

Effects of Killed and Live Attenuated Influenza Vaccine on Symptoms and Specific Airway Conductance in Asthmatics and Healthy Subjects

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Killed and live influenza virus vaccines were given to asthmatics and healthy subjects to investigate symptoms and alterations in their respiratory performance after vaccination. Polyvalent killed influenza virus vaccine was given to 16 asthmatics and live attenuated influenza virus vaccine to 23 asthmatics and 21 healthy subjects. Fourteen of the 16 asthmatics vaccinated with the killed vaccine displayed a significant rise in serum antibody level as measured by a single radial haemolysis in gel (SRH test). 11 of the 23 asthmatics and 14 of the 21 healthy subjects vaccinated with the live attenuated vaccine displayed a significant rise in the SRH test. Among the subjects with no measurable initial antibodies and with a significant rise in the SRH test, one asthmatic vaccinated with the killed vaccine experienced symptoms of common cold with fever and dyspnoea 1 week after vaccination. Three asthmatics and four healthy subjects vaccinated with live attenuated vaccine experienced mild symptoms, mainly rhinorrhoea, cough and sore throat 2 to 3 days after vaccination. No alterations in specific airway conductance in asthmatics or in healthy subjects were observed. We conclude that both killed and live attenuated influenza virus vaccines are tolerated well by asthmatics and appear to be safe for asthma patients.

Key words: asthma; killed influenza vaccine; live attenuated influenza virus vaccine; respiratory viral infections; specific airway conductance; symptoms.

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Respiratory viral infections are often associated with exacerbations of asthma (4, 5, 8, 9). The risk of exacerbation increases during influenza epidemics. Safe and effective influenza vaccines would be of considerable value for patients with asthma (12). However, adverse reactions may be associated with the use of both killed and live attenuated influenza vaccines (1, 2, 11, 13, 16). In the present study, a killed influenza virus vaccine was given subcutaneously to 16 asthmatics and two strains of attenuated influenza virus vaccine intranasally to 23 asthmatics and 21 healthy subjects. Responses to vaccinations were ascertained by symptom records, serologic studies and by measuring airway re-

sistance and thoracic gas volume, and specific airway conductance was calculated from these.

MATERIAL AND METHODS

Patients

Nineteen subjects with mild and 20 with moderately severe asthma, judged from clinical history and need for bronchodilating drugs, were vaccinated. Those with mild disease did not require daily medication and none of the patients were on continuous oral steroids. The routine challenge procedure used in the clinic had shown bronchial hyperreactivity to inhaled

histamine diphosphate aerosol in all patients (7). The patients comprised 13 men and 26 women, whose age range was 16 to 63 years. The mean duration of the disease was 5 years. However, most of the patients had recent asthma with duration under 1 year. Eighteen of the patients had an extrinsic type of asthma as shown by their history and positive results on skin prick testing. Seven patients were smokers. Specific airway conductance (SGaw) was normal in all patients except four with SGaw of 0.074, 0.083, 0.088 and 0.088 $\text{sec}^{-1} \text{cmH}_2\text{O}^{-1}$, respectively, before vaccination.

Healthy subjects

Twenty-one members of the hospital staff (4 men and 17 women) without a history of chest disease, aged 21 to 48 years, participated in the study. Five were smokers, and seven had two or more positive reactions in skin tests. All subjects had normal findings on general physical examination and normal values of SGaw before vaccination.

None of the asthmatics or the healthy subjects had a history of allergy to eggs.

Vaccines

Polyvalent (A/England/864/75, A/USSR/92/77 (H3N2) and B/Hong Kong/8/73 (H1N1) influenza virus vaccine, provided by the manufacturer, Orion (Flupar-Vaccin®, containing 3000 HA units/a dose), was given subcutaneously in a single dose of 0.5 ml to each subject. We used two strains of live attenuated influenza virus vaccine provided by Recherche et Industrie Thérapeutique S.A. (R.I.T.), Victoria 3/75 (H3N2, R.I.T. 4050) and Texas 1/77 (H3N2, R.I.T. 4199). Each vaccine contained approximately 10^7EID_{50} of live influenza virus in one dose. Both vaccines were applied intranasally once to each subject according to the instructions by the manufacturer. During the administration of the solution the patient's head was bent backwards to prevent the extract from flowing into the pharynx. The subjects were divided into three groups according to the vaccine used. Group I comprised 16 asthmatics vac-

inated with Flupar-Vaccin. Group II comprised 13 asthmatics and 12 healthy subjects vaccinated with Victoria 3/75 and Group III comprised 10 asthmatics and 9 healthy subjects vaccinated with Texas 1/77. Group I included no healthy subjects because the use of killed vaccine is common, whereas the characteristics of live vaccines are less well known.

Serologic studies

Serum samples for determination of serologic responses to vaccination were obtained on the day of vaccination and 14 to 28 days later. Changes in serum antibody level were measured by a single radial haemolysis in gel (SRH test) (15). Radial haemolysis plates containing influenza A (Victoria 3/75) virus were used.

Symptom records

The subjects were seen by the investigators before and 2, 3 and 14 or 21 days after vaccination. A questionnaire was given to the patients at each visit and they were asked to write down any symptoms of rhinorrhoea, cough, sore throat, increased dyspnoea, fever, headache, muscle or joint pain and general discomfort. In connection with the visits the patients were asked about symptoms between visits as well as consumption of bronchodilators after the vaccinations. In addition, at each visit the patients underwent physical examination by the same investigator.

Pulmonary function

At each visit, airway resistance (Raw) and thoracic gas volume (TGV) were measured with a constant-volume body plethysmograph (3). The mean of four measurements is reported. The results are expressed as specific airway conductance (SGaw).

Statistical analysis

The significance of changes in SGaw compared with baseline values was evaluated using one-way analysis of variance for dependent groups.

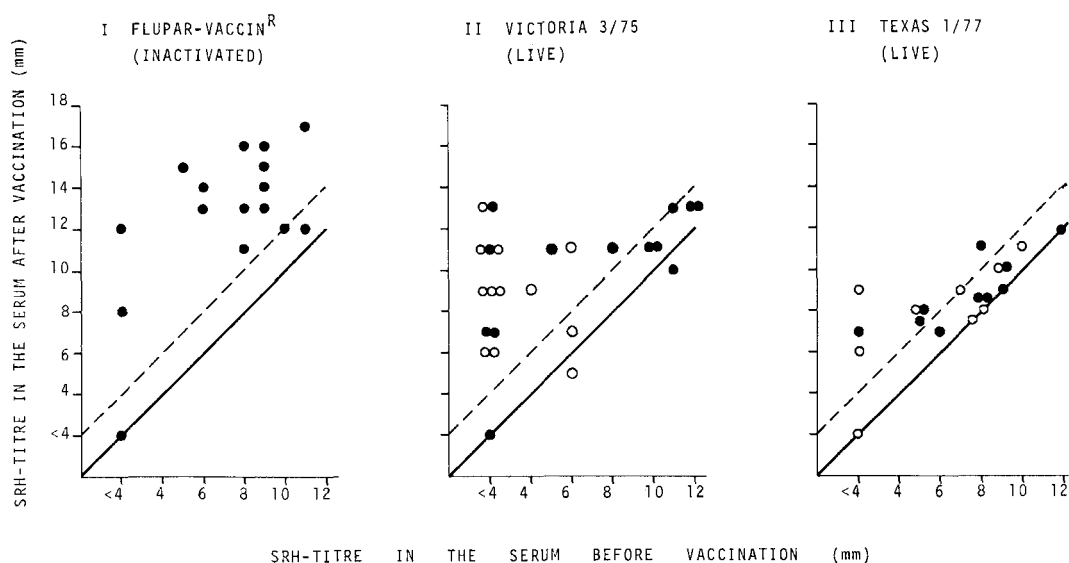


Fig. 1. Changes in serum antibody level to influenza A virus measured by the SRH test. ● = asthmatic patient; ○ = healthy subject. The line of identity is drawn. The dotted line represents the limit of a significant rise (2 mm).

RESULTS

Serologic studies

The serum antibody levels before vaccination varied between and within the three groups (Fig. 1). Group I contained only three asthmatics with no measurable antibodies, i.e. under 4 mm in the SRH test. However, 14 asthmatics displayed a significant rise (at least 2 mm) in serum antibody level after vaccination. In Group II there were five asthmatic patients and eight healthy subjects with no measurable antibodies before vaccination. In this group seven asthmatics and 10 healthy subjects displayed a significant rise in serum antibody level after vaccination. Group III contained only one asthmatic and three healthy subjects with no antibodies before vaccination. Nevertheless, four asthmatics and four healthy subjects displayed a significant rise in serum antibody level after vaccination.

Symptoms

There were no immediate adverse effects of vaccinations in any of the 60 subjects. In Group

I (Flupar-Vaccin) four of the asthmatics who showed a significant rise in the SRH test experienced symptoms. One week after vaccination one of these patients displayed a rise in the serum antibody level from under 4 mm to 12 mm and had rhinorrhoea, cough, sore throat, fever and increased dyspnoea. The remaining three patients had relatively high initial serum antibody levels and they experienced mild symptoms of rhinorrhoea, cough, sore throat and fever 2 to 3 days after vaccination. Two of these were affected with mild dyspnoea and other symptoms.

In Group II (Victoria 3/75), three of four asthmatics with no initial serum antibodies and with a significant rise in serum antibody level experienced mild symptoms of rhinorrhoea 2 days after vaccination. Two to 3 days after vaccination three of the eight healthy subjects with a rise in serum antibody level experienced symptoms of rhinorrhoea, cough, sore throat, headache, muscle or joint pain and general discomfort. Two to 3 days after vaccination two subjects reported fever. Altogether, four subjects had some kind of symptoms that could have been due to the vaccination.

In Group III (Texas 1/77), none of the three

subjects (one asthmatic and two healthy persons) with no initial serum antibodies and with a significant rise in serum antibody level experienced any symptoms after vaccination.

After the vaccinations there was no increase the consumption of bronchodilating drugs among the patients.

Pulmonary function

Specific airway conductance did not change from the baseline after the vaccination in those asthmatics and healthy subjects who showed a significant rise in antibody level in the SRH test. However, the difference between the baseline SGaw and the SGaw after 3 days of vaccination was almost significant in those asthma patients who received Flupar-Vaccin ($F = 5.874$, $P < 0.05$, see Table 1).

DISCUSSION

A significant rise in serum antibody level was observed in 87% of the asthmatics vaccinated with the killed vaccine and in 68% and in 42%

of the subjects vaccinated with the live attenuated vaccines, Victoria 3/75 and Texas 1/77, respectively. According to the results of the SRH test, the killed influenza vaccine seemed to be more effective in boosting antibody levels than the live vaccines. In this respect, however, the live vaccines were also effective in the subjects with low initial serum antibody levels.

The results demonstrated that a killed influenza vaccine, given subcutaneously to asthmatics, produced few, if any, adverse reactions. The side effects of live attenuated influenza vaccines administered by the intranasal route to asthmatics and healthy subjects were also minimal.

No increase in the need for bronchodilating drugs and no significant alterations in respiratory performance, as measured by changes in specific airway conductance, were found after vaccinations. The observations in previous studies have varied. Kiviloog (6) did not detect fever, increased dyspnoea or other side effects in asthmatics after vaccination with a killed influenza vaccine. Bell et al. (2) gave a killed influenza vaccine to children with chronic

Table 1

Mean values of specific airway conductance (SGaw) before and 2, 3 and 14 or 21 days after vaccination in asthmatics and healthy subjects with a significant rise in antibody level in SRH test

Vaccine used	No. subjects		SGaw (sec ⁻¹ cmH ₂ O ⁻¹) Days after vaccination				Significance
			0	2	3	14	
Flupar-Vaccin® (inactivated) asthmatics	14		0.186	0.165	0.153 ¹	0.186 ²	n.s. ($F = 2.449$)
		SD	0.07	0.06	0.06	0.1	
Victoria 3/75 (live) asthmatics	7		0.153	0.143	0.129	0.162	n.s. ($F = 1.816$)
		SD	0.04	0.03	0.04	0.04	
healthy subjects	10		0.218	0.310	0.222	0.216	n.s. ($F = 1.9$)
		SD	0.12	0.32	0.12	0.12	
Texas 1/77 (live) asthmatics	4		0.176	0.164	0.174	0.296	n.s. ($F = 1.579$)
		SD	0.11	0.09	0.07	0.27	
healthy subjects	4		0.242	0.208	0.199	0.232	n.s. ($F = 2.872$)
		SD	0.06	0.03	0.03	0.01	

SD = standard deviation; n.s. = non-significant.

¹ Nearly significant, $F = 5.874$; $P < 0.05$.

² SGaw was measured 21 days after vaccination.

asthma. They observed a significant increase in the need for bronchodilating drugs and a transient decrease in peak expiratory flow rate shortly after vaccination, although severe exacerbation of asthma was rare. They reported a $\geq$ four-fold rise in the serum haemagglutination-inhibition (HI) titre in 78% of the samples of sera examined. The serologic response and the early adverse pulmonary response were not correlated.

Storms et al. (14) used live vaccines and were unable to detect any significant changes in pulmonary function when the emphasis was placed on tests of small airway function. In their study, no significant symptoms were reported by either asthmatics or healthy control subjects after an intranasally administered attenuated live influenza vaccine. A four-fold rise in HI titre was seen in 10 of 20 asthmatics, eight of whom had a low antibody titre prior to immunization. However, Zeck et al. (16) also used live vaccine in patients with chronic lung disease and, 3 weeks after vaccination, observed more pronounced respiratory symptoms and a slight decrease in forced expiratory volume during 1 s (FEV_1). A direct effect of vaccination 3 weeks after the procedure seems unlikely, although delayed effects are possible. Only one of 21 healthy subjects and two of eight patients had seroconversion, as measured by the HI test. In the study by Rosenzweig et al. (13) serial spirometric measurements showed a small but consistent decrease in airflow at low lung volumes in healthy subjects after live attenuated influenza vaccination. HI antibodies increased at least four-fold in nine of 12 subjects whose initial titres were 1:8. These findings do not necessarily disagree with our results because we measured specific airway conductance, which mainly reflects changes in the large airways, whereas the results of Rosenzweig et al. (13) suggest dysfunction of the small airways. In addition, they found no relationship between the spirometric changes and seroconversions.

Perhaps tests designed to detect changes in small airways function would have shown harmful effects of vaccination in our study. However, in general, these tests include deep inspiration and forced expiration manoeuvres, which as

such can influence bronchomotor tone (10). Measurements of airway conductance do not require a deep inspiration, which is the reason for the choice of pulmonary function tests in our study.

The most important question concerning influenza vaccine and asthma is the clinical effect of vaccine on protection against respiratory infections caused by influenza virus. Although both the killed and the live vaccines were effective in boosting serum antibody levels in our study, we cannot say anything about the clinical effect of these vaccines. Instead, the emphasis was placed on another important question, namely: how is the influenza vaccine tolerated by asthma patients.

Although it remains unclear what would happen if these vaccinations were repeated, e.g. once a year, we conclude that both the killed and the live influenza vaccines were well tolerated by our adult patients with mild and moderately severe asthma and that they may be safe for asthmatics.

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