Influence of Anesthetic Regimens on Intestinal Absorption in Rats

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We compared the influence of anesthetic regimens using urethane (U), pentobarbital (P), ether (E), and ketamine/midazolam (K) on the intestinal absorption of several probes using a single-pass perfusion technique in rats. The selected probes were D-glucose (1 m*M*) for the resistance of the unstirred water layer (UWL), D-glucose (100 m*M*) for the capacity of carrier-mediated D-glucose transport, L-glucose, and urea for membrane-limited passive transport, and tritiated water (^3H_2O) for blood flow at the absorption site. The absorbed fraction of D-glucose (1 m*M*) was the smallest for U and the largest for P, suggesting that the resistance of UWL is the largest for U and the smallest for P. The absorbed fraction of D-glucose (100 m*M*) was the largest for P (U = E = K < P), suggesting a higher capacity of carrier-mediated D-glucose transport for P. The absorbed fraction of urea was similar for all anesthetics, while that of L-glucose was the smallest for K (U = P = E > K). Although the results for these two markers of membrane-limited passive transport were inconsistent, the passive permeability of the intestinal membrane may be lower when treating with K. The intestinal absorptions of D-glucose (1 and 100 m*M*), L-glucose, and urea were, in general, lower with any of the anesthetics than under nonanesthesia (N), suggesting increased resistance of UWL and decreased intestinal membrane permeability by carrier-mediated and passive transport under anesthesia. The only exception was the absorption of D-glucose (100 m*M*) under P, which was comparable to that under N. The results were similar when considering the membrane permeability clearance estimated by correcting for the resistance of UWL. The blood flow at the absorption site, estimated from the absorption of ^3H_2O, was decreased under U, compared with N, and increased under K (U < P = E = N < K). The information obtained in this study is useful for the comprehensive interpretation of intestinal absorption data obtained under different anesthetic regimens and the prediction of intestinal absorption *in vivo*.

KEY WORDS: intestinal absorption; rat; anesthetic; urethane; pentobarbital; ether, ketamine; midazolam.

INTRODUCTION

Intestinal perfusion techniques have been used to characterize the intestinal absorption of drugs. Perfusion experiments using laboratory animals such as rats have been performed mostly under anesthetic regimens, e.g., using urethane or pentobarbital (1–5), to facilitate the handling of animals and perfusion procedures. However, anesthesia could affect intestinal absorption and drug disposition. In a comparative study on cardiac output and regional blood flow under various anesthetic regimens, Gumbleton *et al.* found the most severe effects on the hemodynamic profile to occur in rats anesthetized with urethane (6). Another study by Gumbleton *et al.* showed that the renal clearance of gentamicin was lower in anesthetized rats than in unanesthetized rats, and it was the lowest in urethane-anesthetized rats (7). We reported that the resistance of the unstirred water layer (preepithelial diffusional resistance) was larger, and carrier-mediated D-glucose transport and passive L-glucose transport were smaller, in rats anesthetized with urethane than in unanesthetized rats (1). The suppressed intestinal motility in anesthetized rats was suggested as a possible cause of the poorer mixing of intestinal contents, leading to an increased resistance of the unstirred water layer, a decreased effective surface area, and a lower membrane permeability. Thus, anesthetics affect various physiological factors such as blood flow and intestinal absorption. However, the detailed effects of anesthetics on intestinal drug absorption and its mechanism are yet to be investigated. To improve intestinal perfusion techniques, we designed a study examining the influence of various laboratory anesthetic regimens on the intestinal absorption of several probes.

MATERIALS AND METHODS

Materials

[^{14}C]D-Glucose (9.6 GBq/mmol), [^{14}C]L-glucose (1.7 GBq/mmol), [^{14}C]urea (2.1 GBq/mmol), tritiated water (37.0 MBq/g), [^{3}H]inulin (15.8 GBq/g), [^{14}C]inulin (74.0 MBq/g), and Biofluor scintillation cocktail were purchased from New England Nuclear Co. (Boston, MA). Urethane (Tokyo Kasei Kogyo Co., Tokyo), pentobarbital (Nembutal, Dainippon Pharmaceuticals Co., Osaka), ketamine (Ketalar, Sankyo Co., Tokyo), and midazolam (Dormicum, Yamanouchi Pharmaceuticals Co., Tokyo) were commercially obtained. All other reagents were of analytical grade.

Anesthetic Regimens

Male Wistar rats (250–300 g) were used without fasting prior to experiments. The rats were given one of the following anesthetic regimens: U, urethane (1.13 g/4.5 mL/kg, i.p.); P, pentobarbital sodium (50 mg/1 mL/kg, i.p.); E, ether by inhalation through natural spontaneous respiration (animal dose); and K, ketamine (80 mg/1.6 mL/kg) with midazolam (5 mg/1 mL/kg) as an initial i.p. dose followed by ketamine (20 mg/0.4 mL/kg, i.p.) every 30 min for maintenance (6). The anesthetic regimens of urethane and pentobarbital followed those generally reported in the literature.

Perfusion Experiments

Perfusion solutions consisted of 20.1 m*M* $Na_2HPO_4 \cdot 12H_2O$, 47.0 m*M* KH_2PO_4, 101.0 m*M* NaCl (pH 6.4) and contained a ^{14}C-labeled probes with a tracer amount of [^{3}H]inulin, nonabsorbable marker, or tritiated water as a probe with [^{14}C]inulin. The concentration of each probe was adjusted by adding the unlabeled probe.

In situ intestinal single-pass perfusion was carried out using male Wistar rats anesthetized by one of the anesthetic regimens described above. The abdomen of each rat was opened by a midline incision, and a 10-cm intestinal segment, starting 20 cm below the duodenojejunal flexure or

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about 30 cm below the pylorus, was selected. The segment was internally flushed with saline to remove intestinal contents, attached with inflow and outflow cannulas made of polyethylene tubing (internal diameter, 0.3 cm), placed on a flat plate on the abdomen, and perfused at 0.15 mL/min with a peristaltic pump (Minipulse III, Gilson Co., France). The outflow solution was collected for 20 min at 5-min intervals, starting 25 min after the initiation of perfusion. The temperature was monitored at the perfused segment and maintained at 37°C by using a thermostat and a heating lamp.

Perfusion experiments in unanesthetized rats were performed as described in our pervious report (1). Briefly, the surgical operation to attach cannulas was carried out under light ether anesthesia and perfusion was initiated right after the rat regained consciousness in a Bollman cage.

Scintillation cocktail (1.5 mL; Biofluor) was added to the 100-μl aliquots of inflow and outflow solutions, and the radioactivity was determined by liquid scintillation counting.

Data Analysis

The fraction absorbed (F_a) of each probe was estimated as the fraction disappeared from the intestinal lumen, correcting for a minor volume change by using inulin as a nonabsorbable marker:

$$F_a = 1 - \frac{C_{in,I}}{C_{out,I}} \cdot \frac{C_{out}}{C_{in}} \quad (1)$$

where $C_{in,I}$ and $C_{out,I}$ are the concentrations of inulin in inflow and outflow solutions, respectively, and C_{in} and C_{out} are the concentrations in inflow and outflow solutions, respectively. The F_a was determined as the average of those for four sampling periods.

A tube model incorporated with the unstirred water layer to consider the preepithelial diffusional resistance (film model) was used to estimate the intestinal membrane permeability (1). The apparent membrane permeability clearance, or the product of the apparent membrane permeability coefficient and the surface area, for the unit length of intestinal segment was estimated as follows:

$$CL_{a,app} = -\frac{Q}{L} \cdot \ln(1 - F_a) \quad (2)$$

where $CL_{a,app}$ is the apparent membrane permeability clearance; Q is the perfusion rate, 0.15 mL/min in this study; and L is the length of the perfused segment, 10 cm in this study. The $CL_{a,app}$ is related to the membrane permeability clearance ($CL_{am,}$) and the permeability clearance of the unstirred water layer ($CL_{a,aq}$) as follows:

$$\frac{1}{CL_{a,app}} = \frac{1}{CL_{a,m}} + \frac{1}{CL_{a,aq}} \quad (3)$$

Since the intestinal absorption of D-glucose was reported to be unstirred water layer limited at a low concentration such as 1 mM and at a low perfusion rate such as 0.15 mL/min (1), we assumed that $CL_{a,app}$ is equal to $CL_{a,aq}$ for the absorption of D-glucose at 1 mM. Considering that $CL_{a,aq}$ is proportional to the diffusion coefficient, which is inversely proportional to the square root of the molecular weight (M), the $CL_{a,aq}$ of each probe was estimated as follows:

$$CL_{a,aq} = CL_{a,aq}(G, 1\ mM) \cdot \frac{\sqrt{M_g}}{\sqrt{M}} \quad (4)$$

where $CL_{a,aq}$ (G, 1 mM) is the $CL_{a,aq}$ of D-glucose at 1 mM and M_g is the molecular weight of D-glucose. Finally, $CL_{a,m}$ was estimated from the estimates of $CL_{a,app}$ and $CL_{a,aq}$ using Eq. (3).

Statistical significance was examined by Student's t test, taking the data in unanesthetized rats as controls and also taking those in urethane-anesthetized rats as controls. The anesthetic regimen using urethane is widely used and the standard procedure in our laboratory.

RESULTS

The intestinal absorption of D-glucose is known to be mostly carrier mediated, with a minor passive transport component (1). At a concentration of 1 mM, carrier-mediated D-glucose transport was reported to be in the linear phase of the Michaelis–Menten kinetics, with an apparent K_m of 30 to 50 mM, and the overall absorption process is limited by the preepithelial diffusional process in the lumen, or the permeation of the unstirred water layer (UWL) in the UWL model. The resistance of the UWL was reported to represent 93 and 85%, respectively, of the total resistance in urethane anesthetized and unanesthetized rats at a perfusion rate of 0.16 mL/min. Thus, the absorption of D-glucose at 1 mM was assumed to serve as the marker of the resistance of UWL or preepithelial diffusion. Figure 1 shows the absorbed fraction of D-glucose at 1 mM under various anesthetic regimens. The smallest fraction absorbed in rats anesthetized with urethane suggests the largest resistance of UWL. The fraction absorbed in pentobarbital-anesthetized rats was the largest but still smaller than that in unanesthetized rats in our preceding report (1). Thus, the resistance of the UWL was found to be increased by all anesthetic regimens tested in this study, compared to that in unanesthetized rats.

For all anesthetic regimens tested, the absorbed fraction

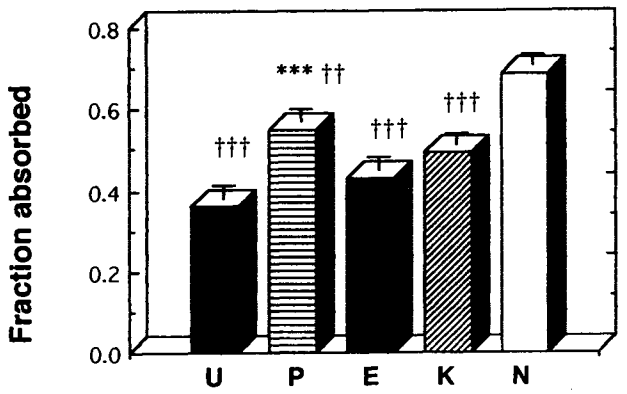

Fig. 1. Influence of anesthetic regimens on the intestinal absorption of D-glucose (1 mM). U, urethane; P, pentobarbital; E, ether; K, ketamine/midazolam; N, nonanesthesia [data from Yuasa *et al.* (1)]. Results are represented as the mean ± SE (n = 6 for N and 3 for the others). Significance level against U: (***) $P < 0.01$. Significance level against N: (††) $P < 0.02$; (†††) $P < 0.01$.

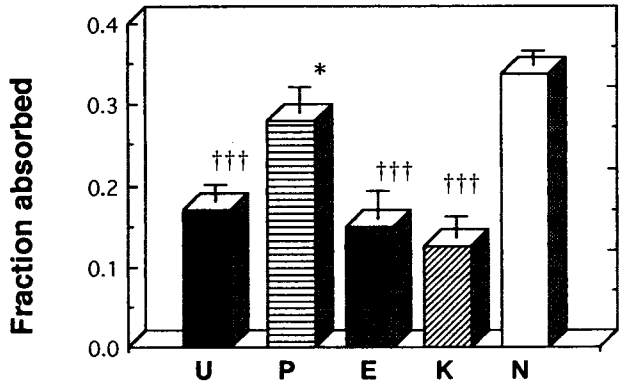

Fig. 2. Influence of anesthetic regimens on the intestinal absorption of D-glucose (100 m*M*). U, urethane; P, pentobarbital; E, ether; K, ketamine/midazolam; N, nonanesthesia [data from Yuasa *et al.* (1)]. Results are represented as the mean ± SE (n = 6 for N and 3 for the others). Significance level against U: (*) $P < 0.05$. Significance level against N: (†††) $P < 0.01$.

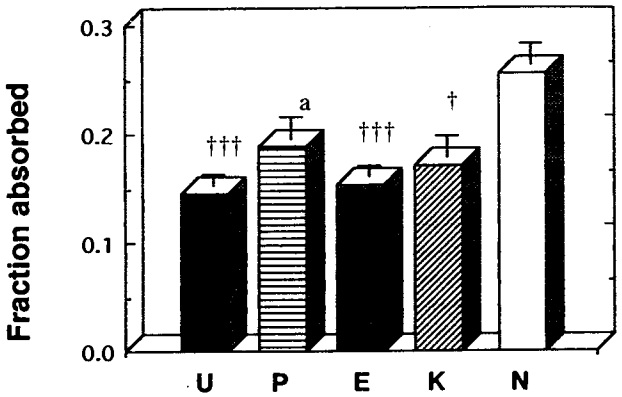

Fig. 4. Influence of anesthetic regimens on the intestinal absorption of urea (0.1 m*M*). U, urethane; P, pentobarbital; E, ether; K, ketamine/midazolam; N, nonanesthesia. Results are represented as the mean ± SE (n = 5 for N and 3 for the others). Significance level against N: (a) $P < 0.10$; (†) $P < 0.05$; (†††) $P < 0.01$.

of D-glucose was decreased by increasing the concentration from 1 m*M* (Fig. 1) to 100 m*M* (Fig. 2), consistent with the significant contribution of the carrier-mediated transport. The absorbed fraction of D-glucose at the saturating concentration of 100 m*M* reflects the capacity of the transport system (1). The absorbed fraction of D-glucose at 100 m*M* in the pentobarbital-anesthetized rats was significantly larger than those in the rats with the other anesthetic regimens and comparable with that in the unanesthetized rats (Fig. 2). This result suggests that the capacity of D-glucose transport is maintained under pentobarbital anesthesia but reduced under the other anesthetic regimens.

The intestinal absorption of L-glucose and urea, which are hydrophylic and poorly membrane permeable, is known to be passive and membrane-limited. The absorbed fraction of L-glucose was the smallest in the rats anesthetized with ketamine/midazolam and similar for the other anesthetic regimens, while the absorbed fraction of urea was similar for all anesthetic regimens (Figs. 3 and 4). These absorbed fractions of L-glucose and urea in anesthetized rats were smaller than those in unanesthetized rats. Although the results for L-glucose and urea were not consistent regarding the effect of ketamine/midazolam, the intestinal membrane permeability by passive diffusion was shown to be decreased by the anesthetic regimens and the effect of ketamine/midazolam may be the strongest.

The absorbed fraction of tritiated water (^3H_2O) was the smallest in urethane-anesthetized rats and the largest in unanesthetized rats and in rats anesthetized with ketamine/midazolam (Fig. 5). The intestinal absorption of ^3H_2O was reported to be blood flow limited and serves as the marker of blood flow at the absorption site (8,9); however, it requires correction for the resistance of UWL (10). After correction for UWL resistance, which is relatively small because of the high diffusivity of ^3H_2O, but not negligible, the intestinal membrane permeability clearance ($CL_{a,m}$) of ^3H_2O can be assumed to represent the blood flow at the absorption site. Tables I and II list the apparent membrane permeability clearance ($CL_{a,app}$) and the membrane permeability clearance ($CL_{a,m}$), respectively. The $CL_{a,m}$ of ^3H_2O was larger in rats anesthetized with ketamine/midazolam than in unanes-

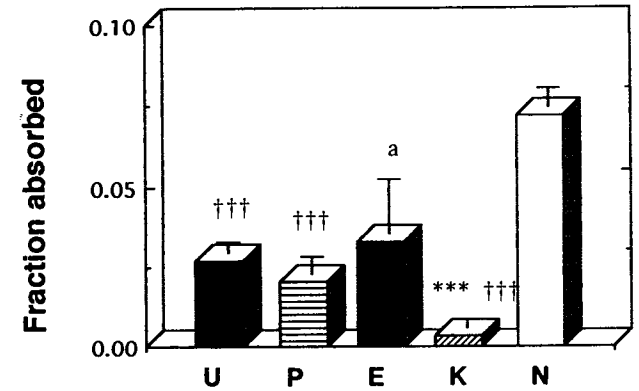

Fig. 3. Influence of anesthetic regimens on the intestinal absorption of L-glucose (1 m*M*). U, urethane; P, pentobarbital; E, ether; K, ketamine/midazolam; N, nonanesthesia [data from Yuasa *et al.* (1)]. Results are represented a the mean ± SE (n = 3). Significance level against U: (***) $P < 0.01$. Significance level against N: (a) $P < 0.10$; (†††) $P < 0.01$.

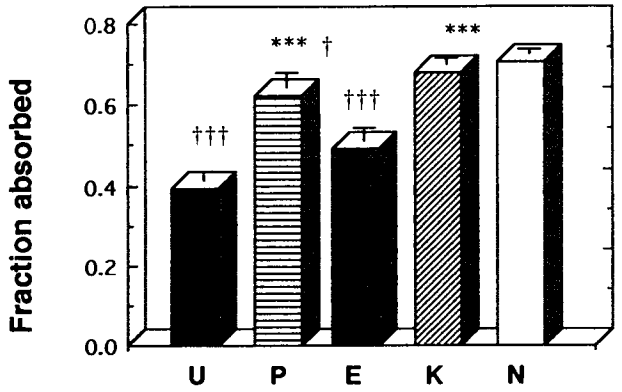

Fig. 5. Influence of anesthetic regimens on the intestinal absorption of tritiated water (0.1 μCi/mL). U, urethane; P, pentobarbital; E, ether; K, ketamine/midazolam; N, nonanesthesia. Results are represented as the mean ± SE (n = 5 for N and 3 for the others). Significance level against U: (***) $P < 0.01$. Significance level against N: (†) $P < 0.05$; (†††) $P < 0.01$.

Table I. Influence of Anesthetic Regimens on Apparent Intestinal Membrane Permeability Clearance ($CL_{a,app}$) in Rats[a]

	$CL_{a,app}$ (μL/min/cm)				
	D-Glucose (1 m*M*)	D-Glucose (100 m*M*)	L-Glucose (1 m*M*)	Urea (0.1 m*M*)	^3H_2O (0.1 μCi/mL)
U	6.66 ± 0.75[f,*]	2.86 ± 0.37[f]	0.30 ± 0.01[f]	2.36 ± 0.16[e]	7.44 ± 0.54[f]
P	11.93 ± 1.04[a,d]	4.89 ± 0.66	0.31 ± 0.03[f]	3.15 ± 0.32	14.64 ± 1.38[b]
E	8.39 ± 0.86[f]	2.44 ± 0.61[f]	0.51 ± 0.27[c]	2.47 ± 0.18[e]	10.38 ± 0.97[f]
K	10.30 ± 1.50[e]	1.98 ± 0.33[f]	0.05 ± 0.03[b,f]	2.84 ± 0.39	17.00 ± 0.72[b]
N	18.23 ± 1.41[b]	6.42 ± 0.45[b]	1.17 ± 0.11[b]	3.79 ± 0.35[c]	15.88 ± 0.61[c]

[a] U, urethane; P, pentobarbital; E, ether; K, ketamine/midazolam; N, nonanesthesia. Data are represented as the mean ± SE (n = 3).
[b] Data from Yuasa *et al.* (1); n = 3 for L-glucose and 6 for the others.
[c] n = 5.
* Signifiance level vs U: (a) $P < 0.02$; (b) $P < 0.01$. Significance level vs N: (c) $P < 0.10$; (d) $P < 0.05$; (e) $P < 0.02$; (f) $P < 0.01$.

thetized rats, suggesting increased blood flow under ketamine/midazolam anesthesia, and it was smaller in rats anesthetized with urethane, suggesting decreased blood flow. Pentobarbital and ether did not appear to affect blood flow.

For D-glucose at 100 m*M*, L-glucose and urea, $CL_{a,m}$'s led to conclusions similar to those reached on the basis of F_a. The $CL_{a,m}$'s of L-glucose and urea were similar to the corresponding $CL_{a,app}$'s, consistent with the suggestion of membrane-limited absorption. However, the absorption of urea was faster than that of L-glucose and more strongly affected by varied UWL resistance among the anesthetic regimens. After correcting for UWL resistance, the influence of the anesthetic regimens on the $CL_{a,m}$'s of urea was marginal, with statistically insignificant effects by pentobarbital and ketamine/midazolam.

DISCUSSION

The apparent membrane permeability clearance ($CL_{a,app}$) of D-glucose (1 m*M*) as a measure of the resistance of the unstirred water layer (UWL) suggested a larger resistance of UWL in anesthetized rats than in unanesthetized rats, in agreement with our previous finding in urethane anesthesia (1) and Anderson and co-workers' finding in pentobarbital anesthesia (2). It may be attributed to the poorer mixing of luminal contents in anesthetized rats because of suppressed intestinal motility of the intestinal segment placed on a flat plate to prevent turbulent flow (1). The different UWL resistances among anesthetic regimens may suggest differences in micromotility, such as villous motility of the small intestine, since we observed little intestinal motility such as peristalsis in any anesthetic regimen.

Urethane, ether, and ketamine/midazolam were suggested to reduce the capacity of carrier-mediated D-glucose transport, compared with that in unanesthetized rats, as shown by the decreases in the absorbed fraction of D-glucose (100 m*M*), where transport is saturated. This reduction in transport capacity could result from a direct effect of the anesthetics on the carrier, an indirect effect on the microenvironment, e.g., Na^+ concentration at the intestinal surface, and/or a nonspecific effect on the intestinal membrane. Anesthetics are known to exert nonspecific effects on biological membranes, changing the structure of phospholipid bilayers and presumably affecting the function of proteins such as carriers (14). Anesthetics may also affect the intestinal surface Na^+ concentration, on which D-glucose transport is strongly dependent, by altering Na^+ transport.

The absorption of passively transported and membrane-limited probes, L-glucose and urea, were affected differently. The $CL_{a,m}$ of L-glucose was decreased in anesthetized rats, compared to unanesthetized rats, to a larger extent than that of urea: by 55% at least for L-glucose (ether) but by 29% at most for urea (urethane and ether). The $CL_{a,m}$ of urea was similar for all anesthetic regimens, while that of L-glucose was significantly smaller with ketamine/midazolam anesthesia than with the others. The transport of L-glucose was strongly diminished in ketamine/midazolam anesthesia. These differences in the anesthetics' effect on absorption of L-glucose and urea may be relevant to the difference in the permeation pathways available for L-glucose and urea as suggested by Tomita *et al.* (15). They reported that only the unrestricted transcellular or paracellular pathway is available to compounds larger than mannitol, while the restricted paracellular pathway as well as the unrestricted pathway is available to smaller compounds such as urea. L-glucose is as large as mannitol and is supposed to be transported via only the unrestricted pathway. The larger decrease in $CL_{a,m}$ for L-glucose than for urea suggests that the unrestricted pathway is affected more than the restricted pathway. Ketamine/midazolam anesthesia may have the strongest effect on the unrestricted pathway.

Table II. Influence of Anesthetic Regimens on Intestinal Membrane Permeability Clearances ($CL_{a,m}$) in Rats[a]

	$CL_{a,m}$ (μL/min/cm)			
	D-Glucose (100 m*M*)	L-Glucose (1 m*M*)	Urea (0.1 m*M*)	^3H_2O (0.1 μCi/mL)
U	5.26 ± 1.21[d,*]	0.32 ± 0.01[e]	2.98 ± 0.25[c]	11.59 ± 1.25[e]
P	8.65 ± 1.93	0.32 ± 0.03[e]	3.73 ± 0.44	24.35 ± 3.51[a]
E	3.68 ± 1.12[e]	0.56 ± 0.30[c]	2.98 ± 0.27[c]	17.35 ± 2.52
K	2.50 ± 0.52[e]	0.05 ± 0.03[b,e]	3.41 ± 0.55	35.83 ± 3.26[b,e]
N	9.63 ± 0.98[b]	1.24 ± 0.12[b]	4.21 ± 0.42[c]	19.92 ± 0.97[c]

[a] U, urethane; P, pentobarbital; E, ether; K, ketamine; N, nonanesthesia. Data are represented as the mean ± SE (n = 3).
[b] Data from Yuasa *et al.* (1); n = 3 for L-glucose and 6 for the others.
[c] n = 5.
* Significance level vs U: (a) $P < 0.02$; (b) $P < 0.01$. Significance level vs N: (c) $P < 0.10$; (d) $P < 0.02$; (e) $P < 0.01$.

The $CL_{a,m}$ of ^3H_2O was larger in the rats anesthetized with ketamine/midazolam than in unanesthetized rats, suggesting increased blood flow in ketamine/midazolam anesthesia. This could result from the pharmacological effect of ketamine, raising blood pressure through sympathetic stimulation (16). The $CL_{a,m}$ of ^3H_2O was not affected by pentobarbital and significantly decreased by urethane. Our finding was in qualitative agreement with that of Gumbleton *et al.*, reporting that intestinal blood flow increased for the anesthetic regimens in the order of urethane, pentobarbital, and ketamine/midazolam (6).

Urethane and pentobarbital have been most widely used for anesthetic regimens in intestinal absorption studies. Comparing these two anesthetics, pentobarbital affected intestinal absorption less. Pentobarbital reduced only the passive transports of L-glucose and urea, while urethane reduced carrier-mediated D-glucose transport, blood flow-limited absorption of ^3H_2O, and passive transports of L-glucose and urea. For transport studies, pentobarbital anesthesia appeared to be more favorable than urethane anesthesia. However, a longer and more stable anesthesia can be expected for urethane than for pentobarbital. The present study does not necessarily discourage the use of urethane for laboratory anesthetic regimens. The information obtained in this study is useful for the comprehensive interpretation of intestinal absorption data obtained under different anesthetic regimens.

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