The Journal of International Medical Research
2003; 31: 215 – 222

Nutritional Value of a Rice-hydrolysate Formula in Infants with Cows' Milk Protein Allergy: a Randomized Pilot Study

E D'Auria[1], M Sala[1], F Lodi[1], G Radaelli[2], E Riva[1] and M Giovannini[1]

[1]Department of Paediatrics and [2]Unit of Medical Statistics, San Paolo Hospital, University of Milan, Milan, Italy

This study was designed to assess whether a rice-hydrolysate formula allows normal growth and adequate metabolic balance in infants with cows' milk protein allergy. Infants (seven females, nine males; aged 6 – 14 months) were randomly assigned to receive a rice-hydrolysate formula (*n* = 8) or a soy formula (control group, *n* = 8). Standardized growth indices (*Z* scores) and biochemical parameters were evaluated during a 6-month treatment period. Infants in both groups showed normal growth patterns during the study, and no adverse reactions were seen. Mean plasma biochemical parameters were within the normal ranges, and did not differ between groups. In conclusion, rice-hydrolysate formula may be a nutritionally suitable alternative for infants with cows' milk protein allergy. Larger studies, with satisfactory power, should be undertaken to confirm these findings.

KEY WORDS: Cows' milk protein allergy; Growth; Infants; Rice-hydrolysate formula; Soy formula

Introduction

Cows' milk protein is the most common cause of food allergy in infants, with 5 – 15% showing suggestive symptoms. Based on strict diagnostic criteria, prevalence rates of 2 – 6% have been reported.[1 – 3]

The main treatment for cows' milk allergy is complete avoidance of cows' milk proteins. Milk, however, is an important source of protein, and omission of cows' milk from an infant's diet could cause growth impairment.[4] The choice of substitute formula is therefore a crucial issue for paediatricians; formula should provide adequate nutrition for normal growth and metabolic function.[5] Current alternative formulae are based on extensively hydrolysed cows' milk, amino acids, or a different (vegetable) protein source, such as soy.

Casein or whey protein formulae, derived from extensively hydrolysed cows' milk, are recommended for infants with cows' milk protein allergy,[6,7] but these formulae have strong, bitter tastes that are difficult to disguise. Infants may therefore refuse these feeds, which has a negative impact on growth. There is evidence of the beneficial effects of extensively hydrolysed cows' milk formulae for infants with cows' milk protein allergy, but data on their nutritional value are few and controversial.[8 – 11] Soy formulae are adequate for growth, cheaper and more palatable than extensively hydrolysed formulae,[12,13] but

because of potential sensitization to soy,[14,15] their use is debatable.[6,7] Alternative vegetable-based formulae use rice protein (*Oryza sativa*). Rice has been recognized as the most hypoallergenic cereal, and has triggered adverse reactions in < 1% of allergic children.[16] Despite the large use of rice in hypoallergenic diets, no data exist regarding the nutritional features of rice protein-based formulae in infants with cows' milk protein allergy.

We aimed to assess whether a rice-hydrolysate formula allows normal growth, and adequate metabolic balance, in infants with cows' milk protein allergy.

Patients and methods

STUDY DESIGN

This was a prospective, randomized, single-centre (San Paolo Hospital, Milan, Italy) clinical trial. The local ethics committee approved the study protocol.

PATIENTS

Infants admitted to our department, for evaluation of atopic dermatitis and food allergy, between March and December 2001, were consecutively recruited to the trial. Written, informed consent was given by the parents. Infants were considered eligible if: they had a gestational age of 37 – 42 weeks inclusive and a birth weight ≥ 2500 g; they were aged 6 – 16 months inclusive; they had an allergy to cows' milk protein; they fulfilled the Hanifin's criteria for atopic dermatitis;[17] and they were not currently being breast-fed. Exclusion criteria were: presence of any metabolic and/or chronic disease; gastrointestinal symptoms; and a positive skin-prick test for rice and/or soy.

METHODS

At enrolment, skin-prick tests with cows' milk, casein, lactalbumin, soy and rice commercial allergen preparations, fresh cows' milk, soy formula and rice-hydrolysate formula were performed. Allergy to cows' milk protein was confirmed by double-blind, placebo-controlled challenge or open challenge, when appropriate.

A computer program, SPLUS 2000 software professional release 3 (Mathsoft, Inc., Cambridge, MA, USA), that assumes all eligible infants have the same probability of being given rice-hydrolysate or soy formula, generated two randomization lists according to gender. Randomization, by individual random numbers, was performed in blocks of 10 subjects. Assignments were made by means of sealed, sequenced, masked envelopes, which were opened on the day of recruitment. To avoid potential interference with the random allocation, the envelopes were prepared by a secretary unaware of the study.

Infants were fed with the assigned formula for a 6-month period.

MEASUREMENTS AND OUTCOMES

On admission, baseline demographic and anthropometric details of the infants and parents, gestational age and parity were recorded. Birth weight and length were obtained from hospital records.

Growth parameters (body weight and length) were evaluated at introduction of the assigned formula (baseline), then prospectively throughout the 6-month period. Anthropometrical measurements were taken, as scheduled by the protocol, at 1 month, 2 months, 4 months and 6 months after starting the formula. The permissible time intervals for scheduled longitudinal growth measurements were ± 5 days for the first two visits and ± 7 days for the third. One experienced examiner (MS), who was not involved in the study and was unaware of the administered formula, took the measurements. At any time, three

measurements were taken for each growth parameter, and the average used for analysis. Fasting, heparinized blood samples were taken, by the same experienced practitioner (FL), at 08.00 ± 30 min, at the beginning and end of the study.

Age, converted to a decimal, was used to calculate standardized anthropometrical indices (*Z* scores). Weight and length *Z* scores (weight for age [WA] and length for age [LA] *Z* scores, respectively) were calculated using the 1990 ANTHRO Pediatric Anthropometry Software Program, Version 1.0 (Centers for Disease Control and Prevention, Atlanta, GA, USA).

Blood samples were centrifuged and plasma levels of albumin, pre-albumin, total protein, iron, urea nitrogen, total and high-density lipoprotein cholesterol, triglycerides and alkaline phosphatase determined enzymatic *in vitro* assays on an automated clinical chemistry analyser (Roche/Hitachi Modular P800, Hoffmann-La Roche, Basel, Switzerland). Plasma amino-acid levels were measured by ion-exchange liquid chromatography (amino-acid analyser; Biochrom 20 PLUS, Biochrom, Cambridge, UK).

The severity of atopic dermatitis was evaluated according to the SCORAD method, established by the European Task Force on Atopic Dermatitis.[18,19]

The nutritional content of the rice-hydrolysate and soy formulae are reported in Table 1. Solid food was introduced between 4 and 6 months, and dietary intake was determined by a 3-day dietary record, every 3 months throughout the study period. The dietary energy and macronutrient intake were comparable between the groups.

STATISTICAL ANALYSIS

Descriptive data were reported as mean, standard deviation (SD) and median, or number of infants and percentage. Analysis of variance was used to compare differences in growth patterns throughout the study, and the non-parametric Mann–Whitney *U*-test was used to compare biochemical data from the two groups. Comparison of the paired data was made using the Wilcoxon test. Statistical significance was set at $P < 0.05$ (two-tailed test). The SPSS package version 8.0 for Windows® (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Eligible infants (seven females, nine males), (mean age [SD], 10.7 [3.1]; median, 11; range, 6 – 14 months) were randomized into two groups – rice-hydrolysate group and control (soy formula) group – each containing eight

TABLE 1:
Energy and macronutrient content of the formulae used in the study

Component	Soy formula	Rice-hydrolysate formula
Protein (g/dl)	1.70	1.54
Lipids (g/dl)	3.23	3.44
Linoleic acid	0.35	0.38
Linolenic acid	0.04	0.04
Carbohydrates (g/dl)	7.24	7.65
Total energy (kcal/dl)	65	68

subjects. There was no significant difference between the groups in the type of feeding, or duration of breast-feeding, before the study commenced. The mean (SD; median) age at introduction of the study formula was 10.1 months (2.5; 10.5) in the rice-hydrolysate group, and 11.2 months (3.4; 11) in the soy group. No significant difference was observed between the groups with respect to demographics and baseline anthropometrics for infants or their parents.

At baseline, SCORAD measurements were > 20 for five patients (three in the rice-hydrolysate group and two in the control group). At baseline and the end of the study, SCORAD scores were not significantly different between the groups.

The coefficient of variation (percentage ratio of SD to mean) of weight and length measurements ranged from 0.7% to 1.2%, and 0.8% to 1.3%, respectively, and the small variability in measurements for individual patients was deemed to yield reliable anthropometrical data.

Mean birth weight and length did not differ between groups. Mean (SD; median) WA *Z* score at birth was 0.08 (0.89; 0.14) in the rice-hydrolysate group and 0.11 (0.77; 0.19) in the control group; mean LA *Z* scores were –0.03 (0.72; –0.10) and –0.01 (0.95; –0.13), respectively.

The pattern of growth indices are shown in Figs 1 and 2. No significant deviation from normal growth was seen for weight or length in either group, and there were no significant differences in the patterns of WA or LA *Z* scores between groups. Average (median) WA and LA *Z* scores ranged from –0.30 (–0.34) to –0.09 (–0.08) and –0.21 (–0.14) to 0.11 (0.15), respectively, in the rice-hydrolysate group; and ranged from –0.10 (–0.21) to 0.07 (0.12) and –0.12 (–0.23) to 0.27 (0.37), respectively, in the control group. Three infants (two in the rice-hydrolysate group and one in the soy group) had WA *Z* scores lower than –1 at baseline and end of the study. In the rice-hydrolysate group, one female patient (aged 7 months, SCORAD > 20 at baseline) impaired the WA *Z* score from

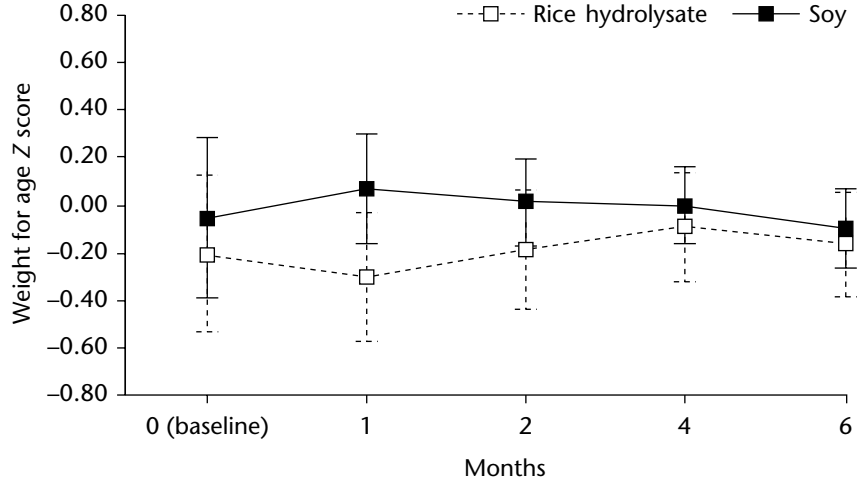

FIGURE 1: Mean (and standard error) weight for age *Z* scores for the rice-hydrolysate and control groups, measured at intervals during the 6-month study period. There was no significant difference between the groups at any time, and no significant difference within the groups over time

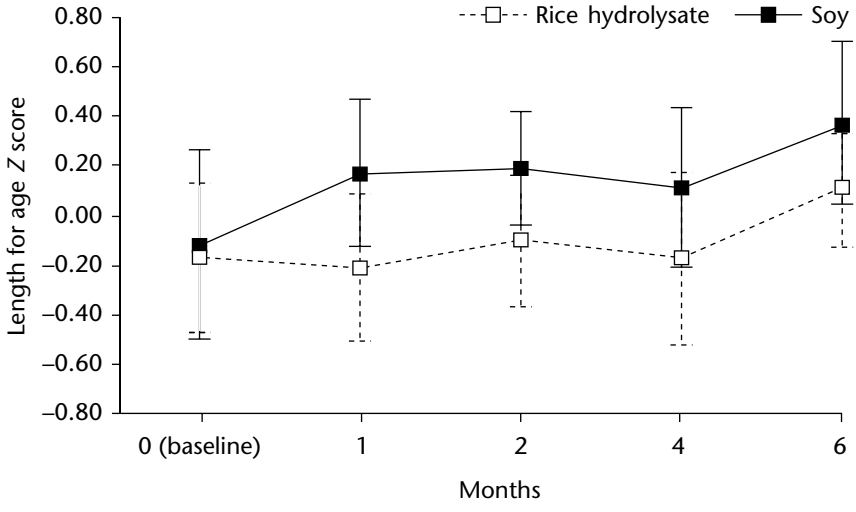

FIGURE 2: Mean (and standard error) length for age *Z* scores for the rice-hydrolysate and control groups, measured at intervals during the 6-month study period. There was no significant difference between the groups at any time, and no significant difference within the groups over time

–0.88 to –1.24. An LA *Z* score lower than –1 at baseline was found in six infants (two in the rice-hydrolysate group and four in the control group), but only one of them, a boy, aged 14 months in the soy group, had an LA *Z* score lower than –1 at the end of the study.

Table 2 shows the biochemical results for all infants at baseline and at the end of the study. The study arms were well balanced for all parameters at baseline, and mean plasma levels were within the normal range in both groups. The mean levels of all biochemical parameters were also within the normal range in both groups at the end of the study, and no significant differences were seen between the groups.

All infants completed the study, and no adverse reactions to the formulae were observed.

Discussion

In infants with cows' milk protein allergy and atopic dermatitis, the atopic status itself may be a risk for impaired growth,[20] but an elimination diet and substitute formula can also influence growth during the first year of life.[4] Identifying well-tolerated diets of adequate nutritional value is therefore crucial.

We aimed to evaluate whether a rice-hydrolysate formula is nutritionally suitable for infants with cows' milk protein allergy, and believe this is the first trial investigating rice-hydrolysate as a feeding formula for infants with cows' milk protein allergy. The matched case–control design was adopted because of its value with small sample sizes.[21] Soy formula was chosen as the control formula, as it has been proven to provide adequate nutrition for infants with cows' milk protein allergy.[12]

Z scores represent the distance, in SD units, from the Centers for Disease Control and Prevention World Health Organization normative reference data adjusted for age and gender.[22] In the control (soy) group, the mean WA and LA *Z* scores throughout the study ranged between the 40th and 60th

TABLE 2:
Results, at baseline and at the end of the study, for all biochemical parameters analysed

		Rice-hydrolysate group			Soy group			
Parameter[a]		**Mean**	**SD**	**Median**	**Mean**	**SD**	**Median**	***P*-value[b]**
Albumin (mg/dl)	Baseline	4.4	0.5	4.3	4.1	0.4	4.2	0.38
	End of study	4.5	0.8	4.2	4.1	0.3	4.1	0.61
Pre-albumin (mg/dl)	Baseline	17.6	2.7	17.2	21.1	3.1	16.8	0.70
	End of study	19.5	3.5	20	18.1	2.1	17.8	0.35
Total protein (mg/dl)	Baseline	6.6	0.4	6.6	6.4	0.3	6.4	0.28
	End of study	6.5	0.2	6.4	6.5	0.2	6.5	0.43
Urea nitrogen (mg/dl)	Baseline	26.7	9.8	26	26.5	6.9	26.5	0.79
	End of study	27.5	6.7	26.5	32.1	8.5	30	0.23
Iron (µg/dl)	Baseline	71.6	29.7	57	82	23.5	80.5	0.32
	End of study	65.7	23.8	62	76.6	24.8	72.5	0.38
Total cholesterol (mg/dl)	Baseline	134.3	28.9	127.5	123	29.9	113.5	0.44
	End of study	136.6	31.9	125.5	136.7	28.1	135.5	0.72
HDL-C (mg/dl)	Baseline	43.4	12.2	42	50.2	13.7	47.5	0.20
	End of study	45.3	14.2	43.5	50.6	14.2	51	0.28
Triglycerides (mg/dl)	Baseline	96.1	50.1	77.5	79.1	36.4	67.5	0.36
	End of study	93.8	45.0	94	62.8	30.6	65.5	0.23
Alkaline phosphatase (IU/l)	Baseline	663.9	148.1	651	543.2	223.0	543.5	0.28
	End of study	673.8	217.4	582	763.6	188.4	736	0.23

[a]No significant variation from baseline to the end of study for any parameter.
[b]Rice hydrolysate versus soy.
SD, standard deviation; HDL-C, high-density lipoprotein cholesterol.

centiles of the reference age- and gender-adjusted growth curves,[22] while in the rice-hydrolysate group, they ranged between the 35th and 55th centiles. This confirms that growth was within the normal range. Independent of the administered formula, 75% (three of four) of the infants showing a marked negative WA and/or LA *Z* score at the end of the study exhibited more severe atopic dermatitis than other infants. This suggests that atopy affects growth, and is in agreement with the findings of other reports.[20,23]

Biochemical parameters were similar in the two groups at baseline and at the end of the study, and were within normal limits. In particular, blood urea concentration, a good indicator of the balance between protein intake and protein used for growth, was unaltered. This shows that replacement of intact proteins by rice-hydrolysed proteins does not increase the metabolic burden.

In conclusion, the rice-hydrolysate formula was adequate for growth and metabolic balance in this small group of infants with cows' milk protein allergy. Larger, more highly powered, longitudinal studies are needed to confirm these results and evaluate the overall effectiveness of rice-hydrolysate-based formulae in infants with cows' milk protein allergy.

• Received for publication 16 December 2002 • Accepted 24 January 2003

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Address for correspondence
Dr E D'Auria
Department of Paediatrics, San Paolo Hospital, Via A di Rudinì 8, I-20142 Milan, Italy.
E-mail: clinped@mailserver.unimi.it