A pilot study of the usefulness and safety of a ready-to-use atopy patch test (Diallertest) versus a comparator (Finn Chamber) during cow's milk allergy in children

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Background: Patch testing is used in the diagnosis of food allergy, especially during delayed manifestations.
Objective: A ready-to-use atopy patch test (APT), the Diallertest, was compared with another APT device, the Finn Chamber, in pediatric cow's milk allergy.
Methods: This prospective study involved 49 children (34.3 ± 17 [mean ± SD] months of age), with cow's milk allergy manifested by atopic dermatitis (10.2%), digestive manifestations (40.8%), or both (49%). All children underwent both APT techniques, with a reading 72 hours after application, followed by a milk elimination diet for 4 to 6 weeks and open cow's milk challenge.
Results: A positive result was seen in 22 (44.8%) versus 13 (26.5%) patients with the ready-to-use and the comparator APTs, respectively. No side effects were recorded. Both techniques were concordant in 67.3% of patients. Of the total 41 open cow's milk challenges, 60.9% had positive results, with 8 patients lost to follow-up. The performances of the ready-to-use and comparator APTs were as follows: sensitivity, 76% (95% CI, 59.2% to 92.7%) versus 44% (95% CI, 24.5% to 63.4%; $P = .02$); specificity, 93.8% (95% CI, 81.9% to 100%) versus 93.8% (95% CI, 81.9% to 100%); positive predictive value, 95% (95% CI, 85.4% to 100%; 1 false-positive result) versus 91.7% (95% CI, 76% to 100%; 1 false-positive result); negative predictive value, 71.4% (95% CI, 52% to 90.7%; 6 false-negative results) versus 51.7% (95% CI, 33.5% to 69.8%; 14 false-negative results); and test accuracy, 82.9% (95% CI, 71.3% to 94.5%) versus 63.4% (95% CI, 48.6% to 78.1%; $P = .05$).
Conclusion: The ready-to-use APT exhibited a good sensitivity and specificity, with no side effects. (J Allergy Clin Immunol 2005;116:1321-6.)

Key words: *Cow's milk allergy, children, ready-to-use atopy patch test*

Food allergy is a common problem in toddlers and small children, involving 8% of French children in a recent population study of food allergy.[1] The current clinically validated method to demonstrate food allergy is elimination and challenge with the suspected food, either using the double-blind, placebo-controlled food challenge (DBPCFC)[2] or according to simplified procedures exhibiting a good correlation with the DBPCFC.[3-6]

For IgE-mediated disorders, skin prick tests (SPTs) guided by clinical history provide a rapid method to screen patients for sensitivity to specific foods. Negative SPT responses essentially confirm the absence of IgE-mediated allergic reactivity with a negative predictive accuracy of greater than 95%,[7] but do not detect delayed-onset, non–IgE-mediated allergies.[6] In the absence of immediate clinical reactions,[8] delayed-onset allergies, most of the time related to a non–IgE-dependent mechanism, still present diagnostic difficulties, a situation specifically of concern during digestive manifestations sometimes associated with eczema in the young child.[9]

Several authors have therefore investigated the use of the atopy patch test (APT) for the diagnosis of non–IgE-mediated food allergy, primarily in patients with atopic dermatitis and digestive disorders.[9-15] The APT results were positive in 89% of children with delayed-onset reactions, despite frequently negative SPT responses.[6,16] Both in clinical practice and in clinical trials, several drawbacks of patch testing originate from its tedious preparation and a lack of standardized antigen preparation, leading to considerable intra-assay and interassay variations.[17] An acceptable standardization of APTs would greatly improve the accuracy of this noninvasive tool for the detection of food allergy. Previous attempts include the development of an optimal vehicle for the allergen inside the patch device.[18]

The aim of our study was to assess the correlation and safety of a ready-to-use APT (Diallertest; DBV-Technologies, Boulogne-Billancourt, France) and compare it with that of another APT (Finn Chamber; Epitest Ltd, Hyrylä, Finland) in the evaluation of pediatric cow's milk allergy (CMA), together with its usefulness in the diagnosis of CMA, as determined by using an open cow's milk challenge.

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Abbreviations used
APT: Atopy patch test
CMA: Cow's milk allergy
CMP: Cow's milk protein
DBPCFC: Double-blind, placebo-controlled food challenge
SPT: Skin prick test

METHODS

Patients

A prospective study was carried out between November 2003 and September 2004 in a population of 49 children (mean ± SD age, 34.3 ± 7 months; range, 5-78 months), 18 girls and 31 boys, enrolled after referral to an outpatient clinic for food allergy. Children exhibited at least one symptom of allergy, the main symptoms being atopic dermatitis (n = 5, 10.2%), digestive manifestations (eg, loose stools, colic, vomiting, gastroesophageal reflux, and failure to thrive; n = 20, 40.8%), and combined manifestations (n = 24, 49%). All abnormal digestive reactions were analyzed by the parent's child and then validated by the physician. Children were not enrolled if maintaining an exclusion diet for cow's milk protein (CMP), presenting with important skin lesions impeding APT application, or having been treated with antihistamines and oral or cutaneous steroid medications for the last week.

Study design

On an outpatient basis, children were routinely tested by means of a blood sample for measurement of specific CMP IgE levels and underwent skin testing on the basis of CMP SPT and CMP APT by using both the ready-to-use technique (Diallertest) and the comparator (Finn Chamber). All enrolled children were randomized for the application of both APT techniques on the right or left side of the back. After the initial standardized evaluation, children were requested to follow a CMP elimination diet based on an extensively hydrolyzed whey protein formula or an amino acid–derived formula for 4 to 6 weeks combined with an open cow's milk challenge. Atopic dermatitis was assessed by using a routine local score on the basis of the severity and extension of eczematous skin lesions as follows: no, mild, moderate, and severe atopic dermatitis. This assessment was performed at enrollment, during the 4 to 6 weeks of the CMP elimination diet, and after the cow's milk challenge. The physician responsible for the open cow's milk challenge was blinded to the results of CMP IgE measurement, SPTs, and both APTs and vice versa. All side effects related to both APT techniques were recorded throughout the study duration according to a questionnaire explained by the research nurse. The protocol was approved by the local ethical committee, and written parental consent was obtained in all cases from both parents.

Specific cow's milk protein IgE (CMP IgE)

Sera CMP IgE was analyzed with the RAST Cap System (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden) calibrated with reference to the World Health Organization standards for IgE. Its specificity was already assessed,[19] and its use in children has already been reported.[20,21] Reference data for specific CMP IgE levels were those of the manufacturer, considering values of less than 0.35 KU/L to be nondetectable.[22,23]

CMP SPT

SPTs were performed with a drop of pasteurized half-skimmed cow's milk on the backs of children if aged less than 12 months and on the volar part of the forearm in those older than 12 months. Histamine dihydrochloride (ALK, Copenhagen, Denmark), 10 mg/mL, and glycerosaline were used as positive and negative controls, respectively. A positive reaction was defined as a wheal diameter 3 mm larger than that elicited by the negative control after 15 minutes.

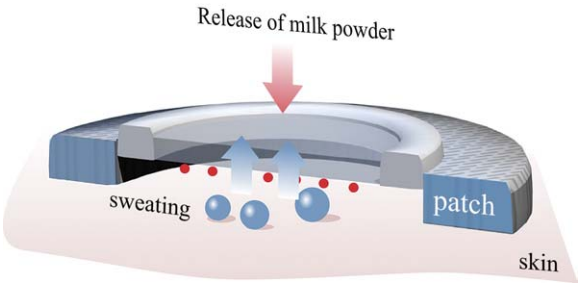

FIG 1. The ready-to-use CMP APT (Diallertest), 26 mm in diameter, consists of 3 parts: (1) a central transparent plastic membrane (11 mm in diameter) of polyethylene charged with electrostatic forces able to retain powdered cow's milk for a long period and to allow a visual monitoring of cutaneous reactions; (2) a biadhesive mousse layer (25 mm in diameter) enclosed by 2 liner sheaths; and (3) an adhesive sheath of nonwoven film.

CMP APT

The comparator CMP APT Finn Chamber. A mixture consisting of two thirds of a powdered cow's milk product (Régilait, Saint-Martin-Belle-Roche, France) and one third of a hypoallergic infantile cow's milk formula with a protein molecular weight of less than 5000 d (Nidal HA; Nestlé, Marne-la-Vallée, France) was diluted in water (13.5 g/100 mL), and 1 drop was applied on uninvolved skin on the patient's back with aluminum cups (Finn Chamber, Epitest Ltd) and Scanpore tape (Alpharma Norgesplaster AS, Vennesia, Norway), the paper inside the chamber being thus soaked with 880 μg of CMP. Isotonic saline solution was used as a negative control.

The ready-to-use CMP APT Diallertest. The ready-to-use CMP APT (Diallertest, DBV-Technologies), 26 mm in diameter, consisted of 3 parts: (1) a central transparent plastic membrane (11 mm in diameter) of polyethylene charged with electrostatic forces able to retain a powdered material for a long period and to allow a visual monitoring of cutaneous reactions; (2) a biadhesive mousse layer (25 mm in diameter) enclosed by 2 liner sheaths (liner 1 and 2); and (3) an adhesive sheath of nonwoven film. The same mixture as the cow's milk–based product used for the comparator CMP APT Finn Chamber was deposited on the central plastic support in the form of microgranules (5-40 μm), forming a homogeneous monolayer retained by electrostatic forces. Each APT thus contained 250 μg of CMP with 60% casein and 40% lactoserum protein (intact and derivatives). The ready-to-use APT serving as a control had the same structure but was deprived of any cow's milk powder in the central part (Fig 1).

Trial design for APT techniques. A telephone call was made 24 hours after application of the APTs to assess the safety of the ready-to-use APT, a specific surveillance of the reaction through the transparent patch membrane being requested from parents. The occlusion time was 48 hours, and the results were read by the same investigator 20 minutes and 24 hours after removal of the devices (ie, at 72 hours). Numeric photographs were taken at 48 and 72 hours and archived into a computer. Reactions were considered as negative, irritation, significant erythema, and erythema with eczema or edema.[6] The reaction was considered positive if at 72 hours the CMP APT exhibited a stronger skin reaction than the negative control (ie,