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(54) Title: NOVEL COMPOSITION

(57) Abstract

Novel vaccine compositions are provided comprising a hepatitis B antigen formulated with aluminium phosphate. The vaccine compositions may additionally contain an inactivated hepatitis A virus, aluminium hydroxide and formol. The combined hepatitis A and B vaccine formulations can, if desired, be administered to human subjects in a 2 dose regimen. Suitable formulations are illustrated.

Novel Composition

Vaccines for the prophylaxis of hepatitis A and hepatitis B infections are well known. For example the vaccine Engerix-B (Trade Mark) from SmithKline Beecham Biologicals is used to prevent Hepatitis B. This vaccine comprises hepatitis B surface antigen (specifically the 226 amino acid S- antigen described in Harford et al. in Postgraduate Medical Journal, 1987, 63 (Suppl. 2), 65-70) and is formulated using aluminium hydroxide as adjuvant. The vaccine Havrix (Trade Mark), also from SmithKline Beecham Biologicals can be used to prevent hepatitis A infections and is also formulated with aluminium hydroxide as adjuvant. This vaccine comprises an attenuated strain of the HM-175 Hepatitis A virus inactivated with formol (formaldehyde); see Andre et al [Prog Med. Virol. 1990, vol 37; p72-95]. The vaccine Twinrix (Trade Mark) which is a combination of the above hepatitis A and hepatitis B antigens may be used to protect against hepatitis A and hepatitis B simultaneously.

European patent 0 339 667 (Chemo Sero) describes the general concept of combining a hepatitis A antigen and a hepatitis B antigen to make a combination vaccine. In that specification it is stated that the adjuvant which is used is not critical: it must only be capable of enhancing the immune activity to a desired extent and not cause any side-effects. It is stated that aluminium gel may be used, in particular aluminium hydroxide gel and aluminium phosphate gel.

PCT application WO 93/24148 (SmithKline Beecham) describes the preparation of vaccines comprising hepatitis B surface antigen in which aluminium phosphate is used as adjuvant. Multivalent combination vaccines which may optionally contain a hepatitis A antigen, are described. The use of formol is not disclosed.

European Patent Number 0 633 784 (SmithKline Beecham) describes novel vaccine formulations comprising a hepatitis B component, particularly hepatitis B surface antigen, in combination with aluminium phosphate, and 3 de-O-acylated monophosphoryl lipid A.

It has now been surprisingly found that vaccines comprising hepatitis B and/or hepatitis A antigens give exceptionally good results if the vaccine is formulated in a specific manner.

Using vaccine formulations according to the invention, it is possible to administer the vaccines in a 2 dose, rather than a 3 dose, regimen.

In a first aspect of the invention, there is provided an aqueous vaccine composition comprising hepatitis B surface antigen which is formulated with aluminium phosphate as adjuvant, the concentration of aluminium phosphate being selected such that there is a ratio of 0.015-0.1mg aluminium phosphate per ug hepatitis B surface antigen.

Preferably the ratio is in the range 0.02 to 0.08mg aluminium phosphate per μg HBsAg.

In a further aspect of the invention an inactivated hepatitis A virus (HAV) may optionally be added to the formulation of the invention, providing a combined hepatitis A plus B vaccine which may be administered in a 2 dose schedule.

The hepatitis A antigen is preferably the HM-175 strain used in the commercial product Havrix (SmithKline Beecham Biologicals).

The concentration of hepatitis A antigen in the vaccine formulation of the invention is preferably about 720-2880 EU units per ml. For the definition of EU units see Andre et al (1990) loc cit.

The compositions of the invention which comprise HAV may additionally comprise aluminium hydroxide, the total amount of aluminium hydroxide generally being 0.05-0.10 mg per ml.

The total amount of aluminium salt per 0.5 or 1 ml dose is normally in the range 0.4-1.0mg.

In the vaccine composition of the invention it is advantageous to add formol (formaldehyde) such that the formol concentration is 10-200$_{\mu}$g per ml.

Preferably the formol concentration is about 20-160 $_{\mu}$g per ml.

Normally the hepatitis B antigen will be hepatitis B surface antigen (HBsAg). The preparation of Hepatitis B surface antigen (HBsAg) is well documented. See for example, Harford et al in Develop. Biol. Standard 54, page 125 (1983), Gregg et al in Biotechnology, 5, page 479 (1987), EP-A- 0 226 846, EP-A-0 299 108 and references therein.

As used herein the expression 'Hepatitis B surface antigen' or 'HBsAg' includes any HBsAg antigen or fragment thereof displaying the antigenicity of HBV surface antigen. It will be understood that in addition to the 226 amino acid sequence of the HBsAg S antigen (see Tiollais et al, Nature, 317, 489 (1985) and references therein) HBsAg as herein described may, if desired, contain all or part of a pre-S sequence as described in the above references and in EP-A- 0 278 940. HBsAg as herein described can also refer to variants, for example the 'escape mutant' described in WO 91/14703. In a further aspect the HBsAg may comprise a protein described as SL* in European Patent Application Number 0 414 374, that is to say a protein, the amino acid sequence of which consists of parts of the amino acid sequence of the hepatitis B virus large (L) protein (ad or ay subtype), characterised in that the amino acid sequence of the protein consists of either:

(a) residues 12 - 52, followed by residues 133 - 145, followed by residues 175 - 400 of the said L protein; or

(b) residue 12, followed by residues 14 - 52, followed by residues 133 - 145, followed by residues 175 - 400 of the said L protein.

HBsAg may also refer to polypeptides described in EP 0 198 474 or EP 0 304 578.

Normally the HBsAg will be in particle form. It may comprise S protein alone or may be as composite particles, for example (L*,S) wherein L* is as defined above and S denotes the S-protein of hepatitis B surface antigen.

Preferably the HBsAg will be adsorbed on aluminium phosphate as described in WO93/24148.

Preferably the hepatitis B antigen is HBsAg S-antigen as used in the commercial product Engerix-B (SmithKline Beecham Biologicals).

The vaccine formulations of the present invention will contain an immunoprotective quantity of the antigens and may be prepared by conventional techniques. Vaccine preparation is generally described in New Trends and Developments in Vaccines, edited by Voller et al., University Park Press, Baltimore, Maryland, U.S.A. 1978. Encapsulation within liposomes is described, for example, by Fullerton, U.S. Patent 4,235,877. Conjugation of proteins to macromolecules is disclosed, for example, by Likhite, U.S. Patent 4,372,945 and by Armor et al., U.S. Patent 4,474,757.

The vaccine compositions of the invention are preferably administered in a 0, 6 month schedule, that is to say a first dose at 0 months and a second dose at 6 months.

The vaccine compositions of the present invention are especially appropriate for adults and are also appropriate for administration to adolescents and children.

The following examples illustrate but do not limit the invention.

EXAMPLES

Example 1. Specific formulations

Specific formulations within the scope of the invention include the following:

a) A vaccine composition for administration to adults which comprises:
40$_{\mu}$g HBsAg
1440 EU HAV
0.85mg Aluminium salt (0.8mg aluminium phosphate plus 0.05mg aluminium hydroxide)
20$_{\mu}$g formol

in a 0.5ml dose

b) A vaccine composition for administration to adults which comprises:
40$_{\mu}$g HBsAg
1440 EU HAV
0.85mg Aluminium salt (0.8mg aluminium phosphate plus 0.05mg aluminium hydroxide)
20$_{\mu}$g formol

in a 1.0ml dose

c) A vaccine composition for administration to adolescents and/or children which comprises:
20$_{\mu}$g HBsAg
720 EU HAV
0.45mg Aluminium salt (0.4mg aluminium phosphate plus 0.05mg aluminium hydroxide)
80$_{\mu}$g formol

in a 1ml dose

d) A vaccine composition for administration to adolescents and/or children which comprises:

20$_{\mu}$g HBsAg

720 EU HAV

0.45mg Aluminium salt (0.4mg aluminium phosphate plus 0.05mg aluminium hydroxide)

80$_{\mu}$g formol

in a 0.5ml dose

Example 2: Study 'HAB 054'

2.1 One group of 47 healthy adult individuals was vaccinated with a vaccine composition (1ml volume) containing:

1440 EU HAV antigen

40$_{\mu}$g HBsAg (S-antigen)

0.8mg $AlPO_4$

0.05mg Aluminium hydroxide

20$_{\mu}$g/ml formol.

This is abbreviated in the tables below to '1440/NF40'

2.2 One group of 47 healthy adult individuals was vaccinated :

a) in one arm with a vaccine composition containing 40$_{\mu}$g of HBsAg formulated with 0.8mg $AlPO_4$, 20$_{\mu}$g/ml formol (hereinafter this composition is abbreviated to 'NF 40') in a 1ml dose; and

b) in the opposite arm with HAVRIX 1440 containing 1440 EU HAV antigen on 0.5mg Aluminium hydroxide and containing 20$_{\mu}$g/ml formol in a 1 ml dose.

The immunization schedule for HAB 054 was 0,6 (i.e. doses administered at month 0 and month 6).

The Hepatitis B serological results at months 2,6 and 7 (seroconversion (SC), seroprotection (SP) and geometric mean titre (GMT)) were unexpectedly high as compared to historical results obtained in another study (HBV NF 021) in which volunteers of the same age group were included.

Study HBV NF 021 (see Table 1) included three groups :

Group 1: Vaccinated with a formulation containing 40$_{\mu}$g of HBsAg on 0.5$_{\mu}$g $AlPO_4$ in 0.5ml volume without formol, schedule 0, 6 months (this is abbreviated in the table to NF 40$_{\mu}$g, 0, 6M)

Group 2: Vaccinated with a formulation containing 20$_{\mu}$g of HBsAg on 0.5$_{\mu}$g $AlPO_4$ in 0.5ml volume without formol, schedule 0, 6 months (this is abbreviated in the table to NF 20$_{\mu}$g, 0, 6M)

Group 3: Vaccinated with an Engerix B formulation (20$_{\mu}$g) using a classical 3 dose immunization schedule of 0, 1, 6 months (third row of data in Table 1)

Results

1) In study HBV NF 021, Hepatitis B serological results at month 7 in groups 1 and 2 were not satisfactory as compared to group 3 (lower SC, SP and GMT +/- 1/3 (500 to 600) of the levels obtained after three doses of Engerix -B (1500)).

2) In study HAB 054, the titres obtained after 2 doses of vaccine were of the same order of magnitude as those that would be obtained following three doses of Engerix B.

TABLE 1:

HBV - NF 021 STUDY

	Serconversion %			Seroprotection %			Geometric Mean Titre		
	Month 2	Month 7	Month 8	Month 2	Month 7	Month 8	Month 2	Month 7	Month 8
NF 40 µg (0.6 M)	50	98	98	16	93	96	5	883	683
NF 20 µg (0.6 M)	42	93	98	6	91	89	3	727	510
Engerix B 20 µg (0.1.6 M)	74	100	100	50	100	100	23	1579	1550

TABLE 2:

HAB 054 study
HAB 2-dose program in adults (0, 6month schedule)
N=94

HAB 054	Seroconversion (in %) Anti-HBs				
	month 2	month 6	month 7	month 9	month 12
HAV 1440/ NF40	75	85	100	100	100
NF 40 (Havrix 1440 in other arm)	80	87	96	97	97
HAV 1440/NF40:	contains 0.85mg Al salts			- 0.8 Al PO_4 20µg formol in 1 ml - 0.05 Al $(OH)_3$	
NF 40:	contains 0.8mg Al PO_4			- 20µg formol in 1 ml	

TABLE 3:

HAB 054 study
HAB 2-dose program in adults (0, 6month schedule)
N=94

HAB 054	Seroprotection (in %) Anti-HBs				
	month 2	month 6	month 7	month 9	month 12
HAV 1440/ NF40	36	62	100	100	100
NF 40 (Havrix 1440 in other arm)	33	57	96	97	90
HAV 1440/NF40 NF 40:	contains 0.85mg Al salts contains 0.8mg Al PO_4			- 0.8 Al PO_4 20µg formol in 1ml - 0.05 Al $(OH)_3$ - 20µg formol in 1ml	

TABLE 4:

HAB 054 study
HAB 2-dose program in adults (0, 6month schedule)
N=94

ANTI-HBs	geometric mean titre - anti-HBs				
	month 2	month 6	month 7	month 9	month 12
HAV 1440/ NF40	8.5	19	2286	1006	632
NF 40 (Havrix 1440 in other arm)	8.8	18	1865	1107	484
HAV 1440/NF40: NF 40:	contains 0.85mg Al salts contains 0.8mg Al PO_4			- 0.8 Al PO_4 20µg formol in 1ml - 0.05 Al$(OH)_3$ - 20µg formol in 1ml	

TABLE 5:

HAB 054 study
HAB 2-dose program in adults (0, 6month schedule)
N=94

HAB 054	S+ % - HAV					
	Day 15	month 1	month 6	month 7	month 9	month 12
HAV 1440/NF40	78	100	100	100	100	100
NF 40 (Havrix 1440 in other arm)	92	98	96	96	100	100
HAV 1440/NF40	contains 0.85mg Al salts		- 0.8 Al PO_4 20μg formol in 1ml - 0.05 Al $(OH)_3$			
NF 40:	contains 0.8mg $AlPO_4$		- 20μg formol in 1ml			

TABLE 6:

HAB 054 study
HAB 2-dose program in adults (0, 6month schedule)
N=94

ANTI-HAV	Geometric mean titre - Anti-HAV					
	day 15	month 1	month 6	month 7	month 9	month 12
HAV 1440/ NF40	337	803	324	10.393	7.408	4077
NF 40 (Havrix 1440 in other arm)	312	722	275	5.748	4.376	2882
HAV 1440/NF40:	contains 0.85mg Al salts		- 0.8 Al PO_4 20μg formol in 1ml - 0.05 Al $(OH)_3$			
NF 40:	contains 0.8mg Al PO_4		- 20μg formol in 1ml			

Example 3: Studies 'HAB 063, HAB071 and HAB 075'

HAB 2 dose program in adolescents aged 11- 18

3.1: Study HAB 063

Vaccine composition comprises:

720 HAV EU / 20$_{\mu}$g HBs Ag

0.25mg Al Salt

40$_{\mu}$g formol

In 0.5ml dose

Results are shown in Table 7.

TABLE 7:

HAB 063 study
HAB 2-dose program in adolescents aged 11 – 18years (0, 6month schedule)
N=52

Antibody	PI (m1)	PI (m2)	PI (m6)	PII(m7)
Anti-HAV				
S+ %	100	96.2	96.2	100
GMT (EL. U/ml)	504	318	199	6874
Anti-HBs				
S+ %	51.9	75	94.2	98.1
Seroprotection rate %	30.8	28.8	71.2	98.1
GMT (mIU/ml)	11	7	19	4110

3.2: Study HAB 071

Two groups were used in this study.

Vaccine composition group 1:

720 HAV EU / 20$_{\mu}$g HBs Ag

0.425mg Al Salt

40$_{\mu}$g formol

In 0.5ml dose and at a schedule of 0, 6 months

Vaccine composition group 2 (Twinrix ™ Junior):

360 HAV EU / 10 $_{\mu}$g HBs Ag
0,225 mg Al Salt
40 $_{\mu}$g formol

In 0.5ml dose and at a schedule of 0, 1, 6 months

TABLE 8:

HAB 071 study

High Dose HAB (Group 1)	PI (m1)	PI (M2)	PI (m6)	PI(m7)
Schedule 0, 6	n=50	n=48	n=49	n=49
Anti-HAV antibodies				
S+ %	100.0	100.0	100.0	100.0
GMT (EL. U/ml)	641	347	161	8151
Anti-HBs antibodies				
S+ %	74.0	70.8	85.7	100.0
Seroprotoection rate %	40.0	27.1	57.1	100.0
GMT (EL. U/ml)	12	9	17	4212
Twinrix ™ Junior (Group 2)	PI (m1)	PI (M2)	PI (M2)	PI(m7)
Schedule 0, 1, 6	n=49	n=48	n=48	n=48
Anti-HAV antibodies				
S+ %	95.9	100.0	97.9	100.0
GMT (EL. U/ml)	336	793	233	6394
Anti-HBs antibodies				
S+ %	61.2	97.9	100.0	100.0
Seroprotoection rate %	36.7	83.3	97.9	100.0
GMT (EL. U/ml)	12	36	202	6330

3.3 Study HAB 075

Two groups were used in this study.

Vaccine composition group 1 (Twinrix ™):

720 HAV EU / 20$_{\mu}$g HBs Ag

0.45mg Al Salt

80$_{\mu}$g formol

In 1ml dose and at a schedule of 0, 6 months

N = 67

Vaccine composition group 2:
1440 HAV EU / 40$_{\mu}$g HBs Ag
0.85mg Al Salt
80$_{\mu}$g formol

In 1ml dose and at a schedule of 0, 6 months
N = 55

TABLE 9:

HAB 075 study

Group			PI (m1)	PI (m2)	PI (m6)	PII(m7)
1						
	Anti-HAV	S+ %	97.0	95.5	100.0	100.0
		GMT	349	193	135	5646
	Anti-HBs	S+ %	62.7	74.6	95.5	100.0
		SP rate %	22.4	32.8	61.2	100.0
		GMT	6	6	13	3046
2						
	Anti-HAV	S+ %	100.0	100.0	100.0	100.0
		GMT	533	318	249	9565
	Anti-HBs	S+ %	67.3	85.5	94.5	100.0
		SP rate %	32.7	41.8	72.7	100.0
		GMT	9	9	26	3497

Example 4: Study 'HAB 084'

HAB 2 dose program in adolescents aged 12 – 15

Two groups were used in this study.

Vaccine composition group 1 (Twinrix ™):

720 HAV EU / 20$_{\mu}$g HBs Ag

0.45mg Al Salt

80$_{\mu}$g formol

In 1ml dose and at a schedule of 0, 6 months

Vaccine composition group 2 (Twinrix ™ Junior):
360 HAV EU / 10$_{\mu}$g HBs Ag
0.225mg Al Salt
40$_{\mu}$g formol

In 0.5ml dose and at a schedule of 0, 1, 6 months

TABLE 10:

HAB 084 study

Group			PI (m1)	PI (m2)	PI (m6)	PII(m7)
1			N=142	N=142	N=142	N=142
(0, 6)	**Anti-HAV**	S+ %	99,3	100	100	100
		GMT	348	244	178	5486
	Anti-HBs	S+ %	80,5	81	93	100
		SP rate %	43	38	68	97,9
		GMT	14	9	20	4948
2			PI (m1)	PII (m2)	PII (m6)	PIII(m7)
(0, 1, 6)			N=148	N=146	N=147	N=147
	Anti-HAV	S+ %	93.2	99.3	99.3	100
		GMT	227	548	298	4174
	Anti-HBs	S+ %	58.1	95.9	99.3	100
		SP rate %	29.1	85.6	98	100
		GMT	9	42	305	5054

Example 5: Study 'HAB 076'

HAB 2 dose program in children aged 1 – 11 years

Vaccine composition comprises:

720 HAV EU / 20$_{\mu}$g HBs Ag

0.45mg Al Salt

80$_{\mu}$g formol

In 1ml dose at a schedule of 0, 1 month

Results are shown in Table 11.

TABLE 11:

HAB 076 study

		PI (m1)	PI (m2)	PI (m6)	PII(m7)
		N=194	N=201	N=197	N=199
Anti-HAV	S+ %	99,5	98,5	98	100
	GMT	434	293	193	11543
Anti-HBs	S+ %	72,7	89,1	93,9	100
	SP rate %	30,3	47,3	78,2	98,5
	GMT	8	11	34	8056

SUMMARY

The clinical results shown in the above examples clearly indicate that a satisfactory immune response is obtained, both for hepatitis A and hepatitis B after the full schedule, that is by Month 7, in children, adolescents and adults.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An aqueous vaccine composition comprising hepatitis B surface antigen; an inactivated hepatitis A virus (HAV); and formol, in which there is 0.015 - 0.1 mg aluminium phosphate per μg hepatitis B surface antigen and 0.05 - 0.10 mg aluminium hydroxide per ml, wherein the vaccine is suitable for administration to human subjects in a two dose schedule.

2. A vaccine composition according to claim 1 in which the formol concentration is about 10 - 200 μg per ml.

3. A vaccine according to claim 1 or claim 2 in which the concentration of HAV is about 720 - 2880 EU per ml.

4. A vaccine composition according to claim 3 for administration to adults which comprises:
40 μg HBsAg
1440 EU HAV
0.85 mg Aluminium salt (0.8 mg aluminium phosphate plus 0.05 mg aluminium hydroxide)
20 μg formol
in a 0.5ml dose.

5. A vaccine composition according to claim 3 for administration to adults which comprises:
40 μg HBsAg
1440 EU HAV
0.85 mg Aluminium salt (0.8 mg aluminium phosphate plus 0.05 mg aluminium hydroxide)
20 μg formol
in a 1.0 ml dose.

6. A vaccine composition according to claim 3 for administration to adolescents and/or children which comprises:
20 μg HBsAg
720 EU HAV
0.45 mg Aluminium salt (0.4 mg aluminium phosphate plus 0.5 mg aluminium hydroxide)
80 μg formol
in a 1.0 ml dose.

7. A vaccine composition according to claim 3 for administration to adolescents and/or children which comprises:
20 μg HBsAg
720 EU HAV
0.45 mg Aluminium salt (0.4 mg aluminium phosphate plus 0.05 mg aluminium hydroxide)
80 μg formol
in a 0.5 ml dose.

8. A vaccine composition according to any preceding claim wherein the hepatitis B surface antigen is the S-antigen.

9. A vaccine composition according to any preceding claim in which the hepatitis A antigen is derived from the HM-175 strain.

10. A vaccine composition according to any preceding claim in which the two doses are administered at 0,6 (i.e. doses are administered at month 0 and month 6).

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