

**Welcome to**  
**34th**  
**Annual Conference**  
**2007**

***Programme Information & Abstracts***

**The Rendezvous Hotel  
Skipton, Yorkshire**

**+** **N S P K U** **+**

The National Society for Phenylketonuria (United Kingdom) Ltd.

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# The Maze of Phenylase

Christineh N. Sarkissian

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Montreal, Quebec, Canada.

Phenylketonuria (PKU) is the result of deficient phenylalanine hydroxylase (PAH) enzyme activity and excess phenylalanine (phe) intake. Mental retardation is a consequence, if therapy is not implemented at birth. PKU can be quite effectively managed with a low phe diet, but patient compliance, perhaps for a lifetime, is difficult and often poor. Therefore alternative therapies are being explored. Tetrahydrobiopterin (BH4) can overcome some of the diminishing effects of a number of PAH enzyme mutants; however, forms of HPA that do not respond to BH4 treatment can benefit from enzyme substitution with phenylalanine ammonia lyase (PAL – commercial name Phenylase). PAL eliminates phe by converting it to harmless metabolites: transcinnamic acid and trace amounts of ammonia. Data from preclinical studies of PAL suggest that we have successfully addressed important technical hurdles required for the development of a potentially safe and effective treatment for individuals with PKU. PAL administered once weekly via subcutaneous injection in a mouse model of PKU resulted in a sustained decrease in blood phe to normal levels for a 12-week period. We have observed restoration of pigmentation and increase in weight in the PAL-treatment groups relative to placebo groups. Antibodies did not have an impact on observed efficacy in either group, nor were there signs of allergic reaction or local injection site reactions. The data suggest that we have a molecule with the essential characteristics required for clinical development.

# Maternal Phenylketonuria

Fiona White

Chief Metabolic Dietitian  
Manchester Children's Hospital

The success of the newborn screening programme for Phenylketonuria (PKU) has resulted in those individuals born with PKU growing up normally with the same career and social aspirations as their peers born without PKU.

Control of blood phenylalanine levels is crucially important in children with PKU in order to maximise their developmental achievement. It is also vital that women with PKU have very strict control of their blood phenylalanine levels prior to and throughout pregnancy. This is to protect the unborn child from the adverse effects of high blood phenylalanine levels in the mother.

Maternal PKU was first described by Charles Dent in 1957. He described a mother with severe mental retardation and PKU who had three children all with mental retardation but who did not have PKU.

In addition to affecting brain development in the unborn baby high blood phenylalanine levels can cause other adverse effects including poor growth, heart defects, behavioural problems and characteristic facial features. The adverse effects are known as the 'maternal PKU syndrome'. We now know that controlling blood phenylalanine levels within strict limits (100 - 250µmol/l) throughout pregnancy minimises these risks.

Ideally women with PKU should plan their pregnancies with the help of a specialist metabolic team. Many women may have been on a normal diet for some years. A number may not have self managed their diet before. Returning to diet prior to conception allows more time to get used to the major changes in dietary intake which are needed, and to achieve target blood phenylalanine levels. Starting diet once pregnant can be harder to achieve with the added stress of needing to reduce

phenylalanine levels quickly at a time when the woman may be suffering pregnancy related symptoms eg morning sickness, weight loss. If a woman with PKU does have an unplanned pregnancy then she should make contact with her PKU clinic as soon as possible for help, advice and support.

Achieving good phenylalanine control throughout pregnancy requires great commitment and support from all those involved. Initially the diet will be even stricter than in childhood to achieve the low phenylalanine levels required. However, phenylalanine tolerance usually increases in the second half of pregnancy, as the baby grows rapidly and its liver starts to metabolise phenylalanine, leading to increases in the allowance of normal protein containing foods (exchanges).

Women with PKU agree that the hard work of adhering to the diet and controlling blood phenylalanine levels throughout pregnancy is worth while when their healthy baby arrives!

# **PKU in the family: Getting off to a good start**

Dr Anna Brazier

Consultant Clinical Psychologist  
Cardiff and Vale NHS Trust

Anna Brazier is a Consultant Clinical Psychologist, based in the University Hospital of Wales in Cardiff. A few years ago she presented a talk jointly with a parent; they described how together they helped a young child take her 'special drink' with less of a fuss.

This year Anna will talk about getting off to a good start with young children and how a good start can provide the basis for helping older children and teenagers to cope with their PKU regime. She will share a approach which is geared to help young people and families find their own solutions to the challenge of PKU; she will also discuss some of the different ways families have found of 'putting PKU in its place'. The talk will be informal and there will be plenty of time for questions and discussion.

## **BH4 and more: research stories from 2006**

Anita MacDonald (on behalf of BCH PKU team),

Birmingham Children's Hospital, Steelhouse Lane, Birmingham, B4 6NH

The year 2006 was a busy year for a number of dietary trials; but the work many people are particularly interested in is the BH4 research.

### **Phenoptin (BH4) trials**

The drug *Phenoptin* is a synthetic form of tetrahydrobiopterin (BH4), a co-enzyme that works in conjunction with the enzyme phenylalanine hydroxylase (that breaks down phenylalanine and is greatly reduced or absent in PKU). Case studies in patients with PKU have indicated that that *Phenoptin* can reduce blood phenylalanine levels in a sub-group of patients who are BH4 responsive. The manufacturers of *Phenoptin* are suggesting that it may help up to 30% of all patients with PKU. To explore this, large, international trials have now been conducted in adults, teenagers and children. Four UK centres (in Birmingham, London [2 centres], and Manchester) have taken part in an extensive 3 part trial recruiting older children and adults. A further trial in children has been completed in the USA.

### **Study 1: A double-blind placebo controlled clinical trial of Phenoptin (BH4) in older children and adults with PKU.**

After 89 subjects had been on an 8 day trial of *Phenoptin* and it had been found to reduce their blood phenylalanine levels by 30% or more, they entered a controlled, blind trial for 6 weeks. Half of them were given the drug *Phenoptin*; and half of them given placebo drug (a dummy drug that looked like *Phenoptin*). They did not know which of the 2 drugs they had been given. They took 10 mg/kg/day of either drug but did not alter their diets. Patients taking the *Phenoptin* had a mean decrease in their blood phenylalanine levels of 236  $\mu\text{mol/l}$  (29%) compared to no change in levels in the placebo or dummy drug group. Before the study started the average blood phenylalanine levels of the 2 groups were quite high (Phenoptin group: 843  $\mu\text{mol/l}$ ; and placebo drug group 888  $\mu\text{mol/l}$ ).

## **Study 2: A 22 week extension study of the *Phenoptin* (BH4) trial using the same subjects.**

Seventy nine patients who took part in the 6 week double-blind trial were then studied for a further 22 weeks. All of the patients were given *Phenoptin* and during the first part of the study all were given 3 different doses: 5 mg/kg/day; 10 mg/kg/day; and 20 mg/kg/day. Their response to each dose determined which of the 3 doses they continued to take in the final 12 weeks. This study found 2 things:

1. The higher dose of *Phenoptin* achieved the greatest reduction in blood phenylalanine levels. A dose of 20 mg/kg/day achieved a reduction in phenylalanine levels of 263  $\mu\text{mol/l}$ ; a dose of 5 mg/kg/day only 100  $\mu\text{mol/l}$ .
2. A once daily dose of *Phenoptin* was sufficient to lower the blood phenylalanine levels over an entire 24 hours.

## **Study 3: A double-blind placebo controlled clinical trial of *Phenoptin* (BH4) in children 4-12 years old with blood levels less than 480 $\mu\text{mol/l}$ .**

This study looked at children only and did not recruit any UK patients. After demonstrating a 30% decrease in blood phenylalanine levels with the *Phenoptin* drug, 45 children entered a 10 week double-blind trial. 75% of the children were given *Phenoptin* and 25% were given a placebo or dummy drug. They were given 20 mg/kg/day of *Phenoptin*. After 3 weeks, the dietary phenylalanine was increased (or decreased if blood levels were too high). The subjects were given phenylalanine powder to alter their phenylalanine intake.

The study found 2 things:

1. In the children taking the *Phenoptin* (before any diet changes were made), they had a mean reduction in blood phenylalanine of 149  $\mu\text{mol/l}$ . Their blood levels only started at a mean of 278  $\mu\text{mol/l}$ .

2. In the *Phenoptin* group the average increase in dietary phenylalanine intake by the end of the study was 21 mg/kg/day (almost 0.5 of a phenylalanine exchange for each kilo of body weight). The placebo or dummy drug group did not alter their phenylalanine intake.

### **Other studies**

Brief updates on other dietary trials will also be given including: the weighing of phenylalanine exchanges; new vitamin and mineral supplements for older patients; and liquid protein substitute for younger children aged 3-10 years.

# The PKU Registers

Alison Munro.

Research Nurse. The UK Newborn screening Programme Center.  
c/o Executive Offices. Great Ormond Street Hospital. London

The UK Phenylketonuria (PKU) register was set up in 1964 with Medical Research Council funding in order to monitor the long-term health and development outcomes of children who had an early diagnosis of PKU through newborn screening. The register is unique in the world because of its national coverage and long history of data collection

Throughout the years, the register has been used to address many important questions, including:

- 1 The relationship between strict, early treatment and childhood development
- 2 Educational progress in children with PKU
- 3 The increased risk of birth defects in children born to women with PKU who are not on treatment.

The findings have led to improved treatment and follow-up for both children and adults with PKU. All individuals born in the UK between 1964 and 1998 and who received a diagnosis of PKU following newborn screening have been placed on the register. Some individuals born before 1964 who were diagnosed later in life (for example, when they had children) have also been reported to the register.

Later data was reported to the register of virtually all pregnancies and births of women with PKU in the United Kingdom between 1978 and 1997. The physical and intellectual development of the offspring of these women was also recorded.

Data collection for the register carried on continuously until 1994, after which issues around funding caused some disruption. Funding stopped completely in 1998, and as a result, data collection ceased.

In 2002 the UK Newborn Screening Programme Centre (UKNSPC) was set up to develop standards and monitor the quality of newborn blood spot screening in the UK. The UKNSPC now looks after the PKU register. It aims to make sure that the register can be used for research once more for the benefit of individuals with PKU and their families.

## **The Future**

The UKNSPC proposes to contact all individuals on the register to secure their consent for retention and use of existing data for research. Ethical approval is being sought to contact individuals whose data are included in the register. Initial contact will be through clinics, with tracing through the NHS Central Register and subsequent contact through general practitioners for those no longer attending clinics. There are approximately 2700 individuals on the register, most of whom are born between 1964 and 1998. Families identified as a consequence of the current national audit of children born between 1994 and 2005 and who have a positive newborn screening test for PKU will also be contacted. This audit is being carried out to assess the quality of the PKU newborn screening programme.

Updates on this project and the results of any research study based on the PKU register will be made available and published. No individual whose data has been used for research will ever be identified in any reports or publications. All data presented will be completely anonymous.

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