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Respiratory and humoral immune response to aerosol and intramuscular pertussis vaccine

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SUMMARY

Animal experiments have shown that respiratory administration of pertussis antigen induces a protective immune response. In this study pertussis antibody in human respiratory secretions was measured and the response to aerosol and intramuscular pertussis immunization investigated. Substantial increases in this antibody occurred after aerosol immunization but no changes were found in serum antibody. The reverse was observed after intramuscular immunization. Severe side effects are frequently seen after intramuscular pertussis vaccine in adults but not with aerosol immunization. The latter method may be of value for paediatric medical and nursing personnel exposed to the risk of pertussis infection.

INTRODUCTION

Dow (1940) showed that mice could be immunized by nasal instillation of *B. pertussis* antigens against respiratory challenge with the homologous organism. North & Anderson (1942) suggested that the immunity obtained by this technique was both a general (circulating) specific immunity and a local respiratory immunity in which non-specific factors played a part. Cooper (1952) reported that intranasal instillation of sublethal doses of live *B. pertussis* in mice appeared to induce a general and local immunity to challenge but pertussis vaccine given by this route produced only a local immunity to infection. Andersen (1952) suggested that larger doses of pertussis vaccine given intranasally would induce general as well as local respiratory immunity.

Immunoglobulins are known to be present in the respiratory secretions (Tomasi, Tan, Soloman & Prendergast, 1965) and are associated with specific antibody activity (Alford, Rossen, Butler & Kasel, 1967) which is contained almost entirely in the IgA fraction. Most investigations into respiratory immunization have been conducted with influenza vaccine and the results evaluated by epidemiological studies, respiratory secretory antibody response and by live challenge procedures (Mann *et al.* 1968; Waldman, Mann & Kasel, 1968; Kasel *et al.* 1969; Thomas, 1973). These studies have shown that specific protective antibodies can be induced in respiratory tract secretions by local application of antigens. Holt (1972) restated the suggestions made by North & Anderson thirty years earlier regarding immunity to whooping cough, i.e. there exists a general immunity (involving polymorphs and an opsonin) mobilized by the inflammatory response at the surface

of the respiratory mucous membrane and a local prophylactic immunity involving specific secretory IgA antibodies.

The investigations described in this paper are concerned with the variations in antibody concentrations in respiratory secretions after aerosol and intramuscular immunization with *B. pertussis* vaccine. Holt (1972) attempted to detect antibody to *B. pertussis* in respiratory secretions and sera from an aerosol-immunized Taiwan monkey, using a tissue culture adsorption-inhibition technique, and obtained very variable results. In the investigations described in this paper a radio-immunoassay technique was used to estimate antibody titre to *B. pertussis* in respiratory secretions.

MATERIALS AND METHODS

Vaccines

The intramuscular pertussis vaccine contained 4×10^{10} organisms/ml. (Burroughs Wellcome & Co., London). Respiratory pertussis vaccine was prepared by freeze-drying the intramuscular vaccine and was administered by means of a metered dose pressurized aerosol container (3 Ms Laboratories, Loughborough, England).

Respiratory secretions and sera

Respiratory secretions were obtained from eight human volunteers and examined for protein and IgA content as previously described (Thomas, 1973). Antibody titres in respiratory secretions were examined by passive haemagglutination (Cruickshank, Duguid & Swain, 1965) and a radio-immunoassay technique (Restall, Thomas & Pennant, 1973) adapted from the method described by Rosenthal, Hayashi & Notkins (1972). Since the IgA content of the nasal secretion samples (and hence the antibody concentrations) varied considerably from one sample to another a standardization procedure was adopted to make the samples comparable. The following formula was used $\frac{\text{counts/second} \times 100}{\text{IgA content}}$. Antibody titres in sera were assayed by the passive haemagglutination method, using the vaccine strain of *B. pertussis* to coat the sensitized sheep cells.

Immunization and sampling procedures

Six adult volunteers received 3 doses of 0·5 ml. of vaccine intramuscularly at monthly intervals. Serum and respiratory secretion samples were obtained before immunization and 3 weeks after the last dose of vaccine. Eight adult volunteers received one dose of aerosol vaccine inhaled via the nostrils (equivalent to 0·5 ml. of the vaccine given intramuscularly). Serum and respiratory secretion samples were obtained before immunization and 3 weeks after immunization.

RESULTS

Passive haemagglutination

Antibody was not detectable in any of the respiratory secretion samples by this method (nor by slide or tube agglutination) from the two groups of volunteers.

Table 1. *Serum antibody titres for* Bordetella pertussis *by passive haemagglutination method, in aerosol immunized and intramuscularly immunized volunteers*

Aerosol immunization			Intramuscular immunization		
	Reciprocal serum titres			Reciprocal serum titres	
Volunteer no.	Before immunization	After immunization	Volunteer no.	Before immunization	After immunization
1	4	4	9	2	16
2	8	8	10	8	32
3	4	4	11	8	128
4	4	2	12	4	32
5	8	8	13	8	16
6	2	4	14	4	32
7	4	4			
8	4	8			

Table 2. *Radio-immunoassay of antibody to* Bordetella pertussis *in respiratory secretions from aerosol immunized and intramuscularly immunized volunteers*

	Before immunization			After immunization			
Volunteer no.	IgA (μg./ml.)	c/s	c/s × 100 / IgA	IgA (μg./ml.)	c/s	c/s × 100 / IgA	Difference
1 aer*	59·3	338	570	28·0	307	1096	+526
2	50·5	265	525	28·0	213	760	+235
3	71·3	112	157	11·7	55	470	+313
4	39·7	225	567	15·5	208	1342	+775
5	25·0	236	944	20·7	266	1285	+341
6	28·0	96	343	8·8	87	989	+646
7	14·1	117	830	30·0	258	860	+ 30
8	18·2	145	797	20·7	280	1353	+556
						Average difference	+428
9 i.m.†	11·0	35	318	20·7	74	357	+39
10	11·0	83	754	15·5	134	864	+110
11	39·0	780	2000	11·7	259	2214	+214
12	49·0	170	346	31·5	96	305	−41
13	12·0	25	208	44·2	84	190	−18
14	27·0	91	337	20·7	69	333	−4
						Average difference	+50

* Aer = aerosol immunized. † i.m. = intramuscularly immunized.
c/s = counts/second.

Serum antibody to *B. pertussis* (Table 1) was present in all the samples from both groups. No significant changes were seen in the aerosol post-immunization serum titres while five of the six intramuscular post-immunization titres showed four-fold or greater increases.

Radio-immunoassay

B. pertussis antibody was present in all the respiratory secretion samples from both groups (Table 2). Significant changes were evident only in the aerosol post-immunization samples.

DISCUSSION

Serum antibody titres to *B. pertussis* are frequently relatively low in adults (Kendrick *et al.* 1969; Abbott, Preston & Mackay, 1971). Even after several intramuscular injections antibody titres do not rise remarkably (Abbott *et al.* 1971). The titres for the intramuscularly immunized volunteers (Table 1) are similar to those described by other workers. It is thus not surprising that increases in serum antibody titres were not recorded after aerosol immunization with only a third of the quantity of antigen given to the intramuscularly immunized group.

Detection of antibody to *B. pertussis* in respiratory secretions required the sensitivity of the radio-immunoassay technique. The results in Table 2 show a reversal of the situation compared with serum antibody. Substantial increases in antibody titre were observed in all of the samples from the aerosol-immunized volunteers, while the intramuscularly immunized group showed only small increases in titre in half of the samples. The numbers involved however are small and similar investigations in larger groups are obviously desirable to verify these observations.

Holt (1972) suggested that the antibody present in respiratory secretions acts by inhibiting adhesion of the organism to the cilia of the mucous membrane while the serum antibody has a bactericidal effect exerted when inflammatory changes in the mucous membrane permit transudation of serum proteins. Under these circumstances aerosol immunization (with the dose of antigen given in this investigation) appears to induce only the prophylactic protective mechanism since serum antibody concentrations were unchanged. Larger doses, up to the level of the intramuscular regimen, may however influence serum antibody.

Aerosol immunization against whooping cough cannot at this stage be recommended for use in infants but it may have a place in the protection of adults, especially those exposed to infection such as doctors and nursing staff concerned with paediatric infectious diseases. Outbreaks of whooping cough in adults are known to occur (Editorial, 1968). Intramuscular immunization of adults is often associated with severe side effects (as was observed during the course of this investigation). Aerosol administration of the *B. pertussis* antigens was not accompanied by any side effects in the eight volunteers (nor by the author who received four doses by this route). For adults aerosol immunization would be a much preferred method of protection.

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