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IMMUNOBIOLOGICAL PARALLELS IN STUDYING DRY AND LIQUID VACCINE AEROSOLS IN EXPERIMENTS ON ANIMALS

by

N. B. Yegorova, V. N. Yefremova, S. F. Fedyayev

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Н н	*Н н*	N, n	Э э	*Э э*	E, e
О о	*О о*	O, o	Ю ю	*Ю ю*	Yu, yu
П п	*П п*	P, p	Я я	*Я я*	Ya, ya

*ye initially, after vowels, and after ъ, ь; e elsewhere. When written as ë in Russian, transliterate as yë or ë. The use of diacritical marks is preferred, but such marks may be omitted when expediency dictates.

GREEK ALPHABET

Alpha	A	α	*α*	Nu	N	ν	
Beta	B	β		Xi	Ξ	ξ	
Gamma	Γ	γ		Omicron	O	ο	
Delta	Δ	δ		Pi	Π	π	
Epsilon	E	ε	*ϵ*	Rho	P	ρ	*ϱ*
Zeta	Z	ζ		Sigma	Σ	σ	ς
Eta	H	η		Tau	T	τ	
Theta	Θ	θ	*ϑ*	Upsilon	T	υ	
Iota	I	ι		Phi	Φ	φ	ϕ
Kappa	K	*κ*	κ *ϰ*	Chi	X	χ	
Lambda	Λ	λ		Psi	Ψ	ψ	
Mu	M	μ		Omega	Ω	ω	

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Russian	English
sin	sin
cos	cos
tg	tan
ctg	cot
sec	sec
cosec	csc
sh	sinh
ch	cosh
th	tanh
cth	coth
sch	sech
csch	csch
arc sin	$\sin^{-1}$
arc cos	$\cos^{-1}$
arc tg	$\tan^{-1}$
arc ctg	$\cot^{-1}$
arc sec	$\sec^{-1}$
arc cosec	$\csc^{-1}$
arc sh	$\sinh^{-1}$
arc ch	$\cosh^{-1}$
arc th	$\tanh^{-1}$
arc cth	$\coth^{-1}$
arc sch	sech^{-1}
arc csch	csch^{-1}
rot	curl
lg	log

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IMMUNOBIOLOGICAL PARALLELS IN STUDYING DRY AND LIQUID VACCINE AEROSOLS IN EXPERIMENTS ON ANIMALS

Report II. Sensitizing Action of Tetanus Toxoid Aerosol Depending on the Fractional-dispersive Composition

N. B. Yegorova, V. N. Yefremova and S. F. Fedyayev
Moscow Institute of Vaccines and Sera im. Mechnikova (Submitted 15 July 1970)

The immunization of animals with an aerosol of tetanus toxoid with adjuvant (complex typhoid antigen) causes the formation of considerable amounts of antitoxin in their blood regardless of the aggregate state and the fractional-dispersive composition (FDC). However, during the immunization of guinea pigs with liquid aerosol we noted a significant deviation of the animals, while vaccination with dry aerosol in a wide range of aspiration doses (1-7 SU [EC - serum units] did not cause the same thing (Yegorova et al., 1969).

The purpose of the present investigation was the study of the dependence of the harmful aftereffects of vaccination (one of the criteria of which is the degree of senstization of the organism) on the FDC of the vaccine aerosol.

It follows to state that the question of the degree of damaging action of aerosols depending on the FDC is not new.

It was studied by many investigators on models of bacterial and toxin aerosols (Druett et al., 1953; Goodlow et al., 1961, Lamanna, 1961, etc.). It was shown that the infecting and toxic action of aerosols increased with a decrease of particle size. As concerns the dependence of the sensitizing action of aerosols on particle size, then on this problem there is only the single report of Lamanna (1961). The latter testifies to the fact that sensitization by an aerosol of egg albumin, containing 77.4% particles up to 1.3 μm in size caused a lethal anaphylactic reaction in 80% of the guinea pigs, while sensitization of the animals with a 7 times greater dose of aerosol, made up primarily of larger particles (from 7.5 to 10.5 μm), caused a similar reaction all told in only 6.6% of the pigs. A study of this question relative to vaccine aerosols will make it possible to determine their most rational FDC, which will ensure not only a high degree of effectiveness, but also a safe vaccination.

In this report we will present materials pertaining to the intensity of anaphylactic action of aerosols of tetanus toxoid of different particle size and aggregate state. For resolving this question the guinea pigs were immunized one time and twice with dry and liquid aerosols, consisting of a mixture of tetanus toxoid and typhus antigen, and also of only the tetanus toxoid with a different FDC.

Two modes of dispersion of the preparation were selected for obtaining the liquid aerosol: in one case the vaccine was transferred into the aerosol under a pressure of 1.5 atm of compressed air, in the second under a pressure of 2.5 atm. The FDC of the aerosols obtained was determined with the help of a photoelectronic dispersion meter. During the dispersion of tetanus toxoid with typhus antigen both modes ensured the obtaining of aerosols which consisted of particles up to 8 μm, but based on the content of the individual fractions they differed significantly. (Table 1) In the first mode of dispersion particles up to 2 μm made up less than 50% by weight (average 45.7±1.7%) in the aerosol, particles larger than 4 μm - 15±1.4%. The aerosol which was obtained as a result of dis-

persion in the second mode differed considerably from the previous one by the greater content of particles up to 2 μm (63.5±2.5%) and by the lesser content of larger particles - a magnitude of 4-8 μm (2.2±0.46%). In the dry aerosol, created with the spraying of tetanus toxoid and typhus antigen, the particles from 2 to 4 μm comprised 1.5%. The fractions of particles from 8 to 25 μm (90.2%) were predominant in it. Furthermore a study was also made of the liquid aerosol of tetanus toxoid per se, which with the selected mode of spraying contained 35-40% of particles up to 2 μm.

Table 1. FDC of an aerosol of tetanus toxoid with adjuvant depending on the method of dispersion and the aggregate state

(1) Агрегатное состояние аэрозоля	(2) Группа	(3) Средняя весовая концентрация (в % ± m) частиц аэрозоля разных размеров (в мк)					
		0,5—2	2—4	4—8	8—13	13—25	25
(4) Жидкий	1-я	45,7±1,7	39,3±2,5	15,0±1,4			
	2-я	63,5±2,5	34,3±2,4	2,2±0,46			
Сухой (5)	3-я		1,5±0,09	8,3±0,88	19,1±1,1	56,6±0,95	14,6±1,57

(6) Достоверность разности (P) между группами:

1-й и 2-й	<0,05	>0,05	<0,05
1-й и 3-й		<0,05	>0,05
2-й и 3-й		<0,05	<0,05

Key: (1) Aggregate state of aerosol; (2) Group; (3) Average weight concentration (in %±m) of aerosol particles of different size (in μm); (4) Liquid; (5) Dry; (6) Reliability of difference (P) between groups:.

Immunization of the animals with liquid aerosol of tetanus toxoid with adjuvant was conducted in parallel tests, in which under different conditions the same amount of preparation was dispersed. The method of immunization, detailed characteristics of the vaccinating preparations and the appraisal of the anaphylactic reaction (which in our work is the test of the sensitizing action of the vaccine aerosol) are described in a previous report (Yegorova et al., 1969). In all the groups of animals immunization was carried out with doses which ensured a high level of antitoxin in the blood.

The titers of antitoxin in all the test animals (regardless of the aggregate state and FDC of the aerosol with which they were vaccinated) after the first inoculation fluctuated within the limits of 0.01-0.1 IU/ml, after the second immunization in the majority of the guinea pigs it was 40-50 IU/ml in the blood. At the same time the intensity of the anaphylactic reaction in the guinea pigs which were inoculated with the tetanus toxoid with adjuvant in the form of a liquid aerosol of different FDC turned out to be different (Table 2). In the group of guinea pigs immunized with the liquid aerosol with a lesser content of the fine fraction (45.7±1.7%) the index of intensity of anaphylactic shock comprised 33.2±13.3% after the first and 48.7±11.6% after the second inoculation. In animals immunized by an aerosol of the same preparation, but containing a larger number of particles up to 2 μm in size (63.5±2.5%), this index considerably exceeded those indicated above and was equal respectively to 72.7±9.1 and 79±7.5%.

Manifestation of severe and fatal anaphylactic shock in the first group of animals after the single and double immunization was recorded in a small number of animals (22±13.8% after the first and 27.2±9.5% after the second inoculation). In the second group of animals (vaccinated with an aerosol containing 63.5±2.5% particles up to 2 μm) a similar picture of shock in analogous periods of observation was noted in 66.6±9.7 and 65.5±9.5%, i.e., 2-3 times more often. It has to be pointed out that in this same group of animals along with the increase of intensity of anaphylactic reaction we noted their death following immunization. All told out of 69 guinea pigs vaccinated under these conditions 16 died from serohemorrhagic pneumonia. In the group being compared there were no deaths of animals following vaccination*. [* A detailed study of the morphological changes in the organs of animals which had been vaccinated with the aerosol of different FDC is the subject of a special report.]

Thus a direct correlation was revealed between the nature of the FDC of a vaccine aerosol and the harmful aftereffects of vaccination, the indices of which in this case were the severity of the anaphylactic reaction and the death of animals following immunization.

From the point of view of evaluating the role of the FDC of vaccine aerosols in the development of sensitization of an organism, and also the influence of the typhus antigen on the anaphylactic properties of the toxoid it was interesting to study the anaphylactic reaction in guinea pigs which had been immunized by a liquid aerosol of tetanus toxoid per se. In our tests such an aerosol contained 35-40% of particles up to 2 μm in size. The titers of antitoxin in the blood of the animals which had been immunized under these conditions fluctuated within the limits of 10-100 IU/ml, with the exception of 2 pigs, in which 1 IU/ml was contained in the blood. In the process of vaccination there were no deaths among the animals. We recorded the manifestations of a severe and fatal shock in the animals of this group after the first inoculation in 30±14.4% and after the second - in 27.3±13.3% of the cases (see Table 2). Consequently, based on the severity of the anaphylactic reaction to the aerosol the administration of liquid tetanus toxoid per se approximated the reaction in the animals which were immunized with an aerosol of the same preparation with adjuvant which contained less than 50% of particles up to 2 μm in size ($P > 0.05$). This testified to the fact that the addition of typhus antigen did not intensify the anaphylactic action of the tetanus toxoid.

During the study of the sensitizing effect of dry aerosol of tetanus toxoid with adjuvant the manifestations of the anaphylactic reaction in guinea pigs which had received a 1-7 SU dose of preparation were expressed to a considerable degree (Table 3). After the first immunization a severe reaction was noted only in one pig out of 16 (6.2±6.0%), after the second inoculation - in 20.8±8.3% of the animals. With a considerable increase of aspiration dose (to 20-25 SU) there was a tendency for intensification of the manifestations of anaphylactic shock. Especially demonstratively in this case the severity of the shock increased after the first

Table 2. Anaphylactic reaction in guinea pigs immunized with a liquid aerosol of tetanus toxoid with adjuvant and per se of different FDC

(1) Препарат	2 Группа	3 Характер ФДС аэрозоля	4 Аспирационная доза (в ЕС)	5 Интенсивность реакции после иммунизации: 6 первой — число животных в опыте	+++	++	+	±	9 индекс интенсивности шока (в %±m)	10 частота тяжелого и смертельного шока (в %±m)	7 второй — число животных в опыте	+++	++	+	±	9 индекс интенсивности шока (в %±m)	10 частота тяжелого и смертельного шока (в %±m)
11 Столбнячный анатоксин с адъювантом	1-я	13 Менее 50% частиц размером до 2 мк	0,4—5,0	9		2	1	4	2	33,2 ±13,3	22,2 ±13,8	22	3	3	8	6	2	48,7 ±11,6	27,2 ±9,5
	2-я	14 Более 50% частиц размером до 2 мк	0,4—6,0	24	8	8	6	2		72,7 ±9,1	66,6 ±9,7	29	17	2	8	2		79 ±7,5	65,5 ±9,5
12 Столбнячный анатоксин per se	3-я	15 Менее 50% частиц до 2 мк	8—15	10	3	—	4	3		52,5 ±15,7	30,0 ±14,4	11	1	2	5	3		52,3 ±14,2	27,3 ±13,4
		16 Достоверность разности (p) между группами	1-й и 2-й							<0,02	<0,02							<0,05	<0,01
			1-й и 3-й							>0,05	>0,05							>0,05	>0,05
			2-й и 3-й							<0,05	<0,05							<0,05	<0,05

Key: (1) Preparation; (2) Group; (3) Nature of FDC of aerosol; (4) Aspiration dose (in SU); (5) Intensity of reaction following immunization; (6) first; (7) second; (8) number of animals in test; (9) index of intensity of shock (in %±m); (10) frequency of lethal and severe shock (in %±m); (11) Tetanus toxoid with adjuvant; (12) Tetanus toxoid per se; (13) Less than 50% of particles up to 2 μm in size; (14) More than 50% of particles up to 2 μm in size; (15) Less than 50% of particles up to 2 μm; (16) Reliability of difference (p) between groups.

Table 3. Anaphylactic reaction in guinea pigs immunized with different doses of dry aerosol of tetanus toxoid with adjuvant

Группа	Аспирационная доза (в ЕС)	2 Интенсивность и тяжесть реакции после иммунизации: первой — число животных	+++	++	+	±	3 индекс интенсивности шока (в %±m)	4 частота тяжелого и смертельного шока (в %±m)	второй — число животных	+++	++	+	±	3 индекс интенсивности шока (в %±m)	4 частота тяжелого и смертельного шока (в %±m)
1-я	1—7	16	1	1	4	5	6	25±10,8	6,2±6,0	24	2	3	11	7	1	47,5±11,9	20,8±8,3
2-я	20—25	7		3		3		57,5±18,6	57,1±18,7	13	4	2	6		1	65±8,9	46,1±13,8
5 Достоверность разности (P) между группами								>0,05	<0,02							>0,05	>0,05

Key: (1) Group; (2) Aspiration dose (in SU); (3) Intensity and severity of reaction following immunization; (4) first; (5) second; (6) number of animals; (7) index of intensity of shock (in %±m); (8) frequency of severe and lethal shock (in %±m); (9) Reliability of difference (P) between groups.

inoculation (57.1% against 6.2%). In the case of aspiration of large doses of dry tetanus toxoid with adjuvant the death of animals was observed in 3-5 days following immunization (4 pigs out of the 23 vaccinated died from serohemorrhagic pneumonia).

In comparing the degree of sensitizing effect of dry and liquid aerosols with different FDC it can be noted that the intensity of the anaphylactic shock and the percentage of animals in which a severe and lethal shock was observed were virtually unique during the immunization with dry aerosol in doses of 1-7 SU and the liquid containing less than 50% of particles up to 2 μm in size. With the repeated increasing of the dose of dry aerosol the degree of the anaphylactic reaction was raised to the level noted during the immunization with liquid aerosol containing more than 50% of particles up to 2 μm in size. At the same time the intensity of the anaphylactic reaction in all the guinea pigs which were vaccinated by means of an aerosol was lower than in the case of the generally accepted subcutaneous method of immunization with sorbed tetanus toxoid. In the last case the index of intensity of shock during challenge with the same dose of tetanus toxoid was equal to 92.5-90.5% (Yegorova, 1968; Yegorova et al., 1969).

The investigations carried out make it possible to approach the solution of the problem of the rational composition of aerosol vaccines which would ensure a high degree of effectiveness with a minimal sensitizing effect.

CONCLUSIONS

1. The nature of the degree of dispersion of a vaccine aerosol of tetanus toxoid with adjuvant plays a leading role in the development of sensitization and the death of guinea pigs following single and double immunization.

2. The harmful aftereffects of vaccination are connected with the damaging action of an aerosol which contains more than 50% of particles up to 2 μm in size.

3. A rational selection of the FDC of a vaccine aerosol ensures a high level of antitoxin in the blood of guinea pigs

(10-100 IU/ml) without their death in the process of immunization and an insignificant degree of sensitization of the immediate type.

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