ENZYME POTENTIATED DESENSITISATION (EPD)

LOW-DOSE ANTIGEN (LDA – USA)

Introduction

Multiple allergies are far more common than reactions to a single factor: people with asthma often react to common dust, dust mite and moulds; symptoms of hay fever occur as a result of reaction to a number of grass or tree pollens; digestive problems are often linked with numerous food items. Whenever possible, simple avoidance of these factors is often enough to clear the symptoms and makes good sense. Patients with inhalant allergies may benefit from regular use of efficient air filters and often lose their symptoms when on holiday in places with low humidity. Others have to omit from their menu only a few foods, known to cause them problems. Approximately 80% of patients find this approach satisfactory.

Sometimes, it is very difficult or practically impossible to prevent symptoms in this way (e.g. having to give up wheat and other grains; asthma from allergy to a loved pet, allergic rhinitis from common dust). In these cases, **desensitisation** (switching-off) of the allergies is the most effective method of treatment. Many patients who require this have been ill with multiple allergies for a number of years and may have tried other methods, including conventional treatments and symptom controlling medications, without success.

In the 20th century, different types of desensitisation have been used in the western medicine with variable success. One of these methods has been used by many doctors in the U.K. to prevent symptoms of hay fever, by means of tiny injections of pollen given pre-seasonally. This type of desensitisation was withdrawn from general use in Britain, in the mid-eighties as it had caused rare but severe allergic reactions (bronchospasm or anaphylactic shock). In the last twenty years, this has been succeeded to an extent, by the **"sub-lingual" immunotherapy**, which is mainly helpful with common inhalant allergies (eg dust mites, pollens and animal dander)

In the last 45 years, two other methods have been developed and have been used by doctors with special interest in allergic conditions:

(i) **Neutralisation method ("low-dose" immunotherapy)**, which uses "provocation (skin) tests" to determine the concentration of each allergic factor, which can turn an allergy off. This requires self-administered injections for maintenance. It is available in very few allergy centres in the U.K. and is more popular in the USA, especially amongst a few ENT surgeons and some private clinics. We use this method in our Clinic for suitable problems.

(ii) **Enzyme Potentiated Desensitisation**.We also use this method for its safety, efficiency and comparatively low cost.

Origins-Availability

This method of treatment/prevention of allergies was invented by a brilliant immunologist Dr. Len McEwen, a pharmacologist, at St. Mary's Hospital, Paddington, literally a few yards from the point where penicillin was first discovered. EPD is manufactured in Italy, under sterile conditions; as it is an unlicensed product (i.e. not a drug), it is available only on a "named patient" basis; EPD is not an "alternative" medicine. Since the early 1980's it has been used by several doctors, specialising in allergy, in Europe (Austria, Germany, Italy, Greece) Canada, USA, Australia and New Zealand.

Description-Mode of Operation

The EPD comes in various "cocktails" of inhalants, foods or chemicals. Allergens are present in each cocktail in concentrations much more diluted than a skin prick test - each allergen is present in fractions of a ml (eg 1:1,000,000 for aero-allergens – 1:10,000,000,000,000 for foods and chemicals !). When mixed with a specific enzyme (beta-glucuronidase), each cocktail is activated and causes a gentle exposure of one's immune system to the allergens it contains. Amongst the various cells of the immune system, it is thought to stimulate the behaviour of T-supressor cells (lymphocytes responsible to work against allergens). This explains the delayed therapeutic effect of EPD and the reason why repeated booster doses are necessary until a good response is established.

Over 45 years of use and millions of treatments, EPD has not caused one severe or life-threatening reaction. As there is a theoretical risk with any form of desensitisation, standard medications are on hand, at the time of treatment, for any allergic reactions. Doctors using EPD are careful to follow protocols recommended by the manufacturers and will only administer the injections, if appropriate and as frequently as necessary. The Medicines and Healthcare Regulatory Agency has recognised that EPD does not have the same risk for severe reactions as the ordinary incremental desensitisation (or sub-cutaneous immunotherapy, discovered by Drs Noon and Freeman in 1911). However, all forms of desensitization for allergy, for regulatory purposes, are described as "unlicensed medicinal products" (their nature precludes them from serious investment by the pharmaceutical sector).

Response Rate

A pessimistic forecast is that EPD will fail in 20% of all patients treated. The rest will experience variable degrees of improvement. Audits place the effectiveness of EPD very high (>80%) providing that instructions are followed strictly. The majority of failures are linked with patients who give up treatment too early or do not follow instructions, i.e. overwhelming the treatment with exposure to perfumes, wrong diet or pets. Depending on the duration of their condition prior to EPD, some patients start feeling better after a few doses but some respond sooner. A small percentage take longer to see results. For this reason, failure of EPD can only be accepted if the environmental, dietary and nutritional advice have been followed meticulously and treatment has been received over a two year period. To ensure good response, instructions should be followed strictly. Occasionally, patients who did not benefit from their treatment during the first pollen season will become immune to various seasonal allergens, if given further booster doses during subsequent years.

Investigations

Treatment is usually recommended when there is satisfactory proof of allergy. This can be obtained with standard tests (IgE, skin prick test, RAST) in the case of classic allergies like asthma, atopic eczema, hay fever, etc. Food or chemical allergies may require different tests (e.g. elimination diet, IgE/IgG-4 screens). It is often essential to assess one's nutritional needs by means of mineral and vitamin screen before supplements can be recommended. Specific tests for heavy metals are recommended, when their presence is suspected e.g. mercury from mercury dental fillings, lead, aluminium and others.

Indications/Aims of EPD

Any type of allergy (IgE/Type I or other sensitivities) including allergies to inhalants, food or chemicals, where simple measures of avoidance are impossible or extremely difficult, are likely to benefit. Conditions, which respond to desensitisation range from "classic" allergies (asthma, eczema, rhinitis, hay fever, urticaria) to "masked" allergies, when a "non allergic" / immune mechanism is suspected (arthritis, colitis/Crohn's disease, digestive problems, hyper-activity, recurrent infections, irritable bowel, migraine, mood changes, paediatric problems, psoriasis /other skin complaints and weight problems).
Other objectives include:

a. Improved diet and limited or normal contact with one's allergens.
b. Phasing out, cessation of various medications, when a person becomes free of symptoms.
c. Prevention of symptoms arising from newly acquired allergens, eg cats.

Preparation

As EPD is highly diluted, it is important to avoid overwhelming it by using the food(s)/chemical(s)/inhalant(s) which it contains at the time of the injection. It is therefore recommended to reduce or avoid exposure to any items in your environment, which might jeopardise the strength of the treatment e.g. diet with low-risk foods around injection time; avoid perfumes and pets if you are being desensitised against such inhalants. Many patients are advised to use specific combinations of antifungals and antibiotics prior to the time of treatment, in order to reduce fungal and bacterial activity in the intestine (see EPD Reminder Sheet).

Administration

An injection of 0.05ml is given intradermally (very superficial into the skin) in a way to form a small blister. This method might cause a small local irritation and stings for a few seconds; this ensures a slow absorption through the skin, minimising the risk of side-effects. This is the most frequently used approach. In recent years, American colleagues have found it working well, if placed inside the lower lip in young children.

Contra-indications

EPD is occasionally used with children under 5 and never under 2 years or during the first three months of pregnancy; it is not an appropriate form of treatment for peanut or bee sting allergy. In case of previous local or generalised reactions (local swelling larger than the size of a hen's egg or urticaria after treatment) EPD may require a cover with oral steroids. EPD can be wasted if it is given; (i) in a variety of circumstances, known to inactivate it (ii) at the same time with certain drugs or nutrients working as anti-oxidants (see EPD Reminder Sheet).

Side Effects

During the early stages of treatment, symptoms such as muzzy head, headache, tiredness, low spirits are not uncommon but last no more than a few days to a couple of weeks. Occasionally, there is a temporary aggravation of the same symptoms EPD is used for (i.e. congestion in rhinitis or wheezing in asthma). Most of these problems gradually clear and the treatments can be spaced out, when the patient is symptom free. Many patients return for annual booster doses, to ensure their immune system preserves its acquired tolerances.

Cost of Treatment

The cost depends on the type of problem to be treated: desensitisation for hay fever requires two to three injections in the first year and one or two annually thereafter, depending on one's response. The cost of treatment for inhalant allergies or food/chemical intolerance will normally be (£400.00 – £940.00 p.a.). Most insurance companies reimburse the costs of various investigations but not treatments. Please check with your insurance before the start of your treatment.

Duration of Treatment

This varies considerably from person to person. Most of the conditions dealt with by doctors specialising in allergies, are long-term and persist in spite of receiving various other (conventional or unconventional) treatments. They stem from a disorder of the immune system and they are not incurable, as many doctors and patients believe. With this background, their treatment is often complex and time consuming. EPD is usually given as a course of 2-3 monthly treatment, over a two year period, with further booster doses given 1-3 times a year, when symptoms have resolved. After that, an effective way to determine the time of the next booster dose is to let the patient return if/when the symptoms recur. This can happen regularly with some, rarely with others.

EPD & the Medical Profession

Generally, the medical profession remains sceptical about lesser known treatments, not adopted by hospital medicine or not widely publicised in the medical press. Whilst EPD has been subjected to rigorous trials (see below) it has been lacking the potential for investment by the pharmaceutical industry and its methods require considerable time to learn. Today, its availability remains limited to a number of private allergy doctors/clinics. A growing number of doctors refer patients for this type of desensitisation and there are several allergy centres using this technique in the USA, Canada, Australia and several European countries. Clinical/scientific research papers on EPD have been published in many medical journals, some of which appear below, along with a list of books available from book shops and libraries.

Medical References

Placebo-controlled trials of EPD

1. Fell P. & Brostoff J. (1988) A single dose desensitisation for summer hay-fever. Results of a double blind study. Eur.J of Clin. Pharmacology (1990) 38:77-79. single dose of placebo or EPD. Unlimited doses of intranasal steroid aerosol and antihistamine were allowed to "comfort". No difference of symptom scores but significantly less drug consumption in EPD group. No side-effects reported.
2. Austarita C. Scala G. et al. Effects of Enzyme Potentiated Desensitisation in the treatment of pollinosis. A double blind placebo-controlled trial. J of Invest Allergology & Clin Immunol. (1996) 6(4):248-255. Single dose EPD or placebo. Escape drug intranasal disodium cromoglycate. Side-effect: transient headache after 24 hours reported in 20% of subjects. Highly significant difference in symptom scores. CD8+ T-lymphocytes significantly increased in actively treated group after six months. Expected rise in total IgE during pollen season was significant in placebo group but not in actively treated group.
3. Longo G. Poli F. et al. Efficacia clinica di un nuovo trattamento iposensibilzzante, (Enzyme Potentiated Desensitisation) nella terapia della pollinosi. Riforma Med. (1992) 107:171-176. Single dose of EPD or placebo. Escape drug oral terfenadrine (antihistamine). Highly significant difference in symptom scores. No side effects.
4. Businco L. et al. Enzyme Potentiated Desensitisation in children with asthma & mite allergy: a double blind study. J Invest Allrgoi & Clin Immunology (1996) 6(4):270-276. Two doses of EPD or placebo given between September and December 8 weeks interval. Assessment in 3 month follow-up. Significant large reduction of days with asthma and days with drug consumption. Conjunctivial provocation test; 10-fold increased threshold in actively treated group. No side-effects
5. Egger J. Stolla A. & McEwen L.M. Controlled trial of hyposensitisation in children with food-induced hyperkinetic syndrome. Lancet (1992) 339:1150-1153. Behaviour previously shown to be affected by multiple foods. Three doses of EPD or placebo at 8-10 week intervals. End-point: ability to eat previously harmful foods regularly in normal quantities without deterioration of behaviour. Significant differences were observed in the actively treated group. No side-effects ($p<0.001$).
6. Egger J. McEwen L.M. & Stolla A. Hyposensibilisierung bei narhungsmittelinduzierter Migrane. Aktuelle Neuropadiatrie (1992) 287-291. Previously established reactions to multiple specific foods. Three doses of EPD or placebo at 8-10 week intervals. End point: ability to resume a normal diet and remain free from attacks of migraine. Significant improvement in the EPD group. No side-effects ($p<0.001$).
7. McEwen L.M. A double blind controlled trial of Enzyme Potentiated Desensitisation for the treatment of ulcerative colitis. Clin Ecology (1987) 5:47-51. No attempt at diagnosis of allergy. Normal diet continued. Stratified randomisation to ensure equal distribution of subjects admitted to the trial during an exacerbation and of subjects on sulphasalazine. 5 doses of EPD or placebo were given single blind in 10 months. No differences were observed during the 10 month period. During the 16 month follow-up there was a significant reduction of "severe events" (Sigmoidoscopy grade 3, and 5-day steroid regime) in the actively treated group.

Other references

1. McEwen L.M., Ganderton M.A., Wilson C.W.M., Black J.H.D. Hyaluronidase in the treatment of allergy. Brit.Med.J(1967)2:507-508.
2. McEwen L.M., Mary Nicholson, Kitchen I., Sheila Whiter. Enzyme Potentiated Hyposensitisation III: Control by sugars and diols of the immunological effects of beta-glucuronidase in mice and patients with hay-fever. Annals of Allergy (1973) 31:543-550.
3. McEwen L.M., Enzyme Potentiated Hyposensitisation V:Annals of Allergy (1975)35:98-103.
4. Scadding G.K., Brostoff J. Low dose sub-lingual therapy in patients with allergic rhinitis due to house dust mite. Clin.Allergy (1986)16:483-491.
5. Anderson N.H., Jeppesen F., Schioler T. et al. (1987) Treatment of hay fever with sodium cromoglycate, hyposensitisation or a combination. Allergy 42:343-346.
6. Challacombe S.J., Brostoff J. Hyposensitisation iin Food Allergy & Intolerance. London: Balliere Tindall (1987) 983-984.
7. **Wikipedia – Enzyme Potentiated Desensitisation**

Also

1. The Guide to Food Allergy & Intolerance. Dr. J. Brostoff & Linda Gamilin (1988).
2. Allergy & Intolerance: A Complete Guide to Environmental Medicine. Drs. G. Llewith, J. Kenyon & D.Dowson: Green Print (1992)112-113.
3. Effective Allergy Practice. A Document on Standards of Care and Management for the Allergy Patient. Brit.Soc. of Allergy, Environmental & Nutritional Medicine (1994)7.
4. 12 Ways You Can Beat Your Allergies. Readers' Digest (May 1995) 51-54.

Cost per dose: £185