

susceptibility is uncertain. Although many of the children were prescribed doses of metoclopramide above those recommended by manufacturers, relative overdosage, as discussed earlier, does not account for the differences in age and sex. Therapeutic overdosage in the 12-19 year age group may contribute to the high reporting rate, but exclusion of those patients who were prescribed a relative overdose from the analysis means that the sex difference in reporting becomes more pronounced in this age group (table V). As we do not have details of prescribing dosages to the community as a whole assessment of the dose response relation in terms of adverse reactions is impossible. Plasma concentrations and clearances of metoclopramide, however, were similar in children suffering from acute extrapyramidal reactions to those not suffering.¹⁰ Furthermore, prescribing a relative overdose does not account for the age related pattern of reports in the age groups over 20 years, and we therefore favour a pharmacodynamic explanation. This would be supported by the observation that the prolactin response to intravenous metoclopramide, which is due to the dopamine antagonist action of the drug, was substantially greater in 17-20 year old women than men.¹¹ Moreover, an age related decline in density of D₂ receptors has been shown to occur in the striatum of the rat¹² and in the caudate nucleus, putamen, and frontal cerebral cortex of man.¹³

Only a fairly small proportion of patients were apparently receiving other drugs (table III). Generally, therefore, adverse interactions probably do not account for most of the reactions. Major tranquillisers, oral contraceptive steroids, and lithium, however, are known to precipitate acute extrapyramidal reactions in susceptible patients, and their concurrent use may exacerbate any tendency to extrapyramidal reactions with metoclopramide. Several patients were receiving opioid analgesics or dextropropoxyphene (table III). Delitala *et al* recently reported that morphine enhances the prolactin releasing effect of intravenous metoclopramide,¹⁴ and it is possible that opioids enhance the sensitivity of D₂ receptors within the basal ganglia.

Although acute dystonic-dyskinetic reactions to metoclopramide are self limiting and rarely cause permanent damage, their morbidity is high and many patients reported to the Committee on the Safety of Medicines were admitted to hospital. In the light of present evidence it would seem wise to exercise care in the use of this drug in young people, and especially girls and young women.

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Egg and cows' milk hypersensitivity in exclusively breast fed infants with eczema, and detection of egg protein in breast milk

ANDREW CANT, R A MARSDEN, P J KILSHAW

Abstract

Forty nine eczematous infants who were still solely and exclusively breast fed and who had never received anything but breast milk were studied for evidence of sensitisation to foods. Thirty four similar infants without eczema formed a control group. The eczematous infants were divided into three groups according to clinical criteria:

(1) definite atopic eczema; (2) possible atopic eczema; (3) atopic eczema unlikely. Twenty three infants showed cutaneous hypersensitivity to foods, usually egg and cows' milk. Seven of 14 infants in group 1 and nine of 20 in group 2 were sensitised compared with four of 15 in group 3 and three of 34 controls ($p < 0.01$). Ovalbumin was detected in breast milk from 14 of 19 mothers tested after ingestion of egg, the concentrations being the same for mothers feeding eczematous and normal infants.

Breast fed babies developing eczema may be sensitised by foods eaten by their mothers.

St George's Hospital Medical School, London SW17 0RE

ANDREW CANT, MRCP, MRC research fellow, department of child health
R A MARSDEN, MRCP, consultant dermatologist

Department of Nutrition, National Institute for Research into Dairy-
ing, Shinfield, Berkshire

P J KILSHAW, PHD, principal scientific officer

Correspondence to: Dr Cant.

Introduction

Despite continuing controversy^{1,2} it is widely believed that breast feeding partially protects against the development of allergic disease, including atopic eczema.^{3,4} This protective effect is not complete, however, as breast fed children sometimes

develop allergic disease, particularly atopic eczema, while still being exclusively breast fed, and there are reports of such infants whose eczema was provoked by foods in their mother's diet.^{5,6} A recent study suggests that children may be immunologically sensitised to foods they have never knowingly been given; a small proportion of exclusively breast fed infants were observed to suffer immediate hypersensitivity reactions on first exposure to egg or cows' milk.⁷

Over 50 years ago the passage of egg protein into human milk

allergic disease in a first degree relative. Possible atopic eczema was diagnosed if the baby fulfilled the criteria for definite atopic eczema but did not scratch, or whose rash had an atypical distribution, or who did not have a first degree relative with allergic disease. Other eczematous babies were classified as "atopic eczema unlikely," and babies with seborrhoeic dermatitis were included in this group. Mothers whose babies had always had normal skin served as controls.

Skin prick tests were carried out on the forearms of both mothers and babies using negative control, positive control (histamine 1 mg/ml), cows' milk, hens' eggs, wheat, chocolate, mixed nuts, cod, mixed grass

TABLE I—Skin test reactions to food and inhaled allergens in exclusively breast fed infants with eczema or normal skin

	Skin diagnosis			Controls
	Definite atopic eczema	Possible atopic eczema	Atopic eczema unlikely	
No in each group	14	20	15	34
Mean age (weeks)	14	12	13	13
No (%) giving skin test reactions to food	7 (50)	9 (45)	4 (27)	3 (9)*
Major	7 (50)	5 (25)	0	0**
Minor only	0	4 (20)	4 (27)	3 (9)
No (%) giving skin test reactions to inhalants	2 (14)	1 (5)	0	0

* $\chi^2 = 12.53$, $p < 0.01$; ** $\chi^2 = 24.34$, $p < 0.001$.

TABLE II—Total and major skin test reactions to individual food and inhaled allergens in exclusively breast fed infants with eczema or normal skin

Allergen	Definite atopic eczema (n = 14)		Possible atopic eczema (n = 20)		Atopic eczema unlikely (n = 15)		Controls (n = 34)	
	Total	Major	Total	Major	Total	Major	Total	Major
Egg	7	7	5	4	3	0	1	0
Cows' milk	5	4	2	1	—	—	1	0
Chocolate	—	—	2	2	—	—	—	—
Wheat	1	1	1	0	—	—	1	0
Cod	—	—	—	—	—	—	—	—
Nuts	—	—	1	0	1	0	—	—
House dust	2	2	—	—	—	—	—	—
Cat fur	—	—	—	—	—	—	—	—

was shown by a Prausnitz-Küstner test,⁸ and recently egg and cows' milk proteins in human milk have been quantified using a solid phase radioimmunoassay.⁹ Thus breast fed children who develop allergic disease may do so because they become sensitised to foods eaten by their mothers.

We have studied a group of solely breast fed infants with eczema for evidence of cutaneous hypersensitivity to food proteins. The passage of egg protein into breast milk was also studied, comparing mothers of eczematous infants with mothers of normal infants.

Patients and methods

Mothers nursing infants with eczema were recruited through parent support groups or by referral from their doctors. All were seen by a paediatrician (AJC) and a dermatologist (RAM). A careful history of infant feeding was taken and the mothers asked if complementary bottles of formula milk had ever been given. Special attention was paid to any separation of mother and baby during the neonatal period, to the feeding policy of the unit in which the baby was born, and to any times when the baby was looked after by someone else and possibly given complementary feeds. Only infants still solely and exclusively breast fed were included in the study. A history of allergic disease (asthma, eczema, hay fever, and immediate reactions to food) in first degree relatives was obtained. Distinguishing atopic eczema from seborrhoeic dermatitis (which is probably not an atopic disease) is difficult in early infancy, so clinical criteria similar to those of Yates *et al* were used.¹⁰ The infants were examined and assigned to one of the following three categories: definite atopic eczema; possible atopic eczema; atopic eczema unlikely.

Definite atopic eczema was diagnosed if the infant scratched or had a rash on the cheeks or forehead and over the extensor surfaces of the limbs with relative sparing of the napkin area and there was a history of

pollens, mixed tree pollens, house dust, house dust mite, cat fur, and ragweed. Commercially available extracts were used (Bencard) except for the histamine solution, which was prepared by the hospital pharmacy. The diameter of each weal and flare was measured in millimetres and the size of any reaction to the negative control subtracted. Reactions with a weal greater than 3 mm diameter were classified as "major."

Eleven mothers of eczematous infants with a positive skin prick test reaction to egg and eight mothers of control babies with negative skin test reactions abstained from egg for 24 hours and then took one raw egg. Breast milk samples were taken two, four, and six hours later. The samples were assayed for ovalbumin by radioimmunoassay, as described.⁹

Results

We studied 105 mothers and babies. All the babies were less than 6 months old and most were between 3 and 4 months of age. Initially all mothers said that their babies were solely breast fed, but on close questioning, although no infant had received solids, 22 were found to have been given complementary feeds of formula milk, 18 by their mothers in the neonatal period and four by nurses or relatives. Cows' milk formula had been given to 19 infants and soy formula to three. Only one infant had received more than four bottles of formula in total.

Of the 83 babies solely and exclusively breast fed, 49 had eczematous rashes, 14 being classified as definite atopic eczema (group 1), 20 as possible atopic eczema (group 2), and 15 as atopic eczema unlikely (group 3). The 34 control infants had normal skin. Seventeen of the controls had a first degree relative with allergic disease. Seven infants in group 1, nine in group 2, four in group 3, and three of the controls reacted to foods ($p < 0.01$; table I). Half of the babies in group 1 gave major reactions to foods compared with a quarter of those in group 2 and none in group 3 or the control group ($p < 0.001$; table I). Nearly all the reactions were to egg and cows' milk (table II).

Hens' egg ovalbumin was detected in breast milk from 14 of the 19 mothers challenged and was present at maximum concentrations of between 0.2 and 4.0 ng/l, usually appearing two or four hours after challenge (no ovalbumin was detected in breast milk taken before the egg challenge). The frequency of detection and the amount found were the same regardless of whether the mothers were feeding eczematous infants with positive skin prick test reactions to egg or babies with normal skin (table III).

Discussion

All the babies referred were said to be solely breast fed, yet—although none had received solids—a third had received a few complementary bottles of cows' milk or soy formula. The importance of such exposure to these milks is not clear, but it illustrates the need for great caution when considering the results of retrospective studies of infant feeding and allergic disease.^{11 12}

Despite the fact that all the babies studied were still solely and exclusively breast fed, 16 (47%) of the 34 infants with definite or possible atopic eczema gave positive skin prick test reac-

with a weal greater than 3 mm diameter are more likely to indicate significant hypersensitivity.²⁰ In our study there was a slightly more clear cut association between atopic eczema and cutaneous hypersensitivity when only "major" reactions were considered, but smaller responses probably also indicate the presence of reaginic antibody and thus infant sensitisation, and there was a highly significant correlation between reactions of any size and the presence of eczema.

We have not documented the route by which sensitisation to egg and cows' milk occurred, but hens' egg ovalbumin was detectable in breast milk samples from most of the mothers tested, and the concentrations were very small and within the range reported by Donnally.⁸ In our study the frequency of detection of antigen and the concentrations of antigen found were the same in breast milk samples from mothers feeding eczematous infants and mothers feeding normal infants. Therefore, if infants are sensitised by food antigen in breast milk the development of hypersensitivity seems to depend not on the amount of antigen reaching the infant, as has been suggested,⁶ but on the exquisite immune responsiveness of certain infants to minute amounts of antigen.

TABLE III—Detection of egg protein in breast milk samples from mothers feeding eczematous infants with positive skin prick test reactions to egg and mothers feeding infants with normal skin and negative skin prick reactions to egg

	Eczema and positive skin test reaction to egg	Normal skin and negative skin test reaction to egg
No of infants	11	8
Mean age (weeks)	17	13
No (%) whose mothers' milk contained ovalbumin	8 (72)*	6 (75)*
Range of ovalbumin concentrations ($\mu\text{g/l}$)	0.2-4.0	0.4-4.0
Mean ovalbumin concentration ($\mu\text{g/l}$)	1.6†	2.4†

*Not significantly different by Fisher's exact test ($\chi^2 = 1.113$).

†Not significantly different by Student's *t* test.

tions to egg or cows' milk, and 12 (35%) gave major reactions. Thus not only had they been exposed to these food proteins while still exclusively breast fed but they had also developed hypersensitivity to them. Our findings are consistent with the results of Hattevig *et al*, who detected egg and milk specific IgE in breast fed babies by radioallergosorbent test.¹³ Although there are case reports of breast fed infants with allergic symptoms (urticaria, eczema, wheezing, vomiting, and diarrhoea) provoked by foods in their mother's diet,^{5 6} it is remarkable that such a high proportion of solely breast fed babies selected only because of an eczematous rash showed hypersensitivity to foods that they had never been given directly. Egg and cows' milk were by far the most common food allergens, and the predominance of reactions to these particular food proteins is curious, though their importance as common allergens in childhood is borne out by other studies.^{7 14 15}

Not only did the positive skin test results provide evidence for very early sensitisation to egg and cows' milk but they appeared to distinguish babies with atopic eczema (according to our criteria) from those with less easily classified rashes and seborrhoeic dermatitis. Half the babies in the definite atopic eczema group gave major cutaneous reactions, whereas none in the group classified as atopic eczema unlikely or in the control group did so. It might be argued that the control infants gave negative reactions because they were not from atopic families. Seventeen of the 34 control infants had a first degree relative with allergic disease, however, and none of these gave a major cutaneous reaction, though two gave minor reactions. Our findings are consistent with those of Yates *et al*, who observed that eczematous infants giving a positive IgE radioallergosorbent test reaction to egg and cows' milk in early infancy all had atopic eczema at 1 year of age, whereas similar infants with a negative reaction to these foods had normal skin at 1 year.¹⁶ Although we performed skin prick tests rather than radioallergosorbent tests, both detect reaginic antibody and correlate in infants of this age.^{5 17-19} It has also been suggested that skin test reactions

Sensitisation, however, may occur by other routes. IgE antibodies to food proteins have been detected in cord blood and there is persuasive evidence that these antibodies are of fetal origin, suggesting that they have been evoked by food antigens crossing the placenta.²¹ Alternatively adventitious environmental contact with these ubiquitous food proteins may be relevant, and the minute amounts of egg and cows' milk antigen in breast milk are similar to those commonly found contaminating the hands.⁹ It is also conceivable that autoanti-idiotypic antibodies to maternal food antibodies cross the placenta and that some may present an internal image of the antigen and act as an immunogen.²²

We have not shown that food antigens in human breast milk cause eczema in breast fed babies. Nevertheless, our findings suggest that maternal avoidance of egg and cows' milk may benefit the breast fed baby with eczema, and controlled studies to test this are needed. Perhaps more important they pose the question, Will maternal avoidance of these foods in pregnancy and lactation prevent sensitisation and so enhance the protective effects of breast feeding^{3 4} and the late introduction of solid food^{23 24} in the prevention of allergic disease? Despite all the studies of infant feeding and allergic disease, a complete answer cannot be given until the effect of maternal diet during pregnancy and lactation has been studied in prospective controlled trials.

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Does stopping smoking delay onset of angina after infarction?

LESLIE E DALY, IAN M GRAHAM, NOEL HICKEY, RISTEARD MULCAHY

Abstract

This study was designed to determine the relation between stopping smoking and angina after infarction in survivors of an acute coronary attack. The study population comprised 408 men aged under 60 who survived a first attack of unstable angina or myocardial infarction by 28 days and were smoking cigarettes at the time of their attack. These patients were followed up for an average of nine years. Three hundred and eighty four were alive at the one year follow up examination, when the presence or absence of angina together with habits of smoking were recorded. The prevalence of angina at one year was 19.5% in the 241 who had stopped smoking cigarettes compared with 32.2% in those who had continued ($p < 0.01$). Six years later, however, the prevalence of angina after infarction was the same in the two groups.

It is concluded that the onset of angina after infarction can be delayed by stopping smoking cigarettes but that this effect is not maintained in the long term.

Introduction

The greater chance of survival for those who stop smoking cigarettes after a coronary attack is well documented,¹⁻¹⁰ but only one report (with negative findings) mentions explicitly the relation between stopping smoking cigarettes and subsequent

angina pectoris.⁸ This paper examines this question in a long term follow up study of 408 men who smoked and survived a first attack of unstable angina or myocardial infarction and were entered into the St Vincent's Hospital heart study.

Patients and methods

Between 1 January 1965 and 31 December 1975, 555 consecutive men aged under 60 who survived a first attack of unstable angina or myocardial infarction by at least 28 days were admitted into a long term follow up study. Diagnostic criteria for entry to the study have been previously published.¹ This report concentrates on the 408 (73.4%) of those patients who were smoking one or more cigarettes daily in the three months before their attack. Of these, 81 (19.9%) had a diagnosis of unstable angina.

A uniform programme of rehabilitation and secondary prevention included advice in hospital and at follow up against smoking. Routine drugs such as anticoagulants or β blockers were not used. Follow up data were recorded annually at a special clinic, and 384 of the 408 patients who smoked before the study began were alive at their first ("one year") examination (mean time to examination was 13.8 months). Subsequent long term follow up of these 384 patients was almost complete when this report was written. By the end of 1983, 188 had died and all but nine (2.3%) had their last follow up examination in 1982 or 1983. The mean duration of follow up to death or last examination was 8.3 years (range 0.1-17.7), with an average of 8.1 annual examinations.

In addition to age and the severity of the first attack, baseline characteristics recorded at entry to the study included blood pressure, serum cholesterol concentration, results of a glucose tolerance test, habits of exercise, consumption of cigarettes and alcohol, anginal state before admission, and measurements of height and weight. Only patients with angina for at least three months before their first attack were classified as having angina before infarction. Smoking and anginal state are the two characteristics at follow up reported here. At each examination a smoker who had stopped smoking for at least three months was defined as a "stopped smoker." A high degree of veracity in the stated smoking habits of a sample of these patients has been reported.¹¹ For both first and follow up examinations the presence or absence of angina pectoris was based on symptoms reported to the investigators.

Statistical techniques included χ^2 and t tests, logistic regression, and an adaptation of the clinical life table of Kaplan and Meier.¹² Significance was determined at a two sided 5% level.

Cardiac Department, Department of Preventive Cardiology, and Department of Community Medicine and Epidemiology, St Vincent's Hospital and University College, Dublin 4, Ireland

LESLIE E DALY, MSc, PhD, lecturer in biostatistics
IAN M GRAHAM, MB, MRCP, director of research in cardiology
NOEL HICKEY, MD, MRCP, lecturer in epidemiology
RISTEARD MULCAHY, MD, MRCP, professor of cardiology

Correspondence and requests for reprints to: Professor Mulcahy, Department of Preventive Cardiology, St Vincent's Hospital, Dublin 4, Ireland.