AMERICAN ACADEMY OF PEDIATRICS

Committee on Nutrition

Soy Protein-based Formulas: Recommendations for Use in Infant Feeding

ABSTRACT. The American Academy of Pediatrics is committed to the use of maternal breast milk as the ideal source of nutrition for infant feeding. Even so, by 2 months of age, most infants in North America are formula-fed. Despite limited indications, the use of soy protein-based formula has nearly doubled during the past decade to achieve 25% of the market in the United States. Because an infant formula provides the largest, if not sole, source of nutrition for an extended interval, the nutritional adequacy of the formula must be confirmed and the indications for its use well understood. This statement updates the 1983 Committee on Nutrition review[1] and contains some important recommendations on the appropriate use of soy protein-based formulas.

ABBREVIATION. IgE, immunoglobulin E.

BACKGROUND

Although soy protein-based nutrition has been used during infancy for centuries in the Orient, the first use of soy formula feeding in this country was in 1909.[2] In 1929, Hill and Stuart[3] proposed soy protein-based feeding for infants with intolerance to cow milk-based feeding.

Before the 1960s, soy protein-based formulas used soy flour, which imparted a tan color and nutty odor to the formula, and infants consuming it often had diarrhea and excessive intestinal gas. These features and symptoms were attributed to residual indigestible carbohydrates in the soy.[4,5] Since the mid-1960s, a soy protein isolate has been used, reducing these concerns and greatly increasing acceptance of the product.

COMPOSITION OF ISOLATED SOY PROTEIN-BASED FORMULAS

The isolated soy protein-based formulas currently on the market are all free of cow milk-protein and lactose, and prepared so they that provide 67 kcal/dL. All are iron-fortified and meet the vitamin, mineral, and electrolyte specifications addressed in the 1976 guidelines from the American Academy of Pediatrics for feeding full-term infants [6] and established by the US Food and Drug Administration.[7]

The protein is a soy isolate supplemented with L-methionine, L-carnitine, and taurine to provide protein at 2.45 to 3.1 g/100 kcal or 1.65 to 2.1 g/dL. The harvested soybean is processed by removal of the hull to yield a pulp that is then refined to soybean oil and soybean flake. The defatted flakes are processed into soy flour, soy protein isolate, or soy cotyledon fiber. Soy protein isolate is extracted in a slightly alkaline solution and precipitated at the isoelectric point of 4.5 to yield a purity of at least 90% soy protein on a dry basis.[8]

Supplementation with L-methionine began by the early 1970s. In 1979, Fomon et al[9] demonstrated improved biological quality of the protein with the addition of sulfur-containing amino acids. Subsequent studies in 1986 demonstrated that at a protein intake of 1.8 g/100 kcal, methionine was required to improve nitrogen balance, whereas at intakes of 2.2 and 2.6 g/100 kcal, methionine supplementation improved weight gain, urea nitrogen excretion, and albumin synthesis.[10] Before the routine supplementation of soy protein formulas with methionine, infants with undiagnosed, untreated cystic fibrosis were particularly at risk for severe hypoalbuminemia and edema when fed soy proteins, a risk that remains in soy, cow milk, and breastfed infants with cystic fibrosis until the initiation of pancreatic enzyme therapy.[11,12]

Carnitine, which is required for the optimal mitochondrial oxidation of long-chain fatty acids, is deficient in foods of plant origin and is added to soy formula to the level in breast milk, as is taurine, an amino acid that is abundant in human milk. Taurine functions as an antioxidant and, along with glycine, is a major conjugate of bile acids in early infancy.

The fat content of soy protein-based formulas is derived primarily from vegetable oils. The quantity of specific fats varies by manufacturer and is usually similar to those in the corresponding cow milk-based formula. The fat content ranges from 5.3 to 5.5 g/100 kcal or 3.6 to 3.8 g/dL. The oils used include soy, palm, sunflower, olein, safflower, and coconut.

Carbohydrate is provided lactose free, as corn starch, corn starch hydrolysate, tapioca starch, or sucrose, with content ranging from 10.0 to 10.2 g/100 kcal or 6.7 to 6.9 g/dL. Polysaccharide, in the form of supplemented soy fiber, has been added to one soy protein-based formula.[13]

Until 1980, mineral absorption from soy formulas was erratic because of poor stability of the suspensions and the presence of excessive soy phytates in the formula.[14] Not surprisingly, conflicting results of studies addressing the adequacy of bone mineralization were reported.[15–17] With the present formulations, bone mineralization, serum levels of calcium and phosphorus, and alkaline phosphatase levels in full-term infants through 6 to 12 months of age are

equivalent to those seen with cow milk-based formulas.[17–19] Because soy protein isolate formulas still contain 1.5% phytates and up to 30% of the total phosphorus is phytate-bound, the total phosphorus and calcium content of the formulas is ~20% higher than in cow milk-based formula, while still maintaining the mandated calcium to available phosphorus ratio (1.1 to 2.0:1).

The soy phytates and fiber oligosaccharides also bind iron and zinc.[20] All soy-based formulas thus are iron-fortified and have proved as effective as iron-fortified (12 mg/L) cow milk-based formulas in the prevention of iron deficiency in infants.[21,22] With radiolabeled zinc, the highest absorption of zinc is from human milk (41%) and the lowest is from soy formula (14%).[23] All soy protein-based formulas thus are zinc-fortified.[20,23] In one infant, the phytates may have interfered with the uptake of exogenous thyroid hormone, binding the T4 within the lumen, increasing fecal loss, and reducing the efficacy of oral thyroid hormone.[24]

Early studies revealed that the full nutritional value of soybean protein is achieved only after heat has been applied. Subsequent studies confirmed the presence of a number of heat-labile factors with biological activity in soybean-based products. The most prominent of these factors is a soybean protease inhibitor with the properties of an antitrypsin, antichymotrypsin, and antielastin.[25] Soybean protein isolate, as heated for infant formulas, removes 80% to 90% of this protease inhibitor activity and renders it nutritionally irrelevant. There also are heat-stable factors that remain in the soy protein isolate, including the low-molecular-weight fibers, phytates, saponins, and phytoestrogens.

The phytoestrogens demonstrate physiologic activity in rodent models and, per unit of body weight, the infant's potential intake of phytoestrogen from isolated soy protein-based formula is higher than that demonstrated to influence the menstrual cycle of humans.[26] Very limited human data to date, however, suggest that soy phytoestrogens have a low affinity for human postnatal estrogen receptors and low potency in bioassays.[25] A number of studies are addressing this issue at this time.

In 1996, the American Academy of Pediatrics issued a statement on aluminum toxicity in infants and children and discussed the relatively high content of aluminum in soy-based formulas.[27] Although the aluminum content of human milk is 4 to 65 ng/mL, that of soy protein-based formula is 600 to 1300 ng/mL.[8,28–31] The source of the aluminum is the mineral salts used in formula production. Aluminum, which makes up 8% of the earth's crust as the third most common element, has no known biological function in humans.[28] The toxicity of aluminum is traced to increased deposition in bone and in the central nervous system, particularly in the presence of reduced renal function in preterm infants and children with renal failure. Additional potential sources of aluminum include total parenteral nutrition solutions, renal dialysis fluids, and aluminum-containing antacids. Because aluminum competes with calcium for absorption, increased amounts of dietary aluminum from isolated soy protein-based formula may contribute to the reduced skeletal mineralization (osteopenia) observed in preterm infants and infants with intrauterine growth retardation.[32] Term infants with normal renal function do not seem to be at substantial risk for aluminum toxicity from soy protein-based formulas.[8]

SOY PROTEIN-BASED FORMULAS IN TERM INFANTS

Numerous studies have documented normal growth and development in term neonates fed methionine-supplemented isolated soy protein-based formulas.[8,33–37] Average energy intakes in infants receiving soy protein formulas also are equivalent to those achieved with cow milk formula.[8] The serum albumin concentration, as a marker of nutritional adequacy, also is normal,[8,10,34,38] and bone mineralization also is equivalent to that documented with cow milk-based formula.[15–19] Additional studies confirm that soy protein formulas do not interfere with the normal immune responses to oral immunization with polio vaccine.[39,40]

SOY PROTEIN-BASED FORMULAS IN PRETERM INFANTS

Preterm infants who weighed from 1500 to 1800 g and were fed methionine-supplemented soy protein-based formulas demonstrated significantly less weight gain, less length gain, and lower serum albumin levels than that achieved with cow milk-based formulas.[41] With lower birth weights, ie, <1500 g, data conflict; one study demonstrated equivalent growth and plasma protein levels,[42] whereas another demonstrated significant reductions in both.[43]

All three studies of preterm infants agreed, however, that serum phosphorus levels were lower in the preterm infants fed soy protein-based formula and, when measured, the alkaline phosphatase levels were higher.[41,42] As anticipated from these observations, the osteopenia of prematurity is reportedly increased in low birth weight infants receiving soy protein-based formulas.[44,45] Even with supplemental calcium and vitamin D, radiographic evidence of increased osteopenia was present in 32% of 125 preterm infants fed soy protein-based formula.[45]

When combined with concerns about aluminum toxicity, the failure to achieve equivalent growth rates or albumin levels consistently and the reduced bone mineralization lead to the conclusion that soy protein-based formulas should not be fed to low birth weight preterm infants. The newer cow milk protein-based formulas designed for preterm infants are clearly superior.

USE IN DISORDERS OF CARBOHYDRATE METABOLISM

When strict dietary lactose elimination is required in the management of infants with galactosemia or primary lactase deficiency, the soy protein formulas are safe and cost-effective. Soy protein-based formulas with sucrose as the carbohydrate are contraindicated in sucrase–isomaltase deficiency and in hereditary fructose intolerance.

Results of studies in animal models using a diabetes-prone rat suggested an increased frequency of diabetes when ingesting a soybean meal diet. However, when soy protein isolate or hydrolyzed soy protein feedings were used, no significant increase in diabetes was noted. This suggests that the factor contributing to the increased frequency of diabetes in this animal model is not the soy protein present in infant formulas.[46]

USE IN ACUTE DIARRHEA AND SECONDARY LACTASE DEFICIENCY

Because of the role of lactose-free soy protein-based formulas in the management of long-term lactose restriction, a number of studies have addressed the role of these formulas in the recovery from acute infantile diarrhea complicated by transient lactase deficiency. After immediate rehydration, most infants can be managed successfully with continued breastfeeding or standard cow milk or soy formula.[47,48] In an extensive review, Brown[47] noted that the dietary failure rate of lactose-containing formulas was 22%, whereas that of lactose-free formulas was 12%. In a study comparing breast milk, cow milk-based formula, and soy protein-based formula, no difference was found in the rate of recovery from rotavirus or nonrotavirus diarrhea based on nutritional therapy.[49] Although not significant from the perspective of nutritional compromise, the duration of diarrhea has been reported to be shorter in infants receiving soy protein-based formula.[50,51] The duration of liquid stools may be reduced further by adding additional soy polysaccharide fiber[52] or by resuming a mixed-staple diet.[53]

ANTIGENICITY OF SOY PROTEIN-BASED FORMULAS

Any ingested large molecular weight protein is a potential antigen to the intestinal immune system. In soy protein isolate, 90% of the pulp-derived protein resides in two major heat-stable globulins: β-conglycin, with a molecular weight of 180 000, and glycinin, with a molecular weight of 320 000. The former has three subunits, and the latter has six.[54] After enteric digestion, the number of potential antigens generated at the mucosal surface is enormous.[55] As a result, the in vitro demonstration of antigen-specific antibody can be difficult. The antigenicity of soy protein, suspected since 1934,[56] was documented in low-risk infants by Eastham et al[57] in 1982. Intrauterine sensitization has been documented by demonstrating antigen-specific antibody in human amniotic fluid.[58]

Severe gastrointestinal reactions to soy protein formula have been described for >30 years[59] and encompass the full gamut of disease seen with cow milk protein in infancy—enteropathy, enterocolitis, and proctitis. Small-bowel injury, a reversible celiac-like villus injury that produces an enteropathy with malabsorption, hypoalbuminemia, and failure to thrive, has been documented in at least four studies.[60–63] To date, those afflicted have responded to the elimination of soy protein-based formulas and are no longer sensitive by 5 years of age. Severe enterocoli-

tis manifested by bloody diarrhea, ulcerations, and histologic features of acute and chronic inflammatory bowel disease also has been well described in infants receiving soy protein-based formulas.[64–68] They respond quickly to elimination of the soy formula and introduction of a hydrolyzed protein formula. Their degree of sensitivity to soy protein during the first few years of age can remain dramatic; thus, casual use of soy-based formula is to be avoided.[68,69] Most children, but not all, can resume soy protein consumption safely after 5 years of age. In addition, up to 60% of infants with cow milk protein-induced enterocolitis also will be equally sensitive to soy protein.[68–70] It is theorized that the intestinal mucosa damaged by cow milk allows increased uptake and, therefore, increased immunologic response to the subsequent antigen soy. Eosinophilic proctocolitis, a more benign variant of enterocolitis, also has been reported in infants receiving soy protein-based formula.[70–73]

These dietary protein-induced syndromes of enteropathy and enterocolitis, although clearly immunologic in origin, are not immunoglobulin E-mediated, reflecting instead an age-dependent transient soy protein hypersensitivity.[74] Because of the reported high frequency of infants sensitive to both cow milk and soy antigens, soy protein-based formulas are not indicated in the management of documented cow milk protein-induced enteropathy or enterocolitis.

ALLERGENICITY OF SOY PROTEIN-BASED FORMULAS

Recognizing that soy protein is antigenic does not mean that soy protein is highly allergenic. To address immunoglobulin E (IgE)-mediated hypersensitivity to soy protein-based formula, three types of studies have been performed. The first addresses the frequency with which proven allergy develops in healthy infants fed cow milk- or soy protein-based formulas. The second addresses the same question in infants at high risk according to a family history of allergic responses to dietary protein. The symptom is usually eczema, and the high-risk history usually includes a family history of atopic disease (eg, asthma, allergic rhinitis, or eczema). The third type of study addresses the response of infants with proven cow milk allergy to subsequent ingestion of soy protein-based formula. The problem with these studies is with the definition of allergy, which included fussiness, colic, emesis, a positive RAST antibody, and/or a positive double-blind, placebo-controlled challenge.

In a prospective study of healthy infants fed breast milk, cow milk formula, or soy-based formula, Halpern et al[75] documented allergic responses to soy in 0.5% of infants and to cow milk in 1.8%. This frequency is consistent with the summary by Fomon[76] that in 3 decades of study of soy-based formulas, <1% of soy formula-fed infants had adverse reactions. In a national survey of pediatric allergists, the occurrence of allergy to cow milk was reported at 3.4%, whereas allergy to soy protein was reported to be 1.1%.[77] Two large studies of infants with atopic dermatitis addressed the frequency with which a

double-blind, placebo-controlled challenge with soy protein was positive. Sampson[78] documented soy positivity in 5% of 204 patients, whereas Businco et al[79] implicated soy in 4% of 143 children.

Prospective studies of high-risk infants suggest that soy protein-based formula has no relative value over cow milk formula in the prophylaxis or prevention of allergic disease.[80-84] Furthermore, the use of soy protein-based formula during the first 3 months of age does not reduce the frequency of positive antibody responses to cow milk formula introduced later in infancy.[85] When human milk feeding is supplemented with soy formula in high-risk infants, the anticipated frequency of eczema by 2 years of age is not significantly reduced.[79,80,86,87] Interpretation of these data is obscured by multiple alterations in the maternal diet and by environmental stimuli. The issue of delay in allergic disease, as opposed to the prevention of allergic disease, awaits the result of long-term investigations. Fortunately, true anaphylaxis after soy protein exposure has been reported only once.[88] According to the data now available, isolated soy protein-based formula has no advantage over cow milk-based formula for supplementing the diet of a breastfed infant.

Two studies documented the frequency of tolerance to soy protein in a small number of children with documented allergy to cow milk protein as defined by a positive skin test and positive double-blind, placebo-controlled challenge. The rate of combined positivity to cow milk and soy approximated 10%.[89,90]

TREATMENT OF COLIC WITH SOY PROTEIN-BASED FORMULA

Colicky discomfort, apparently abdominal in origin, is described by the parents of 10% to 20% of infants during the first 3 months of age.[91] Although many factors have been implicated, parents frequently seek relief by changing infant formula. Although some calming benefit can be attributed to the sucrose[92,93] and fiber content,[13] controlled trials of cow milk and soy protein-based formulas have not demonstrated a significant benefit from soy.[94,95] The value of parental counseling as to the cause and duration of colic seems greater than the value of switching to soy formula.[96] Because most colicky behavior diminishes spontaneously between 4 and 6 months of age, any intervention at that time can be credited anecdotally.

CONCLUSIONS AND RECOMMENDATIONS

1. In term infants whose nutritional needs are not being met from maternal breast milk or cow milk-based formulas, isolated soy protein-based formulas are safe and effective alternatives to provide appropriate nutrition for normal growth and development. Isolated soy protein-based formula has no advantage over cow milk protein-based formula as a supplement for the breastfed infant.
2. Because soy protein-based formulas are lactose-free, they are appropriate for use in infants with galactosemia and hereditary lactase deficiency.
3. Parents seeking a vegetarian-based diet for a term infant can be advised to use isolated soy protein-based formula.
4. Most previously well infants with acute gastroenteritis can be managed after rehydration with continued use of human breast milk or standard dilutions of cow milk-based formulas. Isolated soy protein-based formulas are indicated when lactose intolerance has been documented.
5. The routine use of isolated soy protein-based formula has no proven value in the prevention or management of infantile colic.
6. The routine use of isolated soy protein-based formula has no proven value in the prevention of atopic disease in healthy or high-risk infants.
7. Infants with documented cow milk protein-induced enteropathy or enterocolitis frequently are as sensitive to soy protein and should not be given isolated soy protein-based formula routinely. They should be provided formula derived from hydrolyzed protein or synthetic amino acid.
8. Most infants with documented IgE-mediated allergy to cow milk protein will do well on isolated soy protein-based formula.
9. Soy protein-based formulas are not designed or recommended for preterm infants who weigh <1800 g.

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