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A Comparative Review of the Pharmacokinetics of Boric Acid in Rodents and Humans

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ABSTRACT

The pharmacokinetics of boric acid (BA) have been studied in animals and humans. Orally administered BA is readily and completely absorbed in rats, rabbits, and humans, as well as other animal species. In animals and humans, absorbed BA appears to be rapidly distributed throughout the body water via passive diffusion. Following administration of BA, the ratio of blood : soft tissue concentrations of boron (B) is approx 1.0 in rats and humans; in contrast, concentrations of B in bone exceed those in blood by a factor of approx 4 in both rats and humans. In rats, adipose tissue concentrations of B are only 20% of the levels found in blood and soft tissues; however, human data on adipose tissue levels are not available. BA does not appear to be metabolized in either animals or humans owing to the excessive energy required to break the B—O bond. BA has an affinity for *cis*-hydroxy groups, and it has been hypothesized to elicit its biological activity through this mechanism.

The elimination kinetics of BA also appear to be similar for rodents and humans. BA is eliminated unchanged in the urine. The kinetics of elimination were evaluated in human volunteers given BA orally or intravenously; the half-life for elimination was essentially the same (approx 21 h) by either route of exposure. In rats, blood and tissue levels of B reached steady-state after 3–4 d of oral administration of BA; assuming first-order kinetics, a half-life of 14–19 h may be calculated. The lack of metabolism of BA eliminates metabolic clearance as a potential source of interspecies variation. Accordingly, in the absence of differences in metabolic clearance, renal clearance is expected to be the major determinant of interspecies variation in pharmacokinetics. Because glomerular filtration rates are slightly higher in rats than in humans, the slight difference in half-lives may be readily explained.

The most sensitive toxicity end point for BA appears to be developmental toxicity in rats, with a No Observed Adverse Effect Level (NOAEL) and Lowest Observed Adverse Effect Level (LOAEL) of 55 and 76 mg BA/kg/d, respectively. Mean blood B levels in pregnant rats on gestation day 20 in the pivotal developmental toxicity study were reported to be 1.27 and 1.53 mcg B/g at the NOAEL and LOAEL, respectively. Blood B concentrations in humans are well below these levels. Average blood B levels in the most heavily exposed worker population at a borate mine was 0.24 mcg B/mL, and the estimated daily occupational exposure was equivalent to 160 mg BA/d. Blood B levels in the general population generally range from 0.03 to 0.09 mcg B/mL. These blood B values indicate an ample margin of safety for humans.

In summary, the pharmacokinetics of BA in humans and rodents are remarkably similar, and interspecies differences in pharmacokinetics appear to be minimal.

Index Entries: Boron, boric acid; kinetics; pharmacokinetics; absorption; distribution; metabolism; excretion.

INTRODUCTION

Boron (B), the fifth element in the periodic chart, is ubiquitous in the environment, where it is found combined with O to form compounds called inorganic borates (e.g., borax). Natural sources of borates in the environment include soils, rocks, surface and ocean waters, and the atmosphere.

B in the form of borates has long been recognized as an essential plant micronutrient for the growth and viability of plants *(1)*. Recently, there has been a growing body of evidence that B may be an essential element for frogs *(2)*, fish *(3)*, rats *(4)*, and humans *(5–12)*, as well as for plants.

The major sources of B exposure are diet and drinking water. Fruits, vegetables, and nuts are especially rich in B. Rainey et al. *(13)* recently studied daily dietary B intake, evaluating the food consumption records of over 25,000 Americans over several days. The median, mean, and 95 percentile B intake for all participants were 0.76, 0.93, and 2.4 mg B/d, respectively.

The toxicity of boric acid (BA) has been thoroughly investigated and reviewed *(14–20)*. Based on studies in laboratory animals, the two most sensitive end points of toxicity are developmental and reproductive toxicity *(21)*. Risk assessment of BA typically involves extrapolation from laboratory animals to humans. One potential source of variation between laboratory animals and humans derives from interspecies differences in pharmacokinetics.

The purpose of this article is to review the comparative pharmacokinetics of BA in animals and humans. Specifically, this article reviews

the absorption, distribution, metabolism, and excretion of BA, as well as blood levels associated with effects. Because of the importance of the developmental toxicity study of BA in rats *(22)* as a potential pivotal study for risk assessment, particular attention is paid to pharmacokinetics in rats. Although this review focuses on BA specifically, it has applicability to other common inorganic borates that rapidly dissociate to BA under conditions of physiological pH.

ABSORPTION

Oral Absorption

BA given orally is readily and completely absorbed in humans and animals. In adult human volunteers, Schou et al. *(23)* found 94% of a single oral dose of 500 mg BA (131 mg B) was excreted via the urine. Jansen et al. *(24)* evaluated the absorption of a single aqueous dose of 750 mg of BA in a group of six male volunteers; more than 92% of the BA was excreted in the urine. A similar degree of oral absorption based on urinary excretion of B was observed in volunteers drinking curative spa waters with a high B content, providing a daily dose of approx 100 mg B for 2 wk *(25)*.

In animals, BA has also been shown to be readily absorbed from the gastrointestinal tract. Among the species studied were rats *(26)*, rabbits *(27)*, sheep *(28)*, and cattle *(29, 30)*. Thus, humans and animals appear to absorb orally administered BA similarly.

Dermal Absorption

There is negligible absorption of BA across intact skin in humans and animals. Maibach *(31)* reported minimal dermal absorption of BA in human volunteers. Earlier studies showed little evidence of dermal absorption in human infants *(32)* and adults *(33)*. Dermal absorption across nonintact skin varied with the vehicle used; greater absorption was observed with aqueous-based vehicles compared to oil-based vehicles (e.g., ointments) *(34)*. Only traces of boric acid in ointment penetrated the skin of infants with moderate diaper rash.

Dermal absorption of BA in animals is minimal. BA (5%) was applied topically to 10–15% of the body surface of rabbits with an occlusive dressing for 1.5 h/d for four consecutive days *(27)*. Minimal amounts of BA were absorbed across intact skin and slightly abraded skin of rabbits as measured by excretion of B in urine. Absorption was greater in rabbits with more seriously damaged skin. In rats given BA in an ointment, urinary excretion accounted for only 1% of the administered dose *(35)*. However, as in humans, BA applied to damaged skin of rats in an aqueous jelly was absorbed, with 23% of the administered dose appearing in the urine.

DISTRIBUTION

BA is distributed similarly in humans and animals. It is rapidly distributed throughout body water. After administration of BA, B levels in soft tissues are equivalent to those found in plasma, whereas bone B levels appear to be higher than those found in plasma or soft tissues.

In humans, a greater concentration of B in bone was reported relative to other tissues. Bone B concentrations were determined on 116 ashed samples from 33 human cadavers *(36)*. The concentration of B in bone was 61 ± 2 mcg/g (mean ± SE). In another study *(37)* involving a single human cadaver, B concentrations were determined in bone and 11 other tissues; bone B levels were appreciably higher than in other tissues. However, the bone B concentration reported in this study was only 0.9 ppm, a fraction of the value reported in the earlier study; the authors of the two studies were unable to resolve this discrepancy in findings. Nevertheless, these early human studies suggested that B is found in higher concentrations in bone relative to other tissues. More recently, Ward *(38)* examined B concentrations using a more sophisticated neutron activation analytical technique in a variety of human tissues, including bone, from 14 normal individuals and 18 individuals with rheumatoid arthritis. High B levels were found in bone, hair, and teeth.

Jansen et al. *(39)* concluded from pharmacokinetic studies of human volunteers that there is no tendency for B to accumulate following a single iv injection of 600 mg of BA (105 mg B). In a recent study of workers occupationally exposed to borate dust, there was no progressive accumulation of B across the work week as measured by blood and urine levels *(40)*.

In rats, Ku et al. *(26)* studied the tissue distribution of B in reproductive, accessory sex organs, and other selected tissues in adult males given BA in the diet, providing about 100 mg B/kg/d for up to 7 d. Similar to studies in humans, bone achieved the highest concentration of B in rats, reaching levels two to three times those observed in plasma, and bone B levels continued to increase throughout the 7 d of exposure (Fig. 1). In contrast, adipose tissue concentration of B was only 20% of the plasma value, a finding consistent with the lack of accumulation of B. Except for bone and adipose tissue, all tissues examined exhibited B levels comparable to the levels found in plasma. Accumulation of B in bone has also been reported in older studies in rats *(41)*.

In rats, soft tissue levels of B reached steady-state within 3–4 d when BA was given in the diet or drinking water for 28 d *(42)* or 9 wk *(43)*. Thus, B does not accumulate in soft tissue with time in either rats or humans.

Levels of B were determined in mice. The highest concentration of B in untreated mice was found in bone, 26 mcg/g dry wt *(44)*. In another study in mice *(45)*, investigators observed similar concentrations of B in brain, heart, liver, muscle, spleen, and kidney cortex. The highest con-

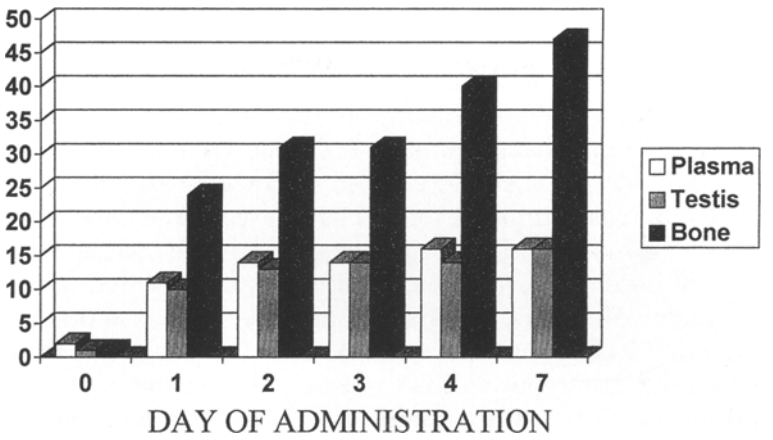

Fig. 1. B levels (mcg B/g) in plasma and tissues of male rats given BA in the diet. Adapted from ref. *(26)*.

centration was reported in papillary region of the kidney. Bone concentration was not determined in this study.

In summary, the distribution of B appears to be similar in humans and animals in several important respects:

1. B is quickly distributed throughout body water.
2. B does not accumulate in soft tissue.
3. B concentrations in soft tissues are equivalent to plasma concentrations.
4. B levels are higher in bone than in any other tissue.

METABOLISM

BA is not metabolized in humans or animals. The metabolism of BA by biological systems is not possible owing to the high energy requirements (523 kJ/mol) needed to break the B—O bond *(46)*.

Other inorganic borates convert to BA at physiological pH in the aqueous layer overlying mucosal surfaces prior to absorption. Additional support for this derives from studies in which more then 90% of administered doses of inorganic borates are excreted in the urine as BA.

In vivo and in vitro studies indicate that BA has a strong affinity for *cis*-hydroxy groups. This may explain the higher concentrations of BA in bone owing to binding to the *cis*-hydroxy groups of hydroxyapetite. This binding to *cis*-hydroxy groups may also provide a plausible mechanism of action for the biological effects of BA. However, this binding is reversible and concentration-dependent, and as such, affected by clearance mechanisms.

EXCRETION AND ELIMINATION

In both humans and animals, BA is excreted unchanged in the urine regardless of the route of administration. It is rapidly excreted, with a half-life of <24 h in humans and animals. BA is slowly eliminated from bone.

In humans, 99% of a single iv dose of BA was excreted in the urine, and the half-life was estimated to be 21 h, based on a three-compartment pharmacokinetic model *(39)*. In another study by the same investigators, 94% of an oral dose of BA (aqueous solution) was recovered in the urine of a group of male volunteers, and more than 50% of the oral dose was eliminated in the first 24 h, consistent with the 21-h half-life in the iv study *(24)*. In evaluating the case reports of BA poisonings, Litovitz et al. *(47)* found a mean half-life of 13 h, with a range of 4–28 h; however, because of the nature of these case reports, confidence in the estimated doses and times of exposure is low.

In animals, elimination half-lives have not been stated explicitly in the scientific literature, but they may be estimated based on data in the literature. Using the data of Ku et al. *(26)* and assuming first-order kinetics for elimination, the half-life in rats may be estimated to be <14–19 h. Similarly, the pharmacokinetic data of Farr and Konikowski *(48)* may be used to estimate a half-life of BA of approx 1 h in mice.

The major determinant of BA excretion is expected to be renal clearance. Rats and mice generally have faster rates of renal clearance than humans do. On the basis of renal clearance rates, one would expect rats and mice to clear BA more rapidly than do humans.

Renal clearance of BA in humans was estimated to be 39 and 55 mL/min/1.73 m^2 in two studies involving volunteers *(39,48)*. In comparison, renal clearance of BA in mice *(48)* was estimated to be 40 mL/min/1.73 m^2. There were no estimates of renal clearance rates for BA in rats. The similarity in the renal clearance rate reported in humans and mice is puzzling, since mice would be expected to clear BA more rapidly; this unexpected result may be related to the methodological and analytical limitations of a pharmacokinetic study that is 35 yr old *(48)*. Based on comparative renal plasma flow and assuming no tubular reabsorption, one might expect rats and mice to clear BA 2.6 and 3.6 times, respectively, more rapidly than humans.

BLOOD LEVELS

Background levels of blood B in the human population have been reported by various investigators to be in the range of 0.03–0.10 mcg/g *(16,49–52)*. Typical dietary intake of B in the diet is approx 1 mg B/d *(13)*. Assuming a 70-kg person, the estimated daily dietary dose of B is approx 0.014 mg B/kg/d (the equivalent of about 0.07 mg BA/kg/d). In a study of workers occupationally exposed to borates in a mine, Culver et al. *(40)*

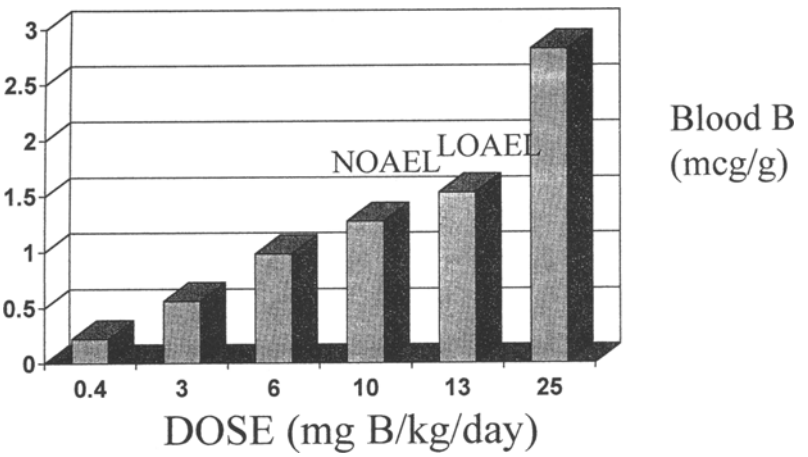

Fig. 2. Blood B (mcg/g) in pregnant rats given various doses of BA in the diet. Adapted from ref. *(53)*.

found an average blood B concentration of 0.24 mcg B/mL among the highest exposed group of workers; the dose received via inhalation was estimated to be 0.38 mg B/kg/d or approx 28 mg B/d, based on the results of air monitoring. In pregnant rats, the background blood B level was 0.23 mcg/g *(53)*, approx 2–8 times higher than the background level observed in humans, or approximately the same as the blood level found in the highest exposed population of workers in a borate mine.

In rats, the blood B levels associated with toxicity were much greater than the levels observed in even the most highly exposed human populations, although it is not known whether toxicity is related to peak blood levels or the area under the curve. The results of blood B analysis in pregnant rats in the pivotal rat developmental toxicity study of Price et al. *(53)* are shown in Fig. 2. The average blood B level on gestation day 20 in pregnant rats given the No Observed Adverse Effect Level (NOAEL) dose, which was 9.6 mg/kg/d, on gestation days 0–20 was 1.27 ± 0.30 mcg B/g, approx 5 times greater than the highest blood B level seen in a highly exposed group of male workers in a borate mine.

No blood B data have been reported in the scientific literature for pregnant women. Since renal clearance rates are higher in pregnant women, lower blood B levels are anticipated in pregnant women compared to nonpregnant women or men. Thus, the difference between the blood B level at the NOAEL in pregnant rats vs the maximum level expected in pregant women would be anticipated to provide a considerable margin of safety.

Blood B levels associated with effects of dietary administration of BA on reproduction in male rats may be estimated from the results of testis B analyses performed by Ku et al. *(43)*. Since this study showed a close

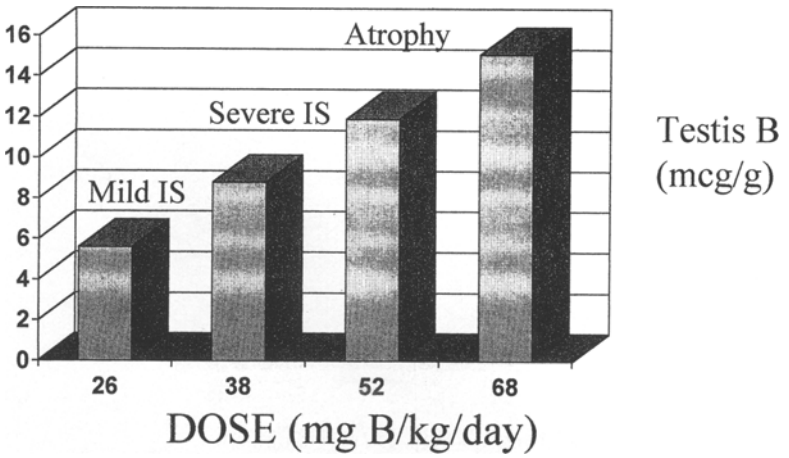

Fig. 3. Testis B levels (mcg/g) and testicular effects in male rats given BA. IS = inhibited spermiation. Adapted from ref. *(43)*.

degree of correlation between plasma and testicular levels of B (*see* Fig. 1), an assumption can be made that testis B levels approximate blood B levels. The lowest dose that had a discernible minor effect (i.e., mild inhibition of spermiation) on the testes of rats was approx 150 mg BA/kg/d (26 mg B/kg/d). This dose level was associated with a testicular B concentration of 5.6 mcg/g (Fig. 3). Making the assumption that blood B and testicular B levels are equivalent, a blood level of 5–6 mcg B/g was associated with mild effects on spermiation. This blood level in rats is 20–24 times greater than the highest mean level seen in the highest exposed worker population in a borate mine.

DISCUSSION AND CONCLUSIONS

The pharmacokinetics of BA appear to be straightforward and reasonably simple. Unfortunately, certain studies of BA were not designed for the primary purpose of evaluating pharmacokinetics. For example, the rat studies of Price et al. *(53)* and Ku et al. *(43)* are toxicologic studies, which included blood or tissue levels as one of many end points. Much of the pharmacokinetic data in humans derive from older studies that would not meet current standards.

Despite the limitations of the existing pharmacokinetic database, it is apparent that fewer potential sources of pharmacokinetic variation exist with BA relative to many other chemicals. Oral absorption is essentially complete in humans and animals. Distribution appears to occur by passive diffusion throughout body water in both humans and animals, and there is no metabolism of BA in humans or animals.

The similarities between humans and animals in the pharmacokinetics of BA have important implications for risk assessment. Reduced uncertainty in pharmacokinetics permits the use of reduced uncertainty factors for risk assessment. The greatest uncertainty exists for the rate of clearance from the body. Since metabolic clearance is not an issue for BA, differences in renal clearance are of paramount importance. Existing studies of renal clearance of BA in humans and animals are limited. The confidence in the selection of appropriate uncertainty factors for BA may be improved by the conduct of state-of-the-art studies of renal clearance.

In conclusion, the pharmacokinetics of BA in humans and animals are similar. In both humans and animals, oral absorption of BA is essentially complete; distribution occurs rapidly throughout body water; metabolism does not occur; urinary excretion is the major route of elimination, with a half-life of <24 h. Our current understanding of comparative pharmacokinetics would benefit from additional studies of the renal clearance of BA. For purposes of risk assessment, the use of reduced uncertainty factors is justified by the similarities in pharmacokinetics.

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