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Disposition of Urea following Intravenous Administration to Rats[1)]

KIKUO IWAMOTO, JUN WATANABE,* KATSUAKI IMAI, MASAHIKO SHIBATA, JUNJI HIRATE, and SHOJI OZEKI

Department of Biopharmaceutics, Faculty of Pharmaceutical Sciences, Nagoya City University, 3-1, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

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To evaluate the distribution, metabolism and excretion of urea in normal rats, plasma concentration profiles, whole-body autoradiograms and urinary, fecal and expiratory excretions following intravenous administration of ^{14}C-urea were investigated. High (1000 mg/kg) and low (0.0675 or 0.117 mg/kg) doses of urea were employed to examine dose-induced differences in the plasma levels and in the whole-body autoradiograms. Plasma radioactivity–time curves were analyzed according to a two-compartment open model. There were no significant differences in almost all of the pharmacokinetic parameters for these two doses. Even in the case of parameters with significant differences (α, β and k_{10}), the dose dependency was considered to be rather small. When these parameters are compared with those for creatinine, k_{12} and k_{21} (which are both transfer rate constants for urea between plasma and tissue compartments) were significantly larger than those for creatinine, while $(V_d')_{extrap}$ for urea was about one-third of that for creatinine. There was also no significant dose dependency in the whole-body autoradiograms. The distribution pattern of urea radioactivity was almost uniform except in the kidney and urinary bladder even at an early stage (at 5 and 20 min). Following the intravenous doses, urea was regarded as being eliminated predominantly *via* the renal route, since more than 80% of the dose was excreted into the urine in 24 h. However, expiratory excretion of the radioactivity was about 12% in 24 h following *i.v.* administration of ^{14}C-urea, while that after *p.o.* administration was approximately 37%.

Keywords——urea; distribution; creatinine; plasma level; urinary excretion; expiratory excretion; volume of distribution; whole-body autoradiography; dose independency

Although urea has been considered to be suitable for use as a model compound for studies on the permeation across biological membranes and/or the distribution in tissues or organs of relatively small, water-soluble and weakly basic drug molecules, there are no detailed reports on disposition or distribution kinetics for urea either in man or in experimental animals.

The reduction of cerebrospinal fluid pressure by urea which was administered intraperitoneally at a relatively high dose (2 g/kg) to rats was monitored periodically by Reed and Woodbury.[2)] They suggested that urea enters two (slowly and rapidly distributed) brain compartments at different rates. On the other hand, distribution kinetics of urea were first (but only qualitatively) studied by determining the plasma elimination curve and urinary excretion of ^{14}C-urea following intravenous administration of 100 or 200 mg/kg as urea to rats which were deeply anesthetized with urethane.[3)]

It has been believed for a long time that urea is the end-product in the metabolism of circulating nitrogenous compounds (amino acids) biosynthesized in the liver and is thus metabolically inert both in man and in experimental animals. However, several reports have appeared demonstrating that the intestinal microflora can substantially destroy urea to form carbon dioxide and ammonia in man,[4–6)] rats[7)] and mice.[8,9)] Furthermore, it has been reported that the cumulative expiratory excretion of $^{14}CO_2$ following subcutaneous or intraperitoneal administration of ^{14}C-urea to rats was about 14[10)] or 35[7)] % of the dose, respectively, in 24 h. In most of the above studies,[4–10)] urea was administered at relatively low doses ranging from a trace amount to approximately 5 mg/head.

Changes in the size of the dose or the condition of subjects or experimental animals may frequently influence the disposition kinetics of certain drugs or chemical substances. In our previous work, two dose levels of creatinine, which might also be regarded as a model compound for studies on the disposition of water-soluble and weakly basic drug molecules in the body, were employed in order to investigate its distribution in rats.[11] However, there is no detailed report describing, on a pharmacokinetic basis, the distribution, metabolism and excretion of urea following intravenous or oral administration at different dose levels, either in normal subjects or in normal unanesthetized experimental animals.

Therefore, the purposes of the present investigation were to estimate and compare several pharmacokinetic parameters obtained by analysis of the plasma radioactivity–time curves following intravenous administration of ^{14}C-urea at two (high and low) dose levels to normal and unanesthetized rats, to examine the distribution pattern of the radioactivity by whole-body autoradiography following the *i.v.* dosings, and to evaluate the urinary, fecal and expiratory excretions of radioactivity following the *i.v.* or *p.o.* administration.

Materials and Methods

Materials——^{14}C-Urea was purchased from New England Nuclear, Boston, Mass., U.S.A. The specific radioactivity was 8.9 or 51.6 mCi/mmol and the radiochemical purity was more than 97%. Ethanolamine used for trapping $^{14}CO_2$ was of solvent grade suitable for liquid scintillation counting (Katayama Chemicals Co., Ltd., Nagoya, Japan). So une-350 (Packard Instruments Co., Downers Grove, I11., U.S.A.) was used for solubilization of fecal samples. All other chemicals were of analytical grade and were used without further purification.

Unlabelled urea was added to the radioactive compound to prepare the high dose (1000 mg/kg) solution which was estimated to produce a blood urea level of more than about a hundred times the endogenous value in rats. On the other hand, the low doses (lower than 0.7 mg/kg in the present experiments) were regarded as too low to affect the endogenous urea level in rats.

Animals——Male Wistar rats weighing 170 to 240 g were used for all experiments. All rats were chronically cannulated into their right external jugular vein with silicone polymer tubing (i.d. 1.0 mm; o.d. 1.5 mm, Dow Corning, Tokyo, Japan) by slightly modifying the method of Upton.,[12] except for rats used in the whole-body autoradiography experiments. Cannu ated rats were used for each experiment 2 d after surgery. In the case of the experiments for measuring excretion or expiration of radioactivity following intravenous or oral administration, rats were fasted for over 15 h before dosing.

Plasma Concentration following Intravenous Administration——Rats were given 9.1 or 10.0 μCi/kg of ^{14}C-urea (0.0675 mg/kg and 1000 mg/kg as low and high doses of urea, respectively) rapidly into the jugular vein. Blood samples (about 250 μl) were withdrawn periodically into small ice-chilled heparinized tubes. Plasma samples were immediately obtained by centrifuging the tubes at 3000 rpm for 15 min. An aliquot (100 μl) of the plasma was used for scintillation counting.

Whole-body Autoradiography——Rats were given 100 μCi/kg of ^{14}C-urea (0.117 mg/kg and 1000 mg/kg as low and high doses of urea, respectively) into the tail vein and sacrificed at 5 and 20 min following the administration by soaking them in dry ice–acetone (−78°C) immediately after light anesthesia with ether. Sections (40 μm) were obtained with a microtome (Yamato 1111, Tokyo, Japan) at about −25°C, and attached to MAG TAPE, NA-70 (Nakagawa Seisakusho Co., Ltd., Tokyo, Japan). After being dried in a freeze-dryer for a few days, the sections were placed in contact with X-ray films (No. 150, Fuji Photo Film Co., Ltd., Nagoya, Japan) for 20 d at 4°C. The films were developed and then fixed to produce the autoradiogram in a conventional manner. To evaluate the distribution pattern of radioactivity using the autoradiograms, the ratio of the darkness in each tissue or organ to that in heart blood was determined by measuring optical density with a Sakura PDA-11 densitometer (Sakura X-Ray Co., Ltd., Nagoya, Japan). Optical density due to the radioactivity in a tissue or organ was usually measured for 5 or 10 points (each point had a diameter of 1 mm) to obtain the mean value. Then the net optical density was calculated from the mean density by subtracting the mean background density.

Urinary, Fecal and Expiratory Excretions following Intravenous or Oral Administration——For the periodical evaluation of urinary excretion, rats were kept individually in Bollman cages (T-451, Tokiwa Kagaku Kikai Co., Ltd., Tokyo, Japan) immediately after intravenous administration of 10 μCi/kg of ^{14}C-urea (0.117 mg/kg and 1000 mg/kg as low and high doses of urea, respectively) and urination was induced by making them sniff at a cotton pad wetted with ether. For the simultaneous evaluation of urinary, fecal and expiratory excretions of radioactivity following intravenous or oral administration of 10 μCi/kg of ^{14}C-urea (0.675 mg/kg and 0.699 mg/kg as urea for *i.v.* and *p.o.* dosing, respectively), rats were housed individually in metabolic cages (KN-450, Natsume, Tokyo, Japan) equipped to capture $^{14}CO_2$ in a mixture of ethanolamine

and methanol (1: 2, v/v) as well as to collect the urine and feces separately. An aliquot (0.5 or 1.0 ml) of the ethanolamine–methanol mixture and an aliquot (100 μl) of appropriately diluted urine were directly used for radioactivity counting. Solid fecal pellets were converted to pasty samples by moistening with distilled water and a part (about 20 to 30 mg) of the paste was utilized for analysis.

Radioactivity Measurement——The radioactivity was determined in a Mark II liquid scintillation spectrometer (Nuclear-Chicago Corporation, Des Plaines, I11., U.S.A.). All samples were directly determined in 10 ml of toluene–Triton X-100 liquid scintillator (PPO 5 g, POPOP 300 mg, toluene 700 ml, Triton X-100 300 ml), except for fecal paste, which was solubilized by adding 1 ml of Soluene-350 before mixing it with the scintillator. The counting efficiencies were automatically determined by the ^{133}Ba external standardization method and cpm values were converted to dpm.

Results and Discussion

Plasma Concentration following Intravenous Administration

Figure 1 shows plasma elimination curves for ^{14}C-urea given to rats at high (1000 mg/kg as urea) and low (0.0675 mg/kg as urea) doses. The results were analyzed by a two-compartment open model as depicted in Fig. 1(A). It was demonstrated that the plasma radioactivity declined in a biexponential fashion in both groups of rats (given high and low doses of urea). Bourne and Barber have demonstrated that a triexponential rather than a biexponential function as fitted to the plasma data gave a much better description of the experimental results in urinary excretion of the compound in deeply anesthetized rats that had been treated with 1.4 g/kg of urethane (*i.p.*).[3] The dose which they employed was 100 or 200 mg/kg as urea, being exactly one-tenth or two-tenths of the high dose in the present study. In addition, they did not report estimated values for pharmacokinetic parameters. It is thus impossible to compare directly the disposition kinetics of ^{14}C-urea obtained by us with their data. Pharmacokinetic parameters as estimated by least-squares regression analysis are summarized in Table I along with those obtained for creatinine given to rats at a low dose (0.0704 mg/kg as creatinine).[11]

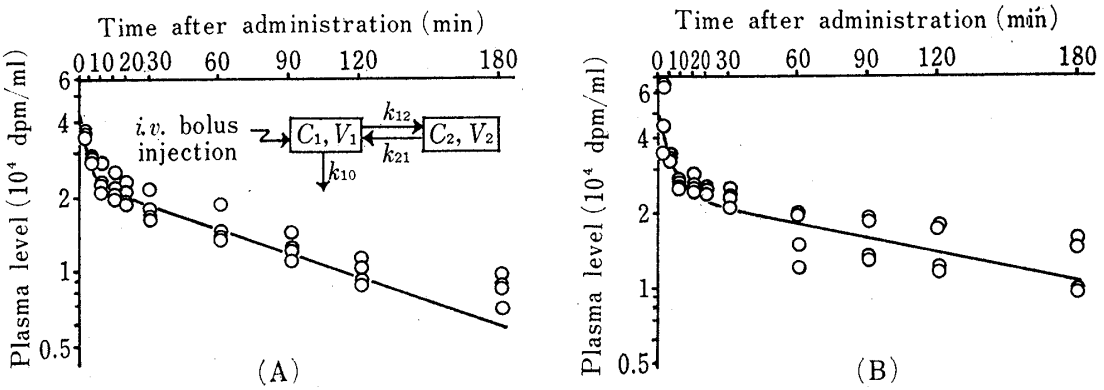


Fig. 1. Plasma Levels of ^{14}C-Urea following Intravenous Administration (10 μCi/kg) of High (A) and Low (B) Doses to Four Rats

(A): high dose (1000 mg as urea/kg).
(B): low dose (0.0675 mg as urea/kg).
The solid lines are the computer-fitted curves (weight(i)$=1/(C_i)^2$).

There were no significant differences in the values of V_1, V_2, AUC, $(V_d')_{extrap}$ and $V_d'_\beta$ estimated for high and low doses. There was also no significant difference in A and B values between the high and low doses when the radioactivity given in the high dose was normalized to be the same (10 μCi/kg) as that in the low dose. In other words, none of the estimated parameters except α, β and k_{10} showed any significant differences which were dependent on the difference in the dose levels. Significantly larger values for α, β and k_{10} were obtained in the case of high dose ($p<0.05$). However, the difference in these parameters was relatively small (approximately 1.4 to 1.9 times) though there was an extremely large (about 1.5×10^4

TABLE I. Pharmacokinetic Parameters for ^{14}C-Urea and ^{14}C-Creatinine following Intravenous Administration to Rats (Value for Parameter ± S.E.[a])

Parameters	Urea		Creatinine (0.0704 mg/kg) ($n=40$)
	High dose (1000 mg/kg) ($n=40$)	Low dose (0.0675 mg/kg) ($n=40$)	
A, dpm/ml	2.08×10^4 $\pm0.36\times10^4$	2.52×10^4 $\pm0.60\times10^4$	5.13×10^4 $\pm2.77\times10^4$
B, dpm/ml	2.36×10^4 $\pm0.10\times10^4$	2.34×10^4 $\pm0.20\times10^4$	7.24×10^3 $\pm7.72\times10^2$ [e]
α, min^{-1}	$2.76\times10^{-1}\pm0.78\times10^{-1}$ [d]	$1.46\times10^{-1}\pm0.56\times10^{-1}$	$8.62\times10^{-2}\pm6.01\times10^{-3}$ [e]
β, min^{-1}	$7.54\times10^{-3}\pm0.73\times10^{-3}$ [d]	$5.16\times10^{-3}\pm0.80\times10^{-3}$	$1.15\times10^{-2}\pm8.48\times10^{-4}$ [e]
k_{10}, min^{-1}	$1.39\times10^{-2}\pm0.17\times10^{-2}$ [d]	$1.03\times10^{-2}\pm0.18\times10^{-2}$	$4.79\times10^{-2}\pm2.28\times10^{-3}$ [e]
k_{12}, min^{-1}	$1.19\times10^{-1}\pm0.43\times10^{-1}$	$6.81\times10^{-2}\pm3.16\times10^{-2}$	$2.91\times10^{-2}\pm3.12\times10^{-3}$ [e]
k_{21}, min^{-1}	$1.50\times10^{-1}\pm0.36\times10^{-1}$	$7.32\times10^{-2}\pm2.57\times10^{-2}$	$2.08\times10^{-2}\pm2.07\times10^{-3}$ [e]
V_1, ml/kg	4.55×10^2 $\pm0.40\times10^2$	4.56×10^2 $\pm0.60\times10^2$	3.79×10^2 $\pm1.88\times10^1$ [e]
V_2, ml/kg	3.63×10^2 $\pm1.60\times10^2$	4.25×10^2 $\pm2.53\times10^2$	5.32×10^2 $\pm8.20\times10^1$ [d]
AUC, dpm·min/ml	3.21×10^6 $\pm0.32\times10^6$	4.71×10^6 $\pm0.81\times10^6$	1.23×10^6 $\pm3.34\times10^5$ [e]
$(V_d')_{extrap}$, ml/kg[b]	8.57×10^2 $\pm0.36\times10^2$	9.48×10^2 $\pm0.81\times10^2$	3.07×10^3 $\pm3.27\times10^2$ [e]
$V_d'_\beta$, ml/kg[c]	8.39×10^2 $\pm1.50\times10^2$	9.10×10^2 $\pm2.44\times10^2$	1.57×10^3 $\pm1.58\times10^2$ [e]
$t_{1/2\beta}$, min	91.9 ±8.9 [e]	134 ±20.8	60.3 ±4.4 [e]

a) W.E. Deming, "Statistical Adjustment of Data," John Wiley and Sons, Inc., New York, 1946.
b) Dose/B.
c) V_1k_{10}/β.
d) Significantly different from low dose of urea at $p<0.05$.
e) Significantly different from low dose of urea at $p<0.01$.

times) difference between the two dose levels. In contrast, the reverse tendency has been observed with creatinine,[11] *i.e.*, the above parameters for the high dose of creatinine were significantly but very slightly smaller than those for the low dose.

Since it was recognized that all the pharmacokinetic parameters estimated for both urea and creatinine[11] exhibited no distinct dose dependency in normal rats, a brief comparison between these two compounds was made only when these were administered in low doses. Relatively large (more than three times) and significant differences were observed in B, k_{10}, k_{21}, AUC and $(V_d')_{extrap}$. The parameters related to elimination, β and k_{10}, were smaller for urea. However, the parameters related to the transfer between compartment 1 and 2, k_{12} and k_{21}, were larger for urea. This suggests that urea is more rapidly and readily distributed in the body than creatinine when administered intravenously. Moreover, $(V_d')_{extrap}$ for urea was approximately one-third of that for creatinine.

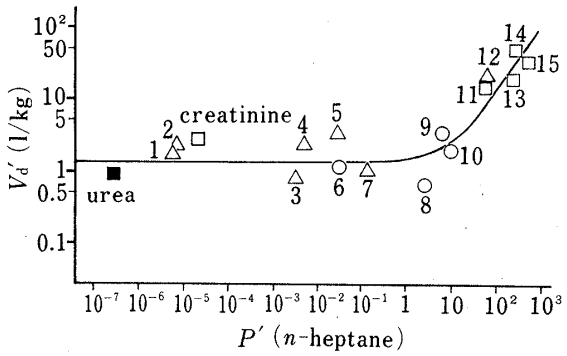


Fig. 2. Relationship between Apparent Volume of Distribution (V_d') and Apparent Partition Coefficient (P') for Basic Drugs

○, rabbits; □, ■, rats; △, dogs. 1, ephedrine; 2, norephedrine; 3, *N*-acetyl-4-aminoantipyrine; 4, torazoline; 5, quinidine; 6, antipyrine; 7, chlordiazepoxide; 8, *p*-toluidine; 9, 3,4-xylidine; 10, *o*-chloroaniline; 11, promazine; 12, fluphenazine; 13, trimeprazine; 14, chlorpromazine; 15, triflupromazine. Values of $(V_d')_{extrap}$ were tentatively used as V_d' in this paper for the chemicals whose blood levels were analyzed by the two-compartment open model.

A certain relationship between apparent volume of distribution (V_d') and apparent partition coefficient (P') for basic drugs has been established by Watanabe and Kozaki,[13,14] indicating that V_d' is almost constant in the region of low P' and increases in the region of high P'. The apparent partition coefficient for urea in an *n*-heptane–water system (at 25°C) has been estimated to be 3×10^{-7}.[15] As shown in Fig. 2, the plot for urea was fairly close to the solid

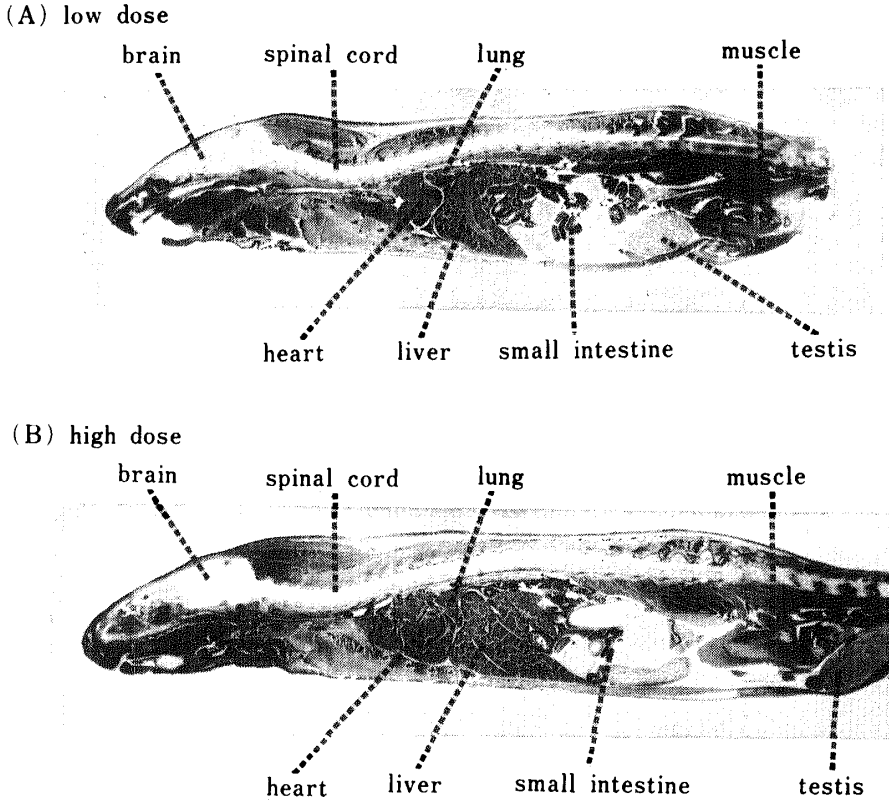


Fig. 3. Autoradiograms showing the Distribution of Radioactivity (Dark Area) in Rats at 5 min following Intravenous Administration of ^{14}C-Urea (100 μCi/kg)

(A): low dose (0.117 mg as urea/kg).
(B): high dose (1000 mg as urea/kg).

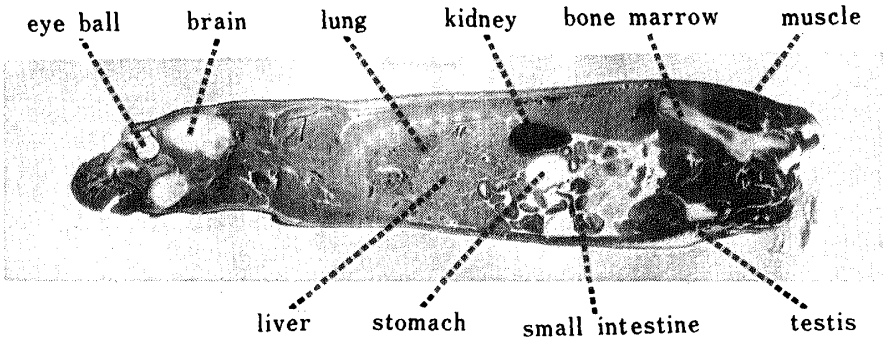
line which was calculated according to the drug distribution model[13,14] as well as to the plot for creatinine.[11]

Whole-body Autoradiography following Intravenous Administration

In order to compare the distribution pattern of urea at high (1000 mg/kg) and low (0.117 mg/kg) doses, whole-body autoradiograms were produced at 5 and 20 min after intravenous administration of ^{14}C-urea (100 μCi/kg), as shown in Fig. 3 and Fig. 4, respectively. The times of 5 and 20 min refer to a time point during the period when the α-phase is predominantly involved and one when the β-phase begins to appear, respectively. At both doses, radioactivity seemed to be distributed almost homogeneously in the liver, muscle, fat or gastrointestinal tract. Table II summarizes the ratio of darkness in various important relatively large organs or tissues to that in heart blood. In spite of the extraordinarily large (about 8500 times) difference between these dose levels of urea, changes in the distribution pattern of the radioactivity seemed to be rather small or insignificant. The ratio in the brain, eye-ball, spinal cord, stomach (both wall and contents) or testis was larger (approximately 1.5 to 6.1 times) at 5 min after the high dose than after the low dose, while that in all other organs or tissues was not altered or decreased (by approximately 20 to 70%) at the high dose. However, the former tendency for the radioactivity in several organs to increase with dose disappeared at 20 min, when the distribution pattern of the radioactivity became almost completely uniform except in the kidney and urinary bladder.

It was noted from a comparison of the distribution pattern following a low dose of urea with that for creatinine[11] that urea tended to be distributed homogeneously earlier than creatinine. This might be explained by the significant differences in the values of k_{12} and k_{21} estimated for these compounds.

(A) low dose



(B) high dose

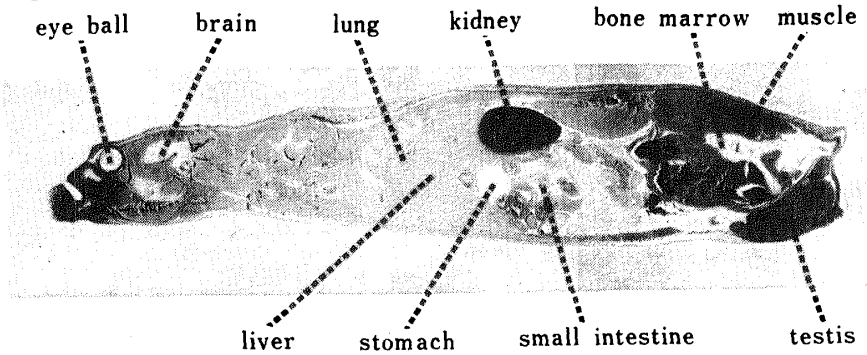


Fig. 4. Autoradiograms showing the Distribution of Radioactivity (Dark Area) in Rats at 20 min following Intravenous Administration of ^{14}C-Urea (100 μCi/kg)

(A): low dose (0.117 mg as urea/kg).
(B): high dose (1000 mg as urea/kg).

TABLE II. Relative Radioactivities of Various Organs or Tissues with Respect to Heart Blood in Autoradiograms of Rats[a)]

Organs or tissues	Low dose[b)]		High dose[c)]	
	5 min	20 min	5 min	20 min
Heart blood	1.00	1.00	1.00	1.00
Adrenal	1.24	1.18	0.976	0.994
Bone marrow	1.29	1.07	0.528	0.834
Brain	0.095	0.242	0.141	0.189
Brown fat	0.495	0.584	0.396	0.526
Eye ball	0.042	0.193	0.074	0.206
Fat	0.106	0.112	0.086	0.269
Kidney (cortex)	2.26	2.14	1.57	2.10
Kidney (medulla)	6.23	5.37	2.74	6.81
Liver	1.30	1.24	0.957	0.983
Lung	0.989	1.13	0.942	0.829
Muscle	1.06	1.52	0.451	1.66
Pancreas	1.53	1.29	0.920	1.20
Salivary gland	0.979	1.20	0.954	1.03
Small intestine (contents)	0.703	0.702	0.285	1.05
Small intestine (wall)	1.29	1.43	0.945	1.22
Spinal cord	0.099	0.230	0.522	0.131
Spleen	1.37	1.15	0.810	1.04
Stomach (contents)	0.007	0.124	0.043	0.000
Stomach (wall)	0.297	0.758	0.534	0.251
Testis	0.544	1.21	1.03	2.00
Urinary bladder	3.00	8.52	3.00	6.81

a) Administered with 100 μCi of ^{14}C-urea/kg.
b) 0.117 mg as urea/kg.
c) 1000 mg as urea/kg.

Urinary, Fecal and Expiratory Excretions following Intravenous or Oral Administration

Figure 5 shows the cumulative urinary excretion of ^{14}C-urea which was determined periodically following intravenous administration of high (1000 mg/kg) and low (0.117 mg/kg) doses. In all the collection periods, there was no significant difference in the excretion percentage except at 2 h ($p<0.05$), though urea appeared to be excreted faster and rather more extensively into the urine when given at a high dose than when given at a low dose, *i.e.* approximately 90 and 80% of the high and low doses, respectively, were excreted in 24 h. The smaller value of k_{10} for urea than for creatinine (Table I) may reflect the fact that the former compound is tubularly reabsorbed to a considerable extent.[11] The tendency described above might be explained by the existence of some saturable mechanism in the tubular reabsorption process. The extent of biliary excretion of ^{14}C-urea was preliminarily determined in rats, and appeared to be only less than 2% of the high and low doses in 12 h following intravenous administration. It was thus supposed that urea was eliminated not exclusively but predominantly *via* the renal route; however, more than about 10% of the *i.v.* dose was possibly eliminated by extra-renal and -hepatic routes.

Since it has been reported that approximately 14 and 35% of subcutaneous[10] and intraperitoneal[7] doses of urea, respectively, were excreted into the expired air of rats, it was necessary to determine simultaneously the exact proportions of urea disposition *via* urinary, fecal and expiratory excretions following *i.v.* or *p.o.* administration. The results obtained by simultaneous collection of urinary and fecal samples and expired air are shown in Table III

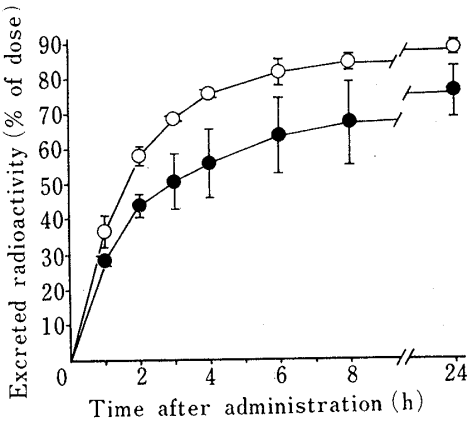


Fig. 5. Cumulative Excretion of Radioactivity in Urine following Intravenous Administration of ^{14}C-Urea (10 μCi/kg) to Two Rats

○: high dose (1000 mg as urea/kg).
●: low dose (0.117 mg as urea/kg).
Each point is the mean value with the range.

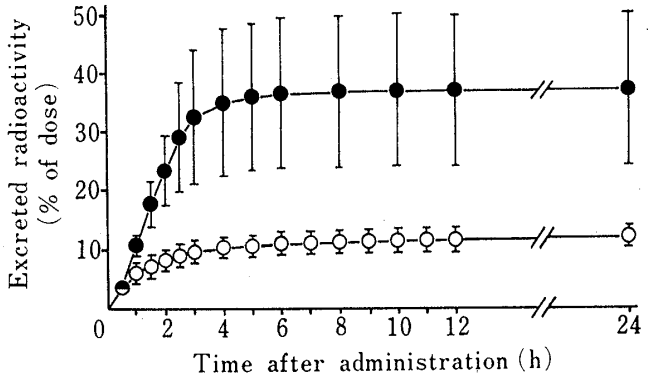


Fig. 6. Cumulative Excretion of Radioactivity in Expired Air following Intravenous (○) and Oral (●) Administration of ^{14}C-Urea (10 μCi/kg) to Rats

Dose: *i.v.*; 0.675 mg as urea/kg, *p.o.*; 0.699 mg as urea/kg. Each point is the mean value±S.D. for three (*p.o.*) or four (*i.v.*) rats.

TABLE III. Cumulative Urinary, Fecal and Expiratory Excretions of Radioactivity in 24 h following Intravenous and Oral Administration of ^{14}C-Urea[a] to Rats

Biological materials	Recovery (% of dose±S.D.)	
	Intravenous ($n=4$)	Oral ($n=3$)
Urine	82.7 ±2.87	55.3 ±12.8
Feces	0.31±0.13	0.26± 0.09
Expired air	12.1 ±1.70	37.0 ±13.7
Total	95.1 ±2.76	92.6 ± 8.04

a) Dose: 10 μCi/kg (0.675 and 0.699 mg as urea/kg for *i.v.* and *p.o.* administration, respectively).

and Fig. 6. Fecal excretion of radioactivity was less than 0.4% of both *i.v.* and *p.o.* doses in 24 h. In contrast, cumulative expiratory excretion of $^{14}CO_2$ in 24 h after *i.v.* dosing was about 12%, which is comparable to the extent found after subcutaneous administration (approximately 14%),[10] while that after *p.o.* administration was about 37%. At all time points except 0.5 h, the cumulative excretion of radioactivity into the expired air was significantly ($p<0.05$) larger than that after intravenous administration, in spite of the relatively larger fluctuation (Fig. 6). A similar fluctuation was also observed in the expiratory excretion of $^{14}CO_2$ after oral administration of ^{14}C-urea to normal mice.[1,16]

It has been reported that the urea decomposition is mostly due to the activity of microfloral urease existing in the gut, especially in the ileocecal portion.[4-9] In normal subjects, the rate of breakdown of endogeneous urea in the gastrointestinal tract has been estimated to be about one-fourth of its production rate.[4-6] On the other hand, a significant reduction in the gut degradation of urea has been demonstrated to occur when rats were eviscerated or during the administration of antibiotics such as neomycin and kanamycin to chronic uremic patients[17] and of antibiotics such as clindamycin, cefazolin, thiophenicol, neomycin and tetracycline to rats.[18] Gut metabolism of urea and/or expiratory excretion of CO_2 as its metabolite has been predicted to be enhanced in renal failure or insufficiency.[17,19] It could, therefore, be concluded that the urea is disposed of from the body not only *via* the renal route but also *via* the intestinal–pulmonary route even following *i.v.* dosing, though it is eliminated predominantly by renal excretion. In the case of *i.v.* administration, most of the $^{14}CO_2$ is supposed to be derived from the radioactivity secreted into the gut lumen, while most or a part of the radioactivity expired into the air following *p.o.* dosing might be due to the intestinal decomposition of unabsorbed ^{14}C-urea.

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References and Notes

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