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Fatty acids in substitute formulas for cow's milk allergy

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Background: The role of dietary fats in food-related allergic symptoms is increasingly being investigated, since the pivotal role of fat-derived inflammatory substances, e.g., leukotrienes, has been realized. The objective of this study was to describe the fatty acid composition of several commercially available infant formulas that are used as substitutes for adapted cow's milk formulas.

Methods: Samples of nine formulas (two soy, two extensively hydrolyzed casein, three extensively hydrolyzed whey, and two amino-acid-based formulas) and human milk as control were analyzed by gas chromatography.

Results: The quantity of fatty acids in the formulas was within the breast-milk range. The percentage of energy derived from fat was below the European Society for Pediatric Gastroenterology and Nutrition recommendations in two cases, but, in the others, it roughly met the recommendations. The percentage of energy derived from linoleic acid was as recommended in all but two cases, where it was higher than recommended. As indicated by a quality indicator, the linoleic to α -linolenic acid ratio, altogether four formulas were within either the recommendations or the analyzed breast-milk range. In three cases, it was 1.5–2.5 and in two cases 4–5 times higher than recommended.

Conclusions: There are recommendations for infant formulas to meet nutritional requirements of fat intake, and the analyzed formulas are in most cases within the suggested ranges. However, little is known of requirements in allergic or inflammatory conditions, and whether these described fatty acid compositions are pro- or anti-inflammatory.

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Attempts to prevent allergies, and treatment of cow's milk allergy, involve using one of several substitute formulas with either hydrolyzed proteins or an alternative protein

source. These formulas are used during infancy, when the quality and quantity of fat in the diet may have long-lasting effects on developmental programming. A quality indicator of the fat composition of foods has been used, the linoleic to α -linolenic acid ratio (LA/ALA). The nutritionally adequate LA/ALA ratio has been fairly well characterized, but the ratio may also have an effect on the balance of the production of the inflammatory mediators, such as leukotrienes and prostaglandins. The effects on the inflammatory reactions may be of special importance for the allergic child. The present work aimed to describe the fatty acid composition of commercially available substitute formulas for cow's milk allergy, and to compare the results with the recommended nutritional and breast-milk ranges, since there are as yet no allergic or inflammatory recommendations.

Material and methods

Nine substitute infant formulas for cow's milk-allergic patients available in Finland were chosen. These included two soy formulas – 1) Dietta-Soija®Semper-Medifood – 2) Nutri-Soija®Nutricia—two extensively hydrolyzed casein formulas – 3a and 3b) Nutramigen®Bristol-Meyers-Squibb, – 4a and 4b) Pregestimil®Bristol-Meyers-Squibb—three extensively hydrolyzed whey formulas – 5) Pepti-Junior®Nutricia – 6) Peptidi-Tutteli®Valio Ltd, – 7) Profylac®ALK—and two amino-acid formulas – 8) Neocate®SHS – 9) Nutri-Junior®Nutricia. Powdered formulas were dissolved in water, as instructed by the manufacturers. Samples of two to three batches of each formula were analyzed. Later the fatty acid composition of Nutramigen and Pregestimil was changed, and the new formulations (3b and 4b) were also analyzed.

Fifteen human milk samples obtained from the milk bank of Tampere University Hospital (Finland) were controls (donated by mothers 2–26 weeks after delivery). According to the usual protocol of the milk bank, milk was expressed from both breasts several times during a day. The samples were stored at 4°C (maximum of 2 days), and thereafter at –70°C (maximum of 1 month before analysis).

After dilution of milk samples with physiologic saline (1:10), lipids were extracted from 50- μ l aliquots with chloroform methanol (2:1 v/v), according to Folch et al. (1). After saponification with KOH-ethanol, the fatty acids were esterified with 2% H₂SO₄ in dry methanol. The methyl esters were analyzed with a Hewlett-Packard model 5890 gas chromatograph equipped with a 25 m, 0.32 mm i.d. NB-351 fused silica capillary column (HNU-Nordion Ltd,

Helsinki, Finland) and a flame ionization detector. Fatty acids were identified by comparing the peaks with known standards, and quantified as a weight percentage of the sum of the 25 major peaks from 8:0 to 22:6n-3. For quantification of total fatty acid content, triheptadecanoate (tri-15:0) was used as an internal standard. The percentage of energy derived from fat was calculated from the manufacturer's description of the fat and energy content of the respective formula.

Results

The quantity of fatty acids in the formulas was within the breast-milk range (Table 1). The percentage of energy derived from fat was below the European Society for Pediatric Gastroenterology and Nutrition (ESPGAN) recommendations (2) in two cases (formulas 3a and 4a), whereas, in others, it roughly met the recommendations, with a tendency of higher than recommended percentage. The percentage of energy derived from linoleic acid was as recommended in all cases, except in two where it was higher than recommended (formulas 3a and 5). Compared to human milk, the total n-6 PUFA (polyunsaturated fatty acid) content of the formulas was strictly the same in one case (formula 8) and close to the analyzed human milk value in two cases (formulas 1 and 2). At the same time, the total n-3 PUFA content was clearly low in two cases (formulas 5 and 7), and similar to human milk in one (3a). All of the n-3 PUFA in all formulas was ALA. According to the recognized quality indicator, the LA/ALA ratio, altogether four formulas were within either the recommendations or the analyzed breast-milk range (formulas 1, 2, 6, and 8). In three cases, it was 1.5–2.5 (formulas 3a, 4a, and 9) and in two cases 4–5 times (formulas 5 and 7) higher than recommended (Fig. 1). After a change in fatty acid composition (formulas 3b and 4b), the LA/ALA ratios were 12.1 and 19.2, in the two formulas, respectively.

Discussion

The quality of fat in substitute formulas used in cow's milk allergy has received little attention. Most cow's milk-allergic patients are atopic, and the substitute formulas are a major component of these infants' diet. Lately, the pivotal role of inflammation in the allergic condition has been realized. A recent review on prevention of asthma

Table 1. Fatty acid (FA) composition of substitute infant formulas for cow's milk allergy (mean of two to three batches) and human milk ($n=15$, mean $\pm$ SD). 1: Dietta-Soija, 2: Nutri-Soija, 3a: Nutramigen old, 3b: Nutramigen new, 4a: Pregestimil old, 4b: Pregestimil new, 5: Pepti-Junior, 6: Peptidi-Tutteli, 7: Profylac, 8: Nutri-Junior, 9: Neocate

	Soy		Casein				Whey			Amino acid		Human milk
	1	2	3a	3b	4a	4b	5	6	7	8	9	
SAT	32.48	33.05	13.65	38.00	48.89*	58.60*	58.12*	43.78	35.64	33.67	26.48	42.24 $\pm$ 3.50
MONO	51.42	50.48	28.38	38.80	16.75	19.52	13.62	38.30	45.44	51.03	53.79	44.30 $\pm$ 2.82
n6PUFA	13.39	13.49	54.36	21.41	32.07	20.76	27.31	16.10	18.32	12.50	18.33	11.17 $\pm$ 1.46
LA (18:2n-6)	13.35	13.46	54.36	21.41	32.03	20.76	27.26	16.06	18.29	12.44	18.27	10.30 $\pm$ 1.42
DLA (20:3n-6)	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.30 $\pm$ 0.06
AA (20:4n-6)	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.35 $\pm$ 0.06
3PUFA	2.57	2.81	1.96	1.76	1.69	1.08	0.46	1.67	0.42	2.60	1.26	2.19 $\pm$ 0.32
ALA (18:3n-3)	2.57	2.81	1.96	1.76	1.69	1.08	0.46	1.67	0.42	2.60	1.26	1.66 $\pm$ 0.30
EPA (20:5n-3)	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.06 $\pm$ 0.05
DHA (22:6n-3)	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	nd	0.31 $\pm$ 0.11
Fat g/dl	3.4	3.6	2.6	3.4	2.7	3.8	3.6	3.5	3.3	3.4	3.5	3.48 $\pm$ 1.4
Fat E%	46.4	49.1	34.9	43.7	34.7	45.9	47.0	47.1	45.0	46.5	43.7	
LA E%	4.9	5.4	14.6	7.9	8.8	7.7	12.1	6.9	6.0	4.9	6.6	
LA/ALA	5.2	4.8	27.7	12.1	18.9	19.2	59.6	9.6	43.4	4.8	14.5	6.45 $\pm$ 1.34

ESPGAN recommendation (Ref. 2); fat 40–45 E%, MONO approximating that of human milk, LA 4.5–10.8 E%, LA/ALA as in human milk (around 10).
 SAT: saturated FA; MONO: monounsaturated FA; PUFA: polyunsaturated FA; LA: linoleic acid; DLA: dihomogamma-linolenic acid; AA: arachidonic acid; ALA: α -linolenic acid; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid; nd: not detected; E%: percentage of energy. * Medium chain triglycerides included.

found dietary fats to be one of the few factors which could be manipulated to decrease the incidence of allergies (3).

The fatty acid content of substitute formulas is shown here to be highly variable, and in several cases different from that of human milk, which is considered the model food for infants. The total n-6 PUFA content of the analyzed

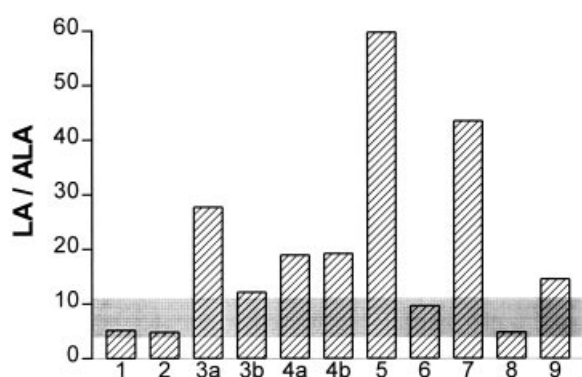


Figure 1. Ratio of linoleic to α -linolenic acid (LA/ALA) in nine substitute infant formulas for cow's milk allergy: 1: Dietta-Soija®, 2: Nutri-Soija, 3a: Nutramigen/old, 3b: Nutramigen/new, 4a: Pregestimil/old, 4b: Pregestimil/new, 5: Pepti-Junior, 6: Peptidi-Tutteli, 7: Profylac, 8: Nutri-Junior, 9: Neocate. Shaded horizontal bar shows European Society for Pediatric Gastroenterology and Nutrition recommendations (Ref. 2) and human milk range.

formulas was well above the analyzed human milk values in all but one case. The n-3 PUFA content varied, being significantly low in two, low in three, and high in three, and in only one case similar to human milk. When the n-3 PUFAs are considered separately, it has to be recognized that all of the n-3 PUFA in the formulas is α -linolenic acid, in clear contrast to human milk, which also contains very long-chain n-3 PUFAs. Interestingly, it has been reported that the breast-milk of mothers whose children have newly developed atopic eczema is low in very long-chain polyunsaturated fatty acids (4). Despite reservations on the method used, that study did highlight the role of fats in atopy.

Recommendations on the fats of infant formulas have been compiled; e.g., by ESPGAN (2). The endorsed linoleic to α -linolenic acid ratio (around 10) is central, and is a prerequisite for balanced synthesis of n-6 and n-3 very long-chain polyunsaturated fatty acids. Only four of the substitute formulas originally met this quality criterion. High intake of linoleic acid may be detrimental to health, by inhibiting ALA metabolism, by disturbing the balance of eicosanoid synthesis, or by excessive lowering of HDL cholesterol. It is important that the formulas intended for allergic infants be nutritionally adequate also in this respect,

and this seems to be increasingly appreciated by the producers of such formulas. The new formulations of both Pregestimil and Nutramigen take this nutritional quality of the fatty acid composition into account.

Traditionally, it has been thought that to treat cow's milk allergy, it suffices to reduce or eliminate the protein antigen content of the special formula used during the cow's milk elimination diet. More recently, it was shown that the quality of formula fat, other components being equal, can significantly affect intestinal integrity in food-sensitized mice; hypothetically, via effects on leukotriene synthesis (5). It has been shown that the gastrointestinal tract of atopic, food-allergic infants is inflamed (6). The role of the fatty acid composition of formula has not been studied in a controlled setting in human infants allergic to cow's milk and consuming any of the substitute formulas; at least, we have not been able to find any such studies by extensive literature searches. In a randomized, controlled setting, a recent paper

examined the effect in asthmatic children of n-3 ("anti-inflammatory") and n-6 ("proinflammatory") fatty acids on the severity of the disease: no beneficial effect of extra intake of n-3 fatty acids could be demonstrated after 6-month intervention (7). Clearly, the role of fatty acids in allergy merits further study, considering their nutritional as well as pro- or anti-inflammatory effects in various patient groups.

In conclusion, the fatty acid composition of the substitute formulas meets the nutritional recommendations for healthy infants in most cases. Evaluated with the LA/ALA ratio, two of the formulas remain nonphysiologic. Although no recommendations for the allergic or inflammatory conditions exist, experimental animal data suggest that the fatty acid composition is also of consequence in food allergy. The possibility of providing the allergic infant with a nutritionally adequate formula which also acts therapeutically by decreasing the gut inflammatory reaction should be explored.

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