LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

March 28 2011

A registry based comparative cohort study in four Swedish counties of the risk for narcolepsy after vaccination with Pandemrix - A first and preliminary report, by the Medical Products Agency.

ABSTRACT

During the summer 2010 an increased reporting of cases with narcolepsy suggesting a relationship to vaccination with Pandemrix was observed in Sweden. A similar increase in reporting was seen in Finland but not in other European countries. The concerns raised by these observations initiated safety investigations at the national and European level. The current report presents results from a Swedish registry study, based on a 5.3 million population, comparing the risk of narcolepsy in vaccinated versus unvaccinated individuals from October 2009 through December 2010. The incidence of narcolepsy in vaccinated children born from 1990 and later was 4.06 cases per 100,000 person years, compared with an incidence of 0.97 cases per 100,000 person years in unvaccinated, yielding a relative risk of 4.19 (95% CI: 1.76-12.1). No corresponding increase in risk was seen in adults. The median latency from vaccination to diagnosis of narcolepsy was 8 months. Although showing a lower risk estimate the results are in line with the findings in a recent Finnish study. The data from this Swedish registry based cohort study provide strengthened evidence that vaccination with Pandemrix in children/adolescents is associated with an increased risk of narcolepsy. However, due to inherent methodological limitations the final interpretation of the study results, in particular for the understanding of a presumed causal relationship, needs to be supported by further investigations and extended observation time.

INTRODUCTION

A nation-wide vaccination program against pandemic influenza A/H1N1 using Pandemrix was carried out in Sweden from October 2009 through March 2010, with an average national coverage of about 60 percent. Starting during the summer 2010, an increasing number of spontaneous adverse drug reaction (ADR) reports on cases of narcolepsy was observed in Sweden, especially in children/adolescents. The number of reported cases in the age 19 and younger exceeded the expected number. These observations suggested a possible association between narcolepsy and vaccination with Pandemrix inthese age-groups. A similar increase in ADR reports in children/adolescents was observed in Finland.

A recent report (February 2nd, 2011) from a registry study in Finland suggested a 9-fold increase in the risk of narcolepsy in conjunction with Pandemrix vaccination. Even though an increased reporting rate of narcolepsy has not been noted in other counties, an EU regulatory procedure was initiated in September 2010 (Art 20) to evaluate this signal in a European setting.

A preliminary analysis of data from Stockholm, Sweden performed in October 2010 did not yield a sufficient number of cases of narcolepsy for any firm conclusions.

The current report contains preliminary data from a larger study population comprising four counties/regions (57 % of the Swedish population). Cohorts of vaccinated (with Pandemrix) and non-vaccinated subjects were followed to the end of 2010.

METHODS

Study population

The study population was defined as all individuals resident in the counties/regions of Stockholm, Skåne, Västra Götaland and Östergötland on October 1st 2009. These regions were chosen to cover a sufficiently large sample of the Swedish population (5.3 out of 9.3 millions, 57 %). Furthermore, these regions had relatively easily accessible vaccination and health care data. No nationwide vaccination register is available in Sweden. Registry data was collected and analysed in accordance with the national regulations governing pharmacovigilance procedures and data protection.

Exposure to Pandemrix vaccine

Data were retrieved from regional vaccination registries. All health care institutions and schools participating in the vaccination campaign were obliged to register every individual vaccinated for subsequent inclusion in the regional vaccination database. Pandemrix was the only pandemic H1N1 vaccine used in Sweden. The H1N1 vaccination campaign in Sweden lasted from mid-October 2009 through March 2010. Estimated vaccination coverage and population sizes in the four counties are presented in Table 1. Individuals who received at least one dose of the vaccine were defined as exposed. The present analysis did not take into account whether a second dose was given or not.

Outcomes and definitions

Prevalent disease was defined as individuals with at least one occasion of care registered in the respective county health care database with a diagnosis of narcolepsy (ICD code G47.4) before October 1st 2009 (i.e before onset of the pandemic period). The length of the period used for identifying prevalent cases from the health care databases differed between the counties. Data in the Östergötland county was available from 1997, in Stockholm from 1998, in Västra Götaland from 2000 and in Skåne from 2001.

Incident new cases were defined as individuals with a first registration of a diagnosis of narcolepsy from October 1st, 2009 in those non-vaccinated or after the first vaccination among those vaccinated.

Statistical analyses

All subjects registered in the respective county October 1st 2009 without a known diagnosis of narcolepsy were followed until December 31 2010, date of narcolepsy diagnosis, death or migration from the county, whichever came first. In the cohort of vaccinated subjects the follow-up time was defined as *exposed* from the date of vaccination until the end of follow-up. Vaccinated subjects

contributed with exposure time in the unvaccinated cohort from October 1 to the date of vaccination. The incidence rates in the vaccinated and unvaccinated cohorts, respectively, were calculated as the number of persons diagnosed with an incident registration for narcolepsy in the health data bases, divided by the person years at risk. Exact confidence intervals for the incidence rates were calculated assuming Poisson distributed number of events. The relative risk, vaccinated versus unvaccinated cohorts, was calculated as the corresponding ratio of incidence rates. Exact confidence intervals for relative risk were calculated through exact confidence intervals for binomial proportions.

The estimates of historical incidence were based on national data of patients obtaining their first diagnosis of narcolepsy between 2005 and 2008 in an in-hospital setting or at an ambulatory care visit at specialist clinics. Due to the fact that registration of specialist ambulatory care visits in the nationwide registries started 2001 only the later years could be used for an operational definition of incident cases, allowing at least a four years washout period of ambulatory care visits to exclude prevalent cases. The historical incidence was estimated as the number of new cases between 2005 and 2008 divided by the population size for the corresponding years, obtained from Statistics Sweden. The historical incidence was compared with the observed incidence in the study period assuming Poisson distributed number of observed cases.

RESULTS

The population size and vaccination coverage in the four counties are presented in Table 1. The overall mean vaccination percentage for children was 67.1 percent and for adults 51.0 percent with some regional differences.

Among those born 1990 or later (19 years and younger at the time of the pandemic period, i.e. children/adolescents), 38 cases of narcolepsy were observed in vaccinated individuals versus 6 in the non-vaccinated group.

The corresponding numbers for those born before 1990 were 26 and 26 cases. Descriptive statistics on age and gender of the cases is shown in Table 2.

The incidence of narcolepsy among vaccinated children born from 1990 and later was 4.06 cases per 100,000 person years, compared with an incidence of 0.97 cases per 100,000 person years among unvaccinated. These rates yield a relative risk of 4.19 (95% CI: 1.76-12.1) for vaccinated children/adolescents as compared with non-vaccinated.

The incidence rates among adults was 1.16 per 100,000 person years for vaccinated and 0.96 person years for unvaccinated, corresponding to a relative risk of 1.21 (95% CI: 0.67-2.17). The county specific estimates for the two age groups are displayed in Table 3 and Table 4, respectively. No apparent differences between the four counties, with respect to incidence rates or to relative risk estimates, were observed. However, the power of detecting such differences is limited.

Based on national patient register data obtained from the National Board of Health and Wellfare concerning in hospital admission and ambulatory care visits at special clinics the average historical incidence of narcolepsy between 2005 and 2008 was 1,04 per 100,000 (95% CI 0.92-1.16) person s20

years and older and 0.46 per 100,000 (95% CI 0.32-0.60) in persons under 20 years of age. The historical incidence in adults is almost identical with the incidence among both vaccinated and unvaccinated during the study period. The historical incidence in children was about half of that observed for the unvaccinated during the study period, however this difference is not statistically significant (P=0.10).

Figure 1 presents the distribution of the time interval between the date of vaccination and diagnosis of narcolepsy in subjects born 1990 or later. The median latency was 261 days with a range of 61 to 408 days and an interquartile range of 160 to 319. The distribution in males and females was similar. Among all of the 38 vaccinated cases 20 were registered with a diagnosis of narcolepsy after August 1st 2010, including 15 cases diagnosed after September 1st 2010.

DISCUSSION

This large register based cohort study in more than half of the Swedish population shows a fourfold increased incidence of narcolepsy diagnoses in children/ adolescents vaccinated with Pandemrix as compared to unvaccinated individuals. The relative risk estimate translates into an absolute risk of 3 cases of narcolepsy in 100,000 vaccinated adolescents/children. Importantly no increase in risk is seen in adults. It is also noteworthy that the incidence rates for narcolepsy in adults irrespective of vaccination status were similar to historical national registry based rates during the years before the pandemic period (i.e. about 1/100,000).

The results from this study are in line with those of a recent Finnish registry study in children/adolescents; although the increase in risk was lower in the current study. A direct comparison of the study results may not be valid since the two studies differed with respect to several aspects,e.g. definition of risk time for observation and of onset of disease.

A strength of the current study is that the study population represents a large sample of the Swedish population. The vaccination coverage is relatively uniform throughout the counties studied and does not compromise the results to a significant extent. Additional strengths include the availability of population based vaccination registration and of local health databases in the studied counties enabling the definition of exposed and non-exposed cohorts as well as a complete follow-up from the start of the pandemic period in October 2009 and trough 2010.

Differences between the two populations (socio-demografic etc) are not corrected for in this analysis. Such factors may have influenced the observed outcome. However, the fact that no differences were observed in adults speaks to some extent against such imbalance being an important contribution to the conclusions. One weakness of the current study is that some cases may not yet be registered in the databases. However, the use of these county health data bases provide continuously updated data as compared to national health care databases that are updated only once yearly. An ongoing nationwide case inventory study, aiming to collect all cases of narcolepsy through hospital departments and sleep laboratories will serve as a validation of the number of cases retrieved from registries. In the case inventory study the date of diagnosis will be identified as the date of first narcolepsy symptom as described in the medical record. This will provide more detailed information that may improve the possibilities to assess the relationship between onset of disease

and time of vaccination. In the present registry based study, only date for registration of diagnosis was available.

An important caveat with the present study is that the incidence of narcolepsy is based on the time of diagnosis rather than the time of onset of disease. Our estimates of incidence may be biased if the time interval between disease onset and a registered diagnosis has been shortened during the study period. This may be caused by the media attention around this issue and/or by the medical profession even before media was alerted. The observed difference in incidence in unvaccinated subjects during the study period is twice as high as the estimated incidence in the period 2005-2008. Even if this difference is non-significant it could potentially be explained by such shortening of latency during our study period. Furthermore, if this shortening of the latency period is more pronounced in vaccinated than among unvaccinated it would result in a biased estimate of the excess risk attributed to vaccination in the present study. With additional data on the latency between disease onset and diagnosis in vaccinated and unvaccinated cases during the study period and for cases prior to the study period the amount of such a bias can be elucidated. The phenotypic expression of the disease may also affect the latency. Therefore detailed information of symptoms for the cases before and during the study period has to be gathered. The future incidence of narcolepsy among vaccinated persons will also be important to monitor since it will shed light on the nature of this problem.

The lower vaccination coverage in the young age group in the Skåne region raises some concern. The vaccination frequency among persons born between 1990 and 1993 is only 45% compared to 64% in the remainder of the population. Since the two unvaccinated cases in Skåne were born between 1990 and 1993, a potential incompleteness in the vaccination registration in this subgroup may misclassify these cases as unexposed resulting in an underestimation of the risk.

The validity of the diagnoses of the cases ascertained from the county health care databases has not yet been investigated. This validation will be part of the case inventory study mentioned above, in which the medical records of the cases will be scrutinized and assessed by clinical experts. Possible misclassification in the current study is however assumed to be independent of vaccine exposure. The consequence of such misclassification would be an attenuation of the risk difference.

This study did not take other factors possibly confounding the results into account. Genetic predisposition, ongoing influenza at the time of vaccination , history of previous recurrent infections, and individual autoimmune reactivity have all been proposed as additional risk factors. Further detailed studies of how patient phenotype, genetics, environmental factors may contribute to the pathogenesis of narcolepsy and its possible relationship to vaccination are needed.

CONCLUSION

In conclusion, this study shows a fourfold increased incidence of narcolepsy in children/adolescents vaccinated with Pandemrix compared to non-vaccinated subjects in the same age group. There was no change in the risk for adults. Even though methodological limitations may have affected the magnitude of the estimated risk the data from this Swedish registry based cohort study - in addition to the excessive number of ADR reports in Sweden as well as the recent Finnish registry data -

provide strengthened evidence that vaccination with Pandemrix in children/adolescents is associated with an increased risk of narcolepsy. Further research is needed to confirm these findings in the Swedish population and additionally, to analyse in detail how Pandemrix exposure, as such or in combination with other factors could be causally related to narcolepsy.

ACKNOWLEDGEMENTS

Essential contributions to this report was made by Fredrik Granath, senior biostatistician, Dept of Clinical Epdemiology, Karolinska Institutet, who performed the scientific analyses of data and by Anders Liljeberg, Skåne, Kersti Osmin and Mikael Hoffmann, Östergötland, Kristina Narbro and Eva Österberg, Västra Götaland and Göran Lord and Åke Örtqvist, Stockholm who delivered population and health care data from their respective counties.

TABLES AND FIGURES

Table 1. Population sizes and vaccination coverages in the four counties of the study population

County	Born from 1990 and later		Born before 1990	
	Population	% vaccinated	Population	% vaccinated
SLL	483021	66.8	1519505	47.8
Skåne	307593	56.2	976909	52.6
VGL	365379	73.9	1214046	51.8
ÖGL	98440	77.2	327506	58.3
ALL	1254433	67.1	4037966	51.0

SLL, Stockholm County; Skåne, health care region; VGL, Västra Götaland Health Care Region, ÖGL, Östergötland county.

Table 2. Age at diagnosis and gender distribution of observed narcolepsy cases by exposure status

Age group	Vaccinated	N	Age at diagnosis				Gender
	Yes/No		Mean	Std Dev	Min	Max	Females/Males
Children/adolescents	No	6	15.00	4.51	7	20	5/1
	Yes	38	13.00	3.75	3	20	19/19
Adults	No	26	48.34	17.63	22	83	17/9
	Yes	26	44.84	19.19	22	91	16/10

Table 3. Incidences of diagnosed narcolepsy, relative risk estimates (RR), and 95% confidence intervals (CI), among vaccinated and unvaccinated children/adolescents

	Vaccinated				Unvaccinated				Vacc. vs Unvacc.	
County	#Events	Risk time*	Rate	95% CI	#Events	Risk time*	Rate	95% CI	RR	95% CI
SLL	11	3.583	3.07	(1.53-5.49)	2	2.403	0.83	(0.10-3.01)	3.69	(0.80-34.2)
Skåne	10	1.928	5.19	(2.49-9.54)	2	1.848	1.08	(0.13-3.91)	4.79	(1.02-45.0)
VGL	16	3.005	5.33	(3.04-8.65)	2	1.549	1.29	(0.16-4.66)	4.12	(0.97-37.0)
ÖGL	1	0.840	1.19	(0.03-6.63)	0	0.388	0.00	(0.00-9.51)	∞	(0.01-∞)
ALL	38	9.355	4.06	(2.87-5.58)	6	6.188	0.97	(0.36-2.11)	4.19	(1.76-12.1)

*100,000 person years

Table 4. Incidences of diagnosed narcolepsy , relative risk (RR) estimates, and 95% confidence intervals (CI), among vaccinated and unvaccinated adults

	Vaccinated				Unvaccinated				Vacc. vs Unvacc.	
County	#Events	Risk time*	Rate	95% CI	#Events	Risk time*	Rate	95% CI	RR	95% CI
SLL	9	7.985	1.13	(0.52-2.14)	11	10.695	1.03	(0.51-1.84)	1.10	(0.40-2.91)
Skåne	9	5.636	1.60	(0.73-3.03)	6	6.382	o.94	(0.35-2.05)	1.74	(0.55-0.96)
VGL	5	6.878	0.73	(0.24-1.70)	8	8.130	0.98	(0.42-1.94)	0.74	(0.19-2.56)
ÖGL	3	2.108	1.42	(0.29-4.16)	1	1.942	0.51	(0.01-2.87)	2.76	(0.22-145)
ALL	26	22.457	1.16	(0.76-1.70)	26	27.149	0.96	(0.63-1.40)	1.21	(0.67-2.17)

*100,000 person years

Figure 1. Distribution of number of days between Pandemrix vaccination and diagnosis registered in health databases among persons born from 1990 (children/adolescents)