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# Elimination of Creatinine Following Intravenous Administration to Chronically $CCl_4$-Treated Rats[1)]

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The plasma levels of creatinine following intravenous administration to chronically (4 months) $CCl_4$-treated rats, which have been extensively used as an experimental model of cirrhosis, were compared with those of control rats.

The total body clearance of creatinine in chronically $CCl_4$-treated rats (6.95 ml/min/kg) was about 70% of the control value (9.85 ml/min/kg). This result suggested that the kidney as well as the liver is impaired by $CCl_4$ treatment. This means that the renal clearance of drugs whose elimination is mainly dependent on the kidney might be decreased by $CCl_4$ treatment.

**Keywords**——creatinine; plasma level; carbon tetrachloride-treated rat; total body clearance; renal clearance

In the preceding papers, the authors reported the disposition of creatinine and urea, which are water-soluble and are considered to pass through the water-filled pores of biological membranes easily, in nephrectomized rats,[2)] hereditary muscular dystrophic mice,[3)] hyperthyroid mice,[4)] and convulsed rats.[1)]

Many agents are known to induce liver disease, and some can also affect the kidney.[5)] However, precise assessments of the change of kidney function have not been carried out. Carbon tetrachloride is known to cause acute cellular injury in both liver and kidneys,[5)] and chronically $CCl_4$-treated rats, which are the most common experimental model for cirrhosis,[6)] have been well investigated as regards the toxic action on the liver. However, an accurate assessment of the effect of chronic $CCl_4$ treatment on the kidney, which is a very important organ in drug elimination, has not been made, in spite of its significance in relation to studies on the disposition of drugs using the above cirrhotic model.

In this paper, creatinine, for which the total body clearance is nearly equal to the sum of the clearances due to glomerular filtration and tubular secretion in rats,[7,8)] was selected as a model compound, and the elimination of exogeneous creatinine from plasma was examined in chronically $CCl_4$-treated rats and control rats to clarify the effect of chronic $CCl_4$ treatment on the kidney function.

## Experimental

**Chemicals**——[carbonyl-$^{14}$C]Creatinine hydrochloride (specific activity, 12.0 mCi/mmol) was purchased from Amersham International, Amersham, England. The radiochemical purity was greater than 98%. All other chemicals were of analytical grade and were used without further purification.

**Animals and $CCl_4$ Treatment**——Male Wistar rats, 9 weeks old, were purchased from Shizuoka Agricultural Cooperative of Experimental Animals, Hamamatsu, Japan, and were divided into two groups. The rats in one group were given a mixed solution of $CCl_4$: olive oil = 1 : 1 (v/v) subcutaneously twice a week for 4 months (1 ml/kg).[6)] The rats in the other group (control) were kept without any treatment for 4 months. All rats were chronically cannulated into the left external jugular vein with silicone polymer tubing (i.d. 1.0 mm; o.d. 1.5 mm, Dow Corning Co., Ltd., Tokyo, Japan) by the method of Upton.[9)]

**Plasma Levels of $^{14}$C-Creatinine Following Intravenous Administration**——Rats were given 10 $\mu$Ci/kg of $^{14}$C-creatinine (942 $\mu$g/kg as creatinine) intravenously into the external jugular vein. Blood samples (250 $\mu$l) were withdrawn periodically into small heparinized and ice-cooled tubes. Plasma samples (100 $\mu$l) were obtained by centrifuging the tubes at 3000 rpm for 15 min and then were dissolved in 0.5 ml of Soluene-350 (Packard Instrument Co., Downers Grove, Ill., U.S.A.).

**Radioactivity Measurement**——The radioactivity was determined in a Mark II liquid scintillation spectrometer (Nuclear-Chicago Corporation, Des Plaines, Ill., U.S.A.). All samples were determined with 10 ml of a toluene–Triton X-100 liquid scintillator (PPO 5 g, POPOP 300 mg, toluene 700 ml, Triton X-100 300 ml). The counting efficiencies were automatically determined by the $^{133}$Ba external standard ratio method and cpm was converted to dpm.

## Results and Discussion

Chronically $CCl_4$-treated rats have been used as the most general experimental model for cirrhosis.[6] However, little information relating to the effect of chronic $CCl_4$ treatment on the kidney is available at present. In this paper, the elimination of exogeneous creatinine from plasma was examined in chronically $CCl_4$-treated rats and control rats.

Creatinine is not metabolized in rats[7] (though the microflora in the gastrointestinal tract can metabolize[10] creatinine) and it is quantitatively excreted into the urine following intravenous administration to rats.[10] Therefore, all of the radioactivity in plasma obtained following intravenous administration of $^{14}$C-creatinine was regarded as originating from $^{14}$C-creatinine.

Plasma level-time data (Fig. 1) following intravenous administration of $^{14}$C-creatinine to chronically $CCl_4$-treated rats and control rats were analyzed on the basis of a two-compartment open model, and the estimated pharmacokinetic parameters are summarized in Table I. It is clear from Fig. 1 that the elimination of creatinine from plasma was delayed in $CCl_4$-treated rats as compared with the control. The rate constants relating to elimination, $\beta$

TABLE I. Pharmacokinetic Parameters for $^{14}$C-Creatinine Following Intravenous Administration to Chronically $CCl_4$-Treated Rats and Control Rats (Value for Parameter ± Standard Error[a])

| Parameter | $CCl_4$-treated ($n=8$)[b] | Control ($n=8$) |
|---|---|---|
| $A$ (dpm/ml) | $5.85\times10^{4}$[c] $\pm6.10\times10^{3}$ | $6.58\times10^{4}$ $\pm6.05\times10^{3}$ |
| $B$ (dpm/ml) | $1.24\times10^{4}$ $\pm1.78\times10^{3}$ | $1.11\times10^{4}$ $\pm1.07\times10^{3}$ |
| $\alpha$ ($min^{-1}$) | $5.31\times10^{-2}$[d] $\pm7.51\times10^{-3}$ | $6.74\times10^{-2}$ $\pm6.67\times10^{-3}$ |
| $\beta$ ($min^{-1}$) | $5.93\times10^{-3}$[d] $\pm8.05\times10^{-4}$ | $8.66\times10^{-3}$ $\pm5.74\times10^{-4}$ |
| $k_{10}$ ($min^{-1}$) | $2.22\times10^{-2}$[d] $\pm2.18\times10^{-3}$ | $3.41\times10^{-2}$ $\pm2.49\times10^{-3}$ |
| $k_{12}$ ($min^{-1}$) | $2.26\times10^{-2}$ $\pm4.17\times10^{-3}$ | $2.48\times10^{-2}$ $\pm3.60\times10^{-3}$ |
| $k_{21}$ ($min^{-1}$) | $1.42\times10^{-2}$[c] $\pm2.52\times10^{-3}$ | $1.71\times10^{-2}$ $\pm1.71\times10^{-3}$ |
| $V_1'$ (ml/kg) | $3.13\times10^{2}$ $\pm2.91\times10^{1}$ | $2.89\times10^{2}$ $\pm2.38\times10^{1}$ |
| $V_2'$ (ml/kg) | $5.00\times10^{2}$ $\pm1.36\times10^{2}$ | $4.19\times10^{2}$ $\pm8.14\times10^{1}$ |
| $(V_d')_{extrap}$ (ml/kg)[e] | $1.79\times10^{3}$ $\pm2.57\times10^{2}$ | $2.00\times10^{3}$ $\pm1.93\times10^{2}$ |
| $(V_d')_\beta$ (ml/kg)[f] | $1.17\times10^{3}$ $\pm2.24\times10^{2}$ | $1.14\times10^{3}$ $\pm1.46\times10^{2}$ |
| $AUC$ (dpm·min/kg) | $3.19\times10^{6}$[d] $\pm4.56\times10^{5}$ | $2.26\times10^{6}$ $\pm2.00\times10^{5}$ |
| $t_{1/2\beta}$ (min) | $1.17\times10^{2}$[d] $\pm1.59\times10^{1}$ | $8.00\times10^{1}$ $\pm5.30\times10^{0}$ |
| $k_{10}\cdot V_1'$ (ml/min/kg) | $6.95\times10^{0}$[d] $\pm9.40\times10^{-1}$ | $9.85\times10^{0}$ $\pm1.08\times10^{0}$ |

a) W. E. Deming, "Statistical Adjustment of Data," John Wiley and Sons, Inc., New York, 1946.
b) The number of input data, each of which is the mean for three rats.
c) Significantly different from the value for the control at $p<0.05$.
d) Significantly different from the value for the control at $p<0.01$.
e) $(V_d')_{extrap}=(\text{dose})/B$.
f) $(V_d')_\beta=V_1'\cdot k_{10}/\beta$.

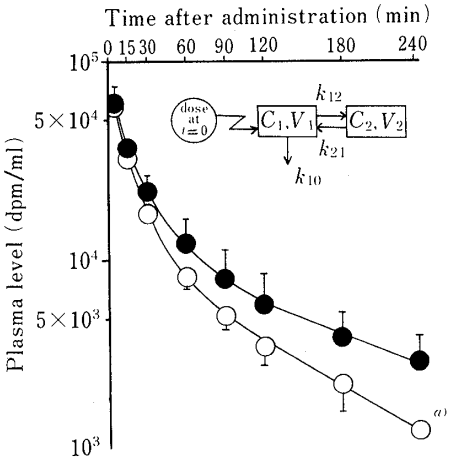


Fig. 1. Plasma Levels of $^{14}$C-Creatinine Following Intravenous Administration to Chronically $CCl_4$-Treated Rats (●) and Control Rats (○)

Each point represents the mean ± S.D. for three rats (*a*): mean for two rats). The points without a vertical bar have S.D. values smaller than the circles. The plots are computer-fitted curves (weight $(i)=1/C_i^2$, where $C_i$ is the plasma level).

and $k_{10}$, in $CCl_4$-treated rats were about 0.7 times those in the control rats ($p<0.01$). The distribution volumes, however, $V_1'$, $V_2'$, $(V_d')_{extrap}$ and $(V_d')_\beta$, were much the same in $CCl_4$-treated rats and the control ($p>0.05$), and the total body clearance ($k_{10}\cdot V_1'$) for $CCl_4$-treated rats (7.0 ± 0.9 ml/min/kg) was slightly but significantly ($p<0.01$) lower than that for the control (9.9 ± 1.1 ml/min/kg). This result suggests that the kidney as well as the liver is impaired by $CCl_4$, treatment, since the total body clearance of creatinine is almost equal to the sum of the clearances due to glomerular filtration and tubular secretion in rats.[7,8] This means, therefore, that the renal clearance of drugs whose elimination is mainly dependent on the kidney might be decreased by $CCl_4$ treatment.

## References and Notes


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