Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Risk of bursitis and other injuries and dysfunctions of the shoulder following vaccinations

L.H. Martín Arias [a], R. Sanz Fadrique [a,*], M. Sáinz Gil [a], M.E. Salgueiro-Vazquez [b]

[a] Centre for Drug Surveillance (CESME), Valladolid University, Spain
[b] Area Pharmacology, Departament of Medicine, Oviedo University, Spain

ARTICLE INFO

Article history:
Received 6 October 2016
Received in revised form 12 July 2017
Accepted 17 July 2017
Available online xxxx

Keywords:
Immunization
Vaccination
Vaccine
Shoulder injury
Deltoid bursitis
Frozen shoulder

ABSTRACT

While vaccination injection site adverse reactions are usually mild and transient in nature, several cases of bursitis and other shoulder injuries have been reported in the medical literature. However, these lesions are not included in vaccine label inserts.

To identify the characteristics of post-vaccination shoulder injuries and those of patients and involved vaccines, as well as their potential causes, a systematic review of the cases of vaccination-related bursitis and other shoulder injuries reported in the literature and notified to the Spanish Pharmacovigilance System database (FEDRA) have been conducted.

We found 45 cases of bursitis and other shoulder injuries that appeared following the vaccine intramuscular injection given into the deltoid muscle (37 from the systematic review of the literature, and 8 from the scrutiny in the Spanish Pharmacovigilance System database, FEDRA). All the patients were adult, 71.1% females, with a mean and median age of 53.6 years (range: 22–89). The most frequently involved vaccines were influenza and pneumococcal vaccines, respectively; followed by diphtheria-tetanus-pertussis, diphtheria-tetanus toxoid, human papillomavirus, and hepatitis A vaccines. The most frequent shoulder lesion was bursitis. Most of patients required medical care due to severe local pain and arm mobility restriction. In a majority of cases, symptoms started 48 h post vaccination.

Subdeltoid or subacromial bursitis and other shoulder lesions may be more common than suspected. Such lesions predominantly affect women. The cause may be related to antigens or adjuvants contained in the vaccines that would trigger an immune or inflammatory response. However, they are more likely to be the consequence of a poor injection technique (site, angle, needle size, and failure to take into account patient's characteristics, i. e., sex, body weight, and physical constitution). Therefore, vaccination-related shoulder injuries would be amenable to prevention.

Contents

1. Introduction

The painful shoulder is one of the most common chief complaints in the primary medical care setting. The annual incidence

* Corresponding author at: School of Medicine, C/Ramón y Cajal, 7, 45005 Valladolid, Spain.
E-mail address: mrsanzfadrique@redfarma.org (R. Sanz Fadrique).

http://dx.doi.org/10.1016/j.vaccine.2017.07.055
0264-410X/

among people aged 40–45 years is estimated to be 1–2%, while this figure may be as high as 26% in those aged over 65 years [1]. The shoulder complaint is associated with some occupational and sport activities and a number of traumatic and medical conditions. However, it is often associated with vaccination as well.

Most vaccines are given into the deltoid muscle, where a number of bone structures, joints, tendons and bursae (i. e. subacromial and subdeltoid) converge. Injection site pain, erythema, inflammation and induration are frequent post-vaccination adverse effects, though they are most often mild and transient in nature [2–4]. Shoulder injuries involving deeper areas located far from the injection site are rare [5], and its relationship with vaccination is unclear so far. The occurrence of these complications may be related to an inappropriate vaccine administration technique [6–9]. Of note, autoimmune mechanisms mediated by both viral antigens and vaccine adjuvants/preservatives [10,11], as well as the individual patient's physical characteristics [12] may be additional contributing factors.

After the recent reporting of several notifications on suspected shoulder injuries and dysfunctions potentially caused by the intramuscular administration of vaccines to the Spanish System for Pharmacovigilance of Human Use Drugs (SEFVH), the present study was designed to characterise these adverse reactions. To this aim, we conducted a systematic review of both the cases described in the literature and those reported to the SEFVH.

2. Methods and materials

We conducted a search in the FEDRA (Adverse Reaction Data of the Spanish Pharmacovigilance System) database of the SEFVH (Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano) based on the following criteria: (1) spontaneous notifications, which excluded notifications from studies reported in the medical literature; (2) involvement of a vaccine as the suspected drug; and (3) occurrence of an adverse reaction coded in the MedDRA (Medical Dictionary for Regulatory Activities) [13] terminology as "*HLGT-Synovial and bursal disorders*" *OR "Tendon, ligament and cartilage disorders*". The search period covered from 1982 to 31-12-2015.

Also, we conducted a systematic review of the articles published in the literature involving shoulder injuries or dysfunctions, in which the suspected cause was vaccination into the deltoid muscle. The literature search was based on the following web sites: PubMed, Embase, and Web of Science (WoS), targeting all articles published through 30-May-2016. The following search strategy was used: (*shoulder injury OR shoulder pain OR shoulder dysfunction OR deltoid bursitis OR adhesive capsulitis OR frozen shoulder) AND (immunization OR vaccin∗).* The search was not restricted by language or animal species, and the period was unrestricted.

We excluded the cases in which the injury or dysfunction involved a body part other than the shoulder, those with bilateral involvement (i. e. both shoulders), and those in which previous traumas, dysfunctions or other conditions of the shoulder had been diagnosed before vaccination or had been caused by a systemic or underlying disease, such as neuropathy, plexopathy or radiculopathy, or by traumatic or surgical causes. Three cases were an exception, because the patients had been diagnosed with the following conditions before vaccination: osteoarticular disease and arthritis [16], osteoarthritis, osteoporosis and hypothyroidism [20], and rheumatoid arthritis and osteoarthritis [21]; however, severe pain, stiffness or mobility range restriction of the shoulder had started after vaccination.

3. Results

Within the study period, 216,968 spontaneous notifications were identified in the FEDRA database, of which 13,717 (6.3%) were related to immunization. Twenty-one of these cases consisted of vaccination-associated dysfunctions of the tendons, cartilages, ligaments and bursae, and eight met the study eligibility criteria (Table 1). Fig. 1 displays the flowchart for the article selection and case extraction process.

Based on the systematic review, we found 67 medical articles at PubMed, Embase, and WoS, of which 11 were excluded due to duplication, 9 because they involved non-human, 13 because they reported conditions unrelated to those in our study, and 4 because they dealt with diagnostic and therapeutic issues. Consequently, we selected 30 articles for complete reading, of which, the review articles were excluded, since they included cases that had been previously selected for our study (3). Also, we discarded the review articles reporting neuropathy, plexopathy, and radiculopathy (7) or autoinmmune or inflammatory diseases (7). In addition, three articles were retrieved from the manual review of relevant papers. Ultimately, we found 16 articles describing cases that fulfilled the study elegibility criteria. Thirty-seven cases were taken from these 16 articles for the study purposes (Table 2). All the selected articles were either clinical cases or case series.

By adding the results from FEDRA notifications to those from the search on the above databases, we created a case series (n = 45) of vaccination-associated injuries or dysfunctions involving the shoulder (Tables 1 and 2).

All the patients were adults. Their mean and median age were 53.6 and 54.5 years (age range: 22–89), respectively. The mean and median age for the FEDRA cases were 58.4 and 55.5 years (age range: 38–83), respectively, and for the cases found by means of the systematic review were 52 and 51 years (age range: 22–89), respectively. In estimating the age medians, the series reported by Atanosoff et al. was excluded, because the authors did not state the age of individual cases, but only the series mean age (i. e., 50 yrs. [range: 26–83 yrs.]). In our case series, most of patients were females (71.1% vs. 28.9%); the percentage for each sex separetely in FEDRA database was 62.5% vs. 37.5%, while it was 73% vs. 27% in the systematic review.

Table 1
Cases of shoulder injuries related to the administration of vaccines reported to Spanish Pharmacovigilance System (SEFVH).

Id	Reporting year	Age	Sex	Vaccine	Symptom onsets	Diagnosis
1	2008	56	F	TD	a few days	Bursitis
2	2009	46	M	Flu	4 days	Subacromial/subdeltoid bursitis
3	2010	53	F	Flu	7 days	Subacromial/subdeltoid bursitis
4	2010	38	F	Flu	2 months	Bursitis
5	2012	76	M	Flu	a few hours	Tenosynovitis
6	2014	55	F	Flu	1 month	Focal tendinosis and bursitis
7	2014	60	M	PPV	a few hours	Bursitis
8	2015	83	F	Flu	1 day	Tendonitis

M = Male. F = Female. Flu = Influenza (seasonal or pandemic) vaccines. PPV = 23-valent pneumococcal polysaccharide vaccine. TD = diphtheria, tetanus toxoid vaccine.

Please cite this article in press as: Martín Arias LH et al. Risk of bursitis and other injuries and dysfunctions of the shoulder following vaccinations. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.07.055