Long-term protective effect of post-exposure Havrix™ administration during viral hepatitis Type A outbreaks

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Abstract. Administration of human normal immunoglobulin (HNIG) post-exposure has been routinely used in Slovakia for outbreak control of hepatitis A, but requires deep intramuscular injection, provides only short-lived protection and is a human blood product. The protective effect of post-exposure administration of an inactivated hepatitis A vaccine was evaluated during 10 outbreaks in Slovakia. Direct contacts of confirmed hepatitis A cases received either: a single dose of hepatitis A vaccine (n = 2171) or immunoglobulin (HNIG, n = 3837). In the HNIG group the number of hepatitis A confirmed cases dropped within the first 7 weeks, however the decrease was not as rapid or as marked as that observed in the vaccinated group where the number of hepatitis A cases dropped within the first 4 weeks after vaccination. Among contacts, 67 cases of hepatitis A were detected during the maximum incubation period of 45 days: 16 cases (0.7%) in the vaccine group and 51 cases (1.3%) in the HNIG group (p < 0.05). After two and three years respectively, 50 and 39 volunteers who had previously received one dose of hepatitis A vaccine received a booster dose and anti-HAV antibodies were measured. Differences in anti-HAV antibody GMCs before and after the booster were statistically significant. The longer time interval (3 years instead of 2) between primary vaccination and booster administration did not seem to impact the magnitude of the booster response. The results of this study show that active post-exposure immunisation with only one dose of inactivated vaccine confers high and long-term protection and effectively controls viral hepatitis A outbreaks.

Key words: Hepatitis A vaccine, Human immunoglobulin, Hepatitis A infection, Outbreak control

List of abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ELISA = enzyme-linked immunosorbent assay; GMC = geometric mean concentrations; HAV = hepatitis A virus; HNIG = human normal immunoglobulin; Ig = immunoglobulin; IgG = immunoglobulin G; IgM = immunoglobulin M; mIU/ml = milli-international units per milliliter; ml/kg = milliliter per kilogram; p = p-value; t = Student’s statistic

Introduction

Hepatitis A remains a serious public health problem, affecting children and adults worldwide. Although hepatitis A is often perceived as a benign infection, up to 15% of infected individuals will have a protracted or relapsing course [1]. Hepatitis A infection occasionally results in fulminant hepatic failure [2, 3] and the case fatality rate in the United States is between 0.3% and 1.8%, with the highest rates observed in older adults [1]. Although less common in the industrialized world compared to developing countries, high incidences of hepatitis A virus (HAV) infection may occur in specific ethnic groups and communities that may contribute to the onset or progression of hepatitis A outbreaks [4, 5].

In the Slovak Republic, hepatitis A among the Gypsy population remains a serious public health problem [6–9]. In Slovakia an excess morbidity from HAV infection in 1979 resulted from an explosive outbreak after widespread consumption of imported frozen products (Figure 1). A rapid decrease in morbidity after 1979 and 1980 (from 222.2 to 89.6 per 100,000 inhabitants) has been followed by a continuous steady decline over the last 22 years; from 61.4 per 100,000 in 1981 to 8.2 per 100,000 in 2002 [9]. The ongoing decline is the result of improved diagnosis, reporting and isolation of HAV infected patients, strict observance of anti-epidemic measures around the focus of infection and improved waste management. Small local outbreaks continue to occur every year, primarily among schoolchildren and Gypsy
communities [10]. An extensive outbreak in Kosice caused a slight rise in overall hepatitis A incidence in 1993 (Figure 1).

Post-exposure administration of human normal immunoglobulin (HNIG) to direct and indirect contacts of HAV infected individuals has been routinely used in Slovakia for preventing further spread of the disease. When administered within two weeks of exposure, HNIG is considered to be 80% to 90% effective in preventing clinical hepatitis A [1]. Protection is short-lived, lasting less than 3 months unless larger doses are given. The use of HNIG has proved unpopular due to the necessity of a painful deep intramuscular injection and prevailing apprehension with regard to the use of human blood products. Furthermore, failure of HNIG prophylaxis has been well documented [1] and has been observed in the context of hepatitis A outbreaks [11]. With no specific treatment available to date, inactivated hepatitis A vaccines have been used as an alternative to HNIG for the control of outbreaks in Slovakia, Alaska, as well other countries [12–15]. However few studies have directly compared the effectiveness of post-exposure vaccination and HNIG. We investigated the protective effect of post-exposure administration of an inactivated Hepatitis A vaccine compared to HNIG in school settings, during hepatitis A outbreaks in Slovakia.

Materials and methods

The study was conducted in two parts: The first part was an open multicentric comparative study carried out in the period from December 1993 to November 1995 in which direct contacts (i.e., those in close daily contact including family members, attending the same day-care centre and/or using the same lavatory in a school) of patients with laboratory confirmed HAV infection during outbreaks in Slovakia (occurring mainly in school communities) were randomly assigned to receive a dose of hepatitis A vaccine or HNIG. HAV cases were confirmed by clinical observation, biochemical testing (ALT and AST levels) and serology (IgM and IgG).

Oral informed consent was obtained from the contact or parent/guardian of each contact. Subjects in the vaccine group underwent serological testing prior to vaccination. Blood samples from these contacts were examined for the presence of IgM and IgG total anti-HAV antibodies by ELISA assay (Sorin, Italy, 10 mIU/ml cut-off). Seronegative contacts were then given a single dose of an inactivated Hepatitis A vaccine (Havrix™ 360‡ [≤ 18 years] or Havrix™ 720‡ [≥ 19 years], GlaxoSmithKline Biologicals, Belgium). The contacts in the second group were given HNIG (Norga Imuna [0.02 ml/kg], Sarisske Michalany, Slovak Republic) without prior examination of the presence of anti-HAV antibodies, as part of the routine HAV control measures in Slovakia.

Clinical cases of HAV infection were recorded 15–45 days after vaccination in vaccine recipients taking into account 14 days required for development of detectable antibody after vaccination and the minimum and maximum incubation period of HAV. Cases were recorded between 8–45 days in HNIG recipients taking into account the 7-day window of opportunity for HNIG administration after exposure recommended in Slovakia.

The second part of the study was a booster study conducted between March and April 1997, in two of the outbreak regions. A booster dose of Havrix™ 720 Junior monodose was randomly offered to children aged 5–9 and 10–14 years who had previously received a vaccine dose in the first part of the study and who resided in the towns of Kosice and