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TOXICOKINETICS

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Serum and urinary boron levels in rats after single administration of sodium tetraborate

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Abstract The pharmacokinetics of boron was studied in rats by administering a 1 ml oral dose of sodium tetraborate solution to several groups of rats ($n = 20$) at eleven different dose levels ranging from 0 to 0.4 mg/100 g body weight as boron. Twenty-four-hour urine samples were collected after boron administration. After 24 h the average urinary recovery rate for this element was 99.6 ± 7.9. The relationship between boron dose and excretion was linear ($r = 0.999$) with a regression coefficient of 0.954. This result suggests that the oral bioavailability (F) of boron was complete. Another group of rats ($n = 10$) was given a single oral injection of 2 ml of sodium tetraborate solution containing 0.4 mg of boron/100 g body wt. The serum decay of boron was followed and found to be monophasic. The data were interpreted according to a one-compartment open model. The appropriate pharmacokinetic parameters were estimated as follows: absorption half-life, $t_{1/2a} = 0.608 \pm 0.432$ h; elimination half-life, $t_{1/2} = 4.64 \pm 1.19$ h; volume of distribution, $Vd = 142.0 \pm 30.2$ ml/100 g body wt.; total clearance, $C_{tot} = 0.359 \pm 0.0285$ ml/min per 100 g body wt. The maximum boron concentration in serum after administration (C_{max}) was 2.13 ± 0.270 mg/l, and the time needed to reach this maximum concentration (T_{max}) was 1.76 ± 0.887 h. Our results suggest that orally administered boric acid is rapidly and completely absorbed from the gastrointestinal tract into the blood stream. Boric acid in the intravascular space does not have a strong affinity to serum proteins, and rapidly diffuses to the extravascular space in proportion to blood flow without massive accumulation or binding in tissues. The main route of boron excretion from the body is via glomerular filtration. It may be inferred that there is partial tubular resorption at low plasma levels. The animal model is proposed as a useful tool to approach the problem of environmental or industrial exposure to boron or in cases of accidental acute boron intoxication.

Key words One compartment model · Experimental boron exposure · Volume of distribution · Total clearance · Biological half-life

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Introduction

Boron is an element of importance in nutrition, occupational health, toxicology, and environmental science. Recently, the Expert Committee on Trace Elements in Human Nutrition of the World Health Organization concluded that boron is probably essential in human nutrition (WHO 1996). Boron compounds are of great importance in strategic materials such as semiconductors, ceramic and electronic devices (Hines et al. 1995; Roig-Navarro et al. 1997). As the use of boron compounds widens, reports have steadily increased of industrial pollution (Temple and Linzon 1976; Mambetalin and Skal'nyi 1992) and of deleterious effects in workers resulting from boron exposure (Garabrant et al. 1984; Woskie et al. 1994).

In nature, boron-polluted volcanic areas are seen in various regions of the world (Stoner et al. 1977). Reports of boron-exposed populations have been published by several researchers (Minoia et al. 1987; Barr et al. 1993). Boron compounds are utilized as insecticides (Appel 1992) or as medicines (Borrelly et al. 1991). Moore (1997) indicated the risk of exposure to boric acid in infants when it is used as a household insecticide for cockroach control. In humans the symptoms of acute poisoning include: nausea, vomiting, diarrhoea, dermatitis. A lethal effect was reported when an extraordinarily high amount of boron was ingested in a suicide attempt (Restuccio et al. 1992).

The human daily boron intake from four different countries is reported in the range 0.93–2.82 mg/day (Coughlin 1996). Since boron is an element that is essential for plant growth (Blevins and Lukaszewski 1994),

foods of plant origin are the natural sources of the element. Boron is known to be easily, rapidly, and completely absorbed from the gastrointestinal tract and the entire ingested amount is excreted by the urine (Hove et al. 1939; Kent and McCane 1941; Jansen et al. 1984a, b). Although there are many reports related to boron acute or chronic toxicity, there are few dealing with the fundamentals of boron metabolism; thus the kinetics in experimental animals have not been clearly established to date.

In this study, several groups of rats ($n = 20$) were given an oral injection of 1 ml of a solution of sodium tetraborate ($Na_2B_4O_7 \cdot 10H_2O$) at one of eleven dose levels ranging from zero to 0.4 mg of boron/100 g body wt. After the administration of boron, 24-h urine samples were collected and boron was analyzed to calculate the recovery rates of the element. Also, to study the pharmacokinetics of boron, a group of rats ($n = 10$) was given a single oral dose of $Na_2B_4O_7 \cdot 10H_2O$ containing 0.4 mg boron/100 g body wt. and six pharmacokinetic parameters: absorption half-life ($t_{1/2a}$), elimination half-life ($t_{1/2}$), volume of distribution (Vd), total clearance (C_{tot}), the maximum boron concentration in serum after administration (C_{max}), and the time needed to reach C_{max} (T_{max}) were calculated by means of a one-compartment open model. These basic indices have been poorly examined in cases of acute boron intoxication. Therefore the present study was designed to evaluate further the effect of a high dose of boron on urinary and serum concentrations of the element. We propose that our animal model may be used as a basis for studies in human exposed subjects.

Materials and methods

Animals

Thirteen-week-old SPF Wistar male rats (Japan SLC, Hamamatsu, Shizuoka, Japan) weighing 240–260 g were used in this study. For convenience, rat body weight was approximated to be 250 g. The animals were fed standard rat chow MM-3 from Funabashi Farms, Funabashi, Chiba, Japan. Throughout the study rats were allowed to eat and drink tap water ad libitum while maintained in a temperature-controlled room at 22 ± 1 °C and 50–60% relative humidity, with illumination cycles of 12 h/day, from 0800 to 2000 hours.

Chemicals

Sodium tetraborate ($Na_2B_4O_7 \cdot 10H_2O$) of 'guaranteed reagent' analytical grade was obtained from Nakarai Tesque, Kyoto, Japan. The compound is a bright white powder with a purity of 99.0–103.0%. The 18.25 MΩ · cm-distilled water was obtained via an ultra-pure water system model CPW-102 equipped with a CPW-100-CSS filter from Advantec Toyo, Tokyo, Japan. The boron solutions were prepared from these sources by appropriate dilution as required for our study.

Dosing and sample preparation

After verifying their good health for 1 week, different groups of rats ($n = 20$) were given a single oral injection of 1 ml of a sodium tetraborate solution at one of each of the concentrations: 0, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 mg/l as boron. Following the administration of boron the animals were allowed to drink tap water ad libitum, but not to eat. Twenty-four-hour urine samples from the rats in each group were collected into test bottles avoiding fecal contamination. The volume of each sample was recorded and centrifuged at 3000 rpm for 5 min. The supernatant was stored at −20 °C until needed for analysis.

A group of ten rats was given an oral injection of 2 ml of sodium tetraborate solution (500 mg/l as boron) containing 0.4 mg of boron/100 g body wt. This dose corresponds to 1.74% of the acute oral LD50 in rats, 6.83–15.3% of the lowest observed adverse effect level (LOAEL) which is known to cause chronic adverse effects to the male reproductive system in rats and 22.9% of the no observed adverse effect level (NOAEL) (Hubbard and Sullivan 1996). The animals were anesthesized with ether and 0.5–1 ml blood samples were drawn directly from the heart at 0 (control), 1, 2, 3, 4, 5, 6, 12, and 24 h after the administration of boron. Each sample was centrifuged at 3000 rpm for 5 min and the serum was stored at −20 °C until needed for analysis.

Analytical procedure

Boron concentrations in urine and serum were determined by means of inductively coupled plasma emission spectrometry (ICPES) on a Hitachi model P-5200 3600/1200 following a slight modification of the procedure previously reported (Usuda et al. 1997a).

Calculations

The curves of serum boron after oral administration were fitted to the exponential equation (Eq. 1), from which the appropriate kinetic parameters were derived.

$$[B] = INT(e^{-ket} - e^{-kat}) \quad (1)$$

where [B] is the serum boron concentration; ka is the absorption rate constant for boron; ke is the elimination rate constant of boron; t is the time in hours; and INT represents the extrapolated y-intercept in the experimental plots.

The absorption half-life ($t_{1/2a}$) was calculated by dividing 0.693 by ka; the elimination half-life ($t_{1/2}$) was calculated by dividing 0.693 by ke. The area under the concentration-time curve (AUC) was calculated by a trapezoidal rule. The total plasma clearance was calculated as C_{tot} = (dose F)/(AUC), where dose F is the fraction of the dose absorbed. The apparent volume of distribution (Vd) was calculated as C_{tot} divided by ke. The maximum boron concentration in serum after administration (C_{max}), and the time needed to reach the maximum (T_{max}) were also evaluated.

The statistical differences between the two groups were established using Student's unpaired t-test. A value of $P < 0.05$ was considered statistically significant. The values are reported as the mean ± standard deviation. All of the experiments described in this paper were performed following the guidelines of the Japanese Association for Laboratory Animal Science (JALAS) for the use of experimental animals.

Results

The recovery rates of boron in the 24-h urine samples are shown in Table 1. The average recovery ($n = 20$) was 99.6 ± 7.9%. Figure 1 shows an excellent linear relationship between the boron excretion in 24-h urine and the given dose ($r = 0.999$). The x-coefficient value of 0.954 for this regression is suitably concomitant with the urinary recovery rate. For practical purposes and considering these results, the bioavailability of boron after oral administration (F) is considered to be 100%.

Table 1 Boron recovery rate in 24-h urine after administration of a 1 ml oral dose of sodium tetraborate solution to several groups of male Wistar rats ($n = 20$) at eleven different dose levels ranging from 0 to 0.4 mg/100 g body weight as boron

Administration dose (mg/100 g body wt.)	Urinary boron excretion (μg/day) Mean ± SD	Recovery in 24-h urine (%)
0	32.2 ± 33.7	–
0.04	121.0 ± 18.8	121.0
0.08	193.6 ± 30.2	96.8
0.12	306.6 ± 25.6	102.2
0.16	388.1 ± 41.8	97.0
0.20	463.7 ± 77.4	92.7
0.24	573.8 ± 46.4	95.6
0.28	682.2 ± 55.1	97.4
0.32	771.5 ± 41.7	96.4
0.36	882.5 ± 50.3	98.1
0.40	987.5 ± 168.9	98.7
		Average 99.6 ± 7.9

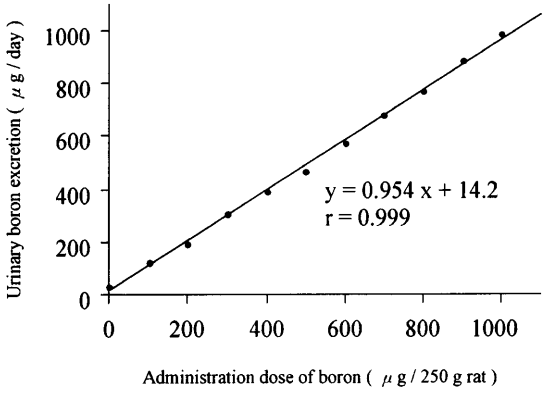

Fig. 1 Relationship between boron intake and urinary excretion in male Wistar rats ($n = 20$)

As shown in Fig. 2, the time-dependent variations of serum boron concentrations after a boron single dose of 0.4 mg/100 g body wt. showed a sharp increase immediately after the oral injection followed by monophasic declines. Good fits to a one-compartment model were obtained. The values for the pharmacokinetic parameters were determined as described in the experimental section and are shown in Table 2.

The administered boron was absorbed with a $t_{1/2a}$ of 0.608 ± 0.432 h. The maximum value C_{max} of 2.13 ± 0.270 mg/l was seen at T_{max} of 1.76 ± 0.887 h following the administration. The gradual decrease of serum boron after the peak concentration was observed with a $t_{1/2}$ of 4.64 ± 1.19. The Vd and C_{tot} were found to be 142 ± 30.2 ml/100 g body wt. and 0.359 ± 0.0285 ml/min per 100 g body wt., respectively.

Discussion

Regarding the relationship between a given dose of boron and the amount of urinary excretion, Kent and McCance (1941) reported that after a single dose (352 mg) of boron as boric acid was given to humans, urinary recovery was >90%. Jansen et al. (1984a) reported that when a single parenteral dose of boric acid (750 and 1473 mg) was given to males >50% of the

Fig. 2 Serum boron levels following a single oral injection of 0.2 ml of sodium tetraborate solution containing 0.4 mg of boron/100 g body wt. to male Wistar rats. The superimposed curve was obtained from the one-compartment model with the pharmacokinetic parameters shown in Table 2

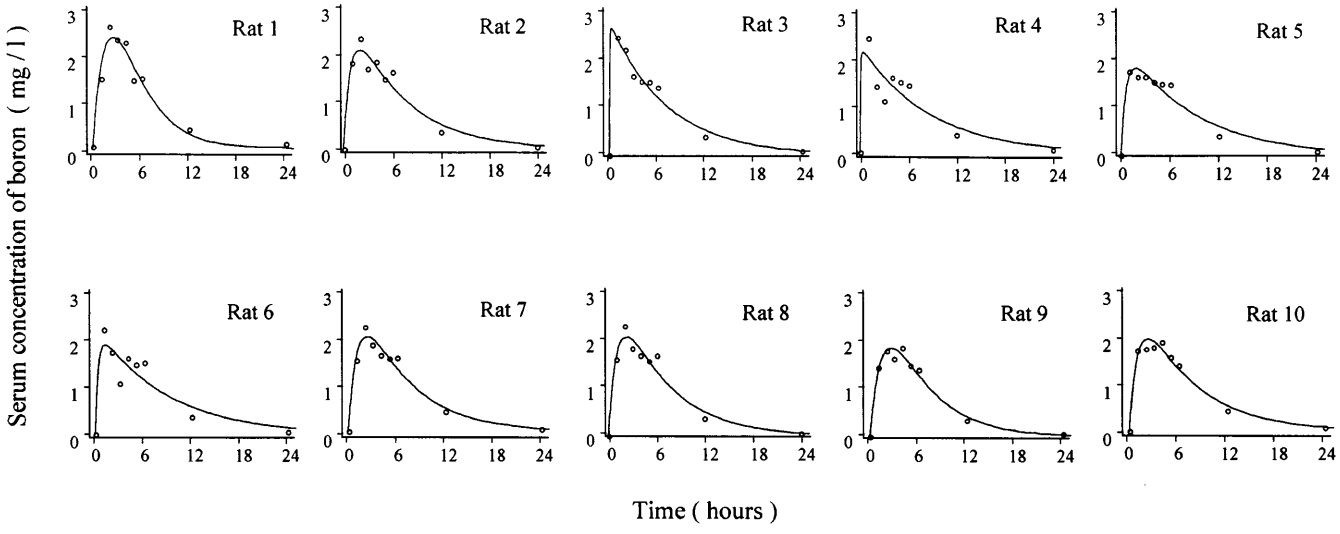

Table 2 Boron pharmacokinetics in male Wistar rats ($n = 10$) after a single oral dose of 2 ml of sodium tetraborate solution containing 0.4 mg of boron/100g body wt. The pharmacokinetic parameters are as defined in the Introduction and Eq. 1

Rat	INT (–)	*ke* (1/h)	*ka* (1/h)	*Vd* (ml/100 g body wt.)	AUC (mg·h/l)	C_{tot} (ml/min per 100 g body wt.)	$t_{1/2e}$ (h)	$t_{1/2a}$ (h)	C_{max} (mg/l)	T_{max} (h)
1	13.4	0.310	0.500	78.6	16.4	0.406	2.24	1.39	2.33	2.52
2	3.37	0.150	1.18	136	19.6	0.340	4.62	0.587	2.18	2.00
3	2.87	0.139	20.5	140	20.5	0.325	4.99	0.0338	2.76	0.245
4	2.30	0.118	18.0	175	19.4	0.344	5.87	0.0386	2.21	0.281
5	2.50	0.117	1.53	173	19.7	0.338	5.92	0.453	1.87	1.82
6	2.29	0.113	2.73	182	19.4	0.343	6.13	0.254	1.91	1.22
7	3.67	0.164	0.876	134	18.2	0.367	4.23	0.791	2.03	2.35
8	3.77	0.165	0.911	130	18.7	0.356	4.20	0.761	2.12	2.29
9	4.52	0.195	0.652	126	16.3	0.410	3.55	1.06	1.89	2.64
10	3.25	0.148	0.979	145	18.6	0.358	4.68	0.708	1.97	2.27
Average	4.19	0.162	4.78	142	18.7	0.359	4.64	0.608	2.13	1.76
SD	3.31	0.580	7.66	30.2	1.40	0.0285	1.19	0.432	0.270	0.887

given dose was eliminated during the first 24-h period; mean recovery in the 96-h urine was 93.9 and 92.4%, respectively. Considering the results previously reported, it is expected that the administered boron was almost entirely absorbed from the gastrointestinal (GI) tract and completely excreted in the urine.

As described in Fig. 1, the boron excretion in 24-h urine showed an excellent linearity to the corresponding dose, with an *r*-value of 0.999, and with an *x*-coefficient number obtained from the regression analysis equation of 0.954. As shown in Table 1, the recovery rate of boron in the 24-h urine showed a very high rate with an average value of 99.6 ± 7.9%. This led us to assume that bioavailability of boron (F) was 100% for all practical purposes.

Regarding the absorption and elimination of orally administrated boron, Hove et al. (1939), who gave 5 ml of milk containing 50 μg of boron to rats, reported that after 1 h only 6.25 μg boron were found in the GI tract. In humans, half lives for boron have been reported as $t_{1/2}$ of 1 day (Teshima et al. 1992; Moseman 1994). Farr and Konikowski (1963) examined the renal blood clearance of sodium pentaborate in patients with intracranial malignant tumors and in mice, reporting values of 39.1 ml/min and 40.0 ml/min, respectively; the values were more than twice the urea clearance in rats. Taking these previous results into account, boron seems to be absorbed from the gastrointestinal tract into blood and excreted into urine via the kidney with extreme rapidity.

The pharmacokinetic parameters for boron obtained in this study are summarized in Table 2. The values of 4.78 ± 7.66 h^{-1} for *ka* and 0.608 ± 0.432 h for $t_{1/2a}$ indicate the easy and rapid absorption of boron from the gastrointestinal tract. The values for $t_{1/2}$ and *Vd* were compared to those of inulin in the literature (Sugimoto et al. 1993). Inulin is a polysaccharide of D-fructose, which resides in extracellular spaces and is not able to diffuse into the intracellular space because of a large molecular weight of 5000–6300.

When the respective $t_{1/2}$ for boron and inulin were compared, that of boron was approximately 5 times longer than that for inulin, giving values of 4.64 ± 1.19 and 0.26 ± 0.05 h, respectively (Sugimoto et al. 1993). These authors stated that the inulin distribution volume for rats weighing between 200 and 250 g was 34.0 ± 4.79 ml/100 g body wt., while Kato et al. (1987) reported that inulin distribution volume was 34.0 ml/100 g body wt. in 8-week-old rats. Our obtained value of *Vd* for boron was 142 ± 30.2 ml/100 g body wt., which is approximately 4.2 times that for inulin and approximately 1.4 times that of body weight.

Wiley (1907) suggested that boric acid was found in human perspiration and milk. Ku et al. (1991) examined the tissue disposition of boron in rats fed 9000 ppm boric acid and reported that a rapid increase in plasma and tissue boron was observed 1 day after the start of exposure with the exception of adipose tissue. Silaev et al. (1977) gave boric acid in a dose of 1 g/kg orally to albino rats for 2 weeks and found that the changes in the nuclei and cytoplasm of both spermatozoids and spermatids were revealed at early stages of their formation. These results are considered strongly to support the possibility of boron diffusion from the intravascular space into the extra- and intra-cellular spaces.

The obtained value of *Vd* may suggest that boron diffuse more easily in body fluid than inulin, showing no affinity to either serum protein or cellular components. components. If an extensive or strong binding between plasma protein and boric acid exists, a small volume of distribution may result. If extensive tissue uptake or accumulation occur, a far larger volume of distribution than body weight may be expected. In a study of patients under hemodialysis, we previously demonstrated the low percentage of strong binding between serum constituents of macromolecules and boric acid (Usuda et al. 1996, 1997b). The results reported in this study seem to support our previous observations.

The value of *Vd* for boron found in this study, which accounted for 1.47 times that of body weight, suggested that boron could be distributed throughout the intracellular spaces. However, Poller and Sauerwein (1995), who treated human melanoma cells as a monolayer in

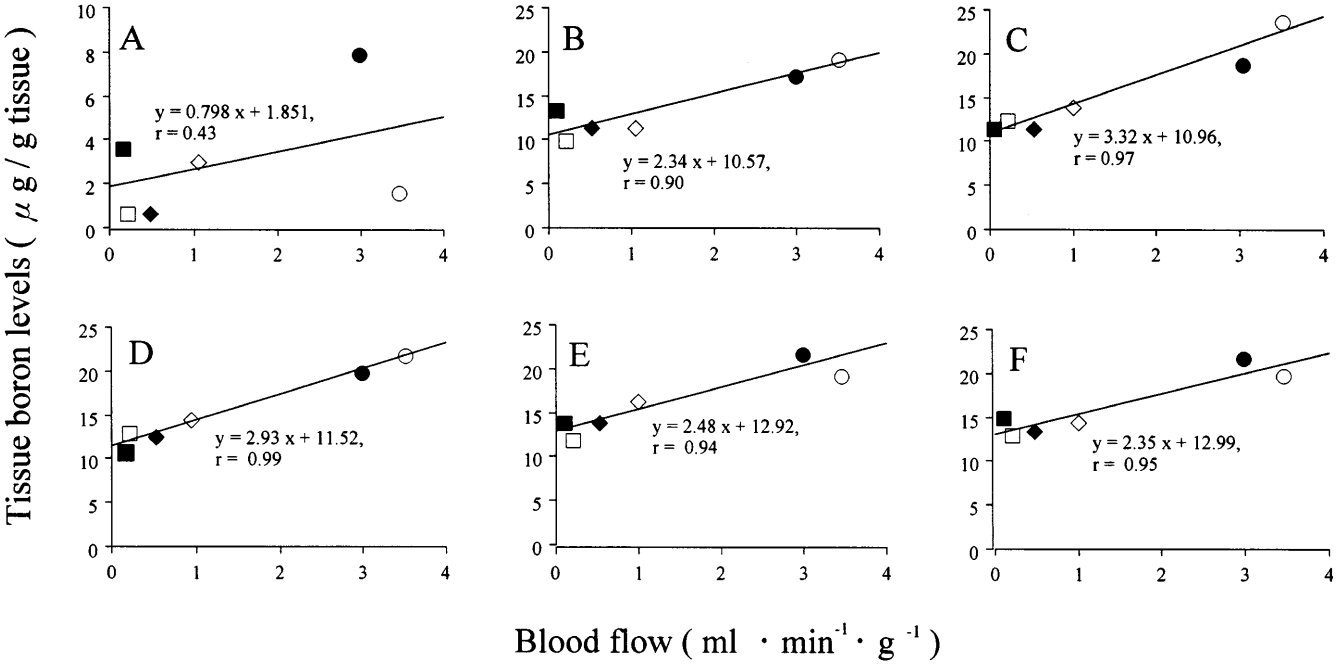

Fig. 3A–F The relationship between tissue boron levels (liver, □; kidney, ○; muscle, ■; large intestine, ◇; brain, ◆; and adrenals, ●) in rats following exposure to 9000 ppm boric acid (Ku et al. 1993) and organ blood flow in rats (Mulder et al. 1994). **A** Controls; **B** 1 day-; **C** 2 days-; **D** 3 days-; **E** 4 days- and **F** 1 week after treatment

the presence of boric acid in vitro, showed that boric acid was found only in the extracellular space. Also, Capala et al. (1996) showed that boron in the form of boric acid did not have a tendency to accumulate in malignant and normal cells in vitro.

The experiments of Ku et al. (1991) revealed that all tissues other than tibia and fibula bones did not show appreciable increase of boron plasma levels. Their data showed high tissue-boron levels in kidney and in brain. As shown in Fig. 3, it is evident that there is an excellent relationship between tissue boron levels in the boric acid-treated rats and the organ blood flow in rats as determined by Mulder et al. (1994). This indicates that boric acid in serum was in a diffusable form and thus able to reach the organs simply in proportion to the tissue blood flow, except in bones.

MacPherson and Tothill (1978) stated that the blood flow value of tibia and fibula in 200–300 g rats was 0.147 ml/g per min. When the blood flow value of tibia and fibula are substituted in equations 2–8, shown in Fig. 3B–F, the bone boron levels reported by Ku et al. (1991) are 10–11 times higher than the theoretically calculated values. This result suggests that the boron may have some affinity for bone and, since bone is very different from other tissues, bone also differs with respect to boric acid diffusion. It may be assumed that a substance exists, which has high affinity to boron-boric acid or for the active utilization of boron in bone, although this is still to be proven. Also, although bone accumulates trace amounts of boron, the amount of deposition seems to be too small to have a significant effect on the results of the pharmacokinetic study.

The clearance of inulin in rat is reported to be (all values in ml/min per 100 g body wt.): 1.17 by Capasso et al. (1987); 1.14 by Cortes et al. (1987), and 1.045 by Wall et al. (1987). The boron/inulin clearance ratio (C_{tot}/C_{in}) $\gg 1$ implies tubular secretion, which is an additional excretion mechanism apart from glomerular filtration, and $\ll 1$ tubular excretion (Bowman and Rand 1986). Our obtained value of C_{tot} for boron was 392.2 ± 36.8 μl/min per 100 g body wt., which is approximately 50–75% of the rats' inulin clearance reported in the literature.

The clearance of endogenous creatinine, which has been used in the rat as an index of glomerular filtration rate (GFR; all values in ml/min per 100 g body wt.), is reported to be 0.432 (Homsi et al. 1996), 0.459 (Bergstrom et al. 1996), and 0.43 (Shehata et al. 1994). Namnum et al. (1983) have stated that creatinine is reabsorbed along the nephron at normal plasma levels and is not a reliable marker of GFR compared to inulin in the rat. The boron/endogenous creatinine clearance ratio (C_{tot}/C_{cr}) revealed that our obtained boron clearance is 90% of the clearance of endogenous creatinine.

These values of C_{tot}/C_{in} and C_{tot}/C_{cr} seem to be too large to account for extensive tubular reabsorption and too small for the extensive tubular excretion mechanism. This suggests glomerular filtration with substantial partial passive reabsorption, which depends on such factors as urine -flow rate, -pH, or -boron concentration.

In previous studies, Farr and Konikowski (1963) reported that the boron clearance for a 21 g mouse at a boron dose of 2.5 mg per 100 g body wt. was more than double the urea clearance in rats reported by Farr and Smadel (1936). Their value is >6 times that of the present study, which is only 1.30–1.64 times (mean 1.44 times) of the rat urea clearance found in the literature of

0.250 ml/min per 100 g body wt. (Whiting et al. 1982) and lower than the value obtained by Farr and Konikowski (1963). These results suggest that net boron transport across the renal tubule may be bidirectional and that transport may be influenced by plasma boron levels. At low plasma levels, boron may be reabsorbed along the nephron, whereas net secretion, or inhibition of reabsorption, are associated with elevated plasma boron.

From our results, it may be concluded that orally administrated boric acid is absorbed from the gastrointestinal tract into blood quite rapidly and with complete (assumed 100%) bioavailability. The boric acid absorbed in the intravascular space does not have a strong affinity to serum proteins and diffuses rapidly to the extravascular space in a manner that is proportional to blood flow, without massive accumulation or binding in tissues. The main route of boron excretion from the body is via glomerular filtration. It is possible that at low plasma levels there is partial tubular reabsorption of boron.

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