Journal of Pediatric Gastroenterology and Nutrition
43:364–371 © September 2006 Lippincott Williams & Wilkins, Philadelphia

Adequacy and Safety of an Infant Formula With a Protein/Energy Ratio of 1.8 g/100 kcal and Enhanced Protein Efficiency for Term Infants During the First 4 Months of Life

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ABSTRACT

Objective: Excess protein in infant formula may lead to renal overload and play a role in later obesity. The objective of this controlled, prospective, randomized, double-blind study was to assess the suitability and safety of a modified protein content infant formula and its noninferiority as compared to a conventional formula.

Patients and Methods: Healthy term infants age <7 days were either breast-fed or randomized to be fed exclusively with a conventional casein-predominant formula (protein/energy ratio: 2.6 g/100 kcal) or the isocaloric whey-predominant study formula (protein/energy ratio: 1.8 g/100 kcal) for 120 days. Primary outcome was daily weight gain between D0 and D120 (noninferiority criterion: difference in daily weight gain ≤4 g). Secondary outcomes were daily gain in weight, length, head circumference and body mass index at monthly intervals. Tolerance and safety were assessed at each visit.

Results: 162 infants were enrolled, 84% of the formula-fed infants and 36% of the breast-fed infants completing the study. Mean daily weight gain from D0 to D120 in the formula-fed groups differed by 0.38 g/day [95% CI: −2.59; 1.83] signifying the noninferiority of the study formula. Secondary outcomes did not differ between the 2 groups at any time and were comparable to outcomes in the breast-fed group. Tolerance was good and adverse events were not different between study groups.

Conclusions: The whey-predominant study infant formula with a protein/energy ratio of 1.8 g/100 kcal and enhanced protein efficiency is safe and not inferior to a conventional formula in ensuring normal growth during the first four months of life. ***JPGN 43:364–371, 2006.*** **Key Words:** Infant formula—Protein content—Protein/energy ratio—Whey-predominant—Breast-feeding. © 2006 Lippincott Williams & Wilkins

INTRODUCTION

Breast milk by itself fulfills the nutritional requirements of healthy term infants up to 6 months of age (1). Infants who are not breast-fed require infant formulas of high nutritional quality, meeting the requirements for both nitrogen and indispensable amino acids for maintenance of the body and growth. The composition of infant formulas, intended to sustain infants during the first 4 to 6 months of life and fully satisfying their nutritional requirements, is regulated within the European Union by Directive 91/321/EEC (2). To compensate for the lesser quality of bovine milk and soy proteins, the only protein sources allowed by the Directive, infant formulas have a higher protein content than human milk.

The minimal protein/energy ratio for infant formulas based on cow's milk and soy protein is defined in Directive 91/321/EEC as 1.8 and 2.25 g/100 kcal, respectively. The lower limit of 1.8 g/100 kcal for infant formulae based on cow's milk is also specified by the US Food and Drug Administration (3), and has been endorsed by the European Society for Paediatric Gastroenterology and Nutrition (4), the Codex Alimentarius (5), and the Committee on Nutrition of the American Academy of

Received July 11, 2005; accepted April 19, 2006.

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Pediatrics (6). Data on breast-fed infants from 1 to 6 months of age published by Dewey et al. showed that protein requirements were 10%–26% lower than previously estimated in the Joint FAO/WHO/UNU Expert Committee Report of 1985 (7,8).

Renal capacity to concentrate urine is low in infants during the first 2 to 3 months of life (9). For this reason, inappropriate protein intake, resulting in excessive generation of urea, may lead to metabolic stress on the kidneys. This is clearly illustrated by the increased serum urea nitrogen and overall increase in plasma amino acid concentration observed in formula-fed infants as compared to breast-fed infants (10). In addition to the short-term effects of infant feeding on growth and health, there is growing evidence that both the quality and quantity of nutrient supply during early infancy have important consequences on disease risks in later life (11). The lower protein content of human milk as compared to infant formulas based on cow's milk and soy protein, has been postulated to play a role in the reduced risk of later obesity associated with breast-feeding (12). Because excessive protein intake does not appear to have any beneficial effects on the health of young infants and children, it should be avoided (13).

The ESPGHAN Committee on Nutrition advocated the systematic nutritional and safety evaluation of breast milk substitutes (14). In its report on the revision of essential requirements for infant and follow-on formulas approved on April 4, 2003, the Scientific Committee on Food proposed no change in the minimum crude protein content of 1.8 g/100 kcal for infant formulas based on intact cow's milk protein. However, the Committee recommended that any infant formulas with this minimum protein content should be subjected to adequate clinical testing of its nutritional adequacy (15).

A growth study in infants should be performed if the formula is modified in any way that could reasonably be expected to have an effect on growth (e.g., by the introduction of new or markedly modified nitrogen sources). The growth study should have a duration of at least 3 months, preferably starting from birth, and include, as a minimum, monthly measurements of the growth parameters weight, length and head circumference (15). According to the guidelines published by the Agence Française de Sécurité Sanitaire des Aliments (AFSSA – French Food Safety Agency), the nutritional adequacy of the formula should be assessed by 2 independent trials (16).

By improving the quality of the proteins in infant formulas, it may be feasible to reduce the quantity of protein. Such an improvement has been made possible by the use of a protein mix based on cow's milk whey protein sources permitting achievement of an amino acid profile closer to that of human milk. As a first step, Ziegler *et al*. showed using metabolic balances that an whey-predominant, whey-modified infant formula with a protein/energy ratio of 1.8 g/100 kcal enabled infants to maintain nitrogen retention at levels identical to those observed in infants receiving a regular formula with a protein/energy ratio of 2.2 g/100 kcal (17). Lower urinary nitrogen excretion was suggestive of a reduced metabolic load. Räihä *et al*. showed that this modified protein content formula met the needs of normal term infants in comparison with a conventional infant formula with a protein/energy ratio of 2.2 g/100 kcal (18).

The aim of the present controlled, prospective, randomized and double-blind study was to confirm in a larger sample of children that an infant formula with a protein/energy ratio of 1.8 g/100 kcal and enhanced protein efficiency is safe and adequate to ensure growth of healthy term infants from birth to 4 months of life.

PATIENTS AND METHODS

Study Population

This controlled, prospective, randomized and double-blind feeding study, performed from February 2003 to March 2004, included 2 cohorts of formula-fed infants born at full term. A cohort of breast-fed infants constituted the control group. Infants were enrolled by 6 pediatricians located in Lille, Marseilles, Paris and Reims, working both in a maternity ward and in outpatient pediatrics. Inclusion criteria were as follows: healthy term newborn girls or boys; gestational age from 37 to 42 weeks; birth weight between 2500 and 4200 g; age less than 7 days. Breast-fed infants were to be exclusively breast-fed from birth onwards and were expected to remain exclusively breast-fed for 120 days. Formula-fed infants could have been breast-fed for up to 72 hours after birth and were to be fed exclusively with an infant formula before enrollment. Infants with current illnesses and/or deformities, including cardiovascular, gastrointestinal or hepatic diseases, were excluded.

Feeding

Formula-fed infants were randomly assigned to receive during 120 consecutive days either a conventional casein-predominant infant formula with a protein content of 2.6 g/100 kcal and a casein/whey ratio of 70/30 (IF [infant formula] 2.6) or the study infant formula with a protein content of 1.8 g/100 kcal and a casein/whey ratio of 30/70 (IF 1.8) (Table 1). The vegetable fat mix was identical in both formulas, with the following composition: coconut oil (22%); corn oil (13%); palm oil (46%); rapeseed oil (19%). The proportion of fatty acids was as follows: saturated fatty acids (44.4%); monounsaturated fatty acids (37.1%); polyunsaturated fatty acids (18.5%). Casein sources were skimmed milk and potassium caseinate for IF 2.6 and skimmed milk for IF 1.8.

The protein content reduction of the study infant formula has been made possible through the development of a protein mix based on cow's milk protein sources enabling to achieve an amino acid profile closer to that of human milk, in particular lowering threonine and increasing tryptophan levels (Table 2). The whey fraction was obtained from demineralized sweet whey proteins stripped of casein glycomacropeptide, low in tryptophan and rich in threonine, by ion exchange process (patent WO 98/56702 A1). The randomization procedure was established using a computer-generated randomization table

TABLE 1. *Main compositional characteristics of the conventional casein-predominant infant formula (IF 2.6) and the modified, whey-predominant protein content study infant formula (IF 1.8)*

	Quantities per 100 mL reconstituted formula	
	IF 2.6	IF 1.8
Energy (kcal)	67	67
Proteins (g)	1.7	1.2
Casein (%)	70	30
Carbohydrates (g)	7.8	7.5
Lactose (g)	5.4	6.4
Malto-dextrins (g)	2.4	1.1
Lipids (g)	3.2	3.6
Minerals (mg)	255	245
Calcium (mg)	48	41
Phosphorus (mg)	25	21
Iron (mg)	0.8	0.8
Potential renal solute load (mOsm/L)	139	111

(Proc PLAN SAS). The isocaloric formulas were supplied by Nestlé-France in powder form and reconstituted by the parents just before consumption, according to the recommendations printed on the product labels. Breast milk or infant formula constituted the sole source of energy during the whole study period (i.e. no complementary feeding was started before the end of the study).

Follow-up and Anthropometric Assessments

Study visits took place at enrollment (D0) and after 15 (± 4) days (D15), 30 (± 4) days (D30), 60 (± 4) days (D60), 90 (± 4) days (D90) and 120 (± 4) days (D120; i.e., at the end of follow-up). At each visit, weight (in grams), length (in millimeters) and head circumference (in millimeters) were measured by standard procedures. Weight gain was expressed in grams/day, and length and head circumference gains were both expressed in millimeters/day. Daily gains in weight, length and head circumference were derived from the measurements made at 2 consecutive visits. Body mass index (BMI) was evaluated by dividing the weight (kg) by the square of the length in meters (m^2).

The daily volume of formula intake was calculated as the mean of daily consumptions (in milliliters) recorded by the parents in a dietary book for 3 days before and 3 days after each visit (except for D0 and D120, when the mean consumption was calculated from the values recorded on the 3 days following the visit and the 3 days preceding the visit, respectively). Daily energy (in kcal) and protein intake (in grams) were calculated on the basis of the volumes recorded and the energy and protein content of each formula. Intakes were expressed per kilograms of body weight.

Frequency and consistency of stools (soft, watery, hard) were recorded by parents for 3 days before each visit. During the visits, the investigators recorded any adverse event reported by the parents or found during clinical examination of the infant. The investigator assessed the overall tolerance and acceptability of the formulas separately at each visit, using a 4-point scale (very good, good, poor, very poor).

All medical events were recorded (including interim health status). Safety was assessed by the incidence of adverse events overall and by system organ, using the preferred terms of MedDRA (version 7.1). Because the duration of exposure (number of days on study formula or breast-feeding) was markedly lower for breast-fed infants, the immediate incidence of adverse events (i.e., the number of new events by day of exposure and by patient), was determined both overall and for gastrointestinal events.

TABLE 2. *Amino acid profile of the casein-predominant conventional infant formula (IF 2.6) and the modified whey-predominant protein content study infant formula (IF 1.8)*

	Grams of amino acid per 100 g proteins	
Amino acid	IF 2.6	IF 1.8
Leucine	9.5	11.7
Methionine	2.7	2.4
Cystine	1.1	2.3
Phenylalanine	4.5	4.5
Threonine	5.1	5.3
Tryptophan	1.6	2.1
Arginine	3.3	4.4
Alanine	3.7	5.0
Aspartic acid	8.1	10.9
Glutamic acid	20.8	19.3
Glycine	1.8	2.6
Proline	9.2	7.6
Serine	6.3	5.2
Isoleucine	6.2	5.7
Lysine	8.5	9.8
Tyrosine	5.4	3.9
Valine	6.6	5.8
Histidine	2.5	2.4

Calculations and Statistical Analysis

This study was designed to assess the noninferiority of an infant formula with an protein content of 1.8 g/100 kcal as compared to a conventional formula with a protein content of 2.6 g/100 kcal. The primary outcome was daily weight gain between D0 and D120, analyzed in the per protocol (PP) population. The zero hypothesis to be rejected was that consumption of the conventional formula would lead to a weight gain superior by 4 g/day to that achieved with the modified protein content formula. A difference in daily weight gain of less than 4 g was chosen as a criterion of noninferiority to ensure that the cumulative growth difference after 120 days of study (i.e., 480 g) would be less than the standard deviation for weight of a reference group of French infants (660 g at 4 months of age for both males and females) (19).

The population size was estimated taking as the population variance the standard deviation (5.7 g/day) of the formula-fed reference group described by Fomon et al. (20). Under these conditions (with a power of 80% and a 2-sided risk of error of 0.025), a PP population comprising 32 patients per group was required. The PP population was defined as randomly assigned infants presenting no deviation from the protocol (i.e., those meeting the inclusion criteria and completing the follow-up of 120 days). In view of the absence of randomization inherent in the choice of breast-feeding, the group of breast-fed infants was not considered for the statistical analysis.

The secondary outcomes were daily gains in weight, length, head circumference and BMI at monthly intervals. The analysis of these outcomes was performed on the intent-to-treat group (ITT), corresponding to all patients included who were either breast-fed or formula-fed at least once and who were evaluated at least at D15. The statistical analyses were performed using the software SAS for Windows 8.2 (SAS Institute, Cary, NC). The analytical models took into account the center effect as an explicative variable with fixed effect, and the value at D0 as covariable. Data were expressed as mean ± standard deviation (SD).

Analysis of the primary outcome was based on the 95% confidence interval of the difference in daily weight gain from D0 to D120. Analyses of secondary outcomes were performed using a 2-way analysis of variance (ANOVA) for quantitative data and either Fisher exact test or Wilcoxon's test, with an alpha level of 5%, for qualitative data. Finally, the effect on anthropometric parameters of the sex of the infant, smoke exposure during gestation and the socio-professional category of the family head was evaluated.

Ethics

The study was performed according to the principles of the Declaration of Helsinki. The study protocol and consent procedure were approved by the ethical committee of the Lille University Hospital. Before each infant's inclusion in the study, a consent form was signed by both parents after having been informed of the design and objectives of the study, and the ability to withdraw their child from the study at any time.

RESULTS

Study Population

One hundred and sixty-two infants were enrolled, 6 of whom were not assessed after D0. The intention-to-treat (ITT) population comprised 156 infants: 55 in the breast-fed group, 50 in the IF 2.6 group and 51 in the IF 1.8 group. Among the 101 randomized patients of the ITT population, 38 in the IF 2.6 group and 36 in the IF 1.8 group were eligible for inclusion in the PP population. The dropout rate was 64% in the breast-fed group and 16% in both formula-fed groups. The baseline characteristics of the infants are listed in Table 3. The groups did not differ significantly with regard to sex ratio, age and anthropometric characteristics. The mean age of the infants at inclusion was approximately 4 days.

Anthropometric Parameters

The primary and secondary outcomes in the 2 formula-fed groups are reported in Table 4. The analyses were not corrected for sex, smoke exposure during gestation and socio-professional category of the family head because these factors did not affect comparison of the results between the infant formula feeding groups. The difference in mean daily weight gain from D0 to D120 for the PP population (primary outcome) between IF 1.8 and IF 2.6 was 0.38 g/day, with a 95% confidence interval of −2.59 (1.83 g/day) (Table 4). This interval did not include the tolerance value of 4 g/day, signifying the noninferiority of the modified protein content infant formula with a protein/energy ratio of 1.8 g/100 kcal relative to the conventional formula with a protein/energy ratio of 2.6 g/100 kcal. Moreover, there was no difference between the 2 infant formula groups with regard to secondary outcomes (i.e., weight, length, head circumference and BMI) at any of the time intervals considered (D15, D30, D60, D90, and D120) (Table 4). D15 data are not shown.

Formula Intake

Formula consumption decreased during the study in both groups from 159.6 ± 20.8 mL/kg at D30 to 120.1 ± 14.8 mL/kg at D120 in the IF 2.6 group and from 146.1 ± 22.4 mL/kg at D30 to 113.8 ± 12.9 mL/kg at D120 in the IF 1.8 group (Table 5). The 2 groups did not differ significantly with regard to the evolution of formula

TABLE 3. *Baseline characteristics of breast-fed infants and infants fed the casein-predominant conventional infant formula (IF 2.6) or the modified protein content study infant formula (IF 1.8) (ITT population)*

	Breast milk	IF 2.6	IF 1.8
Number of infants (males)	55 (28)	50 (28)	51 (27)
Age at inclusion, days (mean ± SD)	4.4 ± 1.4	4.2 ± 1.3	4.4 ± 1.1
Birth weight, g (mean ± SD)	3436.7 ± 370.1	3315.6 ± 402.1	3334.7 ± 398.4
Birth length, cm (mean ± SD)	50.3 ± 1.7	50.1 ± 1.9	49.7 ± 2.0
Smoke exposure (%)	6	24	14
≥10 cigarettes/day (n)	0	5	1
Socio-professional category of family head (%)			
Company director	9	10	6
Senior manager	59	32	36
Middle manager	15	26	28
Employee	13	30	16
Operator	4	2	14

TABLE 4. *Daily gain in weight, length and head circumference, and BMI (mean ± SD) in infants fed the conventional infant formula (IF 2.6) or the modified protein content study infant formula (IF 1.8)*

Outcome	IF 2.6	IF 1.8	*P* (ANOVA)
Primary outcome*:			
Weight gain (g/day)			
D0–D120	29.3 ± 3.7	29.7 ± 5.4	NS
Secondary outcomes**:			
Weight gain (g/day)			
D0–D30	34.9 ± 6.8	36.5 ± 7.8	NS
D30–D60	33.4 ± 6.0	31.7 ± 7.9	NS
D60–D90	25.0 ± 6.2	25.8 ± 6.6	NS
D90–D120	24.3 ± 8.4	23.4 ± 6.6	NS
Length gain (mm/day)			
D0–D30	1.46 ± 0.59	1.49 ± 0.54	NS
D30–D60	1.14 ± 0.34	1.07 ± 0.44	NS
D60–D90	1.12 ± 0.54	1.02 ± 0.39	NS
D90–D120	0.86 ± 0.35	0.89 ± 0.35	NS
Head circumference gain (mm/day)			
D0–D30	0.88 ± 0.31	0.92 ± 0.26	NS
D30–D60	0.59 ± 0.20	0.58 ± 0.17	NS
D60–D90	0.44 ± 0.17	0.45 ± 0.18	NS
D90–D120	0.39 ± 0.18	0.38 ± 0.15	NS
BMI (kg/m^2)			
D0	12.78 ± 1.14	13.10 ± 1.03	NS
D30	14.39 ± 1.20	14.82 ± 1.14	NS
D60	15.69 ± 0.99	16.02 ± 1.10	NS
D90	15.99 ± 1.09	16.57 ± 1.06	NS
D120	16.66 ± 1.31	16.90 ± 1.16	NS

*Per protocol population (IF 1.8: n = 36; IF 2.6: n = 38); **ITT population (IF 1.8: n = 51; IF 2.6: n = 50); NS: difference statistically nonsignificant.

intake during the entire follow-up period (P = 0,16). However, significant differences in formula intake between the groups were recorded at D30, D60 and D120, infants fed IF 1.8 consuming significantly less formula than infants fed IF 2.6. Consequently, energy intake was also lower in the IF 1.8 group, the same differences in energy intake being observed between the 2 groups at D30, D60 and D120. As expected, protein intake was significantly lower in the IF 1.8 group at all visits. D15 data are not shown.

Tolerance and Adverse Events

Stool characteristics changed between D0 and D120 with a similar progression in the 2 groups of formula-fed infants. The stool frequency was 3.6 ± 1.5/day and 3.8 ± 1.5 at D0, and 1.4 ± 0.6 and 1.4 ± 0.7 at D120 in the IF 2.6 and IF 1.8 groups, respectively. No significant difference in stool frequency between the groups was detected at any visit. Stools were judged to be predominantly soft for 90% and 88% of the infants in the IF

TABLE 5. *Daily formula consumption, and daily energy and protein intake (mean ± SD) in infants fed the conventional infant formula (IF 2.6) or the modified protein content study infant formula (IF 1.8)*

Variable	IF 2.6 (n = 50)	IF 1.8 (n = 51)	*P* (ANOVA)
Volume (mL/kg)			
D30	159.6 ± 20.8	146.1 ± 22.4	0.005
D60	138.1 ± 16.8	126.7 ± 16.6	0.0007
D90	124.5 ± 16.4	120.5 ± 13.1	NS
D120	120.1 ± 14.8	113.8 ± 12.9	0.03
Energy intake (kcal/kg)			
D30	106.9 ± 14.0	97.9 ± 15.0	0.005
D60	92.5 ± 11.2	84.9 ± 11.1	0.0007
D90	83.4 ± 11.0	80.7 ± 8.7	NS
D120	80.4 ± 9.9	76.2 ± 8.7	0.03
Protein intake (g/kg)			
D30	2.7 ± 0.3	1.7 ± 0.3	<0.0001
D60	2.3 ± 0.3	1.5 ± 0.2	<0.0001
D90	2.1 ± 0.3	1.4 ± 0.2	<0.0001
D120	2.0 ± 0.2	1.4 ± 0.2	<0.0001

NS: difference statistically nonsignificant.

TABLE 6. *Anthropometric parameters of breast-fed infants (mean ± SD)*

	Weight gain (g/day)	Length gain (mm/day)	Head circumference gain (mm/day)	BMI (kg/m^2)
D0–D30 (n = 50)	34.2 ± 11.4	1.38 ± 0.55	0.91 ± 0.30	14.41 ± 1.31
D30–D60 (n = 43)	28.6 ± 9.3	1.08 ± 0.34	0.55 ± 0.18	15.35 ± 1.42
D60–D90 (n = 31)	21.2 ± 9.6	0.99 ± 0.50	0.43 ± 0.27	16.34 ± 3.86
D90–D120 (n = 25)	17.0 ± 8.0	0.91 ± 1.09	0.36 ± 0.16	16.02 ± 1.47

2.6 and IF 1.8 groups, respectively, at D0 and for 86% and 87%, respectively, at D120.

Overall tolerance was considered to be good or very good in 98% of the infants in both groups at D120. At least 1 adverse event occurred in 79% of infants fed IF 2.6 and in 85% of infants fed IF 1.8, without any significant difference when expressed as immediate incidence per follow-up day (0.013 ± 0.02 in both groups). The incidence of gastrointestinal adverse events was 0.011 ± 0.02 and 0.012 ± 0.02/day and per patient in the 2 formula-fed groups, respectively (NS). No formula-related serious adverse event was reported during the study in either group.

Breast-Fed Infants

The anthropometric characteristics of the breast-fed infants are reported in Table 6 (D15 data not shown). The stools of breast-fed infants were predominantly liquid (67% of infants at D0 and 52% at D120) and stool frequency was 4.8 ± 1.9 at D0 and 1.8 ± 1.3 at D120. Sixty percent of the breast-fed infants presented at least 1 adverse event. The incidence of adverse events per follow-up day was 0.009 ± 0.011, the incidence of gastrointestinal adverse events being 0.005 ± 0.011.

DISCUSSION

It is generally considered that a normal growth pattern in infants means that their nutritional needs are satisfactorily fulfilled. Our study showed a similar gain in weight, length and head circumference in healthy term infants fed during the first 4 months of life exclusively with a modified protein content infant formula having a protein/energy ratio of 1.8 g/100 kcal (IF 1.8) as compared to a regular infant formula with a protein/energy ratio of 2.6 g/100 kcal (IF 2.6). BMI was also similar in both groups. Protein intake was significantly lower in infants receiving IF 1.8 at every monthly interval from 1 to 4 months of age and no compensatory increase of infant formula intake was observed. Indeed, both the volume of formula consumed and the energy intake were significantly lower at 1, 2 and 4 months of age in infants receiving IF 1.8.

Fomon et al. showed that energy intake from 8 through 55 days was significantly higher in infants receiving a formula with a protein/energy ratio of 1.7 g/100 kcal than in a formula-fed reference group of infants (20). Weight gain was also significantly superior to that of infants in the formula-fed reference group or a breast-fed reference group. BMI was significantly higher than that observed in either reference group, suggesting more fat accumulation in infants fed this low-protein content formula. Fomon *et al.* concluded that an infant formula with a protein/energy ratio of 1.7 g/100 kcal was adequate for growth, but may not be safe. In the present study, the lower levels of formula and consequently total energy intake at 1, 2 and 4 months of age, associated with a normal growth pattern from birth to 4 months of age, confirm the adequacy and safety of this infant formula with enhanced protein efficiency and a protein/energy ratio of 1.8 g/100 kcal as compared to a conventional formula with a protein/energy ratio of 2.6 g/100 kcal.

The Human Nutrition Committee of the French Food Safety Agency recommended that the nutritional adequacy of an infant formula representing a significant compositional change (in terms of energy content or protein sources) be assessed by 2 independent trials (16). In accordance with these recommendations, 2 independent studies, namely the study performed by Räihä et al. and the present study, confirmed the nutritional adequacy of IF 1.8 (18). The control formula used in our study had compositional differences as compared with that used in the study of Räihä et al. The major protein source was casein instead of whey, and the protein content was 2.6 g/100 kcal instead of 2.2 g/100 kcal. Our choice of using a control formula with a protein content of 2.6 g/100 kcal was solely motivated by the wish to reflect as closely as possible the usual type of feeding of non-breast-fed French infants. More than 90% of the infant formulas available on the French market have a casein-predominant protein content.

A further difference between the 2 studies was that all infants in our study were included before 7 days of age, whereas in the study reported by Räihä et al., infants up to 28 days of age could be included. Räihä et al. showed no differences between infants fed IF 1.8 and those fed the standard formula, in terms of weight and length gain and BMI. Head circumference was not measured in their study. No differences in energy intake were observed between the formula-fed groups, whereas protein intake was lower in infants fed IF 1.8. Plasma urea levels of the infants receiving the infant formulas were close to those found in breast-fed infants.

The safety of the study formula was also demonstrated in our study by the absence of any significant difference in the overall incidence of adverse events or the incidence of gastrointestinal adverse events between infants fed IF 1.8 and those fed the control formula.

The SCF report recommended comparison of the growth parameters of infants fed a modified infant formula with those of breast-fed infants, keeping in mind that maximal weight gain does not necessarily mean optimal weight gain (15). The absence of randomization inherent in the choice of breast-feeding precludes a statistical comparison of the formula-fed and breast-fed populations. The weight gain of breast-fed infants during the first month of life was, however, similar to that of formula-fed infants, but appeared to be slightly slower thereafter, with a difference in mean daily weight gain of 3.5 g during the 4-month study period.

There was no difference in length and head circumference gain between breast-fed and formula-fed infants. It is well known that the growth pattern of breast-fed infants differs from that of formula-fed infants (21,22), the average weight gain of the former being lower. However, evidence to date suggests that there are no apparent adverse consequences associated with the slower weight gain of breast-fed infants: they do not differ in activity level, they experience less illness and appear to have enhanced cognitive development (22,23). Our group of breast-fed infants was characterized by a high dropout rate. Only 36% of infants in this group were exclusively breast fed at the age of 4 months (i.e., at completion of follow-up). This poor compliance with long-term exclusive breast-feeding is related to the low median duration of breast-feeding in France, estimated to be 10 weeks in a prospective survey of 150 breast-feeding mothers (24).

Excess protein intake in infancy induces an unnecessary stress on metabolism and renal function. A high protein intake after weaning in young rats results in increased kidney growth and glomerular filtration rate exceeding the concomitant increase in body weight (25). In human adults, a high protein intake is similarly associated with increased kidney size (26). Recently, Schmidt found that kidney growth and serum urea nitrogen were significantly increased in partially or fully formula-fed 3-month-old infants compared with breast-fed infants. This effect was more pronounced in boys than in girls (27). The authors suggested that this structural effect may reflect an adaptive response to the hyperfiltration induced by the increased protein intake. The changes in relative kidney size were temporary, as they were no longer evident at 18 months of age when all children received a normal mixed diet. Whether there are any long-term consequences of early increased renal load on later kidney function remains to be elucidated.

It has been suggested that a high-protein intake early in life could increase the risk of adiposity later in life. However, this issue remains controversial. Two studies from France and Italy showed that protein intake (as a percentage of total energy intake) at the age of 2 years and 1 year, respectively, was positively correlated with BMI at the age of 8 and 5 years, respectively (28,29). However, 2 other studies performed in the United Kingdom and Denmark found no effect of early protein intake on any measure of body fat (30,31). More investigation is necessary to gain further insight into the relationship between protein intake in early infancy and obesity later in life.

CONCLUSIONS

The results of the present study confirm the safety of a whey-predominant infant formula with a protein/energy ratio of 1.8 g/100 kcal and enhanced protein efficiency, and its noninferiority to a conventional casein-predominant formula with a protein/energy ratio of 2.6 g/100 kcal in ensuring the normal growth of healthy term infants from birth to 4 months of age. The lower protein/energy ratio of the study formula as compared to the conventional formula resulted in a significantly lower protein intake and no compensatory increase of formula consumption was seen. The modified protein content formula was well tolerated and was not associated with an overall incidence of adverse events or an incidence of gastrointestinal adverse events significantly different from those observed in infants receiving the conventional formula.

Provided that the amino acid content is modified in order to permit achievement of an amino acid profile closer to that of human milk and that a growth study is performed to ensure the suitability and safety of the formula, it is possible to feed term infants from birth to 4 months of age an infant formula with a protein content at the lower range of the protein contents endorsed by most pediatric societies and regulatory authorities (i.e., 1.8 g/100 kcal).

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