

## The role of hypoallergenic formulas in cow's milk allergy and allergy prevention: report of a workshop held in March 1995 at St Mary's Hospital NHS Trust, Newport, Isle of Wight, UK

D. W. HIDE

*Clinical Allergy Research Unit, St Mary's Hospital NHS Trust, Newport, Isle of Wight, PO30 5TG, UK*

The role of so-called hypoallergenic (HA) formulas in cow's milk allergy (CMA) and in allergy prevention was discussed at this year's workshop organized by the Clinical Allergy Research Unit at St Mary's Hospital NHS Trust, Newport, Isle of Wight, UK and chaired by Dr Brian Wharton, Director General of the British Nutrition Foundation. The subject was selected as it was thought there was considerable confusion among general practitioners and paediatricians in the United Kingdom on the appropriate use of these formulas. Although a substantial number of infants in North America and mainland Europe are given such formulas, either at the behest of the doctor or the choice of the mother, only a very small number of British babies receive HA formula. Even unhydrolysed soya-based formulas, available over the counter in the United Kingdom, are given to only 3% of the infant population whereas it is estimated that at least 20% of United States infants receive a soya milk at some time.

David Hill (Melbourne) reviewed recent work from his department which has demonstrated that there are three groups of infants within the cow's milk allergy complex. These have differing patterns of symptoms and show different laboratory results on investigation. The first group show a classical IgE-mediated reaction with immediate skin rash and features of anaphylaxis. The second group, generally not showing IgE sensitization, develop symptoms within hours of milk ingestion. The third group may not reveal their milk intolerance for many hours or some days after ingestion. Their symptoms may be gastro-intestinal with respiratory tract or cutaneous late reactions in addition.

Although many infants and small children eventually tolerate cow's milk they also are likely to develop other atopic disorders, eczema, asthma and rhinitis. Hill's

series is no doubt weighted towards the severe end of the CMA spectrum but over 20% of his patients retained symptomatic CMA 6 years after diagnosis.

A northern hemisphere perspective of CMA was given by Host (Odense). He estimated the incidence of cow's milk protein allergy and intolerance as 2–3%. Although he found a correlation between early exposure to cow's milk formula and subsequent CMA Host questioned whether this was likely to occur as a result of the small volumes of milk protein passed in breast milk which he thought more likely to induce tolerance. He considered that sensitization might take place pre-natally and, unlike most other workers, had been able to demonstrate the presence of specific IgE to cow's milk proteins in cord blood.

Overall the outlook for losing CMA is as good in Denmark as it is in Australia with a recovery rate of 71–87% at 3 years. However, about half the children develop adverse reactions to other foods, especially egg, soy, peanut and citrus fruit. Those with IgE-mediated CMA are also at increased risk of becoming sensitized to inhalant allergens.

Discussion of the therapeutic options in the treatment of CMA was opened by Dean (Southampton) who reviewed the immunological mechanisms involved. The best understood, and perhaps the most important, is that involving IgE antibodies. Dean has shown in a group of patients with CMA that more than half had specific IgE antibodies to more than one hypoallergenic formula. The role of other humoral responses, in particular IgG antibodies, remains in doubt. Cellular immune responses also have received little attention although recently it has been shown that circulating milk-sensitized lymphocytes are depleted in number or function in patients with CMA.

A paper by Rigo (Liege) drew attention to the changes in growth and biochemical parameters that are found when infants are fed on hydrolysed formulas as an

Correspondence: Dr D. Hide, Clinical Allergy Research Unit, St Mary's Hospital NHS Trust, Newport, Isle of Wight, PO30 5TG, UK.

alternative to breast or conventional cow's milk formula. Results varied between the hydrolysates tested and their significance is uncertain. However, a reduced rate of growth and lower plasma protein levels were found with some formulas. Whey hydrolysates showed an increase in plasma threonine and a decrease in tyrosine while soy-collagen hydrolysate gave an increase in glycine and hydroxyproline and a decrease in lysine and cystine. The amino acid pattern of a whey/casein hydrolysate induced a profile close to that of a breast fed infant. Rigo also demonstrated a relative reduction in nitrogen absorption and utilisation in infants fed the whey and soy/collagen hydrolysate while the whey/collagen formula showed reduced absorption of fat, calcium and phosphorus. He had also studied the use of hydrolysates in preterm infants. Again there was considerable variation in the pattern of amino acids compared to that seen with conventional formulas.

It is vital that the nutritional adequacy – and indeed the biochemical consequences – of feeding so-called HA formulas are established before they are launched upon the market. There is more than a suspicion that such information is not available as early as it should be – something that surely would not be permitted by the licensing bodies of other pharmacotherapeutic products.

Some reassurance was given by Heymans (Groningen) who had evaluated two whey hydrolysate formulas in 79 children with cow's milk intolerance. The infants were studied for at least 10 weeks during which time their growth was normal and the severity of the manifestations of allergy decreased.

Isolauri (Tampere) widened the approach to the treatment of food allergy. While she conceded that the majority of cases of milk allergy respond well to extensively hydrolysed cow's milk formulas she argued that new approaches to the treatment of CMA were needed which ensured the completeness of antigen elimination. One possibility would be through the use of synthetic amino-acid derived formulas. Both Isolauri and Hill reported their successful use of one such preparation in multiple food allergy.

Other approaches postulated included immunotherapy to induce antigen-specific hyporesponsiveness and methods to stabilize the intestinal mucosal barrier by changing the gut microflora.

The workshop returned to the practical problems of the management of milk allergy intolerance when MacDonald (Birmingham) reviewed the options available to clinicians. Extensively hydrolysed casein and whey based formulas remain the first choice of many although even these occasionally are not tolerated. She considered that intolerance to soya based formulas had been over-emphasized and that they could be useful in

infants with IgE-mediated milk allergy particularly those with non-gastrointestinal symptoms.

In a view from industry Hudson (Hounslow) outlined the methods used to hydrolyse dairy proteins until 'virtually no antigenic epitopes remain recognisable to the infants immune system'. Hydrolysis is achieved by a combination of heat treatment and enzymatic modification. He claimed that the initial source of protein became less relevant in extensively hydrolysed formulas because the protein was mostly made up of amino acids and small peptides. Among the disadvantages of these formulas Hudson cited palatability and production costs. He believed none of the newer HA formulas had achieved a reduction of antigenicity comparable to the extensively refined casein hydrolysates – which were introduced 50 years ago. He considered that the next development would lie in the use of new enzyme systems that would cleave resistant amino acid sequences and achieve the target million-fold reduction in antigenicity. This could occur without total hydrolysis avoiding the present problems such as those of taste and increased osmolality.

The final part of the workshop was devoted to the use of hydrolysates in allergy prevention programmes. Hide (Isle of Wight) reviewed the published intervention studies. Relatively few workers had reported their experience with HA diets. Those that had usually found a reduction in atopic dermatitis and food related allergy in their intervention group. There was little or no protection against respiratory tract allergy. There was a tendency for rates of allergy in the intervention and control groups to converge as the children were followed through childhood. The Isle of Wight study combined dietary and environmental intervention. High-risk infants were either breast fed with mother on a diet restricting foods considered potentially antigenic, or given an extensively hydrolysed soy/collagen formula. In addition strenuous efforts were made to reduce their exposure to house dust mite by the use of an acaricide. After 4 years the control group had significantly more manifestations of allergy and sensitization as judged by a battery of skin tests than did the intervention children.

A group of high-risk infants exclusively breastfed or given an extensively hydrolysed whey based formula was reported by Halken (Sondborg). These infants avoided cow's milk protein and solid foods for at least the first 4 months of life. A reduction in the cumulative incidence of food allergy and atopic dermatitis was found. Halken claimed that the reduction in CMA at least should be regarded as true prevention as the onset of this condition is almost always in infancy.

Vandenplas (Brussels) reported the use of a partial whey hydrolysate compared with a standard cow's milk formula in infants with at least two first degree relatives

with atopic disease. The major benefit of the milk was less atopic dermatitis but Vandenplas considered the reduction in manifestations of CMA an important observation. He was one of several speakers to call for studies comparing the efficacy of partial and extensive hydrolysates in preventing atopy.

The final paper in the workshop was given by a dietitian, Wolfe (Leeds), who emphasized the benefits of breastfeeding which should be encouraged for all infants. Prevention programmes should only be considered for those at high risk of allergy. Very often the motivation of mothers to follow a difficult regimen is

high. However, there are potential nutritional, social and psychological problems and access to dietary advice is of paramount importance.

The papers presented at the workshop are published as a Supplement to the *European Journal of Clinical Nutrition* (1995) [1].

## Reference

- 1 The role of hypoallergenic formulae in cow's milk allergy and allergy prevention. *Eur J Clin Nutr* 1995; 49:Suppl. 1.

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