Vaccine 30S (2012) A190–A195

Contents lists available at SciVerse ScienceDirect

Vaccine

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

Retrospective hospital based surveillance of intussusception in children in a sentinel paediatric hospital: Benefits and pitfalls for use in post-marketing surveillance of rotavirus vaccines

C. Lloyd-Johnsen[a], F. Justice[a], S. Donath[b,d], J.E. Bines[a,c,d,*]

[a] Rotavirus Group, Murdoch Childrens Research Institute, Melbourne, Australia
[b] Clinical Epidemiology and Biostatistics Unit, Murdoch Childrens Research Institute, Melbourne, Australia
[c] Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Melbourne, Australia
[d] Department of Paediatrics, The University of Melbourne, Melbourne, Australia

ARTICLE INFO

Article history:
Received 9 August 2011
Received in revised form 23 October 2011
Accepted 3 November 2011

Keywords:
Intussusception
Rotavirus vaccines
Post-marketing surveillance

ABSTRACT

Evaluation of the safety of rotavirus vaccines, particularly with respect to the risk of intussusception, is recommended for countries planning to introduce rotavirus vaccines into the National Immunisation Program. However, as prospective studies are costly, require time to conduct and may be difficult to perform in some settings, retrospective hospital based surveillance at sentinel sites has been suggested as an option for surveillance for intussusception following introduction of rotavirus vaccines.

Objective: To assess the value of retrospective hospital based surveillance to describe clinical and epidemiological features of intussusception in children aged <24 months and to investigate any temporal association between receipt of a rotavirus vaccine and intussusception.

Methods: A retrospective chart review of all patients diagnosed with intussusception at Royal Children's Hospital, Melbourne, Australia over an 8-year period including before and after rotavirus vaccine introduction into the National Immunisation Program, was conducted using patients identified by a medical record database (ICD-10-CM 56.1). Patient profile, clinical presentation, treatment and outcome were analysed along with records of immunisation status obtained using the Australian Childhood Immunisation Register.

Results: A 9% misclassification rate of discharge diagnosis of intussusception was identified on critical chart review. The incidence rate of intussusception at the Royal Children's Hospital over the study period was 1.91 per 10,000 infants <24 months (95% CI 1.65–2.20). Intestinal resection was required in 6.5% of infants (95% CI 3.6%, 11.0%). Intussusception occurred within 30 days after vaccination in 2 of 27 patients who had received at least 1 dose of a rotavirus vaccine.

Conclusions: Valuable data on the incidence, clinical presentation and treatment outcomes of intussusception can be obtained from data retrieved from hospital medical records in a sentinel paediatric hospital using standardised methodology. However, there are methodological limitations and the quality of the data is highly dependent on the accuracy and completeness of the patient information recorded, the system of coding and record retrieval.

1. Background

Evaluation of the safety of rotavirus vaccines, particularly with respect to the risk of intussusception, has been a major influence in the approach to clinical development and implementation of rotavirus vaccines [1–4]. When the World Health Organization (WHO) Special Advisory Group of Experts (SAGE) made the global recommendation for rotavirus vaccines in July 2009, it was recommended that post-marketing surveillance activities to detect rare adverse events, including intussusception, should be conducted or strengthened [5,6]. This recommendation was based on the previous experience with the first rotavirus vaccine to be licensed in the USA, the Rotashield vaccine (RRV-TV; Wyeth-Lederle, USA)[2,7]. In hindsight, early clinical trials of the Rotashield vaccine did hint at a possible association with intussusception although these studies were not powered to detect a statistically significant association of a rare association [8]. However, implementation of this vaccine within the National Immunisation Program in the US was

* Corresponding author at: Department of Paediatrics, University of Melbourne, Flemington Rd, Parkville, Victoria, 3052, Australia. Tel.: +61 3 9345 4107; fax: +61 3 9345 6667.
E-mail address: Julie.bines@rch.org.au (J.E. Bines).

0264-410X/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.vaccine.2011.11.015

associated with the detection of a rare association between intussusception and Rotashield® vaccine and the recommendation for the vaccine was suspended 9 months after its introduction [8]. The size of the large clinical trials of Rotarix® (RV1; GlaxosmithKline, Belgium) and RotaTeq® (RV5; Merck, USA) were driven by the need to exclude a risk of intussusception of >1 in 30,000 vaccine recipients [3,4]. Both vaccines were found to be safe and effective [3,4] in the large Phase III clinical trials, however, there remains a concern regarding the risk of rare adverse events, including intussusception, when the vaccines are administered outside the strict administration guidelines of a clinical trial and in regions where the baseline risk of intussusception is high or is unknown [6].

The aim of post-marketing surveillance activities is to detect rare adverse events related to vaccination but that had not been identified or comprehensively evaluated in pre-licensure clinical trials. Although it would be ideal to conduct post-marketing surveillance activities to determine the impact and safety profile of a new vaccine within each local regional context, these studies are expensive and require specific expertise if they are to provide complete and accurate data. Therefore, it is unrealistic to expect all countries that plan to implement rotavirus vaccines into the National Immunisation Program to have the resources needed to conduct post-marketing surveillance of sufficient quality to provide meaningful data [6,9]. One of the challenges facing new vaccines is the assessment of risk in regions where there is limited data on the baseline incidence and severity of diseases that may become the focus of safety investigations. This is particularly true for rotavirus vaccines and intussusception. Although intussusception is a well recognised surgical condition in infants globally, accurate data on the epidemiology and clinical presentation is limited, particularly in developing countries [10]. What data that is available suggests that there may be variability in the baseline incidence of intussusception between regions [1,10], making data on the incidence of intussusception obtained only from post-marketing surveillance activities extremely difficult to interpret.

One of the most common methods to evaluate the impact of introduction of a rotavirus vaccine is done by monitoring admissions for intussusception in a sentinel paediatric hospital and to compare data obtained from medical records in the immediate pre-vaccine and post-vaccination period [11–14]. Although this methodology has a number of limitations, it may provide useful information that may otherwise not be available. Intussusception is a diagnosis that is well suited to sentinel site surveillance as the diagnosis and treatment of this condition requires radiological and surgical expertise that is generally focused at key paediatric hospitals. Failure to diagnose and treat intussusception is usually associated with bowel obstruction, bowel ischaemia, perforation and ultimately death. Therefore, hospital based surveillance may under represent the true incidence and outcome of intussusception, particularly in resource poor settings where access to paediatric diagnostic facilities and treatment is limited [6].

In this study we aimed to assess the potential benefits and pitfalls of retrospective hospital based surveillance for intussusception in a sentinel paediatric hospital. We examined data collected retrospectively using hospital medical records during the period before and after introduction of a rotavirus vaccine into the National Immunisation Program in Australia.

2. Methods

The Royal Children's Hospital (RCH) is a major tertiary care paediatric hospital in Victoria providing for the care of the 70,000 annual birth cohort in Victoria, as well as specialist paediatric care for children with complex conditions from elsewhere in Australia and the Asia-Pacific region. A retrospective chart review was conducted at the Royal Children's Hospital over an 8-year period (July 1, 2001 to July 1, 2009). This period included 6 years prior to the introduction of Rotateq® into the National Immunisation Program and 2 years following this introduction. The medical records of all children aged <24 months admitted to the Royal Children's Hospital over the study period with a discharge diagnosis of intussusception (ICD-10-CM K56.1) were obtained and systematically reviewed. A standardised data collection form was used to verify the diagnosis of intussusception and to collect additional descriptive data including clinical symptoms, signs, treatment and outcomes. To evaluate the sensitivity of medical record coding at the Royal Children's Hospital over the study period we also conducted a search of the hospital database to identify any additional cases of intussusception that may have been miscoded as other gastrointestinal diseases that are rarely associated with intussusception (such as ICD-10-CM Q43.8: other specified congenital malformations of the intestine; ICD-10-CM K38.8: intussusception of the appendix) as well as for possible complications of intussusception, such as bowel obstruction. This data was compared to previously published data from the same hospital (January 1, 1995 to June 30, 2001) that was collected using the similar methodology [11] Patients with primary idiopathic intussusception confirmed by surgery, air or liquid-contrast enema as level 1 according to the Brighton Collaboration Clinical Case Definition, were included in the analysis [15]. To examine the possibility of a temporal association between receipt of a rotavirus vaccine and intussusception, we obtained vaccination records from the Australian Childhood Immunisation Register [16]. We compared the date of rotavirus immunisation to the recorded date of intussusception diagnosis, the age of each patient at the time of vaccination and the number and date of doses received.

Data were entered and stored in a secure Microsoft Access 2003 database. Incidence rates were calculated using age specific population estimates for Victorian children obtained from the Australian Bureau of Statistics for each year of the study [17]. Ninety-five per cent confidence intervals for incidence rates and their ratios were calculated using standard methods based on Poisson distribution. Poisson regression analysis was used to estimate incidence rate ratios that describe the difference in incidence rate for each age group from the beginning to the end of the study period. Statistical analysis was performed using Stata 10.0 (StataCorp, College Station, TX, USA). This study was approved by the Ethics in Human Research Committee at the Royal Children's Hospital, Melbourne.

3. Results

A total of 258 episodes of IS were identified in 230 children aged 24 months or less over the 8-year study period. Thirty-three patients were excluded from the final analysis. This included 11 patients whose diagnosis was secondary to underlying pathologies such as; Meckel's Diverticulum ($n = 6$), duplication cyst ($n = 1$), prolapsed stoma ($n = 1$) and post operative IS ($n = 3$). In addition, 21 cases of IS were found to be unproven on surgical or radiological investigations, and 1 case lacked sufficient data to make a complete assessment ($n = 1$). Approximately 9% ($n = 28$) of episodes were misclassified or coded incorrectly. Sixty-four cases were identified under codes that could be associated with intussusception and miscoded, although a subset analysis of these cases found no miscoded cases of intussusception. Four cases were not born in Victoria but presented to RCH for diagnosis and treatment of intussusception during the study. As these infants presented sporadically over the 8 years of the study, they did not significantly impact on the incidence rate calculations based on the Victorian birth cohort and were included in the final analysis. Final analysis was performed on the remaining 197 assessable cases.