Micronutrients in Parenteral Nutrition: Boron, Silicon, and Fluoride

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Boron may be beneficial for bone growth and maintenance, central nervous system function, and the inflammatory response, and silicon may be beneficial for bone maintenance and wound healing. Fluoride is not an essential element but amounts provided by contamination may be beneficial for bone strength. Fluoride toxicity may be a concern in parenteral nutrition. Further studies are warranted to determine whether there are optimal amounts of boron and silicon that should be delivered to typical and special population patients receiving parenteral nutrition. In addition, further studies are needed to determine whether providing the dietary guideline of adequate intake amounts of fluoride parenterally would prevent or treat parenteral nutrition osteopenia.

Boron (B) is essential for some organisms in all phylogenetic kingdoms. Among the higher animals that require B are zebra fish and frogs. Boron-deprived male frogs show atrophied testes, decreased sperm counts, and sperm dysmorphology; female frogs show atrophied ovaries and impaired oocyte maturation.[1,2] During rapid cell division in embryogenesis, B-deprived zebra fish zygotes show blebbing of cell membranes, followed by cytoplasmic and yolk extrusion.[3] These changes prevent the completion of the life cycle (ie, deficiency causes impaired growth, development, or maturation such that procreation does not occur), which is a criterion for essentiality.

Although there are data suggesting that B deprivation impairs early embryonic development in mice,[4] the critical experiment showing that B is essential for a mammal to complete the life cycle, or defining a biochemical role for B necessary for life, is lacking. However, B-deprived experimental animals and human beings, when compared with controls fed nutritional amounts of B, show detrimental effects in bone growth and bone maintenance, brain function, and inflammatory response regulation. Boron deprivation impaired alveolar bone formation in mice, and alveolar bone repair after tooth extraction in rats; alveolus osteoblast surface was decreased and quiescent bone-forming surface was increased.[5,6] Boron deprivation decreased vertebral bone volume fraction and trabecular thickness, and increased trabecular separation and structural model index in rats.[7] Boron deprivation exacerbated arthritis induced by an antigen in rats.[8] Boron deprivation impaired cognitive processes of attention and memory, and psychomotor skills in human beings.[9] In addition, low dietary boron has been associated with prostate,[10] cervical,[11] breast,[12] and lung[13] cancer in human beings.

The diverse responses (many that may be secondary to a primary action) reported for low intakes of B have made it difficult to pinpoint a primary mechanism responsible for its bioactivity. However, the chemical characteristics of B may provide some clues as to a mechanism. At the pH of most biological fluids, about 96% of B exists as boric acid, $B(OH)_3$, a Lewis acid that accepts a hydroxyl group during the production of a proton. This property allows boric acid to react with biomolecules with hydroxyl groups to form B esters. Boron ester formation is best when hydroxyl groups are adjacent and *cis*.

The phosphoinositides, glycoproteins, and glycolipids of membranes contain *cis*-hydroxyl groups that may form diester borate polyl complexes, which could act as calcium chelators and/or redox metabolism modifiers[14] affecting membrane integrity and function. Thus, a low B status may impair important hormone receptors and signal transduction functions. Supporting this suggestion are findings showing that B deprivation impairs the actions of some hormones. Boron deprivation reportedly decreases insulin sensitivity[15] and increases the requirement for vitamin D to prevent gross bone abnormalities[16] and the need for exogenous thyroxine for tail resorption in frog development.[2]

Boron as boric acid also readily forms complexes with several biologically important sugars, including ribose, a component of adenosine.[17] S-adenosylmethionine (SAM) and diadenosine phosphates have higher affinities for B than any other currently recognized B ligands present in animal tissues.[18] Diadenosine phosphates are present in all cells and function as signal nucleotides associated with neuronal response. SAM is one of the most frequently used enzyme substrates.[19] About 95% of SAM is converted into S-adenosylhomocysteine, which is important for methylation of DNA, RNA, proteins, phospholipids, hormones, and neurotransmitters.[19] Hydrolyza-

Abbreviations used in this paper: AI, adequate intake; B, boron; F, fluoride; PN, parenteral nutrition; SAM, S-adenosylmethionine; SI, silicon.

0016-5085/09/$36.00
doi:10.1053/j.gastro.2009.07.072

tion of S-adenosylhomocysteine yields homocysteine. High circulating homocysteine and depleted SAM have been implicated in many human diseases including atherosclerosis, osteoporosis, arthritis, cancer, diabetes, and impaired brain function. The finding that B deprivation increased plasma homocysteine and decreased liver SAM levels in rats suggests that B may be bioactive through affecting the formation or use of SAM.[20]

Assessment of Deficiency and Toxicity

Boron is similar to most essential trace elements in that there is no single good indicator of status. About 90% of ingested B is absorbed and then efficiently excreted via the urine.[21] Thus, urinary B assesses only the recent intake. However, urinary B combined with a B intake assessment may give an indication of whether an individual has a low B status. Human beings consuming less than 0.5 mg/day for 2–3 months respond to a nutritional B supplement (3 mg/day).[9,22] Thus, a person on parenteral nutrition (PN) providing less than 0.5 mg B/day and excreting less than 0.5 mg B/day may have a low B status.

Plasma or serum B also may have some value as an indicator of B status. In one human study, a 9.0-fold increase in dietary B (mean from 0.36 to 3.23 mg/day) increased plasma B concentrations 1.5-fold (mean from 64 to 95 ng/mL).[21] In another study, supplementing 43 perimenopausal women with 2.5 mg B/day for 60 days increased the median plasma B concentration from 33 ng/mL (range, 20–67 ng/mL) to 52 ng/mL (range, 28–75 ng/mL).[23] These findings suggest that persons with serum or plasma B concentrations in the lower part of these ranges might be suspected of having a low B status. Plasma or serum B also may be used as an indicator of excessive B intake. Mean blood B concentrations were 68, 347, 585, 450, and 659 ng/mL in people from areas where drinking water provided 0.02, 0.08, 0.3, 0.4, and 0.5 mg B/kg body wt/day, respectively, in the drinking water.[24] Thus, blood B concentrations greater than 300 ng/mL would indicate a B intake in excess of that needed to prevent signs of B deprivation. Plasma or serum B concentrations greater than 1 μg/mL may indicate B toxicity.[25]

Boron is not very toxic when administered orally. Its relatively low toxicity allowed boric acid and borates to be used as food preservatives and in oral medicinal products in the late 19th and early 20th centuries. Toxicity in animals generally occurs only after dietary B exceeds 100 mg/kg. The signs of chronic B toxicity, based mainly on animal findings, include poor appetite, weight loss, and decreased sexual activity, seminal volume, sperm count, and sperm motility.[25]

Dose Range Recommendation for Typical PN-Fed Patients

The Food and Nutrition Board of the National Academy of Sciences set no Recommended Dietary Allowance for B, but did set tolerable upper limits.[26] These tolerable upper limits in mg/day are as follows: adults (≥19 y), 20; adolescents (14–18 y), 17; children (9–13 y), 11; children (4–8 y), 6; and children (1–3 y), 3. In human depletion-repletion experiments, subjects responded to a boron supplement after consuming a diet supplying less than 0.50 mg/day for 63 days.[9,19] An analysis of both human and animal data has suggested that an acceptable safe range of population mean intakes for B for adults could be 1–13 mg/day.[27] Thus, a recommendation that patients receive 1 mg B/day through typical PN could be beneficial for their bone and brain health. A limited number of reports have indicated that most PN solutions do not supply this amount of B, which comes only from contamination of ingredients. The calculated daily intake for B from PN based on analyses of individual components was 0.148 mg/day in one study.[28] In another study, the calculated intake for B in PN based on analyses of individual components was 1.796 mg/day,[29] but actual analysis of the intravenous delivered solution was only between 0.20 and 0.25 mg/day.[30] Urinary analysis of trauma patients receiving PN indicated that they received only about 0.2 mg B/day.[31] These findings suggest that depending on contamination to provide health-giving amounts of B may not be appropriate.

Silicon

Metabolic Function

Silicon (Si) is nutritionally essential for some lower forms of life (diatoms, radiolarians, and some sponges) and may be essential for some higher plants (eg, rice). For more than 35 years, the nutritional interest in Si for higher animals and human beings has focused on its beneficial effects on collagen and glycosaminoglycan formation or function, which could influence bone formation and maintenance, cardiovascular health, and wound healing. Although numerous apparent Si deficiency signs have been described, Si still is not generally accepted as an essential nutrient for higher animals and human beings. The critical experiment showing that Si is essential for a mammal to complete the life cycle, or defining a biochemical role for Si necessary for life, is lacking.

In 1978, Schwarz[32] described the difficulty in defining a biochemical function for Si. He first suggested that Si as an ether- or ester-like derivative of silicic acid had a cross-linking role in connective tissue; the low Si content of connective tissue negated that suggestion. Schwarz[32] subsequently hypothesized, because of the stability of the O-Si-O bond, that Si is involved in binding structures such as cell surfaces or macromolecules to each other. If this hypothesis is confirmed, it would indicate that Si may be involved in the interaction between an extracellular matrix macromolecule and osteotrophic cells such that it affects cartilage composition and ultimately car-