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Press release

Vaccinations against Hepatitis B Virus: a summary of the discussions of the National Advisory Board of Pharmacovigilance of September 30th, 2008

The National Advisory Board of Pharmacovigilance during a meeting the 30 September, 2008, examined the results of a case control study undertaken by Mikaeloff et al, to evaluate the risk of occurrence of a first central demyelinating event in children.

This study performed in the French neuropaediatric "KIDSEP" cohort included children up to 16 years of age having had a first episode of central acute demyelination which could represent the beginning of multiple sclerosis (MS) between on January 1st, 1994 and on December 31st, 2003. It is the third analysis published on this cohort with the aim of finding a possible association between vaccination against hepatitis B and the risk of demyelination including MS. The first two studies published in 2007 did not show an increase in the risk of multiple sclerosis nor of recurrence of MS in the children vaccinated against hepatitis B.

The main statistical analysis does not show an increase in risk after vaccination against hepatitis B whatever the vaccine used, the number of injections and the length of the period in time between vaccination and the first neurological symptoms.

According to the authors, the results of an investigation relating to a sub-group of children having followed the French vaccine recommendations, reported a statistically significant increase in the risk of MS, when a vaccination by Engerix B® had been done more than three years before.

Until now, no epidemiologic study has shown any association between the vaccine against HBV and the occurrence of multiple sclerosis in children. In adults, among a dozen studies which have been carried out, only the Hernan study, published in 2004, showed a significant association in patients vaccinated in the three years before the occurrence of the first symptoms.

The National Advisory Board of Pharmacovigilance considers that:

- The main and major result of this study does not reveal any association between vaccination against hepatitis B and the risk of MS;
- Because of several limits discussed during the meeting, the results of the analysis of the sub-group of children having followed the vaccine recommendations are deemed to be fortuitous.

The National Advisory Board also considered the updated pharmacovigilance data, which did not demonstrate any significant difference between the vaccines, and also the biological assumptions which could explain such a possibility. It also examined the epidemiological data for hepatitis B in France.

The National Advisory Board concluded that these results do not modify its previous conclusions at a meeting on 29 January, 2008. The National Advisory Board confirms that all pharmacovigilance and pharmaco-epidemiological data, evaluated over a period of more than 13 years in children and adults, has not called the benefit /risk ratio of the vaccine against Hepatitis B virus into question.

The summary of the discussions of the National Advisory Board of Pharmacovigilance of 30 September, 2008 are public.

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Vaccination against the Hepatitis B virus: summary of the National Advisory Board of Pharmacovigilance of September 30th, 2008

The National Advisory Board of Pharmacovigilance examined:

- The results of a case control study carried out on the French KIDSEP neuropaediatric cohort evaluating the risk of occurrence of a first event of acute CNS inflammatory demyelination between 1994 and 2003 after vaccination against hepatitis B virus (HBV) (Mikaeloff Y. *et al. Neurology* 2008, being published);
- Up to date pharmacovigilance data on spontaneous notifications of multiple sclerosis (MS) in children of 15 year old or less vaccinated against HBV during the period of the case control study (1994-2003) (J.L. Imbs, CRPV Strasbourg);
- Data on the mechanistic assumptions likely to explain a link between vaccination against HBV and of an event of acute CNS inflammatory demyelination (V. Gazin, D. Masset, Département de Toxicologie, Afssaps)
- Epidemiologic data on vaccine coverage and hepatitis B in France (D. Levy-Bruhl, InVS);

Background

Following the notification of first acute SNC demyelination events after the administration of vaccines against hepatitis B, an official pharmacovigilance investigation of central and peripheral nervous system demyelinating events was launched in June 1994.

Between 1995 and 1996, successive analyses of the data from spontaneous notification, by the National Advisory Board of Pharmacovigilance, did not support the hypothesis of any possible association between the vaccination against HBV and neurological disorders. Consequently, the Ministry of Health asked the French Agency of Health Products in August 1997 to perform a series of epidemiological studies to evaluate this eventual association.

To date, thirteen epidemiologic studies (three in children) have been performed. None of these studies have shown any statistically significant result in favour of a connection between vaccination against HBV and the occurrence of CNS demyelination disorders, except for one case control study evaluated by the National Advisory Board of Pharmacovigilance on September 21st, 2004 (Hernan Mr. *et al. Neurology* 2004; 63: 838-42). This study evidenced a significant connection between vaccination against HBV and the occurrence of multiple sclerosis (MS) in certain adults of 18 years old or more when vaccinations had been made out in the three years before the appearance of the first symptoms of MS (odds ratio (OR) = 3.1; IC 95% = [1.5; 6.3]). OR was equal to 1.8 and non-significant (IC 95% = [0.5; 6.3]) when the period of observation between vaccination against HBV and the first symptoms of MS was limited to 12 months.

The studies undertaken on the French KIDSEP neuropaediatric cohort made up of children of less than 16 years old in whom an acute SNC demyelinating event had been diagnosed between 1994 and 2003 did not confirm the risk of a recurrence of MS (Mikaeloff Y. *et al. Brain* 2007 Apr; 130 (Pt4): 1105-10) nor any increase in the risk of MS in a child vaccinated against HBV (Mikaeloff Y. *et al. Arch Pediatr Adolesc Med DEC* 2007; 161 (12): 1176-82). The results of these studies were presented at the National Advisory Board of Pharmacovigilance on May 29th, 2007 and January 29th, 2008, respectively.

In September 2008, Afssaps was informed of the forthcoming publication in *Neurology* of the third case control study carried out on the KIDSEP cohort and carried out with the support of the Ministère de la Santé, Afssaps and the ANRS.

Case control study on the risk of occurrence of a central nervous system demyelination event in children vaccinated against Hepatitis B [Y. Mikaeloff and Al. *Neurology* 2008; being published]

Method

This study is a case control study carried out on the French KIDSEP neuropaediatric cohort made up of children of less than 16 years old who had had an acute SNC demyelinating event diagnosed between 1994 and 2003. The principal objective was the evaluation of the risk of occurrence of a first acute SNC demyelinating event (whatever the later progression of the event) in children vaccinated against HBV over various periods following vaccination.

The cases included in the study were patients for whom a first acute SNC demyelinating event had been diagnosed between January 1994 and December 2003.

The controls free of a first acute SNC demyelination event (12 at the most for each case) chosen at random in the general population were paired with the cases on the basis of age (\pm 6 months), sex and geographical localization.

Information on the medical history and underlying diseases of the cases and controls was collected by means of a standardized questionnaire. The validation of vaccine status was based on a copy of the families' health records. The reference date used to compare vaccination history was that corresponding to the first acute SNC demyelination event of the case in question.

The comparison of the cases and controls' vaccination history against HBV before the reference date was carried out using conditional logistic regression.

Results

Overall, 403 patients diagnosed with a confirmed first acute SNC demyelination event were identified from the medical records. The analysis was carried out on 349 cases able to provide a copy of their vaccination records along with 2941 controls.

The results do not show any increase risk of the occurrence of a first acute inflammatory demyelination event in the children in the three years following vaccination against HBV, the result even being very close to a *reduction* of the risk being statistically significant: OR = 0.74; IC 95% [0.54-1.02]) nor in the following years (OR = 0.93; IC95% [0.65-1.31]).

However, a sub-group analysis in the children having respected the vaccine recommendations reveals a significantly increased risk of the occurrence of demyelination events (OR = 1.74; IC 95% [1.03-2.95]) and of MS (OR = 2.77; IC95% [1.23-6.24]) more than three years after vaccination in children vaccinated by Engerix B®.

Discussion

The Members of the National Advisory Board of Pharmacovigilance were informed of the conclusions of the group of expert epidemiologists which was held on September 24th, 2008. They considered that this study had been carried out using satisfactory methodology and in particular, careful checking of the vaccination histories and diagnoses of demyelination. Nevertheless, some important reservations were expressed with respect to the results of the sub-group analyses of this study:

- 1) Taking into account all the sub-group analyses carried out, and thus the multiplicity of tests performed (approximately 160), there is a very big increase in the chance of type I error, and the probability of detecting a significant connection by chance is thus very high. The problem of test multiplicity is all the more worrying as these analyses were carried out without the main results being significant and without an interaction test.

It should also be noted that the results concerning MS published in 2007 in the overall population (with no limiting to subjects having followed vaccine recommendations) did not show any connection to vaccination.

- 2) The justification for an analysis limited to children, following the vaccine recommendations is unclear. It depends on the hypothesis of a possible bias in the responses from the controls, in favour of those children who are generally better vaccinated than the general population, and this could have meant that OR has been undervaluated. It is surprising that this assumption

was maintained given the results provided by the authors concerning the absence of a difference in recommendation compliance rate between the cases and the controls. In addition, the sub-group analysis in the children not following the vaccine recommendations would quite probably have shown the “protective” effect of the vaccine.

Also, the analysis could have been improved by introducing a “compliance” variable into the multivariate analysis model in order to highlight the influence of the total vaccine status of the children on the relation between the specific anti- hepatitis B vaccine and the risk of MS.

- 3) Sub-group analyses considerably reduce numbers and the results highlighted by the authors only relate to a minor proportion of the population initially included in the study. In these sub-analyses, the number of cases of acute demyelination and confirmed MS are respectively 163, i.e. 46.7% of initial number and 72 i.e. 48% of the initial number of children with confirmed MS. All of these reductions in numbers lead to a selection bias which is impossible to assess. In addition, about half of the controls were excluded in order to maintain case-control pairing for the conditional logistic regression model. In particular, for the analysis of compliant subjects, much more than half of the controls were withdrawn. The authors do not discuss this point even though it would have been possible, using a sensitivity analysis for example, not to take pairing into account but to adjust these variables within the non-conditional logistic regression model.
- 4) An increased risk in the sub-group compliant with vaccine recommendations cannot be plausibly explained from a medical point of view. It could suggest an interaction between vaccination HBV and other vaccinations which does not correspond to current scientific knowledge on the subject.
- 5) The results of the analyses carried out according to the length of time between the vaccination and the occurrence of an acute demyelination event are far from coherent. Indeed, in the sub-analysis in children following the vaccination recommendations, OR is 0.45 (IC95% = [0.20-1.01]) for a period ranging between 1 and 2 years i.e. almost significant protection while it moves to 1.50 (IC95% = [0.93-2.43]) when a period of more than three years before the event is considered. The same thing is observed with episodes of MS. In addition, these results are not coherent with the results of Hernan *et al.* which were increased to a significant degree during the ≤ 3 years period. Here, they are not increased when a period of ≤ 3 years before the event is considered.
- 6) To conclude that there is a difference between Engerix B® and the other vaccines because the connection to a risk of MS is significant for Engerix B® and non-significant for the other vaccines comes down to an error of interpretation. Without a significant interaction, such a conclusion is highly debatable, and the OR confidence intervals which overlap to a large extent for the different vaccines, a significant interaction could not be shown.

Comments on the spontaneous notifications of multiple sclerosis collected in children up to 15 years old vaccinated against hepatitis B during the period of the study (J.L. IMBS, CRPV Strasbourg)

The sales figures for the 15-16 years age population were not available, only the annual rate of MS notifications in children up to 15 years old could be estimated, that is to say 0 to 1.36/100 000 vaccinated subjects. This rate can be compared with that estimated by taking into account the vaccines most prescribed against HBV: 0.45/100000 for Engerix B® 10 and 0.64/100000 for Genhevac B®. These values do not indicate that the use of Engerix B® carries any more risk than Genhevac B®.

Evaluation of the mechanistic assumptions supporting a connection between vaccination against HBV and an acute CNS inflammatory demyelination event (V. Gazin, D. Masset, Département de Toxicologie, Afssaps)

A presentation on the vaccines against monovalent recombinant HB virus marketed in France (R. Gibert, DLC Afssaps) was followed by a presentation on the mechanistic assumptions in question.

On a mechanistic level, the authors of the case control study suggest two hypotheses to explain the possible difference in risk between Engerix B® and GenHevac B® vaccines:

- molecular mimicry between neuronal proteins and vaccine antigens and/or yeast protein contaminants from the production system.
- the triggering of an auto-immune reaction by contaminant yeast proteins.

It should be noted that only the Engerix B® vaccine is produced using yeast, GenHevac B® being produced on CHO mammalian cells. The major factor discrediting the involvement of yeast proteins is that the use of yeasts is widespread in biotechnology product production systems and thus far has never even been suspected of causing a first acute SNC demyelination event. In addition, the interaction of the vaccine antigen with a yeast protein would be detected during quality control during the release of the vaccine batches.

The assumption of molecular imitation between the vaccine antigens (AgHBs) and neuronal Myelin Basic Protein (MBP) has been tested by comparing the amino-acid sequences using a computer: no similarity has been detected, which also discredits the idea of molecular mimicry. However, Faure *et al.* (2005) have suggested that fragments of polymerase could be produced in an “accidental” manner near vaccine antigens, and these could contain sequences similar to the MBP likely to set off an autoimmune reaction. Following this reasoning the risk would be higher with GenHevac B® vaccine compared to Engerix®, but is not coherent with the results of the study which would suggest the reverse.

An additional assumption adopted by Afssaps’ ad hoc immunotoxicology group of involves the induction by the vaccine antigens of an envelope protein of endogenous retrovirus related to MSR/V (Multiple Sclerosis associated RetroVirus) which would act as an immune system activator and cause a reduction in tolerance towards endogenous proteins. This assumption is based on the fact that 1) in 80% of MS cases, the envelope protein of the retrovirus is found in the serum, 2) in experimental studies in the animal, the injection of this protein with a vaccine additive and a myelin peptide produces effects similar to human MS. However, the role of this envelope protein in the occurrence of MS remains to be demonstrated (through cause, consequence or coincidence).

In the current state of knowledge, there is thus no robust physiopathological mechanism supporting the hypothesis of cause and effect between vaccination against HBV and the occurrence of a first acute SNC demyelination event but many avenues of research have been opened. Thus, an assessment of the capacity of the vaccine antigens to induce the expression of the retroviral envelope protein in an experimental system *in vitro* could be undertaken.

Updating the epidemiological data on Hepatitis B in France (D. Levy-Bruhl, InVS)

A representative of the Institut de Veille Sanitaire (D. Levy-Bruhl) presented an update on the epidemiological data on Hepatitis B in France reflecting the situation in the general population and in populations at risk. The vaccine coverage in newborns has never been higher than 30%. During the countryside school campaign (1994-1998), vaccine coverage was approximately 76% and the vaccine coverage of the main populations at risk about 40%. The development of vaccine coverage since 1998

has demonstrated insufficient rates for newborns (< 30%), for young teenagers (approximately 40%) and for populations at risk.

In France, since the reintroduction of the mandatory declaration (DO) of acute infections by HBV, the number of annual cases reported from 2003 to 2007 is stable (140 to 180 on average). After correction for under-notification, the incidence of acute hepatitis B is estimated to be between 600 and 800 cases /year compared to approximately 8500 cases/year before 1994. This obvious reduction is also observed in hepatic transplantations for acute hepatitis B liver failure (close to 20/year at the beginning of the nineties compared to 2/year in 2002). These results prove the beneficial impact of the anti-HBV vaccination campaign started in 1994. Estimates of the number of Hepatitis B cases and complications avoided since 1994 via the vaccination of children up to 16 years old are currently being validated and will be presented on October 2nd to the Comité Technique des Vaccinations and Haut Conseil de la Santé Publique.

Conclusions of the discussions of the National Advisory Board of Pharmacovigilance

After deliberation, the National Advisory Board of Pharmacovigilance has adopted (23 votes for, 7 abstentions and 1 vote against) the following conclusions :

- the main result of this study does not demonstrate any link in children between exposure to vaccinations against Hepatitis B Virus and a central acute demyelinating event ;
- because of several limiting factors brought up during the meeting, the National Advisory Board of Pharmacovigilance considers that the results of the sub-group analysis of children having respected vaccine recommendations present the features of a fortuitous result ;
- the benefit /risk ratio of vaccination against HBV, whatever the vaccine used against Hepatitis B, can not be called into question on the basis of this analysis of a sub-group in the paediatric population.

The National Advisory Board of Pharmacovigilance considers however that it is necessary to continue the national follow-up on the pharmacovigilance of vaccines against HBV.

Lastly, the National Advisory Board of Pharmacovigilance will be kept informed of any developments from the immuno-toxicological work being undertaken by Afssaps group of experts.

1 Sadovnick A.D. *et al.*. *The Lancet* 2000,355:549 - 50.

Mikaeloff Y. *and al.*. *Brain* 2007 Apr; 130 (Pt4): 1105-10

Mikaeloff Y. *and Al.* *Arch Pediatr Adolesc Med* DEC 2007; 161 (12): 1176-82