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# Excretion of Creatinine into Gastrointestinal Tract in Renal-artery-ligated Rats

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Excretion of creatinine into gastrointestinal tract was studied using renal-artery-ligated rats as a model of patients suffering from renal failure.

In the rats of first group, both arterial branches of kidney and bile duct were ligated, and a saline solution was sent through the intestinal lumen to perform the intestinal dialysis. In the second group, after ligation of both renal arteries, a fine catheter was sutured with bile duct to collect the bile. After the intravenous administration of creatinine (138 mg or 34 mg/kg) through the femoral vein, the animals were kept for 1 hr until the creatinine level in body-fluid approach to steady state.

Under these steady state conditions, about 170 μg or 70 μg of creatinine was permeated into gastrointestinal tract every 1 hr from upper and lower region of jejunal mucosa after the administration of 138 or 34 mg/kg of creatinine, respectively.

The creatinine concentration in bile was similar to that in blood and about 200—270 μg or 90—110 μg of creatinine was excreted into bile every 1 hr after the injection of 138 or 34 mg/kg of creatinine, respectively.

Creatinine excreted from the intestinal mucosa and bile was collected together by perfusing the saline solution for 3 hr. About 3.5% of creatinine was excreted.

These results suggested that, at least, 20—30% of creatinine in body fluid may be excreted daily into gastrointestinal tract through the intestinal mucosa and from bile in the renal shutdown rats.

Hemodialysis treatment for patients suffering from acute or chronic renal failure is widely provided for removing "Uremic toxins" and controlling the electrolite imbalance.

Recently, some ingestible absorbents, such as activated charcoal, oxystarch, ethylen maleic acid copolymer and aluminum hydroxide gel, have been studied to remove waste metabolites directly form gastrointestinal tract as an additional management technique to assist the artificial kidney or diseased natural kidneys.[2–5] But there are few quantitative studies on the excretion of uremic wastes except urea[6] into gastrointestinal tract under the condition of renal shutdown in man and animals.

In the present study, we describe the excretion of creatinine into gastrointestinal tract through the mucous membrane of jejunum and bile duct in rats, the bilateral renal arteries of which were ligated.

## Experimental

**Animal Experiments**——Male Wistar rats weighing 250 to 400 g were used after fasting for 24 hr. Animals were divided into two groups to perform the intestinal dialysis in the first group and to collect the bile

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2) R.E. Sparks, N.S. Mason, P.M. Meier, M.H. Litt and O. Lindan, *Trans. Amer. Soc. Artif. Int. Organs*, **17**, 229 (1971).

3) R.E. Sparks, N.S. Mason, P.M. Meier, W.E. Samuels, H.M. Litt and O. Linde, *Trans. Amer. Soc. Artif. Int. Organs*, **18**, 458 (1972).

4) D.L. Gardner, R.D. Falb, B.C. King and D.C. Emmerling, *Trans. Amer. Soc. Artif. Int. Organs*, **17**, 239 (1971).

5) Z. Varghese, J.F. Moorhead and M.R. Wills, *Lancet*, **ii**, 985 (1973).

6) O. Wrong, *Med. J. Austr*, **2**, 281 (1967).

in the second group. Under pentobarbital anesthesia, in the rats of the first group, both arterial branches of kidney and bile duct were ligated, and then, jejunum was divided into two parts with equal length and each upper ends were sutured to catheters connected to a flow pump. After the intravenous administration of creatinine solution (138 mg or 34 mg/kg) through the femoral vein, the animals were kept for 1 hr until the creatinine level in body-fluid approach to the steady state. And then, a saline solution was sent through the intestinal lumen by the flow pump at a flow rate of 10 ml/hr after washing the intestinal lumen with 20 ml saline. The saline solution flowing out the intestinal lumen were collected at 1 hr intervals for 3 hr and the concentration of creatinine was determined.

In the second group, after ligation of both renal arteries, a fine catheter which was connected to 2.0 ml volumetric pipet was sutured with bile duct to determine the bile volume at 1 hr intervals for 3 hr.

**Determination of Creatinine**——Determination of creatinine in blood, bile and intestinal dialysate was done using Folin-Tungstic acid method.[7] And the experimental results are expressed as a mean of 3 to 6 experiments.

## Result and Discussion

Following infusion of 138 or 34 mg of creatinine, the blood creatinine level in the normal rats rapidly decreased to normal ranges of 1—2 mg/dl after 1 hr of the infusion, while the blood creatinine level in the renal shutdown rats was kept at high steady state level after 1 hr of the infusion and the concentration of 25 mg and 6.5 mg/dl of creatinine were maintained for more than 3 hr respectively as shown in Fig. 1.

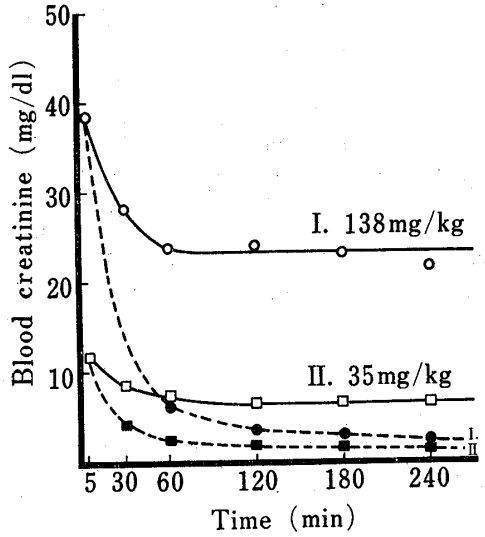


Fig. 1. Blood Creatinine Levels of Normal and Renal-artery-ligated Rats after *i.v.* Administration of Creatinine (○, ●: 138 mg/kg and □, ■: 35 mg/kg)

solid line: renal artery-ligated rats
dotted line: normal rats

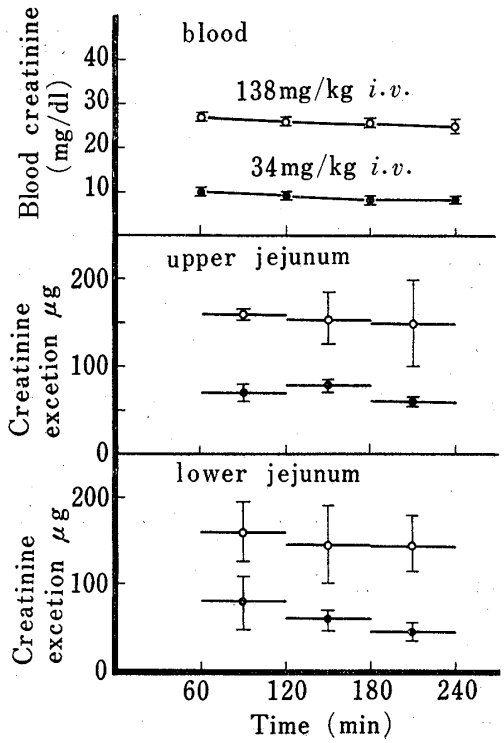


Fig. 2. Creatinine Excretions from Mucous Membrane of Upper and Lower Regions of Jejunum after *i.v.* Administration of Creatinine (○: 138 mg and ●: 34 mg/kg) in Bile- and Renal-artery-ligated Rats

About 170 μg or 70 μg of creatinine permeated into gastrointestinal tract every 1 hr from upper and lower regions of jejunal mucosa after the administration of 138 or 34 mg/kg creatinine

7) R.W. Bonsnes and H.H. Taussky, *J. Biol. Chem.*, **158**, 581 (1945).

respectively as shown Fig. 2, and no differences were observed between the upper and lower regions.

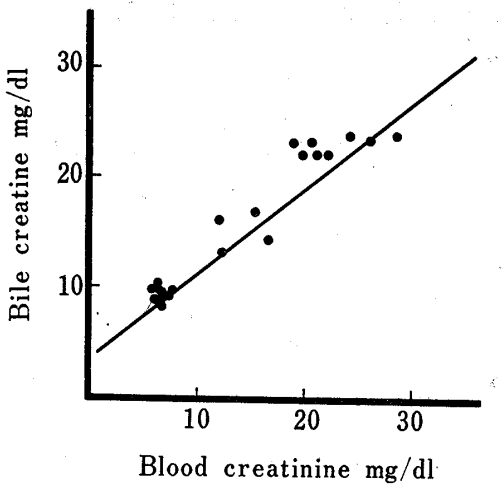


Fig. 3. Relationship between Creatinine Concentration of Blood and Bile in Renal-artery-ligated Rats

About 200—270 μg or 90—110 μg of creatinine was excreted into bile every 1 hr after the injection of 138 or 34 mg of creatinine and the creatinine concentration in bile was similar to that in blood as shown in Fig. 3 at a correlation coefficient 0.9596, ($p<0.01$).

Creatinine excreted from the intestinal mucosa and bile was collected by perfusing the saline solution, as described in experimental section, for 3 hr from 1 to 4 hr after the administration of 138 mg/kg of creatinine in renal-artery-ligated rats. About 3.5% of the creatinine was excreted as shown in Table I. This result was confirmed to be comparable to the result obtained from two individual experiments with the intestine and bile.

The results in this experiment suggested that, at least, 20—30% of creatinine in body fluid may be excreted daily into gastrointestinal tract through the intestinal mucous membrane and from bile in the renal shutdown rats. Similar results on urea excretion were obtained in normal[8] and uremic man.[6]

Table I. Total Excretion of Creatinine into the Gastrointestinal Tract after Intravenous Administration of Creatinine in Renal-artery-ligated Rats

| No. | Body wt g | Dose mg | Excretion mg | % |
|---|---|---|---|---|
| 1 | 280 | 38.5 | 1.5 | 3.9 |
| 2 | 250 | 34 4 | 1.3 | 3.8 |
| 3 | 267 | 36.7 | 1.1 | 3.0 |
| 4 | 280 | 38.5 | 1.2 | 3.1 |
| 5 | 320 | 44.0 | 1.4 | 3.2 |
| 6 | 250 | 34.4 | 1.3 | 3.8 |
| Ave. | 274.5±26.0 | 37.8±3.6 | 1.3±0.1 | 3.5±0.4 |

One hour after the intravenous administration of creatinine (138 mg/kg) in renal artery-ligated rats, creatinine excreted into the intestinal tract from duodenum mucosa, jejunum mucosa and bile was collected by perfusion of the saline solution for 3 hr. The method is described in the experimental section.

We concluded that there is a possibility that the oral administration of encapsulated "binder" of uremic toxins may be useful as a supplemental therapy of hemodialysis for patients suffering from renal failure.

8) M. Walser and L.J. Bodenlos, *J. Clin. Invest.*, **38**, 1617 (1959).