

Are tablets a practical source of protein substitute in phenylketonuria?

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Background: A phenylalanine-free amino acid based protein substitute is necessary to provide the major source of protein in phenylketonuria (PKU). Protein substitutes in PKU are usually given as drinks. These are unpalatable and compliance is often poor. Tablets containing a suitable mixture of phenylalanine-free amino acids (Aminogran Food Supplement, UCB) are now available.

Aims: To compare the effectiveness and acceptability of these tablets with conventional protein substitute drinks.

Methods: Twenty one subjects with PKU, aged 8–25 years, participated in a randomised crossover study. During one phase, subjects received at least 40% of their protein substitute requirements from the amino acid tablets and the rest from their usual protein substitute tablets. During the other phase, they received their usual protein substitute. Each period lasted 12 weeks. Blood phenylalanine concentrations were measured at least once every two weeks and other plasma amino acids were measured at the beginning, at crossover, and at the end of the study. The subjects kept a diary of all protein substitute taken.

Results: Compliance appeared to be better with the new tablets than with patients' usual protein substitutes. Ninety per cent (18/20) recorded that they took the tablets as prescribed, compared with 65% (13/20) fully compliant with their usual protein substitute. Moreover, plasma phenylalanine was lower on the amino acid tablets, and the median difference in blood concentrations between the two groups was 46 $\mu\text{mol/l}$ (95% CI 14.8 to 89.0, $p = 0.02$). Tyrosine increased by a median of 16 $\mu\text{mol/l}$ daily on the amino acid tablets (95% CI 7.1 to 40.5, $p = 0.01$). Most subjects (70%) preferred incorporating the new tablets into their usual protein substitute regimen.

Conclusions: Amino acid tablets are an effective and relatively popular protein substitute in older children, teenagers, and adults with PKU.

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The dietary treatment of phenylketonuria (PKU) is challenging and unpopular with patients. It requires severe restriction of natural protein and the consumption of a "protein substitute". The substitute contains all amino acids other than phenylalanine, and supplies over 75% of protein requirements in patients with classical PKU. Some preparations also contain the daily requirements of vitamins, minerals, and trace elements. Insufficient protein substitute impairs growth and plasma phenylalanine control, and may lead to an imbalance of amino acids across the blood-brain barrier.^{1,2}

Protein substitutes are usually administered as drinks. They taste bitter and have an offensive smell. Most parents have difficulty persuading their children to take them. Patients in one study took an average of one hour per day to drink their protein substitute, and in some cases it took as long as seven hours.³ Many patients fail to take the prescribed quantity of liquid protein substitute,³⁻⁵ and yet there are few reports of alternative methods of administering protein substitutes.

Recently, a new phenylalanine-free amino acid tablet has become available (Aminogran Food Supplement Tablets, UCB). The tablets have no taste or smell. There are few published data concerning the effectiveness of amino tablets in PKU.^{6,7} Here we report a multicentre, open, randomised, two treatment crossover trial to assess the efficacy and acceptability of amino acid tablets compared with conventional protein substitutes in the dietary management of PKU.

SUBJECTS AND METHODS

Subjects

Twenty one subjects with PKU were recruited into the study from three centres (Birmingham Children's Hospital, Newcastle General Hospital, and Temple Street Children's Hospital,

Dublin). Fifteen subjects were female (71%) and the median age was 15 years (range 8–25 years). One subject was less than 10 years of age, 10 were aged 10–15 years, and 10 were over the age of 16 years. Pregnant or lactating women were excluded. The median prescribed intake of protein substitute was 0.9 g/kg/day (range 0.6–2.6). The protein substitutes used before the study were Aminogran Food Supplement powder ($n = 9$), PK Aid 4 powder ($n = 1$), Phlexy 10 drink mix ($n = 4$), XP Maxamum powder ($n = 4$), and Phlexy 10 capsules ($n = 2$). Sixteen of the subjects took additional vitamin and mineral supplements. The mean body mass index (kg/m^2) of the subjects was 21.6 (range 15.2–31.7). The study was approved by the Medical Ethics Committees of South Birmingham Health Authority, Newcastle and North Tyneside Health Authorities, and the Children's Hospital, Dublin. Informed consent was obtained from all subjects, and if aged less than 18 years, from the carers also.

Methods

This was an open, crossover trial. During one 12 week period, subjects took their usual protein substitute (regimen A). During the other 12 week period, subjects took at least 40% of their daily protein substitute requirement as Aminogran Food Supplement Tablets (regimen B). Subjects who chose not to take their full requirement as tablets took the remainder as their usual protein substitute. Subjects or carers kept a daily diary of all protein substitutes consumed. They did not keep a record of daily timing of protein substitute intake. All subjects were instructed to complete their entire protein substitute and for subjects taking their protein substitute as drink this included any sediment. The sequence of the two regimens was randomised. There was no washout period between the two study periods.

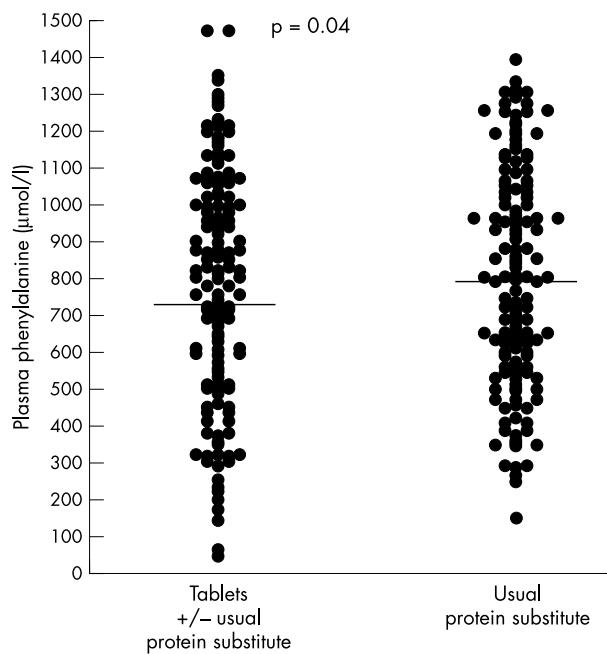


Figure 1 Chart showing the differences for each subject of the phenylalanine concentration changes under regimen B minus those under regimen A, subgrouped by the order of getting the two regimens. Horizontal line represents mean.

Each 1.3 g Aminogran Food Supplement tablet contained 1 g amino acids and 0.3 g carbohydrate. The amino acid composition of the tablets was similar to other protein substitutes used in PKU. In particular, the tyrosine content was 66 mg/g amino acids. The respective tyrosine content of XP Maxamum, Phlexy 10 (capsules or powder), and Aminogran food supplement powder is 90, 97, and 66 mg/g amino acids.

Blood specimens for phenylalanine measurement were collected at home by skin puncture (finger or thumb) at weekly or fortnightly intervals. For each subject, blood specimens were obtained at a consistent time of day, usually before breakfast. The blood specimens were collected either in Starstedt CB 300 heparinised tubes (300 µl) or on Guthrie cards and posted to the hospital. Venous blood samples for plasma amino acid measurement were taken at study entry (baseline) and at the end of weeks 12 and 24. Phenylalanine and other amino acid analyses were undertaken by high-pressure liquid chromatography.

At the end of weeks 12 and 24, subjects rated the acceptability of the treatment received on a 100 mm (in 10 mm divisions) visual analogue scale. Acceptability was defined as palatability, smell, ease of swallowing, and gastrointestinal intolerance.

Statistical analysis

The medians of the weekly/fortnightly plasma phenylalanine concentrations on each protein substitute regimen were calculated for each subject. These and the tyrosine concentrations have skewed distributions, and changes and group comparisons were best analysed using Wilcoxon signed rank and Wilcoxon two sample tests, both with and without allowing for period effects. Results were summarised as the median change in tyrosine and phenylalanine concentrations. A Wilcoxon two sample test was used to compare the acceptability of the two protein substitute regimens, as assessed by the visual analogue scores. The subjects' preferences were analysed using the Mainland-Gart test, which is based on Fisher's exact test, taking into account period effects.

RESULTS

Nineteen subjects (13 female; six male) completed the study. One subject failed to start the study; one subject withdrew during the second treatment period as a result of the usual protein substitute appearing less acceptable after the phase on the amino acid tablets; and in a further subject the tyrosine concentration on the usual protein substitute was unavailable. Therefore, plasma phenylalanine data were available on 20 subjects on regimen B (amino acid tablets), and 19 subjects on regimen A (usual protein substitute). Plasma tyrosine data were available on 20 subjects on regimen B, and 18 subjects on regimen A. Ten subjects had regimen A first and 10 subjects regimen B first.

Dosage of protein substitute

On their usual supplement (regimen A), the median daily dose of prescribed amino acids was 66 g (range 32–75 g). On regimen B, nine (45%) of the subjects took their entire protein substitute as amino acid tablets. The other 11 subjects took between 40% and 65% of their protein substitute as tablets and the remainder as their usual protein substitute. The median daily dose of amino acid tablets was 42 (range 20–75), equivalent to 42 g amino acids. Overall, on regimen B, the median intake/day of amino acids in protein substitute was 60 g (range 48–75 g).

Effect on plasma phenylalanine concentrations

Plasma phenylalanine concentrations were significantly lower when subjects used the new amino acid tablets than when taking their usual protein substitute regimen (fig 1). The median plasma phenylalanine concentration on regimen A was 735 µmol/l, compared with 707 µmol/l on regimen B, but the median difference was 46 µmol/l (95% CI 14.8 to 89.0; $p = 0.02$). However, fig 1 also reveals a significant ($p = 0.04$) order effect in the crossover analysis. In the group receiving the new regimen B amino acid tablets first, the median A – B difference was 75 (95% CI 40.0 to 297; $p = 0.01$), whereas in the group receiving the usual regimen A first, the median difference was only 18 (95% CI –60 to 134).

Effect on plasma tyrosine concentrations

Plasma tyrosine concentrations showed a significant median increase of 16.0 when patients were taking the new tablets on regimen B (95% CI 7.1 to 40.5; $p = 0.01$; fig 2). Plasma tyrosine concentrations in patients on their usual protein substitute (regimen A) were not significantly changed, with a median rise of 1.8 (95% CI –14.5 to 25.8). There was no statistically significant evidence that the order of giving the regimen affected tyrosine change, as under regimen B there were median tyrosine increases of 12 and 40 given before or after regimen A respectively ($p = 0.13$).

Effect on other plasma amino acid concentrations

Plasma concentrations of the essential amino acids, other than phenylalanine, were almost all within normal ranges. The exceptions were isoleucine, leucine, threonine, and valine, which were each low in one patient on regimen A, and lysine, leucine, and threonine, which were each low in one patient on regimen B.

Acceptability of protein substitutes and compliance

Subjects considered that the tablets made their protein substitute regimen more acceptable ($p < 0.05$), according to results recorded by the visual analogue scale. On this scale, higher scores signified a more acceptable regimen. A mean of 57 (SD 35) was scored by patients on regimen A. Patients on regimen B, in which the tablets provided at least 40% of the protein substitute, scored a mean of 82 (SD 16). Overall, 70% of subjects preferred the amino acid tablets compared with conventional protein substitute. Of these 14 subjects, six had the tablets first and eight had them second.

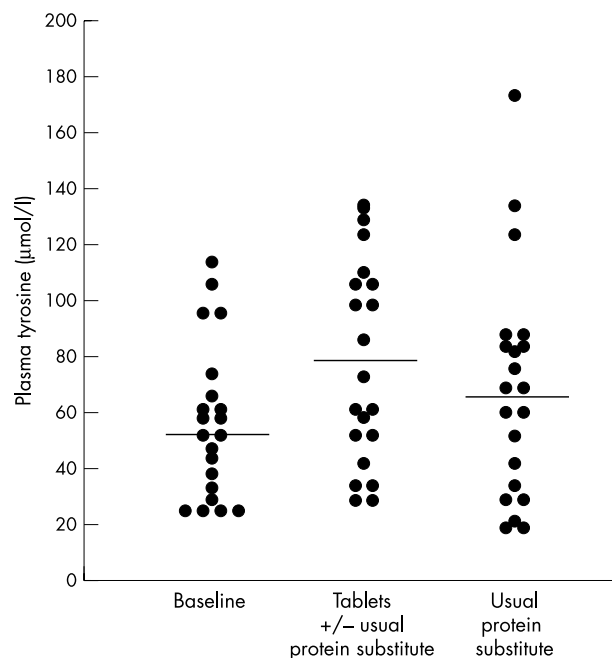


Figure 2 Chart showing the changes for each subject in tyrosine concentration during the periods under regimen A and regimen B. Horizontal line represents mean.

Compliance was better with the amino acid tablets. Thirteen subjects (65%) took the protein substitute as prescribed in regimen A, compared with 18 subjects (90%) for regimen B.

Adverse events

One subject had symptoms which appeared to be related to the Aminogran Food Supplement tablets. The symptoms were moderately severe diarrhoea and mild nausea, both of which started the day after taking the tablets. The diarrhoea continued for two weeks, and the nausea did not resolve while taking the tablets. Another adult subject had a significant weight gain while taking the tablets. Although the tablets were less calorific than the subject's conventional protein substitute powder, she drank large quantities of sugar containing aspartame-free squash to facilitate swallowing the tablets.

DISCUSSION

This study has shown that Aminogran Food Supplement tablets are a useful alternative to existing protein substitutes in those patients with PKU who can swallow large size tablets. The subjects reported that they preferred regimens which included tablets to their usual protein substitutes. Despite the need to take a large number of tablets per day, they reported better compliance. Moreover, the use of tablets was associated with improved plasma phenylalanine control, particularly when protein substitute was administered first, and higher plasma tyrosine concentrations, probably because of improved compliance.

The main limitation of this study was its relatively short duration. It is possible that the novelty of the tablets may have led to better compliance and more favourable acceptability scores than would have been the case with more prolonged use. However, prolonging the study might have reduced recruitment and compliance. Again, to minimise the duration of the study, there was no washout time between protocols, but we have no reason to believe that this caused artefacts. Previous studies have shown that changes in protein substitute intake have an immediate effect on plasma phenylalanine concentrations.^{8,9}

Amino acid tablets have several potential advantages for the older patient with PKU. They have no taste or smell, they do

not appear to affect appetite, and they are easy to take at school or work. Tyrosine is a poorly soluble amino acid and in protein substitute powders given as drinks, tyrosine may be lost in frequently discarded sediment. This will not occur with amino acid tablets. Furthermore, the tablets contain very little carbohydrate, so the daily amount of protein substitute is lower in calories than for most protein substitute drinks. However, this advantage is lost if the tablets are swallowed with high calorie drinks, as occurred in one of our patients. Moreover, the tablets should be taken with carbohydrate if net protein synthesis is to be maximised.¹⁰ Another disadvantage of the tablets is that they contain no vitamins or minerals. Few comprehensive vitamin and mineral supplements are available and compliance with separate vitamin and mineral supplements is poor.¹¹

This is the first full study to support the use of amino acid tablets in PKU. There has been one previous case report, describing a pregnant lady who packed her own capsules with amino acid powder and took 60 capsules daily.⁷ There is also one abstract describing two young adults who chose amino acid capsules in preference to other protein substitutes.⁸ In all three patients, blood phenylalanine control and plasma amino acids were satisfactory.

In summary, Aminogran food supplement tablets are an effective protein substitute for use in PKU. Most of the older children and young adults in this study preferred regimens incorporating these tablets to their existing protein substitute. Since compliance with protein substitute tends to be poor, it is particularly helpful to have an increase in the range of products from which patients can choose.

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