Rotavirus vaccine – haematemesis

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Summary

An investigation in VigiBase was undertaken following a report based on a personal communication describing an otherwise healthy child presenting with recurring haematemesis on the same day after both doses of rotavirus vaccination.

As of March 2020, there were 129 reports of this drug–adverse drug reaction in VigiBase. This is a larger number than expected compared to the background of the database. In 52 of the cases rotavirus vaccine was the only suspected drug and for 42 cases it was the only reported drug. In 33 of the reports, intussusception was co-reported; four of these concerned the withdrawn product Rotashield. For the reports that co-reported intussusception the time to onset of the reaction was generally longer, with just over two weeks as a median, compared to a median of three days for all reports, indicating two different mechanisms for the occurring haematemesis. In two reports a rechallenge was performed by administering a second dose of rotavirus vaccine where the babies afterwards presented with haematemesis a second time. Based on the reports in VigiBase, there is a risk that the vaccine could cause gastroenteritis induced haematemesis in certain individuals, with or without intussusception. Further studies to establish this potential are needed. In the meantime, if haematemesis following rotavirus vaccination occurs, careful reflection is recommended before repeated exposure to the vaccine.

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Introduction

Following a report in the autumn of 2019, based on a personal communication describing an otherwise healthy child with haematemesis occurring on the same day after both doses of vaccinations with rotavirus vaccine, an investigation was sparked at the UMC by looking for more reports in VigiBase. As there were more than one hundred reports of haematemesis for rotavirus vaccine shared worldwide and the number of reports exceed what is expected against the background of the database, of number of reports of rotavirus vaccine and of haematemesis separately, an in-depth investigation was performed.

The initial case report was submitted to the national drug regulatory authority and has subsequently reached VigiBase.

Rotavirus vaccine

Rotavirus vaccine is a live attenuated human rotavirus vaccine indicated for active immunisation against gastro-enteritis caused by rotavirus infection. It is indicated from the age of six weeks, preferably administered before 16 weeks of age, but must be completed before 24 weeks. The vaccination course consists of two doses that should be given at least four weeks apart.[1]

Rotavirus is the most common cause of severe diarrhoea in infants and young children and is easily spread from hand-to-mouth through contact with stools from an infected person. Most children with rotavirus diarrhoea recover on their own. However, some children become very ill with severe vomiting, diarrhoea and life-threatening loss of fluids that requires hospitalisation.[1]

Rotavirus vaccine history

The first company to licence a rotavirus vaccine (RotaShield) was Wyeth Laboratories in 1998, which withdrew the product from the market one year later. It had been approved by the United States Food and Drug Administration (US FDA) for oral administration to infants at two, four and six months in the US. Shortly following licensure, the Advisory Committee on Immunization Practices (ACIP) recommended routine immunization with three oral doses of the vaccine for the prevention of rotavirus disease in infants up to six months. Prelicensure clinical trials showed at that time no statistically significant difference between vaccines and placebo in the rate of intussusception (five of 10,000 recipients of any reassortant vaccine versus one of 4,632 placebo recipients). However, at the end of 1999, 101 cases of intussusception had been reported into the US FDA Adverse Event Reporting System (FAERS), and based on case control studies it was estimated that around 1,200 potential additional cases of intussusception would occur annually in the United States given its current regime, and the vaccine was withdrawn the same year.[2]

Three other vaccines were subsequently licensed: Rotarix, a single-strain human rotavirus vaccine licensed in Europe in 2006, and in the USA in 2008; RotaTeq, a combination of five bovine–human reassortant rotaviruses licensed in the USA in 2006; and the Lanzhou strain of lamb rotavirus, licensed in China and widely used there since 2000.[3] Rotarix and RotaTeq were both extensively tested for safety regarding intussusception and for efficacy, in trials comprising over 60,000 infants for each vaccine.[4] It is not clear whether multivalent vaccines are preferable or whether a monovalent vaccine could effectively prevent the high mortality associated with the first infection by taking the place of the first attack, as has been suggested in some clinical trials. However, full protection against infection and disease is strain specific.[3]

Both Rotarix and RotaTeq have been associated with a low incidence of vaccine attributable intussusception, of the order of 1:51 000 to 1:68 000 in the seven days after dose 1 for both vaccines. This is much less than the vaccine-attributable risk of RotaShield but does not take into account the fact that most cases of intussusception following RotaShield occurred in infants aged over 90 days.[4]

Haematemesis

Haematemesis is the vomiting of blood caused by bleeding in the oesophagus, stomach or duodenum, i.e. bleeding proximal to the duodenal-jejunal junction. The colour and volume of the vomitus is indicative of how long the blood has been in the stomach. Dark blood or 'coffee grounds' suggests a small bleed which has been altered in contact with gastric acid. A larger volume of bright red blood could instead be indicative of a rapid haemorrhage of a larger volume.[5] In a child presenting with haematemesis, the source of bleeding is the upper

gastrointestinal tract, even if it can represent swallowed blood, as in newborns with swallowed maternal blood. Children presenting with bright red blood in the stool or bloody diarrhoea is usually indicative of bleeding in the lower gastrointestinal tract, most likely the colon.[6]

Differential diagnoses of haematemesis in infants includes upper gastrointestinal bleeding, most commonly from esophagitis or gastritis; coagulopathies including those caused by vitamin K deficiencies; platelet disorders, or clotting factor deficiencies; swallowed blood from the nasopharynx or respiratory tract, or swallowed maternal blood, which is the most common aetiology in new-borns. Cases of ingested substances such as red food colourings and dyes have also been described as being mistakenly identified as blood. Less common causes of infant hematemesis include ulcerating gastric tumour, Dieulafoy arterial malformation and hereditary haemorrhagic telangiectasia.[7]

Reports in VigiBase

There were 129 cases, from all geographical regions in the world, of haematemesis reported for rotavirus vaccine in VigiBase, compared to 73 expected based on the background of the database, as of March 2020 (IC_{025} is 0.6). Seven of the reports were related to the withdrawn product Rotashield. The reports came from 17 countries within North and South America, Oceania, Europe and Asia. In 112 cases the doses had been administered between 28 days and 23 months of age, as recommended in the product labels. In two cases the vaccine was administered prior to the age of 28 days, and in two cases the vaccine was administered when the children were two, and four years old. In 13 cases the age when the vaccine was administered was not given. The sex distribution was 39% girls and 61% boys receiving the vaccine (compared with 43% girls and 54% boys for rotavirus vaccine with all reported adverse drug reactions (ADRs) in VigiBase). Sex was unspecified in less than 1% of the reports.

In 82 cases the reports had been marked as serious and five cases were reported as fatal. Unfortunately, there is no information of any performed autopsies which could have given additional background about the cause of death. For the fatal cases one was co-reported with the serious known adverse event intussusception leading to complications and finally death and one baby had been born premature at week 35. In one case the cause of death was stated as that the baby had died in their sleep suffocated from bloody vomit, and in another asphyxiation and accidental death were co-reported with haematemesis.

In 52 cases rotavirus vaccine was the only suspected drug and in 42 cases it was the only reported drug. In most cases the rotavirus vaccine was administered at the same time as other vaccines in childhood vaccination programmes. However, rotavirus vaccine was the only orally administered drug in all but two cases; one patient co-reported nystatin, simeticone and paracetamol and one co-reported glycine/iron against anaemia. Two cases noted a rechallenge.

In 33 of the reports, intussusception was co-reported. Four of these reports concerned the withdrawn product Rotashield. In most cases the vomiting of blood is reported to have happened the same day as the intussusception but in one case the vomiting of blood happened one month prior to the intussusception. In one case the intussusception and haematemesis were co-reported with vaccination failure and a rotavirus infection and gastroenteritis.

Time-to-onset was given on 109 of the reports. The time-to-onset was the same day or within a few days (24 reports, of which only one co-reported intussusception), up until four years (one report) with a median of three days for all the reports. For those cases co-reporting intussusception, the time to onset was more varied, with a median time to onset of 15.5 days (range 0 days ~10 months).

Causality assessment was made in 17 cases. In one of the cases with a rechallenge it was reported as 'definite', in 13 cases it was reported as 'possible', in one 'probable', in one 'unlikely', and one as 'not related'. In the report with causality assessed as 'probable', a six-week old male infant was vaccinated and the reaction occurred the same day as the intake of the vaccine. It was noted that: *"The health authority reported the causality of vomiting and haematemesis to be probably related and the severity to be severe. The patient's outcome was reported to be recovered without sequelae on an unknown date. Dechallenge was reported as "Definite improvement"*. The reporting physician who assessed the case as 'not related' did so because it was not labelled: *"The patient experienced haematemesis*

post vaccination. Time to onset was compatible but the event is unlisted with the vaccine."

Gastroscopy is not mentioned in any of the 129 reports as a means to investigate the cause of the haematemesis, and there are no cases that co-report ulcers of any kind. However, gastroenteritis is co-reported as an adverse drug reaction in seven of the reports. Looking in VigiBase there are 981 cases of gastroenteritis reported for Rotavirus vaccine, compared to 34 expected (IC_{025} 4.73). Only two of the 981 reports additionally mention combined immunodeficiency.

Literature and Labelling

Diarrhoea is a commonly reported gastrointestinal adverse event, abdominal pain and flatulence are listed as uncommon, and intussusception is listed as a very rare but serious adverse event also noted as a special warning in the product label: "As a precaution, healthcare professionals should follow up on any symptoms indicative of intussusception (severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever) since data from observational safety studies indicate an increased risk of intussusception, mostly within seven days after rotavirus vaccination."[1] Haematemesis, or vomiting of blood, is not listed in the UK or US labels. In the US DailyMed, vomiting, diarrhoea intussusception and recurrent intussusception (including death), haematochezia and gastroenteritis with vaccine viral shedding in infants with severe combined immunodeficiency (SCID), are the gastrointestinal disorders that are listed in the label.[1,8] No case reports of haematemesis and rotavirus vaccine were found when a literature search was performed in PubMed.

Haematemesis is described as one of several symptoms of duodenal ulcers following gastroenteritis caused by rotavirus infections.[9,10] In seven of the cases in VigiBase gastroenteritis is co-reported, however there are none that co-report duodenal ulcers. In the European risk management plan for Rotavirus vaccine, chapter 3.2 "Summary of important risks" it is noted under Missing information (information that refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine)): *Long term genetic stability of the vaccine virus strain (concern that genetic variations in the Rotarix vaccine strain could lead to clinical symptoms of Gastroenteritis - GE).* Additionally, under the heading "to present in the next PBRERs/EU PSUR: *An evaluation of all reported cases of rotavirus gastroenteritis (RVGE) after Rotarix vaccination, including confirmed/suspected vaccine failures and those RVGE cases reported after at least one dose, identified through continuous monitoring, with assessment of severity and cumulative reporting rates.*[11]

Discussion and Conclusion

It is known that haematemesis could occur in duodenal ulcers, which are sometimes caused by rotavirus induced gastroenteritis, which is included in the label, although only as "frequency unknown, in infants with SCID". In VigiBase there are 981 reports of gastroenteritis following vaccination with rotavirus vaccine, compared to 34 expected. Only two co-report SCID, indicating that there might be children without this deficiency that are affected by gastroenteritis caused by rotavirus vaccination, potentially also presenting as haematemesis.

Among the 129 reports of haematemesis in VigiBase, the time to onset of the reaction is short and fairly consistent. A majority of the cases were serious and five were fatal. In 52 cases it was the only suspected drug for this reaction and in 42 rotavirus vaccine was the only reported drug. In only three cases were there concomitantly used drugs other than additional childhood vaccines. For the reports with other childhood vaccines concomitantly reported, rotavirus vaccine was the only orally administered vaccine. Two cases reported a rechallenge and causality was set as definite in one of these reports. In the cases that co-reported intussusception, the haematemesis could potentially be explained by a gastric perforation that sometimes occurs as complication of intussusception.[12] However, for the majority of the reports there are no other evident alternative explanations. Vitamin K deficiency could lead to bleeding in infants, but vitamin K shots are recommended to be given to new-borns world-wide.[13-15]

The fact that practitioners judge haematemesis as not related to the vaccine because it is not listed in the label, as is shown in one of the reports shared to VigiBase, is problematic. Failure to see a potential link to the vaccine after the first dose would probably

lead to a second dose being administered and an additional risk to potentially develop haematemesis, such as has been seen among the cases in VigiBase. Several of the cases are severe and deaths have been reported.

Although vaccination with rotavirus vaccine continues to be an important health initiative that prevents serious illness or death for many children worldwide, there is a risk that the vaccine could cause gastroenteritis and haematemesis in certain individuals. Further studies establishing this possibility are needed and, in the meantime, it might be advisable to be vigilant of symptoms. If any occur, before repeated exposure to the vaccine there should be careful reflection.

References

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SIGNAL

WHO defines a signal as:

"Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously". An additional note states: "Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information".*

A signal is therefore a hypothesis together with supporting data and arguments. A signal is not only uncertain but also preliminary in nature: the situation may change substantially over time one way or another as more information is gathered. A signal may also provide further documentation of a known association of a drug with an ADR, for example: information on the range of severity of the reaction; the outcome; postulating a mechanism; indicating an "at risk" group; a dose range which might be more suspect; or suggesting a pharmaceutical group effect or a lack of such an effect by a particular drug.

Signals communicated by UMC are derived from VigiBase, the WHO global database of individual case safety reports. This database contains summaries of individual case safety reports of suspected adverse drug reactions, submitted by national pharmacovigilance centres (NCs) that are members of the WHO Programme for International Drug Monitoring. More information regarding the status of this data, its limitations and proper use, is provided in the Caveat on the last page of this document.

VigiBase is periodically screened to identify drug-ADR combinations that are unknown or incompletely documented. Combinations of such interest that they should be further reviewed clinically are sent to members of the Signal Review Panel for in-depth assessment. The Signal Review Panel consists of experienced international scientists and clinicians, usually affiliated with a governmental or an academic institution. The expert investigates the clinical evidence for the reaction being related to the suspected drug.

The topics discussed in the signals represent varying levels of suspicion. Signals contains hypotheses, primarily intended as information for the national regulatory authorities. They may consider the need for possible action, such as further evaluation of source data, or conducting a study for testing a hypothesis.

The distribution of signals is currently restricted to NCs, regulatory authority staff and their advisers, participating in the WHO Programme. Signals are sent to the pharmaceutical companies when they can be identified as uniquely responsible for the drug concerned. UMC does not take responsibility for contacting all market authorisation holders. As a step towards increased transparency, since 2012 UMC signals are subsequently published in the WHO Pharmaceuticals Newsletter.

National regulatory authorities and NCs are responsible for deciding on action in their countries, including communicating the information to health professionals, and the responsible market authorisation holders, within their jurisdiction.

In order to further debate, we encourage all readers of signals to comment on individual topics.

* Edwards I.R, Biriell C. Harmonisation in pharmacovigilance. Drug Safety 1994;10:93-102.

Responses from industry

Signals on products under patent are submitted to patent holders for comments. Responses from industry are unedited. The calculations, analysis and conclusions are theirs, and should be given serious but critical consideration in the same way as any scientific document. The WHO and UMC are not responsible for their findings, but may occasionally comment on them.

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Caveat Document

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs). Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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