

Administration of Yellow Fever Vaccine in Patients with Egg Allergy

K. Rutkowski P.W. Ewan S.M. Nasser

Allergy Department, Cambridge University Hospital NHS Foundation Trust, Cambridge, UK

Key Words

Anaphylaxis · Desensitization · Egg allergy · Yellow fever vaccine

Abstract

Background: The population of large parts of Africa, South America and travellers to these areas are at risk of yellow fever (YF) with a 50% mortality risk. Yellow fever vaccine (YFV) propagated in hens' eggs confers protection in 95% of the vaccinated. The rate of anaphylaxis for YFV ranges from 0.42 to 1.8/100,000 doses with most cases considered to be due to egg allergy. Egg allergy is a contraindication for the YFV. Nevertheless, the potential fatal sequelae from YF give the incentive to protect everyone at risk irrespective of their allergic status. **Methods:** Six subjects who had had a recent reaction to egg and who were travelling to endemic areas (3 adults and 3 children) underwent skin prick tests (SPT) with undiluted YFV and egg extract. Intradermal tests for YFV were undertaken at a 1:10 dilution. In 4 egg-allergic patients with a positive SPT to YFV, a 7-step desensitization protocol was used. A 2-step (10 + 90%) protocol was used in the 2 subjects with a negative YFV SPT. Premedication was not administered. **Results:** All 6 patients were successfully vaccinated. Four patients completed desensitization: 1 developed mild local erythema at the injection site, 1 had fleeting generalized urticaria with local erythema/angioedema and 2 did not experience any adverse reactions. Patients who received YFV in 2 steps developed no adverse reactions. **Conclusions:** We describe the successful administration of YFV

in 6 egg-allergic patients. The Cambridge Allergy 7-step protocol allows for its safe administration in patients with positive SPT to YFV. A 2-step protocol can be used in patients with negative YFV SPT.

Copyright © 2013 S. Karger AG, Basel

More than 900 million people in tropical Africa and South America as well as nonvaccinated travellers entering endemic areas are at risk of yellow fever (YF), an acute flaviviral haemorrhagic fever transmitted by mosquitoes (genus *Aedes*) [1–3]. Each year, 200,000 new cases occur worldwide with a reported mortality rate of 20–50%. Up to 50% of patients with haemorrhagic complications die and there is no specific treatment. Morbidity and mortality increase steadily due to declining population immunity, deforestation, urbanization and climate change that alter the life cycle of the mosquitoes and stimulate their propagation [2, 4]. Mosquito control in jungle areas is impractical and hence eradication of the YF virus is impossible.

YF vaccine (YFV) is safe, usually affordable and in 95% of cases provides effective immunity within 1 week. It was developed by Theiler and Smith in 1937 and contains an attenuated live 17D YF virus propagated on embryonated hens' eggs [4–6]. Everyone in endemic areas should be immunised. In the developed world, vaccination is relevant for international travellers, military personnel and laboratory staff exposed to the YF virus. It is administered subcutaneously as a single 0.5-ml dose at least 10 days before travelling to an endemic area. The protective level

Table 1. Characteristic of desensitized patients

Patient n	Sex; age years	Reaction to egg, all patients diagnosed in childhood	Egg SPT wheal mm	Egg IgE kU/l	YFV SPT/IDT mm	Other (+) SPT	Indication for YFV	Co-morbidities
1	M; 22	Generalized urticaria, nausea, erythema, vomiting and abdominal pain	5	0.4	4/n.d.	cat	RAF	mild asthma
2	M; 28	Severe facial angioedema	7	n.d.	3/30	none	RAF	none
3	M; 35	Hand and facial oedema	7	1.36	3/12	grass, tree, shrub pollen	RAF	hay fever
4	M; 2	Nausea, vomiting, abdominal pain and generalized urticaria	4	n.d.	0/n.d.	none	travel	seborrhoeic dermatitis and eczema
5	F; 3	Oral pruritus and nausea	5	n.d.	0/n.d.	milk, peanut	travel	milk allergy
6	M; 8	Nausea, vomiting and abdominal pain	20	>100	6/n.d.	milk, peanut	travel	mild asthma, milk and peanut allergy

n.d. = Not done; RAF = Royal Air Force; travel = YFV required due to travel to endemic country.

of YF antibodies is 0.7 IU/ml (depending on the assay) [7]. Re-immunization is required every 10 years for patients at risk, although a single dose probably confers life-long protection [5, 6]. Many countries require an International Certificate of Vaccination from travellers or those arriving from YF-endemic areas [2]. Stamaril (Sanofi Pasteur, UK) is the only WHO-approved YFV available in the UK [3, 8, 9]. YF-VAX (Sanofi Pasteur, USA) is used in the USA [10, 11].

Worldwide, 500 million YFV doses have been administered over the last 7 decades, and in the USA, almost a million doses annually [10]. Analysis of the US Vaccine Adverse Events Reporting System (VAERS) confirms the good safety profile of the YFV. The anaphylaxis rate was 0.42/100,000 doses of YFV alone (1 in 238,000) and 0.8/100,000 (1 in 131,000) when YFV was co-administered with other vaccines. By comparison, the frequency of possible and probable anaphylaxis after MMR vaccination was 0.17/100,000 doses (1 in 587,000) [10, 12–15]. A more recent analysis by VAERS (2000–2006) reveals an increased frequency of anaphylaxis for YFV of 1.8/100,000, although this higher figure may be partially due to increased awareness and reporting [14]. Overall severe hypersensitivity reactions are rare and are considered to be caused mainly by egg protein. Historically, therefore, allergy to egg has been a contraindication for YFV. Potential fatal sequelae of YF, however, make it crucial to protect everyone at risk irrespective of their allergic status.

We describe 7-step desensitization and a 2-step (split dose) protocol for the administration of YFV in 6 egg-allergic subjects.

Methods

Patients

We studied 6 egg-allergic patients requiring YFV who were referred to the University of Cambridge Foundation Hospital Allergy Department between 2006 and 2012. Three British Royal Air Force servicemen aged 22–35 years required vaccination prior to deployment to YF-endemic countries. Three children aged 2–8 years with a history of egg allergy were travelling to their parents' countries of origin (Angola and Cote d'Ivoire). Egg allergy had been diagnosed in early childhood in all subjects (table 1).

Clinical Features

Subjects 1–4 reported unequivocal episodes of acute urticaria and facial angioedema within the preceding 3–9 months with acute abdominal pain (patient 1 and 4) after eating or handling lightly cooked egg. Subject 5 developed intraoral pruritus and nausea after consuming a lightly cooked omelette. Subject 6 experienced several episodes of delayed abdominal pain with nausea and vomiting 3–4 h after eating baked egg. All patients were tolerant of chicken meat and gelatin (table 1).

Methods

Diagnostic work-up included a detailed clinical history, skin prick tests (SPT) with undiluted YFV (Stamaril, Sanofi Pasteur), egg extract (10,000 DU/ml; Allergy Therapeutics, Worthing, UK), 0.9% saline as negative and histamine (10 mg/ml; ALK Abelló, Horsholm, Denmark) as a positive control. Intradermal tests

Table 2. YFV-specific desensitization protocols in egg allergy and a universal US protocol for patients with hypersensitivity to vaccines

YFV protocols									Universal vaccine protocol	
Cambridge interval 30 min no premedication		Muñoz-Cano [12] interval 30 min no premedication		Charpin [23] interval 30 min high-dose premedication					US protocol interval 15–60 min no premedication	
0.1 ml	1:1,000	0.05 ml	1:10	Day 1	MTP 7 a.m.	9 a.m.	0.1 ml	1:1,000	0.05 ml	1:10
0.1 ml	1:100	0.15 ml	neat			9.30 a.m.	0.1 ml	1:100	0.05 ml	neat
0.1 ml	1:10	0.30 ml	neat			10 a.m.	0.1 ml	1:10	0.1 ml	neat
0.05 ml	neat			Day 9	MTP 8 p.m.	–	–	–	0.15 ml	neat
0.1 ml	neat			Day 10	MTP 7 a.m.	8.30 a.m.	0.1 ml	1:10	0.2 ml	neat
0.15 ml	neat				MTP 8 p.m.	9 a.m.	0.1 ml	neat		
0.2 ml	neat			Day 11	MTP 7 a.m.	8.30 a.m.	0.1 ml	1:10		
					MTP 8 p.m.	9 a.m.	0.2 ml	neat		
				Day 12	MTP 7 a.m.	8.30 a.m.	0.1 ml	neat		
						9 a.m.	0.2 ml	neat		

MTP = Methylprednisolone 20 mg i.m.

(IDT) were performed with a 1:10 dilution of Stamaril YFV in 0.9% sodium chloride.

SPT was considered positive if the wheal diameter was at least 3 mm greater than the negative control. IDTs were considered positive if at 20 min the wheal extended beyond the outline of the original 6-mm bleb and erythema developed, according to the recommendations of the European Society of Contact Dermatitis and the European Academy of Allergy and Clinical Immunology [16, 17].

IDT were not undertaken in young children as they were deemed unnecessarily traumatic. Evidence of specific immunoglobulin E (sIgE) to egg was required on either SPT or ImmunoCap but not necessarily both. The same principle was applied to demonstrate sIgE to YFV – positive SPT or IDT but not necessarily both.

Although there is no evidence that YFV or egg SPT predict clinical reactivity after YFV administration, SPT was undertaken on the grounds of safety.

Cambridge Desensitization Protocol

The Cambridge desensitization protocol was used in egg and YFV SPT-positive patients. Seven YFV doses are administered at 30 min intervals (0.1 ml 1:1,000, 0.1 ml 1:100, 0.1 ml 1:10 and then 0.05, 0.1, 0.15 and 0.2 ml of undiluted vaccine to give a total dose of 0.5 ml (the full recommended dose). No premedication was used and the final dose was followed by a 2-hour observation period (table 2).

Two-Step Protocol

Patients with SPT positive to egg but negative to YFV received the vaccine in a 2-step protocol. Initially, 10% of the dose was administered. The remainder of the dose was given after a 30-min observation period if no adverse reaction occurred. Thereafter, patients remained under observation for 2 h (table 2).

Both protocols were undertaken under close medical supervision with resuscitation facilities available. Prior to administration of the vaccine, all patients were well with no pre-existing urticaria/angioedema and they were not taking anti-allergic medication or β -blockers. Written informed consent was obtained from all adult subjects and parental consent was obtained for all children.

Results

Investigations

Skin Tests

All patients had a positive SPT to egg and 4 patients had a positive SPT to YFV. IDT for YFV were undertaken in patients 2 and 3 and were positive at 30 and 12 mm, respectively.

Serology

sIgE to egg was positive in all 3 patients in whom it was measured and ranged from 0.4 to >100 kU/l in the patient with delayed gastro-intestinal reactions to baked egg. It was not measured in any of the 3 patients who had positive SPT to egg.

Outcome of Desensitization

All 6 subjects with egg allergy were successfully vaccinated with YFV. Four patients with a positive SPT to egg and to YFV successfully completed a 7-step desensitization protocol. Patient 1 developed mild local erythema at the injection site to doses 4–6. Patient 2 experienced fleeting generalized urticaria to doses 1–3 and local erythema/angioedema at the injection site after the 4th–7th doses and lasting 6 h. Patients 3 and 6 did not experience adverse reactions during desensitization.

Patients 4 and 5, both with a negative SPT to YFV, were given 1/10th dose of YFV followed by 9/10ths as a split dose with no adverse reaction.

Table 3. Comparison of the two most commonly used YFVs [5, 7, 9]

YFV	Potential allergens
Stamaril (Sanofi Pasteur, UK)	egg protein: 0.067–0.306 µg/0.5 ml dose (mean 0.105 µg/0.5 ml) ^a chicken protein sorbitol E420 lactose no gelatin powder vial: chlorobutyl stopper, aluminium cap solvent pre-filled syringe: halobutyl plunger needle-shield: natural rubber or polyisoprene
YF-VAX (Sanofi Pasteur, USA)	egg content – unknown ^a chicken protein sorbitol gelatin 7,500 µg/dose solvent vial: latex stopper powder vial: no latex

^a Personal communication: Sanofi Pasteur UK (13/5/2012) and Sanofi Pasteur USA (14/5/2012).

Discussion

Almost 1 billion people are at risk of YF [1, 2]. Up to 2.5% of children and 0.1% of adults are affected by egg allergy according to European and US studies [18, 19]. There have been studies on food (including egg) allergy in South Africa [20], but to the best of our knowledge there are no published data on the prevalence of egg allergy in African countries with a high risk of YF virus transmission (e.g. Côte d'Ivoire, Burundi and Angola). Sensitization to egg in South American children ranges greatly, from 5 to 30% [21]. Published evidence on administration of the YFV in this group of patients is surprisingly limited. It is likely that many are denied the vaccine due to egg allergy [22].

Only 2 single case reports of successful desensitization to YFV with two different protocols have been published. Charpin et al. [23] treated a 30-year-old male with a history of anaphylaxis to egg, grass-pollen-allergic rhinoconjunctivitis and chronic urticaria. SPT and RAST to egg were positive. IDT for YFV were positive at 1:1, 1:10, 1:100 and 1:1,000. The patient developed a delayed reaction to 1:1 IDT at 6 h (generalized malaise; no other details given) treated with 20 mg i.m. cortisone. Their protocol was complex and time-consuming with large doses of i.m. methylprednisolone premedication and required a 3-day period of hospitalization between days 9 and 12 of the protocol (table 2).

Munoz-Cano et al. [12] undertook desensitization to YFV in a 42-year-old patient with angioedema and rhinitis after ingestion of cooked egg as well as oral symptoms to raw egg (table 3). SPT and sIgE were positive to egg. SPT and IDT were positive to 1:100 YFV.

The American Academy of Paediatrics published a generic protocol for the administration of vaccines for patients with a history of hypersensitivity reactions (table 3) which is included in the YF-VAX package insert [5, 11]. However, there are no cases in the literature of its application in egg-allergic patients requiring YFV.

There have been no large-scale studies on YFV safety in egg allergy. Roukens et al. [22] investigated the serological response to 0.1 ml YFV administered intradermally in 7 egg-allergic patients. All the patients developed large wheals to YFV IDT (13–35 mm vs. control 0–7 mm) with no systemic symptoms and further vaccination was not undertaken as per Dutch guidelines. Interestingly, this intradermal dose (20% of the recommended dose) induced an adequate protective immune response (average 5.3 IU/ml). However, the longevity of response was not reported and the study was not adequately powered and larger cohorts are needed to validate this approach.

Three commonly administered vaccines are contraindicated in egg allergy: trivalent influenza (TIV), YFV (2 preparations in use; table 3) and tick-borne encephalitis vaccine [5, 9, 18, 24]. There is, however, emerging evidence that TIV with an ovalbumin content below 0.6 µg/0.5 ml can be administered safely to patients allergic to egg as a single or split dose (10 + 90%). Routine SPT to vaccine are not necessary unless there is a strong suspicion of reaction to the vaccine itself or severe anaphylaxis to egg [7, 25–27].

Large studies, similar to those on TIV, are needed in egg-allergic patients requiring YFV. In addition, as in the case of influenza vaccine, multiple-step desensitization should be compared with a 2-step protocol (10 + 90%). Data are emerging on the safe administration of influenza vaccine with an ovalbumin content much higher than YFV in egg-allergic subjects [28]. Therefore, it should be possible to administer Stamaril (Sanofi Pasteur) with a mean content of 0.105 µg/dose in a single dose without skin testing, but due to the small number of patients we have not been able to test this hypothesis. Moreover, we are unable to explain why 4/6 patients in our study had positive SPT to YFV and yet it is rare to find a single egg-allergic subject with a positive SPT to TIV. There are also no data on whether successful desensitization results in long-term tolerance or needs to be repeated if a YFV booster is required.

A history of egg allergy appears to be the most important contraindication for YFV and most cases of anaphy-

laxis to vaccination occur in patients with hens' egg allergy. Other allergens also need to be considered, however (table 3).

According to the manufacturer, YFV may contain residual chicken protein [5, 12]. Kelso et al. [29] successfully followed the universal US protocol and administered YFV to 3 egg-tolerant patients allergic to avian meat with positive SPT to YFV (2 SPT, 1 IDT), turkey, chicken, dove and quail. Immunoblot revealed IgE bands to proteins of similar weight in different avian but none to egg or YFV [29]. It is well known that severe allergy to chicken meat occurs in the absence of sensitization to egg or chicken feathers. Four distinct allergens were identified of size 5, 10, 25 and 40 kDa. They were different to the 70-kDa serum chicken albumin/egg yolk alpha-livetin (Gal d 5) responsible for the bird-egg syndrome [18, 30]. It is uncertain and perhaps unlikely that YFV contains

chicken meat protein and the relationship between avian meat allergy and YFV requires further study.

YF-VAX, but not Stamaril, contains a significant amount of gelatin used as a stabiliser (table 3). Gelatin has been implicated in many cases of anaphylaxis to MMR, varicella and Japanese encephalitis vaccines. Bovine and porcine gelatins are highly cross-reactive, but, interestingly, oral tolerance does not exclude an allergic reaction to injectable gelatin in a vaccine [7, 13, 31].

Conclusion

We have described two protocols allowing for the safe administration of YFV in egg-allergic patients: 7-step desensitization in patients with positive SPT to YFV and a more rapid, 2-step protocol in those with negative SPT to YFV.

References

- Weir E, Haider S: Yellow fever: readily preventable but difficult to treat. *CMAJ* 2004; 170:1909–1910.
- Yellow fever fact sheet. WHO www.who.int (accessed July 21, 2012).
- UK Health Protection Agency. Yellow Fever Fact Sheet. www.nathnac.org/pro/factsheets/pdfs/YF%20March%202010.pdf (accessed July 21, 2012).
- Domingo C, Niedrig M: Safety of 17D derived yellow fever vaccines. *Expert Opin Drug Saf* 2009;8:211–221.
- Sanofi Pasteur. YF-VAX Yellow fever vaccine package insert, 2010.
- Poland JD, Calisher CH, Monath TP, Downs WG, Murphy K: Persistence of neutralizing antibody 30–35 years after immunization with 17D yellow fever vaccine. *Bull World Health Organ* 1981;59:895–900.
- Kelso JM, Greenhawt MJ, Li TJ, Nicklas RA, Bernstein DI, Blessing-Moore J, et al: Adverse Reactions to Vaccines Practice Parameter 2012. *J Allergy Clin Immunol* 2012;130:25–43.
- Salisbury D, Ramsay M, Noakes K (eds): Yellow fever; in: *Immunisation Against Infectious Disease*. UK Department of Health Green Book, updated March 26, 2012, pp 443–454 (accessed July 13, 2012).
- Sanofi Pasteur MSD Ltd: Stamaril package insert, 2010.
- Khromava AY, Eidex RB, Weld LH, Kohl KS, Bradshaw RD, Chen RT, et al: Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. *Vaccine* 2005;23:3256–3263.
- Active immunization; in Pickering LK, Baker CJ, Long SS, McMillan JA (eds): *Red Book: 2006 Report of the Committee on Infectious Diseases*, ed 27. Elk Grove Village, American Academy of Pediatrics, 2006, pp 446–448.
- Munoz-Cano R, Sanchez-Lopez J, Bartra J, Valero A: Yellow fever vaccine and egg allergy: really a problem? *Allergy* 2010;65:533–534.
- Kelso JM: Adverse reactions to vaccines for infectious diseases; in Adkinson NF, Bochner BS, Busse WW, Holgate ST, Lemanske RF, Simons FER (eds): *Middleton's Allergy: Principles and Practice*, ed 7. Philadelphia, Mosby, 2008, pp 1189–1204.
- Lindsey NP, Schroeder BA, Miller ER, Braun MM, Hinckley AF, Marano N, et al: Adverse event reports following yellow fever vaccination. *Vaccine* 2008;26:6077–6082.
- Kelso JM, Mootrey GT, Tsai TF: Anaphylaxis from yellow fever vaccine. *J Allergy Clin Immunol* 1999;103:698–701.
- Brockow K, Romano A, Blanca M, Ring J, Pichler W, Demoly P: General considerations for skin test procedures in the diagnosis of drug hypersensitivity. *Allergy* 2002;57:45–51.
- Barboud A, Goncalo M, Bruynzeel D, Bircher A: Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reaction. *Contact Derm* 2001;45:321–328.
- Clark AT, Skypala I, Leech SC, Ewan PW, Dugué P, Brathwaite N, et al: British Society for Allergy and Clinical Immunology guidelines for the management of egg allergy. *Clin Exp Allergy* 2010;40:1116–1129.
- Caubet JC, Kondo Y, Urisu A, Nowak-Węgrzyn A: Molecular diagnosis of egg allergy. *Curr Opin Allergy Clin Immunol* 2011;11:210–215.
- Poel L, Chen J, Penagos M: Food allergy epidemics – is it only a Western phenomenon? *Curr Allergy Clin Immunol* 2009;22:121–126.
- Kung SJ: Food allergy in sub-Saharan Africa. *J Allergy Ther* 2011;S3:002. DOI:10.4172/2155-6121.S3-002.
- Roukens AH, Vossen AC, van Dissel JT, Visser LG: Reduced intradermal test dose of yellow fever vaccine induces protective immunity in individuals with egg allergy. *Vaccine* 2009;27:2408–2409.
- Charpin J, Vervloet D, Birnbaum J, Tafforeau M, Sentissi S: Yellow fever: desensitization to an anti-amaril 17D vaccine performed on a patient with anaphylaxis to eggs. *Bull Acad Natl Med* 1987;171:1001–1005.
- Fritsch PJ, Helbling A, Ballmer-Weber BK: Vaccine hypersensitivity – update and overview. *Swiss Med Wkly* 2010;140:238–246.
- James JM, Zeiger RS, Lester MR, Fasano MB, Gern JE, Mansfield LE, et al: Safe administration of influenza vaccine to patients with egg allergy. *J Pediatr* 1998;133:624–628.
- Gagnon R, Primeau MN, Des Roches A, Lemire C, Kagan R, Carr S, et al: Safe vaccination of patients with egg allergy with an adjuvanted pandemic H1N1 vaccine. *J Allergy Clin Immunol* 2010;126:317–323.
- Greenhawt MJ, Chernin AS, Howe L, Li JT, Sanders G: The safety of the H1N1 influenza A vaccine in egg allergic individuals. *Ann Allergy Asthma Immunol* 2010;105:387–393.
- Kelso JM: Administration of influenza vaccines to patients with egg allergy. *J Allergy Clin Immunol* 2010;125:800–802.
- Kelso JM, Cockrell GE, Helm RM, Burks AW: Common allergens in avian meats. *J Allergy Clin Immunol* 1999;104:202–204.
- Liccardi G, Szépfalusi Z, Noschese P, Nentwich I, D'Amato M, D'Amato G: Allergy to chicken meat without sensitization to egg proteins: a case report. *J Allergy Clin Immunol* 1997;100:577–579.
- Sakaguchi M, Nakayama T, Inoue S: Food allergy to gelatin in children with systemic immediate-type reactions, including anaphylaxis, to vaccines. *J Allergy Clin Immunol* 1996; 98:1058–1061.