marshall (1972]. The pre-

0340-5761/78/0039/0219/$ 1.00

treatment with SPL changes the uptake of mercury in the liver and kidneys, increases biliary excretion of mercury, increases direct passage of mercury from blood plasma to intestinal lumen, and independently increases the mercury content in erythrocytes (Haddow et al., 1972). The two major metabolic products of SPL are canrenone and thioacetic acid. Canrenone had no effect while thioacetic acid produced an effect similar to that produced by SPL (Klaassen, 1975). In our previously published paper (Cikrt and Tichý, 1975) it was shown that the effect of SPL on biliary excretion of mercury could be limited by the level of "mercury available" in the organism. We have by now given evidence that during the first hours after intravenous administration of $HgCl_2$ to SPL-pretreated animals a certain part of bile mercury is bound on a bile component with a low molecular weight (Tichý and Cikrt, in preparation). A similar picture was found when organic mercury compounds were given (Tichý et al., 1975).

Unithiol (sodium 2,3-dimercaptopropanosulphonate) is a water soluble derivative of BAL which is apparantly more effective in mobilizing mercury. Furthermore Unithiol (UNI) does not produce a redistribution of Hg^{2+} to the brain as observed after BAL treatment. UNI is effective in the treatment of occupational mercury poisoning (Aschbel, 1959), but there are no reports of its effects on alkyl mercury poisoning. This compound increases both urinary as well as fecal excretion of mercury. According to the opinion of Piotrowski et al. (1971) the action of UNI on the urinary excretion of mercury could be explained only partly by simple chelation. Signs of renal tissue damage were observed when the drug was applied following a relatively high dose of mercury (Piotrowski et al., 1971; Cikrt et al., in press). This process seems to limit practical application of this compound for the mobilization and elimination of mercury in human beings.

In the present paper the influence of UNI on the biliary excretion of mercury and combined effect of UNI and SPL on the excretion and distribution of ^{203}Hg in rats were studied.

Materials and Methods

Female Wistar rats (mean weight 200 g) were intravenously given $^{203}HgCl_2$ (in the dose of 120 μg of Hg^{2+} per rat).

SPL Pretreatment. SPL was administered (in the dose of 10 mg of SPL per rat) by gavage into stomach 24, 16 and 2 h before the mercury injection.

UNI Treatment. UNI was injected intramusculary (in the dose of 12.5 mg of UNI per rat) 4 and 7 h after administration of $^{203}HgCl_2$.

UNI + SPL Treatment. Both compounds were injected at same dose and time intervals as described above.

Bile duct was cannulated with polyethylene cannula PE-10 Intramedic. The feces and urine were collected separately. Radioactivities of plasma, urine, feces, and some organs were estimated on a well-type scintillation counter.

The rats were divided into four groups: UNI (only UNI treatment), SPL (only SPL pretreatment), UNI + SPL (combined treatment) and control group (without treatment).

Results and Discussion

Table 1 shows the influence of SPL, UNI or SPL + UNI treatment on the distribution and excretion of $^{203}Hg(II)$ in rats after 24 h after administration of mercury. In these experiments the bile ducts were not cannulated. The results are expressed in percentage rates of the administered dose. We did not find differences between UNI and UNI + SPL groups in the total excretion of mercury, but there were great differences in comparison with the control group. The excretion of ^{203}Hg in UNI group took place almost exclusively via urine, whereas in case of SPL via feces.

Treatment with the combination of SPL + UNI caused marked decrease of the uptake of ^{203}Hg in the kidneys and brain and the level in plasma. In that case the excretion of mercury was increased in both excretion pathways.

Table 2 presents the influence of SPL, UNI or SPL + UNI treatment on the distribution and excretion of $^{203}Hg(II)$ in rats after 10 h after administration of mercury. The results are again expressed as percentage rates of the administered dose. In rats in these experiments the bile ducts were cannulated. The total excretion of ^{203}Hg from the body in both UNI as well as UNI + SPL groups was equal and higher than in SPL group. The biliary excretion of ^{203}Hg during 10 h after mercury administration was the highest in case of UNI + SPL combination. The highest uptake of ^{203}Hg by the liver in case of SPL treatment due to redistribution of mercury was followed by the increased level of ^{203}Hg in the bile in the subsequent period of time. In the kidneys there were no differences between the UNI and UNI + SPL groups. It is interesting in the connection with the fact mentioned above (Table 1) that 24 h after administration of mercury there was a difference between UNI and UNI + SPL groups.

Figure 1 shows the rate of the biliary excretion of ^{203}Hg (expressed as percentage of administered dose per milligram of bile) during 10 h after ^{203}Hg administration. The effect of UNI was significantly higher after SPL pretreatment.

Conclusion

1. UNI-treatment increases markedly biliary excretion of mercury. This effect is time-limited probably due to quick elimination of UNI from the body.

2. After SPL-pretreatment the effect of UNI on the biliary excretion of mercury is significantly higher.

3. In spite of the fact that we did not find any differences between UNI and UNI + SPL groups in the total amount of mercury excreted from the body during first 24 h after administration of $^{203}HgCl_2$ we believed that combination of UNI and SPL is more suitable for the treatment of mercury poisoning in the experiment.

The excretion of ^{203}Hg after UNI + SPL treatment is predominantly via feces. This fact together with the lowest level of ^{203}Hg in the kidneys and plasma might decrease the undesirable toxic renal effect of mercury.

4. According our opinion further research in this field should be a study of combination of two or more chemical agents to enhance the removal of mercury from the body.

Table 1. The distribution and excretion of ^{203}Hg in rats 24 h after administration of mercury

Group	Number of rats	Brain	Kidneys	Liver	Plasma (8.3 ml)	Urine	Feces + GIT content	Total excretion
UNI	4	0.017 ± 0.001	6.3 ± 0.3	3.3 ± 0.2	1.86 ± 0.28	32.8 ± 0.6	11.0 ± 0.9	43.8
SPL	4	0.021 ± 0.0	22.5 ± 2.1	5.2 ± 0.5	0.74 ± 0.13	3.9 ± 1.3	27.9 ± 4.9	31.7
UNI + SPL	4	0.012 ± 0.002	2.7 ± 0.4	4.4 ± 0.5	1.08 ± 0.29	17.2 ± 2.7	29.6 ± 2.3	46.8
Control	4	0.037 ± 0.001	28.1 ± 1.2	10.8 ± 0.9	3.43 ± 0.59	7.4 ± 0.4	7.2 ± 0.6	14.6

UNI: Unithiol treatment (12.5 mg of UNI per rat i.m. 4 and 7 h after administration of ^{203}Hg). SPL: Spironolactone pretreatment (10 mg of SPL per rat by gavage into stomach 24, 16 and 2 h before ^{203}Hg injection). UNI + SPL: Unithiol and Spironolactone treatment (in the same dose and in the same time intervals as described above). ^{203}Hg was administered intravenously in the form of $^{203}HgCl_2$ (120 μg of Hg^{2+} per rat). Values in the table are expressed as percentages of the administered dose of ^{203}Hg (mean values and their 95% confidence intervals). For plasma the results are expressed in terms of the entire plasma volume [8.3 ml per 200 g rat (Spector, 1956)]. GIT: Gastrointestinal tract

Table 2. The distribution and excretion of ^{203}Hg in rats 10 h after administration of mercury

Group	Number of rats	Bile	Brain	Kidneys	Liver	Plasma (8.3 ml)	Urine	Feces + GIT content	Total excretion
UNI	8	5.86 ± 0.57	[a]	3.4 ± 0.2	5.9 ± 0.5	9.8 ± 0.4	19.1 ± 2.6	2.1 ± 0.2	27.1
SPL	4	3.65 ± 0.55	0.033 ± 0.003	34.8 ± 1.3	11.4 ± 1.4	1.8 ± 1.1	4.5 ± 0.6	2.2 ± 0.2	10.3
UNI + SPL	9	16.72 ± 1.64	[a]	2.9 ± 0.2	6.4 ± 0.7	9.2 ± 0.6	8.4 ± 1.9	1.9 ± 0.2	27.0
Control	4	0.28 ± 0.1	0.049 ± 0.004	33.6 ± 1.0	8.2 ± 0.7	2.7 ± 0.2	2.7 ± 0.6	1.7 ± 0.2	4.7

Legend see Table 1.

[a] The sample were not measured

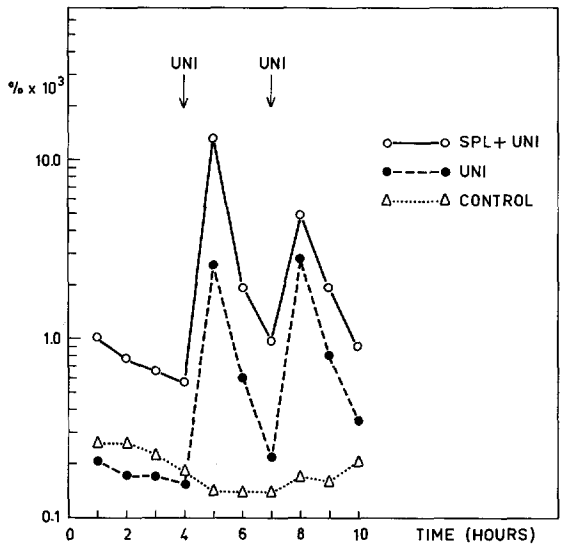

Fig. 1. Biliary excretion of ^{203}Hg during 10 h after administration of $^{203}HgCl_2$. The influence of Unithiol and Spironolactone treatment. Percentage of administered dose of ^{203}Hg excreted per mg of bile per minute ($\times 10^3$)

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Received April 28, 1977