ORIGINAL ARTICLE

Protein substitute dosage in PKU: how much do young patients need?

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Background: The optimal dose of protein substitute has not been determined in children with phenylketonuria (PKU).
Aim: To determine if a lower dose of protein substitute could achieve the same or better degree of blood phenylalanine control when compared to the dosage recommended by the UK MRC.[1]
Methods: In a six week randomised, crossover study, two doses of protein substitute (Protocol A: 2 g/kg/day of protein equivalent; Protocol B: 1.2 g/kg/day protein equivalent) were compared in 25 children with well controlled PKU aged 2–10 years (median 6 years). Each dose of protein substitute was taken for 14 days, with a 14 day washout period in between. Twice daily blood samples (fasting pre-breakfast and evening, at standard times) for plasma phenylalanine were taken on day 8–14 of each protocol. The median usual dose of protein substitute was 2.2 g/kg/day (range 1.5–3.1 g/kg/day).
Results: When compared with control values, median plasma phenylalanine on the low dose of protein substitute increased at pre-breakfast by 301 μmol/l (95% CI 215 to 386) and in the evening by 337 μmol/l (95% CI 248 to 431). On the high dose of protein substitute, plasma phenylalanine concentrations remained unchanged when compared to control values. However, wide variability was seen between subjects.
Conclusions: A higher dosage of protein substitute appeared to contribute to lower blood phenylalanine concentrations in PKU, but it did have a variable and individual impact and may have been influenced by the carbohydrate (+/− fat) content of the protein substitute.

Phenylalanine-free protein substitute is fundamental in the dietary management of PKU. It is based on L-amino acids, supplemented with tyrosine, and may contain added carbohydrate, fat, vitamins, and minerals. In PKU, it supplies 80–85% of protein requirements. The MRC working group[1] recommended that all children treated for PKU should receive a protein substitute. They suggested that the dose could be important, as it is likely to influence blood phenylalanine control. However, there is ongoing debate regarding precise protein substitute requirements in PKU. So far, available data is contradictory and insufficient to help assemble rational recommendations on actual dosage.

There are two schools of thought on protein substitute dosage. In the UK, the MRC[1] guidelines recommend generous quantities of amino acid. It is suggested that children over 2 years should be maintained on a level of 2 g/kg/day. This is higher than the normal protein requirements.[2] A high dose of protein substitute may lead to an increase in nitrogen retention and improve phenylalanine tolerance.[3 4] Administration of protein equivalent in the form of L-amino acids may be poorly utilised[5 6] and a higher intake may be necessary to compensate for ineffective utilisation.

The second view states that there is no reason why children with PKU should have different protein requirements from other children without PKU.[7] This is the preferred view of some centres in the USA[8] and other European countries. For children between the ages of 1–10 years, normal protein requirements are relatively low (1.0–1.2 g/kg/day;[9 2 10] table 1).

If protein equivalent from protein substitute is given to provide normal requirements only and acceptable blood phenylalanine control is achieved, UK patients could significantly reduce the quantity of protein substitute they have to take each day. Protein substitute is unpalatable and expensive and it may be argued that lower doses of protein substitute may improve patient acceptance and compliance.

The aim of this randomised controlled study was therefore to investigate if a lower dose of protein substitute could achieve the same or better level of blood phenylalanine control when compared to the dosage recommended by the MRC.[1] Two different doses of protein substitute were compared in a group of well controlled children with PKU.

METHODS

Subjects

Twenty five children with well controlled PKU from the Birmingham Children's Hospital clinic were recruited. All children followed a strict low phenylalanine diet comprising: (1) a dietary phenylalanine allocation using a 50 mg phenylalanine exchange system (50 mg = 1 g protein); (2) a phenylalanine-free protein substitute; and (3) low phenylalanine foods, e.g. most fruits, many vegetables, and special low protein products, or so called ''free'' foods permitted in usual quantities. There were three inclusion criteria: (1) maintenance of at least 70% plasma phenylalanine concentrations (weekly or fortnightly according to age group) within ranges recommended by the MRC Working Group[1]* in the six months before entering the study; (2) age 2–10 years; and (3) parental ability to take skin puncture blood specimens.

Fourteen girls and 11 boys, with a median age of 6 years (range 2–10 years) fulfilled these criteria and agreed to participate. The median number of 50 mg phenylalanine exchanges allocated was 5.5 per day (range 3−14) with an equivalent median natural protein intake of 5.5 g daily

*Children 0–5 years maintained blood phenylalanine concentrations at 120−360 μmol/l; school age children 120−480 μmol/l.

Table 1 Dietary reference values for protein (g/day)

Age (y)	FAO/WHO/UNU[10]	EU population reference intakes[9]	UK dietary reference values[2]
1–3	14.5	14.7	14.5
4–6	19.7	19	19.7
7–10	28.3	27.3	28.3

(table 2). Subjects continued to take their usual brand of protein substitute throughout the study.

This was taken either as a paste or a drink. Eight subjects used XP Maxamaid (SHS International), eight PKU Gel (Vitaflo), two Minaphlex (SHS International), two Phlexy 10 Drink Mix (SHS International), two PKU Express (Vitaflo), one Aminogran Food Supplement powder (UCB), one Aminogran Food Supplement tablets (UCB), and one Pam 2 (SHS International). The composition of the different protein substitutes is given in table 3. The median dose of protein substitute was 2.2 g/kg/day (range 1.5–3.1 g/kg/day) at the start of the study.

The local research ethics committee (LREC) approved the study. Informed consent was obtained from all parents and assent from all competent children.

Study design

In a six week randomised, crossover, prospective study, two dosages of protein substitute were given and blood phenylalanine concentrations compared. Each dosage of protein substitute was taken for 14 days, with a 14 day washout period in between. The protein substitute was taken three or four times (according to usual practice) throughout the day at standard times for each individual subject.

- Protocol A: Children were given 2 g/kg/body weight per day of protein equivalent from protein substitute (high dose of protein substitute) for 14 days.
- Protocol B: Protein substitute dosage was administered according to UK dietary reference values,[2] i.e. 1.2 g/kg/day of protein equivalent for children (low dose of protein substitute) for 14 days.

Table 2 Age and natural protein intake of subjects

Subject no.	Age (y)	Number of 50 mg phenylalanine exchanges	Total daily natural protein intake (g)
1	10	6	11.2
2	7	9	13
3	7	6	14
4	7	5	6
5	2	3	6
6	5	5	7
7	6	5	7
8	5	6	12
9	9	5	8.6
10	6	9	12
11	2	3.5	5
12	10	6	10
13	6	8	10
14	10	14	21
15	6	6	9
16	3	6	8
17	8	5.5	10
18	5	5.5	8
19	5	5	7
20	7	5.5	13
21	4	3	10.5
22	4	3	7
23	4	3	7
24	2	3.5	5
25	10	7	14

Washout period: Patients took their usual type and dose of protein substitute for 14 days. The median control dose of protein equivalent from substitute was 2.2 g/kg/day (range 1.5 g/kg/day to 3.1 g/kg/day).

The randomisation order was generated in blocks of four. Each subject's randomisation order was retained in a sealed envelope until after the subjects or carers had signed the consent form.

Assessment of plasma phenylalanine concentrations

Twice daily finger prick blood samples (fasting pre-breakfast and pre-evening meal at standard times) were taken on day 8–14 of each trial period by parents/carers. Twice daily blood samples were collected for three days during a baseline and washout period; median phenylalanine concentrations were estimated from morning and evening blood samples. Twice daily blood samples for plasma phenylalanine were taken due to expected diurnal variation in plasma phenylalanine concentrations.[11] Daily bloods were collected between day 8 and day 14 of each trial period to determine any day to day variability in protein substitute dosages. Median phenylalanine concentrations were estimated from morning and evening blood samples for each subject.

Parents or carers had been previously taught how to do thumb skin puncture blood specimens at home. Blood specimens were collected from the home and taken to the laboratory within eight hours of collection of the final specimen by the principal investigator. All blood specimens were centrifuged on receipt and resulting plasma samples stored at –20°C until analysed. Plasma phenylalanine concentrations were measured by high performance liquid chromatography (HPLC).

Assessment of protein substitute and dietary intake

As patients were unlikely to change their protein substitute to one brand or type of protein substitute, subjects took their usual type of protein substitute recommended by the dietician. The protein substitute was taken in three or four dosages at standard timings throughout the day for each individual subject. Patients also followed the same individualised, standard menu between days 8–14 of each protocol. In the first protocol the subjects were randomised to, parents or carers were asked to weigh and record their entire usual food intake between day 8 and day 14. They then repeated the same menu between day 8 and day 14 of the second protocol and documented all food intake. All food and drink was weighed using Salter scales (accurate to 5 g), which parents/carers were instructed on how to use.

Nutritional analysis was calculated using the Microdiet computer program based on *McCance and Widdowson's "The Composition of Foods"*[12] with supplementary data provided by manufacturers.

Statistics

Non-parametric tests for crossover studies (adapted from Wilcoxon signed rank tests) were used to detect differences in plasma phenylalanine concentrations between the two trial periods.

A power calculation indicated that 25 subjects should detect a 30% difference in blood phenylalanine concentrations between the two study protocols at a power of 90%.

RESULTS

The higher dosage of protein substitute was associated with lower blood phenylalanine concentrations in PKU (table 4). When compared with control values, median plasma

Table 3 Nutritional composition of protein substitutes

Protein substitute	Company	Protein equivalent (g/100 g)	Carbohydrate (g/100 g)	Fat (g/100 g)	Energy (kcal/100 g)
Aminogran Food Supplement powder	UCB	97.2 (amino acid)	–	–	400
Aminogran PKU Tablets	UCB	97.2 (amino acid)	Neg	0.19	264
Minaphlex	SHS International	29	38	13.5	390
PAM 2	SHS International	77.5	Nil added	Nil added	310
Phlexy 10 drink mix	SHS International	42	44	–	343
PKU Express	Vitaflo	60	15	<0.5	302
PKU Gel	Vitaflo	42	43	<0.5	342
XP Maxamaid	SHS International	25	51	<0.5	309

phenylalanine on the low dose of protein substitute increased at pre-breakfast by 301 μmol/l (95% CI 215 to 386) ($p < 0.001$) and in the evening by 337 μmol/l (95% CI 248 to 431) ($p < 0.001$) (fig 1). On the high dose of protein substitute, when compared to control values, the median plasma phenylalanine concentrations remained unchanged (they decreased at pre-breakfast by 4.5 μmol/l (95% CI −34 to 23) and in the evening by 6 μmol/l (95% CI −46 to 31).

There was wide variability in changes in blood phenylalanine concentrations between individual subjects. It was not correlated with age, phenylalanine tolerance, or total energy intake. However, there was a reduction in energy intake during administration of the lower dose of protein substitute in protocol B (median reduction 8 kcal/kg/day; range 3–12 kcal/kg/day) and this was positively correlated with blood phenylalanine concentrations ($r = 0.522$; $r^2 = 0.273$, $p < 0.01$) (fig 2). Children who took protein substitute with a higher energy content (higher carbohydrate and fat) had the greatest reductions in energy intake.

DISCUSSION

This is the first randomised, controlled trial to identify that a lower dose of protein equivalent provided by a protein substitute, similar to the safe levels of protein intake recommend by the FAO/WHO/UNU[10] is associated with an increase in blood phenylalanine concentrations. Other studies have observed that lower protein substitute intake adversely affects overall blood phenylalanine control and phenylalanine tolerance but this was in smaller or uncontrolled studies. Duran *et al*[13] observed in six patients with PKU that compliance with protein substitute intake following supervision in hospital led to a significant reduction in blood phenylalanine control. Acosta and Yannicelli[3] showed in 25 infants with PKU given an infant protein substitute containing high quantities of protein equivalent (3.12 g of protein per 100 kcal), that dietary phenylalanine tolerance improved and blood phenylalanine concentrations were lower. In a longitudinal study, Kindt *et al*[4] fed two groups of eight children with PKU different quantities of total protein. One group adhered to the US Recommended Dietary Amounts (median intake 2.0 g/kg/day)[14] and the other group to the lower safe levels (median intake 1.46 g/kg/day) recommended by the Joint FAO/WHO Expert Committee.[15] The RDA group tolerated additional phenylalanine (3–5 mg/kg body weight/day).

Two other studies do not support a high intake of protein substitute. Clemens *et al*[16] gave 10 patients, aged 15–37 years, three different levels of protein equivalent (1.5 g/kg; 0.75 g/kg; and 0.65 g/kg) from a protein substitute consisting of phenylalanine-free essential amino acids and tyrosine only for three months each. For all three levels of protein intake, there was no sign of amino acid imbalance or catabolism. On the basis of these results, Clemens suggested that as long as phenylalanine-free essential amino acids and tyrosine are given, the overall quantity of the protein substitute may be

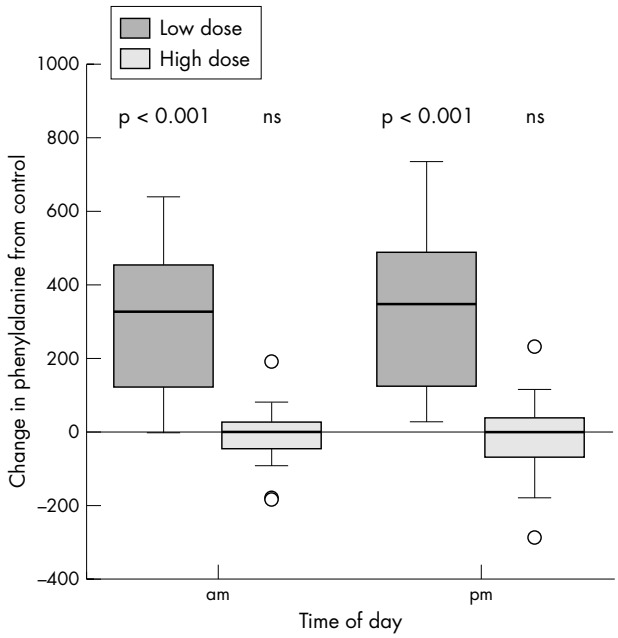

Figure 1 Change in blood phenylalanine concentrations from control values on high and low dose of protein substitute.

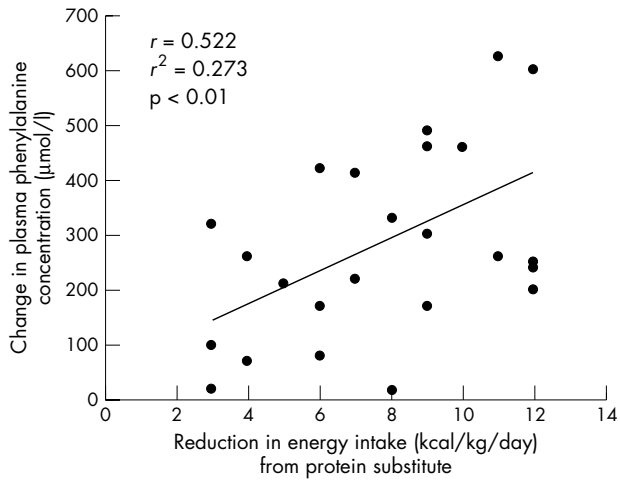

Figure 2 Relation between reduction in energy intake from protein substitute in the two phases of the study and changes in blood phenylalanine concentrations.

Table 4 Differences in blood phenylalanine concentrations between the two protocols

Subject no.	Median morning phe levels on low dose of protein substitute (μmol/l)	Range of phe levels (μmol/l)	Median evening phe levels on low dose of protein substitute (μmol/l)	Range of phe levels (μmol/l)	Median morning phe levels on high dose of protein substitute (μmol/l)	Range of phe levels (μmol/l)	Median evening phe levels on high dose of protein substitute (μmol/l)	Range of phe levels (μmol/l)	Median difference in morning blood phe levels between low and high dose of protein substitute	Median difference in evening blood phe levels between low and high dose of protein substitute	% EAR[2] on low dose of protein substitute	Energy difference per kg/day/body weight between low and high dose of protein substitute
1	200	90–360	240	60–310	100	60–110	40	30–100	100	200	106	3
2	250	200–320	220	180–320	180	130–250	170	140–210	70	50	117	4
3	460	370–480	410	210–430	290	210–350	270	190–350	170	140	96	6
4	530	460–550	510	440–590	200	100–310	170	60–350	330	340	121	8
5	420	300–570	330	180–430	220	200–290	30	<30–70	200	300	81	12
6	770	700–1000	720	670–970	170	130–200	90	50–140	600	630	69	12
7	650	480–770	620	510–690	390	190–560	510	420–530	260	110	95	11
8	720	540–780	650	440–760	230	210–320	190	160–330	490	460	95	9
9	630	550–670	550	480–610	210	150–240	50	40–70	420	500	92	6
10	400	350–470	390	360–450	230	190–380	230	150–350	170	160	87	9
11	180	150–350	130	40–200	170	160–260	90	30–150	10	40	78	7
12	530	480–580	520	500–620	120	90–210	150	30–270	410	370	86	7
13	390	300–430	370	320–420	180	130–210	120	110–180	210	250	79	5
14	530	490–560	540	480–570	270	260–310	260	170–290	260	280	109	4
15	370	340–400	360	320–380	150	140–170	100	70–140	220	260	84	7
16	570	450–640	560	420–600	270	210–290	140	90–290	300	420	80	9
17	680	600–750	690	540–730	220	160–350	100	80–170	460	590	112	10
18	910	810–1000	920	830–940	310	190–400	280	220–300	600	640	108	12
19	460	450–530	400	360–440	140	140–290	115	70–270	320	285	70	3
20	260	210–330	250	170–300	180	130–230	140	100–190	80	110	114	6
21	785	730–930	825	790–990	160	110–190	120	90–150	625	705	96	11
22	440	400–580	420	310–560	190	140–560	260	50–460	250	160	67	12
23	600	540–670	570	470–660	360	200–450	390	210–400	240	180	69	12
24	770	630–860	740	660–820	310	150–520	360	120–420	460	380	68	9
25	140	100–180	90	40–140	120	40–140	26	<30–180	20	64	151	3

phe, phenylalanine.

What is already known on this topic

- Phenylalanine-free protein substitute provides 80–85% of protein requirements in PKU
- The optimal dosage of protein substitute has not been determined in PKU

What this study adds

- This is the first randomised controlled trial to show that a higher dose of protein substitute (as recommended by the MRC in 1993) appears to lower blood phenylalanine concentrations
- The impact of the dosage of protein substitute is variable but its effect is enhanced by an increasing carbohydrate (+/− fat) intake

reduced. However, all these patients were on more natural protein than younger children with PKU, and intake varied between 9 and 26 g/day. Prince *et al*[8] found, in a group of patients aged 4–10 years, the actual amino acid intake from protein substitute decreased from only 0.9 g/kg body weight/day to as little as 0.4 g/kg body weight/day in children over 4.2 years of age. Growth and nutritional biochemistry were not adversely affected, although mean serum phenylalanine increased from 380 to 480 μmol/l. The authors suggested that the increase in serum phenylalanine was just a reflection of increasing patient age, but equally it could have related to reduced intake of protein substitute.

In our study, changes in dosage of protein substitute appeared to have an immediate effect on plasma phenylalanine concentrations. The exact mechanism for the higher blood phenylalanine concentrations on a lower dose of protein substitute is unclear. It may be explained by increased catabolism associated with either a lower amino acid intake or a reduction in energy consumed from carbohydrate or fat added to the protein substitute; the influence of energy on protein utilisation and nitrogen balance is well recognised.[17] It is generally believed that stimulation of protein deposition occurs in response to intakes of dietary energy as well as protein, with dietary carbohydrate more effective than fat.[18] Individual subject phenylalanine tolerance (a possible indicator of disease severity) did not appear to influence the results, although further mutation analysis work has been conducted on this group of patients.

The variable energy content of the different protein substitutes appeared to be an important factor affecting the results. This was controlled for in the study as recruitment would have been difficult if all the patients had been asked to standardise their protein substitute to one type. A disparate group of protein substitutes was therefore used. However, although all subjects had an increase in blood phenylalanine concentrations on lower doses of protein substitutes, subjects consuming protein substitutes with added carbohydrate (+/− fat) at baseline had greater reductions in energy intake on the lower doses and had the greater corresponding increases in blood phenylalanine concentrations. Illsinger *et al*[19] recently showed in subjects with PKU that phenylalanine concentrations decreased with energy supplementation. In contrast, MacDonald *et al*[20] showed that the use of a low carbohydrate protein substitute (15 g/100 g) did not appear to adversely affect phenylalanine control in the majority of a group of 23 teenagers and adults with PKU.

In conclusion, a high dose of protein substitute appeared to lower blood phenylalanine concentrations in PKU. However, it did have a variable and individual impact on overall phenylalanine control. Phenylalanine control may have been influenced by inadvertently increasing the intake of exogenous carbohydrate (+/− fat) added to the protein substitutes on the higher dosage. To further explore the effect of protein substitute dosage, additional controlled studies maintaining a constant intake of carbohydrate and fat are necessary. However, the results of this study do suggest that dosage of protein substitute may have an important role in overall blood phenylalanine control.

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Programme for Global Paediatric Research Symposium and Workshop

Antenatal and intrapartum causes of perinatal asphyxia and stillbirths in developing countries, 5–6 October 2006, Bangkok, Thailand

The Programme for Global Paediatric Research (PGPR) includes paediatric researchers, societies, and other organisations committed to child health. It was formed in January 2004 to address the disparity between the scientific research resources available in high-income countries and the quantity of scientific research focused on the health of children in mid- and low-income countries. PGPR works at the centre of a global network to inform, educate, facilitate international research cooperation and collaboration, and advocate for research to improve the health of all children.

Symposium

PGPR's (www.globalpaediatricresearch.org) fourth symposium will be held October 5, 2006 in conjunction with the 14th Congress of the Federation of Asia and Oceania Perinatal Societies (www.faops2006thailand.org). This three-part symposium will focus on the antenatal and intrapartum causes of perinatal asphyxia and stillbirths in developing countries. Parts 1 and 3 will be comprised of expert presentations providing an overview of the issues and region-specific information. Part 2 will feature platform presentations from abstracts selected following an international call.

Symposium topics

- *Stillbirths* – A global review of interventions and risk factors: Zulfigar Bhutta, Aga Khan University, Karachi, Pakistan
- *The aetiology of stillbirths in developing countries:* Robert Goldenberg, University of Alabama at Birmingham, Birmingham, USA.
- *Unexplained stillbirths and the role of amniotic fluid infections as a possible cause:* Robert Pattinson, University of Pretoria, Pretoria, South Africa
- *Antenatal inflammation and perinatal hypoxia:* Karin Nelson, Neuroepidemiology Branch, NIH, USA.
- *Hypertension/toxemia in relation to perinatal hypoxia and stillbirths:* Peter Von Daedelszen, University of British Columbia, Vancouver, Canada
- *The consequences of perinatal asphyxia in Nepal; can mothers' groups help to reduce the burden?* Matthew Ellis, Centre for Child and Adolescent Health, Bristol University, Bristol, UK.
- *The management of birth asphyxia through village midwives in Cirebon, Indonesia:* Iwan Ariawan, Program for Appropriate Technology for Health (PATH), Jakarta, Indonesia

Call for abstracts

The deadline for abstract submissions is 1 July 2006.

Workshop

At the follow-up workshop on 6 October 2006, colleagues from low-, mid- and high-income countries, with expertise in perinatal asphyxia and stillbirths will meet in order to examine the critical issues and establish clear plans for collaborative study and other action. One of the expected outcomes of the workshop will be a preliminary statement of research needs related to antenatal and intrapartum causes of perinatal asphyxia and stillbirths in developing countries. If you wish to attend the workshop and/or require further information, please contact Dr. Alvin Zipursky, Chair and Scientific Director of PGPR at 416-813-8762; Alvin.Zipursky@sickkids.ca