

MONITORING ADVERSE REACTIONS OF THE CANTGRIP® VACCINE

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Abstract

Post-marketing vaccine safety monitoring is an important component of all vaccination programs. Early detection and quick response to adverse events following immunization can lessen their negative impact on health and on immunization programs themselves. For this reason, the current non-interventional, prospective study developed a method of further evaluating the safety of the Cantgrip® vaccine for influenza virus A(H1N1) manufactured and used in Romania. A total of 371 questionnaires were distributed to the health-care professionals at the moment of the immunization, 309 subjects returned the questionnaires in two weeks' time. The most common injection-site reaction was pain (48.5%). Other local adverse reactions were redness, irritation and induration. The most common systemic adverse reactions reported were: muscle ache (8.7%), chills (2.9%) and sweating (1.9%). Most of the reported adverse reactions following immunization were mild-to-moderate. No life-threatening or adverse events of special interest were reported. The results of our study showed that, for an initial follow up of the studied group of subjects, Cantgrip® proved to be a safe vaccine.

Rezumat

Monitorizarea post-marketing a siguranței vaccinurilor este o componentă importantă a tuturor programelor de vaccinare. Detectarea timpurie și luarea rapidă de măsuri în cazul apariției de reacții adverse poate scădea impactul negativ al acestora asupra sănătății și chiar asupra programelor de vaccinare. Din acest motiv, prezentul studiu non-intervențional, prospectiv, a dezvoltat o metodă de evaluare a siguranței vaccinului A(H1N1) (Cantgrip®) utilizat în România. În cadrul acestui studiu au fost distribuite 371 de chestionare profesioniștilor din domeniul medical, în momentul imunizării, dintre care 309 au returnat chestionarele completate, după două săptămâni. Cea mai întâlnită reacție locală a fost durerea la locul injectării (48,5%). Alte reacții adverse locale raportate au fost roșeața, iritația și indurația. Dintre reacțiile adverse sistemice, cele mai des raportate au fost: mialgia (8,7%), frisonul (2,9%) și transpirațiile (1,9%). Majoritatea reacțiilor adverse raportate au fost ușoare și moderate ca severitate. Nu au fost înregistrate reacții adverse care

să pună în pericol viața pacienților sau reacții adverse de interes special. Rezultatele preliminare ale studiului arată că în cazul grupului studiat, Cantgrip® este un vaccin sigur.

Keywords: influenza A(H1N1) vaccine; safety monitoring; adverse events.

Introduction

At the beginning of 2009, a novel swine-origin influenza A(H1N1) virus was identified as the cause of a rapid-spreading febrile respiratory illness [1, 2]. By June 11, 2009, nearly 30,000 cases of 2009 H1N1 virus infections have been confirmed across 74 countries, compelling the WHO (World Health Organisation) to declare a phase 6 alert level and the start of the 2009 influenza pandemic period [3]. The first confirmed case was documented in Romania on May 23, 2009, and from then on, a total of 7008 people acquired the A(H1N1) virus; in 122 cases the infection has led to death [4]. Mathematical modeling suggests that the most effective means of reducing the effect of the virus pandemic at the medical, sociological and economic level is by mass immunization of the population [5]. In response to the pandemic, the Romanian Public Health Ministry launched on November 26th the National Immunization Campaign using a vaccine produced by the 'Cantacuzino' National Institute of Research and Development in Microbiology and Immunology, Bucharest, Romania. Cantgrip® vaccine was approved for use by the National Medicines Agency and was distributed according to the National Intersectorial Pandemic Intervention Plan, primarily to the health-care professionals [6].

Post-marketing vaccine safety monitoring is an important component of all vaccination programs. Although immunization programs are considered as 'one of the most effective as well as safe of all health interventions', several challenges must be faced for their implementation [7]. Vaccination is expected by both the public and health professionals to be a safe medical intervention that will not lead to harm, mostly because it is generally administered to healthy people (children, pregnant women, active people), in contrast to therapeutic drugs that are taken to cure or alleviate disease. This is an aspect that sets very high standards for the safety and efficacy of vaccines [8, 9].

Studies show that any adverse event or vaccine safety issue may lead to rumors which, if not rapidly and effectively dealt with, can undermine public confidence in the vaccine and have dramatic consequences for immunization coverage and disease incidence [10, 11]. Additionally, the public will need frequent reassurance of vaccine safety when events associated with vaccination are identified, even when these events have other causes and occur at the expected background rates. Inappropriate

assessment of safety data can severely undermine the effectiveness of the vaccination campaigns [12, 13], as is the case with the occurrence of adverse events of special interest such as Guillain-Barré syndrome or Bell's palsy, severe adverse events for which a scrutinizing evaluation of the background rates is imperative [14, 15]. Early detection and quick response to adverse events following immunization can lessen their negative impact on health and on immunization programs themselves. Clinical trials can fail to identify all adverse drug reactions; in fact 51% of serious adverse drug reactions of marketed drugs are not detected prior to approval [16]. This is expected to happen especially when trials involve a small sample population. This was the case of the Romanian A(H1N1) Cantgrip® vaccine, whose safety and effectiveness was tested on 70 adults and 61 elderly healthy subjects [17]. All of these challenges have created the need for comprehensive, efficient and cost-effective systems for post-marketing drug surveillance. For this reason, the present study developed a method of further evaluating the safety of the Cantgrip® vaccine.

Materials and Methods

Study design and objective

The study was designed by the Drug Information Research Center at the University of Medicine and Pharmacy "Iuliu Hatieganu" in Cluj-Napoca, in collaboration with the Territorial Emergency Hospital and the Infectious Disease Hospital from Cluj-Napoca. It is a prospective, non-interventional study that aims to identify and evaluate the adverse reactions of the Cantgrip® influenza vaccine used in Romania. The study was approved by the University Ethics Committee and by the National Medicines Agency.

Questionnaires were developed, containing: (1) open and closed questions seeking demographic details and information on current therapy and disease states; (2) a series of symptoms divided into body systems, with tick boxes and spaces for the addition of other symptoms; these symptoms were the adverse reactions most frequently reported during the early monitorization of the A(H1N1) vaccines available in the European Union, data published on the AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé)[18] and the MHRA (Medicines and Healthcare products Regulatory Agency UK)[19] websites and by the VAERS (Vaccine Adverse Event Reporting System) in the United States [8]; (3) fields where the patient was asked to mention the onset moment, the severity and the duration of each symptom; symptoms' severity was to be graded as mild, moderate or severe; (4) a detachable sheet that asked for the identification of

adverse events of special interest such as Guillain-Barré syndrome, Bell's palsy, neuritis, vasculitis, seizures, encephalitis, demyelinating conditions or anaphylaxis; this particular sheet was to be returned three months after the immunization if such an event was to occur; the monitorization of the adverse events of special interest was recommended by the EMA (European Medicines Agency) through the Pharmacovigilance Plan adopted by the CHMP (Committee for Medicinal Products for Human Use) on 25 June 2009 [20]; (5) a separate sheet providing the description of the symptomatology of the monitored adverse events of special interest [18,19].

In the Infectious Disease Hospital, 138 questionnaires were distributed to the health-care professionals at the moment of the immunization; at the Territorial Emergency Hospital 200 health-care professionals received the questionnaires after immunization. The subjects enrolled in the study were asked to return the questionnaires completed in two week's time.

Each health-care professional enrolled in the study signed an informed-consent form that insured the confidentiality of the information provided in the questionnaire.

All authors vouch for the completeness and accuracy of the data.

Vaccine

The vaccine monitored in the present study is a monovalent, purified, inactivated, unadjuvanted, split-virus vaccine. The seed virus was derived from the A/California/7/2009(H1N1) virus, one of the candidate reassortant vaccine viruses recommended by the WHO [21]. The vaccine was prepared using embrionated chicken eggs with the same standard techniques that are used for the production of seasonal influenza vaccines. One dose of the vaccine (0.5mL) contains 15µg H1hemagglutinine, the surface antigen that determines the immune response, thiomersal as a preservative and a saline solution as a solvent [17].

Each health-care professional enrolled in the study received one dose of Cantgrip® vaccine intramuscularly into the deltoid muscle.

Statistical analysis

Quantitative data was described using the minimum, 1st quartile, median, 3rd quartile and maximum. Qualitative data was described using absolute and relative frequencies. Also 95% confidence intervals were computed for percentage estimates. Qualitative variables were compared with Fisher exact test when expected frequencies were low (<5) in more than 20% of the cells of the contingency table. Otherwise Pearson Chi square (χ^2) test was used. For all statistical tests the two-way p value was used. The critical alfa statistical significance level chosen was 0.05.

Statistical calculations were performed in **R** software environment for statistical computing and graphics, version 2.9.2, using the Rcmdr graphical user interface, version 1.4-10, on a Ubuntu 9.10 Karmic Koala system. Confidence intervals were computed in EpiInfo version 3.5.1 on a Windows 7 system.

Results and Discussion

A total of 309 subjects returned the questionnaires completed. 95.46% of the subjects reported pain at the injection site as an adverse reaction. This symptom is not entirely relevant as an adverse reaction to the vaccine, as the process of injecting the vaccine is itself a source of pain, most of the subjects mentioning as onset time the first 5 minutes and the duration of the reaction a maximum of 30 minutes. 51.5% of the subjects reported other adverse reactions to the vaccine. It is possible that the use of tick boxes for the symptoms could increase reporting rates through suggestion, although there are studies that contradict this theory. However, open questionnaires identify fewer symptoms [16].

The *median* age of the subjects was 37 years (range 20 to 71), 78.96% were female and 21.04% were male. The first quartile was at 29 years and the third at 46 years. This means that 25% of all subjects were younger than 29 years old and 75% of all subjects were younger than 46 years old. The median shows that 50% of all subjects were younger than 37 years old.

Among the female subjects, 66.39% reported adverse reactions, with an incidence of almost double that of the male subjects, which is 38.46% ($\chi^2=16.7595$, $df=1$, $p=0.00004243$ Chi square χ^2 test). It may be possible that the female subjects are more prone to identifying adverse reactions and more willing to admit their existence.

Out of the subjects who reported adverse reactions, 9 had also received the seasonal flu vaccine up to three weeks before or after the immunization with the Cantgrip® vaccine. They reported muscle ache, headache, fatigue, dizziness and arthralgia. It is possible that the symptoms identified by these subjects could represent adverse reactions to the flu vaccines used. Other two subjects had received the hepatitis B vaccine four weeks before the immunization and one subject had received the Gardasil® vaccine three months prior to the immunization with Cantgrip® vaccine. These subjects reported only local adverse reactions such as pain at the injection site, irritation and inflammation, reactions that cannot be produced by the other vaccines used, due to the lack of plausible time relationship to vaccine administration.

Some examples of subjects that reported adverse reactions after vaccination, patients that were also taking other drugs that could account for the reported adverse events, are presented in Table I.

Table I

Possible alternative causes for some reported adverse reactions.

Drugs taken at the time of the immunization	Adverse events following immunization (AEFIs)	Possible alternative causes for the reported AEFIs
<i>Case 1</i> Indapamide and Metoprolol	Fatigue Muscle ache	There are numerous literature reports which suggest that both indapamide and metoprolol can induce fatigue. There are also several reports of myalgia due to metoprolol [22, 23].
<i>Case 2</i> Propranolol, Omeprazole,	Nausea Rhinorrhoea	Nausea has been reported after propranolol and omeprazole use. Respiratory effects including rhinorrhoea have been reported after propranolol use [22].
<i>Case 3</i> Metoprolol, Levothyroxine	Fatigue Arthralgia	Metoprolol can induce both fatigue and arthralgia [22].
<i>Case 4</i> Enalapril, Indapamide and Albuterol	Headache Fatigue	Concurrent use of angiotensin converting enzyme inhibitors and thiazide diuretics may result in postural hypotension which can produce headache and fatigue. Albuterol use can also produce headache and fatigue [22, 23].
<i>Case 5</i> Indapamide, Felodipine, Nonsteroidal anti-inflammatory drugs and Flavonoids (diosmin and hesperidin)	Fatigue Headache	Simultaneous use of nonsteroidal antiinflammatory agents and thiazide diuretics may result in decreased antihypertensive efficacy [24]. Felodipine, hesperidine and diosmin use can produce headache. Diosmin use can also produce fatigue [22].

The vast majority of the drugs used by the subjects who reported adverse reactions are cardiovascular drugs according to the ATC (Anatomical Therapeutic Chemical) classification. Beta-blockers, diuretics, sartans and calcium channel blockers can produce postural hypotension, headache, malaise or dizziness, symptoms that could be mistaken for the adverse reactions following immunization. However, Pearson's Chi-squared test revealed that, in the case of the correlation between the uses of drugs for certain conditions and the adverse reactions reported, the data in our study is not statistically significant ($\chi^2=0.6865$, $df=1$, $p=0.4074$) to support a relationship between the two.

The most frequent disorder among the subjects who reported adverse reactions was hypertension ($n=10$). Other disorders were asthma ($n=3$), bronchitis ($n=2$), thyroid disorders ($n=5$), gastritis ($n=2$), bone disorders ($n=6$), diabetes mellitus type 1 ($n=2$), anemia ($n=1$) and tuberculosis ($n=1$). Patients who already have a certain condition are more likely to report

adverse reactions. Co-morbidities are a risk factor for the high incidence of adverse drug reactions. Symptoms of these conditions could also be mistaken for the adverse drug reactions following immunization with Cantgrip®. But again, Pearson's Chi-squared test revealed that, in the case of the correlation between the existence of certain conditions and the number of adverse reactions reported, the data in our study is not statistically significant ($\chi^2 = 0.006$, $df=1$, $p = 0.9382$) for supporting a relationship between the two.

Many subjects used supplements; others used analgesics and nonsteroidal anti-inflammatory drugs that could hide certain adverse reactions following immunization such as muscle ache, headache, arthralgia, inflammation, tumefaction or irritation. Fisher's Exact Test showed no statistical significance to support the relationship between the use of analgesics and nonsteroidal anti-inflammatory drugs and the reported adverse reactions ($p=1$).

The post-authorization adverse reactions of the Cantgrip® vaccine reported in our study were consistent with the ones included by the manufacturer in the Summary of Product Characteristics [17].

Local adverse reactions are presented in Table II. They represent 65% out of all adverse reactions reported after the immunization. In most of the cases the reactions were of mild severity and resolved in a week's time.

Table II

Incidence and severity of local adverse reactions following vaccination

Local adverse reaction	% within all subjects (95% CI)	Sex	No	% within sex (95% CI)	Severity % within reaction (95% CI)		
					Mild	Moderate	Severe
Injection site pain	48.5 (42.8-54.3)	M F Total	63 236 295	21.1 (16.6-26.1) 78.9 (73.9-83.4) 100	46.8 (34.0-59.9) 45.1 (38.6-51.7) 45.4 (39.6-51.3)	37.1 (25.2-50.3) 40.3 (34.0-46.9) 39.7 (34.0-45.5)	16.1 (8.0-27.7) 14.6 (10.3-19.8) 14.9 (11.1-19.5)
Induration	2.3 (1.0-4.8)	M F Total	0 7 7	0 100 (100-100) 100	0 71.4 (29.0-96.3) 71.4 (29.0-96.3)	0 28.6 (3.7-71.0) 28.6 (3.7-71.0)	0 0 0
Redness	5.8 (3.6-9.2)	M F Total	1 17 18	5.6 (0.1-27.3) 94.4 (72.7- 99.9) 100	100 88.2 (63.6-98.5) 88.9 (65.3-98.6)	0 11.8 (1.5-36.4) 11.1 (1.4-34.7)	0 0 0
Tumefaction	1.6 (0.6-4.0)	M F Total	0 5 5	0 100 (100-100) 100	0 80 (28.4-99.5) 80 (28.4-99.5)	0 20 (0.5-71.6) 20 (0.5-71.6)	0 0 0
Inflammation	0.3 (0.0-2.1)	M F Total	1 0 1	100 (100-100) 0 100	100 (100-100) 0 100 (100-100)	0 0 0	0 0 0
Irritation	6.5 (4.1-10.0)	M F Total	3 17 20	15 (3.2-37.9) 85.0 (62.1-96.8) 100	66.7 (9.4-99.2) 58.8 (32.9-81.6) 60.0 (36.1-80.9)	33.3 (0.8-90.6) 41.2 (18.4-67.1) 40.0 (19.1-63.9)	0 0 0

Systemic adverse reactions are presented in Table III. They represent 20.1% out of all adverse reactions reported in the present study. The most frequent systemic reaction was muscle ache (8.7%) followed by chills (2.9%) and sweating (1.9%). The majority of the systemic reactions were also of mild severity and resolved in maximum one week.

Table III
Incidence and severity of systemic adverse reactions following vaccination

Systemic adverse reaction	% within all subjects (95% CI)	Sex	No	% within reaction (95% CI)	Severity % within reaction (95% CI)		
					Mild	Moderate	Severe
Muscle ache	8.7 (5.9-12.6)	M	3	11.1 (2.4-29.2)	33.3 (0.8-90.6)	66.6 (9.4-99.2)	0
		F	24	88.9 (70.8-97.6)	54.2 (32.8-74.4)	45.8 (25.6-67.2)	0
		Total	27	100	51.9 (31.9-71.3)	48.1 (28.7-68.1)	0
Chills	2.9 (1.4-5.6)	M	1	11.1 (0.3-48.2)	100 (100-100)	0	0
		F	8	88.9 (51.8-99.7)	37.5 (8.5-75.5)	62.5 (24.5-91.5)	0
		Total	9	100	33.3 (7.5-70.1)	66.7 (29.9-92.5)	0
Sweating	1.9 (0.8-4.4)	M	1	16.7 (0.4-64.1)	0	100 (100-100)	0
		F	5	83.3 (35.9-99.6)	40.0 (5.3-85.3)	60.0 (14.7-94.7)	0
		Total	6	100	33.2 (4.3-77.7)	67.7 (22.3-95.7)	0
Fever	1.3 (0.4-3.5)	M	3	25.0 (0.6-80.6)	0	100 (100-100)	0
		F	1	75.0 (19.4-99.4)	33.3 (0.8-90.6)	66.7 (9.4-99.2)	0
		Total	4	100	25.0 (0.6-80.6)	75.0 (19.4-99.4)	0
Facial edema	0.6 (0.1-2.6)	M	0	0	0	0	0
		F	2	100 (100-100)	0	100 (100-100)	0
		Total	2	100	0	100 (100-100)	0
Peripheral edema	0.3 (0.0-2.1)	M	1	100 (100-100)	0	100 (100-100)	0
		F	0	0	0	0	0
		Total	1	100	0	100 (100-100)	0
Arthralgia	2.3 (1.0-4.8)	M	0	0	0	0	0
		F	7	100 (100-100)	42.9 (9.9-81.6)	57.1 (18.4-90.1)	0
		Total	7	100	42.9 (9.9-81.6)	57.1 (18.4-90.1)	0
Itching	0.6 (0.1-2.6)	M	0	0	0	0	0
		F	2	100 (100-100)	100 (100-100)	0	0
		Total	2	100	100 (100-100)	0	0
Rash	0.6 (0.1-2.6)	M	0	0	0	0	0
		F	2	100 (100-100)	50.0 (1.3-98.7)	50.0 (1.3-98.7)	0
		Total	2	100	50.0 (1.3-98.7)	50.0 (1.3-98.7)	0
Hypotension	0.3 (0.0-2.1)	M	0	0	0	0	0
		F	1	100 (100-100)	0	100 (100-100)	0
		Total	1	100	0	100 (100-100)	0
Palpitation	0.6 (0.1-2.6)	M	0	0	0	0	0
		F	2	100 (100-100)	100 (100-100)	0	0
		Total	2	100	100 (100-100)	0	0

Table IV presents the neurological and gastrointestinal adverse reactions reported in our study. Fatigue (12.9%) was the most frequent neurological reaction reported followed by headache (5.5%) and sleepiness (4.5%).

Table IV

Incidence and severity of neurological and gastrointestinal adverse reactions following vaccination

Neurological adverse reaction	% within all immunized (95% CI)	Sex	No	% within reaction (95% CI)	Severity % within reaction (95% CI)		
					Mild	Moderate	Severe
Fatigue	12.9 (9.5-17.3)	M	5	12.5 (4.2-26.8)	60.0 (14.7-94.7)	40.0 (5.3-85.3)	0
		F	35	87.5 (73.2-95.8)	45.7 (28.8-63.4)	51.4 (34.0-68.6)	2.9 (0.1-14.9)
		Total	40	100	47.5 (31.5-63.9)	50.0 (33.8-66.2)	2.5 (0.1-13.2)
Malaise	1.3 (0.4-3.5)	M	0	0	0	0	0
		F	4	100 (100-100)	25.5 (0.6-80.6)	25.5 (0.6-80.6)	50.0 (6.8-93.2)
		Total	4	100	25.5 (0.6-80.6)	25.5 (0.6-80.6)	50.0 (6.8-93.2)
Dizziness	4.5 (2.6-7.7)	M	1	7.1 (0.2-33.9)	100 (100-100)	0	0
		F	13	92.9 (66.1-99.8)	53.8 (25.1-80.8)	30.8 (9.1-61.4)	15.4 (1.9-45.4)
		Total	14	100	57.1 (28.9-82.3)	28.6 (8.4-58.1)	14.3 (1.8-42.8)
Headache	5.5 (3.3-8.8)	M	0	0	0	0	0
		F	17	100 (100-100)	29.4 (10.3-56.0)	52.9 (27.8-77.0)	17.6 (3.8-43.4)
		Total	17	100	29.4 (10.3-56.0)	52.9 (27.8-77.0)	17.6 (3.8-43.4)
Nausea	1.6 (0.6-4.0)	M	0	0	0	0	0
		F	5	100 (100-100)	60.0 (14.7-94.7)	40.0 (5.3-85.3)	0
		Total	5	100	60.0 (14.7-94.7)	40.0 (5.3-85.3)	0
Vomiting	0.6 (0.1-2.6)	M	0	0	0	0	0
		F	2	100 (100-100)	50.0 (1.3-98.7)	50.0 (1.3-98.7)	0
		Total	2	100	50.0 (1.3-98.7)	50.0 (1.3-98.7)	0
Sleepiness	4.5 (2.6-7.7)	M	2	14.3 (1.8-42.5)	100 (100-100)	0	0
		F	12	85.7 (57.2-98.2)	41.7 (15.2-72.3)	58.3 (27.7-84.8)	0
		Total	14	100	50.0 (23.0-77.0)	50.0 (23.0-77.0)	0
Insomnia	0.6 (0.1-2.6)	M	1	50.0 (1.3-98.7)	0	100 (100-100)	0
		F	1	50.0 (1.3-98.7)	100 (100-100)	0	0
		Total	2	100	50.0 (1.3-98.7)	50.0 (1.3-98.7)	0
Irritability	0.3 (0.0-2.1)	M	0	0	0	0	0
		F	1	100 (100-100)	0	100 (100-100)	0
		Total	1	100	0	100 (100-100)	0
Syncope	0.3 (0.0-2.1)	M	0	0	0	0	0
		F	1	100 (100-100)	0	100 (100-100)	0
		Total	1	100	0	100 (100-100)	0

During our study, two unsolicited adverse reactions were reported, namely rhinorrhoea (n=4) and arm fasciculation (n=1).

No life threatening or other serious adverse reactions following immunization were reported (such as thrombocytopenia, lymphadenopathy or angioedema) and no events of special interest. Assessment of the adverse events of special interest is still in progress. If reported, additional data will be published in a follow-up study.

Conclusions

The adverse reactions reported in our study of the Cantgrip® vaccine are similar in nature to the ones reported in the pre-authorisation clinical trials mentioned in the Summary of Product Characteristics [17]. The results

of this research add to the body of scientific medical evidences, showing that for an initial follow up of the studied group of subjects, Cantgrip® proved to be a safe vaccine.

However, the evaluation of the special interest adverse events after immunization is ongoing and if reported, additional data will be provided.

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