Committee on Nutrition

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

Many infant formulas are available as alternatives to breast-feeding. These formulas are necessary and valuable resources in the nutriment of infants, but it is important to evaluate their use and efficacy periodically. Soybean preparations were suggested as a milk substitute by Hill and Stuart in 1929.

Since then, the use of these products has expanded appreciably, and they are used for an estimated 10% to 15% of all formula-fed infants. This increase in use has prompted examination of the following critical issues about the indications for use of soy-protein formulas in infants. (1) Are soy-protein formulas an adequate nutritional substitute for cow's milk-based formulas in full-term infants? (2) Is it appropriate to recommend soy-protein formulas to provide a lactose-free formula, or are there better alternatives? (3) Are soy-protein formulas ever indicated for use in premature infants? (4) What is the evidence for and against the use of soy-protein formulas in the management of cow's milk-protein allergy? (5) What is the role of soy-protein formulas in prophylaxis of allergic disease? (6) What is the evidence for and against the use of soy-protein formulas in the management of "colic"?

Examination of these issues will hopefully, provide a more clear-cut basis for decisions regarding the use of soy-protein formulas and updated recommendations for the role of soy-protein formulas in feeding human infants.

**COMPOSITION OF SOY-PROTEIN FORMULAS**

Soy-protein formulas, although different in carbohydrate and protein source, are similar in composition to cow's milk-protein formulas following the American Academy of Pediatrics, Committee on Nutrition, 1976 recommendations for nutrient levels in infant formulas. Differences include a slightly higher protein level and slightly lower carbohydrate content. The protein source is generally (but not always) soy-protein isolate; the fat is a blend of vegetable oils; and the source of carbohydrate is usually sucrose, corn syrup solids (hydrolyzed corn starch), or a mixture of both. Thus "soy" formulas are called this because soy is used as a protein source. The lactose-free characteristic of these formulas also enhances their use in specific situations.

The quality of a product depends to a considerable extent on its processing. The first infant formulas containing soy protein used fat-free soy flours; as a result, they were dark in color, had a distasteful flavor, and, because of the soluble carbohydrates from the soybean, were the cause of flatus and foul-smelling stools. The development of more refined soy-protein isolate has made the manufacture of higher quality, soy-based formulas possible. Although the specific processing of soy proteins is kept confidential by the manufacturers, the primary objective is extraction of the major protein fraction. Heat treatment of soy protein reduces the activity of trypsin inhibitors and hemagglutinins and enhances protein digestibility and bioavailability of some minerals. For example, although iron absorption appears to be inhibited in soy products, absorption from soy-isolate formulas has been shown to be similar to that from cow's milk protein formula. However, in the processing of isolates, the formation of tightly bound protein-phytic acid-mineral complexes may reduce the availability of some minerals. Zinc in soy also appears to be less well absorbed; however, supplemental zinc absorption does not appear to be impaired. The amount of phytic acid in these formulas and its effect on mineral and trace element availability needs to be more clearly delineated. Carnitine, which is required for the optimal oxidation of fatty acids, is generally found in low concentrations in foods of plant origin as compared to foods of animal origin. Therefore, soy-based formulas contain minimal amounts of carnitine. However, there is insufficient evidence to conclude that carnitine should be added to formulas on a routine basis.
Because soy-protein formula provides the sole source of nutrition for many infants, the adequacy of the amino acids provided by soy protein is important. Fomon et al\textsuperscript{12} showed improved biologic quality of soy-protein isolate with fortification of the first limiting amino acid, methionine. Methionine appears to limit nitrogen retention at deficient levels of intake but not at requirement levels or above, making supplementation unnecessary when the intake of protein is adequate.\textsuperscript{13} However, methionine is now routinely added to all soy-protein formulas manufactured in the United States.

**USE IN FULL-TERM INFANTS**

Normal growth and development in full-term infants fed soy-protein formulas have been well documented in numerous studies.\textsuperscript{14-21} A recent review of this topic by Fomon and Ziegler\textsuperscript{22} reported growth and nitrogen balance studies in infants fed soy-protein formula or cow’s milk-protein formula. No significant differences were found between the two groups of infants in either weight or length. Furthermore, concentrations of serum urea nitrogen, total protein, and albumin did not differ significantly between the infants consuming cow’s milk-based formulas and those consuming soy-protein formulas. However, when expressed in terms of weight gain per unit of energy intake, infants receiving soy-protein formulas had slightly lower rates of weight gain. Although this observation is of some interest, available evidence suggests that formulas using methionine-supplemented, soy-protein isolate promote normal growth and development in full-term, healthy infants.

**USE IN LACTOSE INTOLERANCE AND GALACTOSEMIA**

Soy-protein formulas are lactose-free and supply carbohydrate from either sucrose or corn syrup (hydrolyzed corn starch). Thus, when lactose elimination is required for the management of primary lactase deficiency or galactosemia, soy-protein formula is the feeding of choice. In addition, secondary lactose intolerance resulting from enteric infection or other causes of mucosal damage can be managed with soy-protein formula.\textsuperscript{23-25} After the diarrhea and the intestinal damage have been resolved, resumption of a cow’s milk-protein formula is appropriate (generally 2 weeks after cessation of the diarrhea).

**USE IN PREMATURE INFANTS**

The first report of the result of feeding soy-protein formula in premature infants was that of Omans et al,\textsuperscript{26} who found considerably more variability in weight gain than with feedings of cow’s milk formula. However, these studies were with soy protein not supplemented with methionine. In another comparative study of soy-protein and cow’s milk-protein formulas in premature infants, Naudé et al,\textsuperscript{27} using a methionine-supplemented formula, found reduced weight and length growth and significantly lower serum albumin levels in infants fed soy-protein formula. Shenai et al\textsuperscript{28} in a comparison of cow’s milk-protein formula and soy-protein formula (methionine supplemented), found normal and equal growth in length and weight and similar and normal serum albumin levels between the two groups. The mean BUN values were significantly greater and the nitrogen retention values were significantly lower in the soy-protein fed group; however, the BUN values were in the normal range for premature infants, and the nitrogen retention values were in the normal range of fetal nitrogen accretion rates.

In all three of the feeding studies,\textsuperscript{26-28} serum phosphorus levels were significantly lower in the groups fed soy-protein formula; and, in the two studies in which serum alkaline phosphatase levels were measured,\textsuperscript{27,28} serum phosphorus levels were significantly elevated over levels found in the infants fed cow’s milk-protein formula. Osteoporosis and rickets recently were reported in sick, very low-birth-weight infants. These infants, fed soy-protein formulas for several months, have been found to have this complication.\textsuperscript{29-30} The low calcium content of soy-protein formulas (relative to the needs of the rapidly growing, very low-birth-weight infant) and all standard infant formulas and human milk is a major cause. However, the hypophosphatemia associated with the prolonged use of soy-protein formulas in premature infants probably can accelerate the development of hypophosphatemic rickets. The reason for the hypophosphatemia is not certain, but it may lie with the binding of some of the soy milk phosphorus with phytate in the formula, leading to its unavailability for intestinal absorption.

The use of soy-protein formula in premature infant feeding was encouraged by the initial reports of the efficacy of continuous nasojejunal feeds in the feeding of very low-birth-weight infants. Soy-protein formula was widely used for feeding by this route because the formula osmolality was low, and the lack of lactose seemed to confer an advantage in feeding very low-birth-weight infants who frequently tolerated lactose loads poorly. In particular, soy-protein formulas seemed to be associated with a lower incidence of necrotizing enterocolitis (NEC). However, the effect on the development of NEC probably is more the result of the rate at
which the formula is given and the rapidity of feeding increases than the osmolality, type of protein, or lack of lactose in the formula. Moreover, there are now other commercial formulas that are isosmolar with plasma, even in concentrations of 24 calories per ounce, and these formulas have reduced lactose levels. The disadvantages of the soy-protein formula for very low-birth-weight infant feeding, as discussed here, indicate that these formulas should not be used for prolonged feeding of very low-birth-weight infants. Rather, they should be used only for specific therapeutic indications and for periods of not more than 3 to 4 weeks.

MANAGEMENT OF COW'S MILK ALLERGY

The question of soybean allergenicity aroused interest in 1934 with the report of a patient sensitive to inhaled soybean who lived and worked near a soybean mill.31 Five other persons working in the mill had evidence of allergic disease. Subsequent animal studies32,33 concluded that soybean was a weak sensitizing protein and soy-protein formulas were deemed nonallergenic and recommended for use in managing cow's milk-protein allergic infants.34-36 In 1960, a series of case reports of gastrointestinal and "allergic" reactions to soy protein began to appear.37-44

Serious gastrointestinal reactions to protein included severe vomiting, diarrhea, and weight loss37; flat intestinal mucosa38; a series of four infants with colitis and persistent diarrhea39; and documented systemic allergic manifestations to dietary soy protein.40-42 Additional reports43,44 of soy protein intolerance, comitant with cow's milk-protein intolerance, and positive intracutaneous tests of soybean in allergic children who received soy-protein formula in infancy,45 also were published. Because cow's milk-protein allergy frequently leads to small bowel damage,46 including villus atrophy, mucosal permeability to other proteins can result in an increased systemic uptake and immunologic response to these proteins. Furthermore, at a time of clinical allergic response to cow's milk protein, the uptake of otherwise nonallergenic proteins might result in a similar allergic reaction to these proteins, thus broadening the allergic response.47 Therefore, in infants and children already showing clinical manifestations of allergic disease, a less antigenic formula is warranted (ie, protein hydrolysate).

PROPHYLAXIS OF ALLERGIC DISEASE IN NEWBORN INFANTS

The role of soy-based formulas in the prevention of allergic disease in newborn infants remains controversial. Theoretically, any protein is a potential allergen, and examples of soy-protein allergy have been cited. Two studies in infants with strong family histories of allergy48,49 fed human, soy, or cow's milk-protein formula found no significant difference in the development of allergy from the type of feeding. On the other hand, Taylor et al50 identified allergy-prone infants, compared human milk and elemental feeding with unrestricted conventional dietary regimens for infants, and showed a significant decrease in children exposed to a less antigenic intake. Gruskay51 found similar results in breastfed allergy-prone infants compared with allergy-prone infants cow's milk or soy-protein formula.

Two similar studies in healthy, full-term infants with no genetic history of allergic disease have different interpretations. Eastham et al52 showed lower antibody titers to subsequent cow's milk protein or soy protein in infants fed casein hydrolysate formula for the first three months of life compared with findings in infants fed cow's milk-protein or soy-protein formula. This suggests that soy protein is as antigenic as cow's milk protein and indicates intestinal mucosal barrier maturation as a factor in the development of allergic disease. May et al53 recently found the feeding of soy-protein formula from birth to 112 days did not lessen the antibody response to cow's milk-protein products fed subsequently.

At this time, evidence suggests that soy protein may be less allergenic than heat-treated, cow's milk protein and is probably a better source of nutrition in allergy-prone infants. However, whether or not soy protein represents the optimum form of prophylaxis is still controversial. The extent to which early exposure to antigen affects the subsequent development of allergic disease requires more sophisticated prospective studies to resolve the issue objectively.

TREATMENT OF COLIC

Colic is a frequent symptom complex of abdominal pain and severe crying of presumed gastrointestinal etiology. A multitude of dietary factors (including overfeeding, allergy, and carbohydrate intolerance) have been implicated as possible causes.54,55 However, only occasionally does a change in diet prevent further attacks, with symptoms in most infants resolving spontaneously, by 4 months of age. A recent study of Lothe et al56 compared the effects of cow's milk-protein formula, soy-protein formula, and protein hydrolysate formula in the management of colic. They found symptoms to be unrelated to diet in 29% of the infants;
18% were symptom-free while receiving soy formula; and 53% were unchanged or colic was worse while receiving soy or cow’s milk-protein formula, but the symptoms resolved when casein hydrolysate was given. This raises the possibility that cow’s milk is a precipitating factor in some infants with colic and suggests that it may be most effectively managed by the use of a casein hydrolysate. Any conclusions are tentative at this time and more controlled studies on this common problem are needed.

CONCLUSIONS AND RECOMMENDATIONS

The use of soy-protein formula should be approached with thoughtful consideration of indications for use. Based on the information given here, specific recommendations for the use of soy-protein formula include: (1) in vegetarian families in which animal protein formulas are not desired; (2) in the management of galactosemia, primary lactase deficiency, or the recovery phase of secondary lactose intolerance, animal protein formulas are not desired; (2) in the dietary management of galactosemia, primary lactase deficiency, or the recovery phase of secondary lactose intolerance, these formulas are the least expensive and most available formulas not containing lactose; and (3) in potentially allergic infants (with a family history of atopy) who have not shown clinical manifestations of allergy. However, these infants should be monitored closely for allergy to soy protein.

Instances when soy-protein formula should not be used include: (1) for the routine feeding of premature and low-birth-weight infants; use should be for limited periods, if at all; (2) in the dietary management of documented clinical allergic reaction to cow’s milk protein and/or soy protein formula; and (3) in the routine management of colic.

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