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A double-blind placebo-controlled study of the effect of influenza vaccination on airway responsiveness in asthma

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Introduction

Influenza A infection may cause severe exacerbations of asthma with increased airway responsiveness and airflow obstruction (1). Annual vaccination against influenza is therefore recommended for patients with asthma by the Chief Medical Officer of the Department of Health. However, some patients report exacerbations of their asthma, apparently related to influenza vaccination, and there is reluctance to adhere to the recommended vaccination policy (2). We therefore studied the effect of a current subunit vaccine on symptoms, medication use, spirometry and airway responsiveness in patients with stable asthma.

Patients, Methods and Results

Twenty-two patients (eight male) with a median age of 41 (range 19–71) years participated in the study, which was undertaken in November 1995. All had a forced expiratory volume in 1 s (FEV_1) of greater than 60% of the predicted value (range 60–112%); all had demonstrated >15% reversibility and all were taking inhaled β_2 agonists; 20 were taking inhaled corticosteroids. All were non-smokers and 13 had previously received influenza vaccination. All medications were continued unchanged during the study. Spirometry and airway responsiveness (PD_{20} methacholine) (3) were measured twice at a 2 week interval before vaccination and at 48 and 96 h postvaccination. Patients were assigned in a double-blind fashion to receive either placebo ($n=5$) or 0·5 ml of inactivated surface antigen influenza vaccine (Evans Medical Ltd.) by deep subcutaneous injection ($n=17$). The vaccine contained surface antigens from the three strains of influenza virus recommended for 1995/1996. Patients recorded symptoms, medication use and adverse events.

Eight vaccine recipients reported transient symptoms such as fever, sore throat and malaise, and one developed a reaction at the site of vaccination; no placebo recipient reported any adverse events. Symptoms were mild and resolved within 48 h. No patient reported any worsening of asthma symptoms or increase in medication use. There was no significant difference between mean pre- and post-vaccination spirometry or PD_{20} in either the placebo or active vaccination groups (analysis of variance, ANOVA) (Table 1) and no individual patient showed a change in postvaccination PD_{20} of more than two-fold.

Discussion

Infection with influenza A virus or vaccination with live attenuated influenza vaccine has been shown to cause increased airways responsiveness (1,2). Studies using older killed vaccines gave conflicting results, with some studies showing increased airways responsiveness post vaccination (4,5). More recent studies using modern purified surface sub-unit vaccines show no effect on airway responsiveness or asthma control (6). However, some patients still report exacerbations of their asthma, apparently related to influenza vaccination, and there is reluctance to adhere to the recommended annual vaccination policy (2). Our study showed no evidence of increased airway responsiveness or airway obstruction in patients with stable asthma receiving a modern purified surface antigen sub-unit vaccine. Airway responsiveness is a continuous variable which is distributed normally in the general population. In practice PD_{20} values <200 μg are almost invariably associated with evidence of active asthma, whereas values >1000 μg rarely are. Inhaled steroids usually result in an increase in PD_{20} value. The serial quantification of geometric mean levels of airway responsiveness as PD_{20} offers a powerful method of detecting any general effect on asthmatic activity. Repeatability data from earlier investigations suggest that as few as six subjects would provide an 80% chance of detecting a doubling of asthmatic activity (i.e. a halving of geometric mean PD_{20}) at the 5% level of significance, and 37 would detect a one and a half-fold increase (i.e. a 25% decrement in geometric mean PD_{20} (3). The present investigation consequently had the power to detect a one and a half to two-fold increase in asthmatic activity, though in fact no hint of any increase was seen. We therefore conclude that

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TABLE 1. Mean FEV_1 and PD_{20} (μg) methacholine pre- and postvaccination

		Pre-vaccine 1	Pre-vaccine 2	Postvaccine 48 h	Postvaccine 96 h
Active vaccine	FEV_1 (l)	2·93 (1·46–4·67)	2·89 (1·32–4·20)	2·83 (1·47–4·54)	2·90 (1·40–4·54)
$n=17$	PD 20 (μg)	105 (11–6400)	135 (10–6400)	102 (8–6400)	101 (8–6400)
Placebo	FEV_1 (l)	3·49 (2·16–4·20)	3·54 (2·18–4·78)	3·41 (2·30–4·39)	3·44 (2·20–4·36)
$n=5$	PD_{20}) (μg)	242 (15–6400)	198 (16–6400)	320 (25–6400)	344 (15–6400)

this vaccine does not generally exert any adverse effect on asthma. This and previous similar studies are reassuring and provide support for adherence to current vaccination guidelines. Minor transient symptoms were common after vaccination but were not associated with any increase in airway responsiveness or airway obstruction. It is important to distinguish such systemic symptoms from true exacerbations of asthma when patients report an adverse reaction to previous vaccination.

Although this study shows that a surface antigen sub-unit influenza vaccine does not exert a general adverse effect on airway responsiveness in patients with asthma it does not exclude the possibility that an individual patient may develop an allergic reaction to an influenza vaccine. Differentiation of a true reaction to vaccination from coincidental exacerbations of asthma in such patients would probably require repeat vaccination of the patient under double-blind experimental conditions and such a study has not been performed. Furthermore different vaccines may have different effects, and changes in the vaccine components from year-to-year to allow for antigenic drift of the virus might be important.

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