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RESEARCH PAPER

Effectiveness of hepatitis A vaccination as post-exposure prophylaxis

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ABSTRACT

Hepatitis A (HA) has been a vaccine-preventable disease since 1995. In Catalonia, a universal combined hepatitis A+B vaccination program of preadolescents was initiated at the end of 1998. However, outbreaks are reported each year and post-exposure prophylaxis (PEP) with hepatitis A virus (HAV) vaccine or immunoglobulin (IG) is recommended to avoid cases.

The aim of this study was to assess the effectiveness of HAV vaccine and IG in preventing hepatitis A cases in susceptible exposed people.

A retrospective cohort study of contacts of HA cases involved in outbreaks reported in Catalonia between January 2006 and December 2012 was made. The rate ratios and 95% confidence intervals (CI) of HA in susceptible contacts receiving HAV or IG versus those without PEP were calculated.

There were 3550 exposed persons in the outbreaks studied: 2381 received one dose of HAV vaccine (Hepatitis A or hepatitis A+B), 190 received IG, and 611 received no PEP. 368 exposed subjects received one dose of HAV vaccine and IG simultaneously and were excluded from the study. The effectiveness of PEP was 97.6% (95% CI 96.2–98.6) for HAV vaccine and 98.3% (95% CI 91.3–99.9) for IG; the differences were not statistically significant ($p = 0.36$).

The elevated effectiveness of HAV vaccination for PEP in HA outbreaks, similar to that of IG, and the long-term protection of active immunization, supports the preferential use of vaccination to avoid secondary cases.

KEYWORDS

effectiveness; Hepatitis A; immune globulin; outbreak; post-exposure prophylaxis; vaccine

Introduction

Hepatitis A (HA) is generally an acute, self-limited liver infection caused by the hepatitis A virus (HAV), an enterically-transmitted picornavirus. Infection is expressed in 2 major forms: asymptomatic and symptomatic. Asymptomatic forms are those without elevated serum aminotransferase levels or elevated aminotransferase levels but without symptoms. Symptomatic forms of HA are indistinguishable from those caused by other viral hepatitis and usually present with jaundice and dark urine, but symptomatic HA without jaundice also occurs. The onset may be abrupt with increasing fatigue, malaise, anorexia, fever, myalgia, dull abdominal pain, nausea and vomiting.[1,2] The clinical course of the disease is age dependent and the infection tends to progress to more severe forms in adults.[3] In children aged < 6 years, the infection is asymptomatic in more than 80% of cases[4] or is characterized by non-specific symptoms such as pharyngitis, cough, rhinitis, photophobia and headache. Atypical courses include acute liver failure, cholestatic hepatitis and relapsing hepatitis.[5] The disease may also be complicated by extra-hepatic manifestations.[6] On rare occasions, HAV infection results in fulminant disease with case-fatality rates as high as 60%,[2] and patients with chronic liver disease are at increased risk for severe or fulminant disease requiring urgent liver transplantation due to liver failure. The major factors associated with the worst outcomes include age, underlying liver disease and co-infection with other hepatotropic viruses.[7] Prolonged, relapsing hepatitis of up to one year occurs in 15% of cases.[8]

Although large outbreaks due to exposure to fecally contaminated food have been reported,[9-14] in developed countries the HAV is mainly transmitted person-to-person by the fecal-oral route among close contacts, particularly in day care centers, the household and extended family settings.[15,16]

In 1995, when inactivated HAV vaccines of proven immunogenicity and protective efficacy became available, a vaccination program of people belonging to risk groups was introduced in Catalonia, but the results showed that the impact of vaccination on the global incidence of the disease was small.[17] Therefore, at the end of 1998, a universal program of vaccination of preadolescents aged 12 y with a combined hepatitis A+B vaccine containing 360 Elisa units of HAV antigen and 10μg of hepatitis B surface antigen was introduced.

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Before the licensing of HA vaccines, HA post-exposure prophylaxis (PEP) was based on the administration of standard immune globulin (IG) to exposed people within 2 weeks after exposure. The efficacy of IG is about 80–98% and was first demonstrated in an outbreak at a summer camp in 1944 and has been confirmed by many studies.[18,19] Since IG began to be used as PEP, differences in the potency of different IG lots have been demonstrated and, consequently, its effectiveness also varies.[20,21] An effectiveness of 47% and 87%, respectively, were estimated for 2 IG lots although administration occurred at a similar interval from exposure to the index case.[22] Whether IG completely prevents infection or leads to asymptomatic infection and the development of persistent anti-HAV antibodies (anti-HAV) is probably related to the amount of time between the exposure and IG administration.[18,23] The efficacy of IG administered $\geq$ 2 weeks after exposure in preventing secondary cases has not been established.[2]

The use of IG for PEP has been limited by the licensure of inactivated HAV vaccines for people aged $\geq$ 12 months, usually recommended in a 2-dose schedule,[24] and the benefits of routine administration of one dose have also been reported.[25] Available HAV vaccines are highly immunogenic and at least 95% of healthy children, adolescents and young adults have protective antibody levels one month after receipt of the first dose. One month after a second dose, more than 99% of healthy children, adolescents and adults have protective antibody levels.[24] Adults aged $\geq$ 40 y appear to respond less well than younger adults to a single dose but equally after 2 doses.[26]

The aim of this study was to assess the effectiveness of administering one dose of HAV vaccine and IG in preventing HA cases in susceptible exposed people in outbreaks in Catalonia during 2012–2016.

Results

Of 163 outbreaks of HA reported to the Epidemiological Surveillance Units (ESU) between 2006 and 2012, 112 (68.7%) were selected. The remaining 51 outbreaks were discarded because the parameters analyzed could not be collected correctly: 7.1% of the outbreaks occurred in the community, 14.3% in schools and day care centers, and 62.5% in the family, and in 18 outbreaks (16.1%) the setting involved both family and schools or day care center (Table 1). The mean number of people exposed per outbreak varied according to the setting from 6 per outbreak in community outbreaks to 289 in day care center and school outbreaks.

The determining factor for whether PEP was administered after notification of the outbreak was always whether $\leq$ 14 d had passed since the last exposure. The distribution of outbreaks according to setting and type of PEP is shown in Table 2.

Of exposed people, 2381 (98.7% aged < 40 years) were administered HAV vaccine (2316 received the hepatitis A vaccine and 65 schoolchildren received the combined hepatitis A + B vaccine). There were 17 secondary cases in persons receiving the hepatitis A vaccine and no secondary cases in those receiving the hepatitis A+B vaccine. IG was administered as PEP to 190 exposed persons, in whom one case of HA occurred. We excluded 368 subjects who were simultaneously administered HAV vaccine and IG from the analysis. Finally, 611 exposed persons (mainly in the community and family settings) received neither the HAV vaccine nor IG due to the delay between the onset of the outbreak and ESU technicians becoming aware of it: there were 184 secondary cases in these 611 persons (Table 3).

The effectiveness of HAV vaccine (any type) as PEP was 97.6% (95% CI 96.2–98.6) compared with 98.3% for IG (95% CI 91.3–99.9), but the difference was not significant ($p = 0.36$). No significant differences ($p = 0.62$) were found between persons who received only the HAV vaccine (97.6%; 95% CI 96.1–98.6) and those who received the hepatitis A + B vaccine (100%; 95% CI 84.6–100).

Discussion

The results of this study show that the administration of HAV vaccine as PEP was effective in avoiding secondary cases in HA outbreaks in Catalonia. Various studies have found that HAV vaccine is as effective as PEP in HA outbreaks,[27-32] but few studies have estimated the effectiveness. In a RTC conducted by Victor et al.[33] new infections after PEP were assessed by measuring seroconversion in people aged 2–40 years: the estimated effectiveness of the HAV vaccine was 86% (95% CI 73–99) assuming that IG was 90% effective and 73% (95% CI 47–86) assuming that IG was 80% effective, consistent with the results of a previous study which found HAV vaccine for PEP was 79% (95% CI 7–95) effective in preventing infections as compared with an observational-only control group.[34] The results of the study by Victor et al. were taken into account by the U. S Advisory Committee on Immunization Practices of the CDC, when they recommended the vaccine in persons aged 2–40 y as the preferred PEP option.[35] More recent data from the US indicate that 74% of susceptible adults aged 40–49 y

Table 1. Characteristics of outbreaks by setting. Catalonia, 2006–2012.

Setting	No. of outbreaks	No. of exposed persons	Mean of exposed persons by outbreak	No. of secondary cases	Mean of secondary cases by outbreak
Family	70	549	7.8	110	1.6
Family and school	14	597	42.6	6	0.4
School	13	1336	102.8	28	2.1
Wider community	8	50	6.3	15	1.9
Family and day care center	4	343	85.8	33	8.2
Day care center and school	2	579	289.5	6	3
Day care center	1	96	96.0	6	6.0
Total	112	3550	31.7	204	1.8

Table 2. Distribution of outbreaks according to setting and type of post-exposure prophylaxis. Catalonia, 2006–2012.

Setting	IG	Vaccine	IG and vaccine	No post-exposure prophylaxis	Total
Family	6	20	27	17	70
Family and school	1	8	4	1	14
Family and day care center	0	2	1	1	4
Day care center and school	0	1	1	0	2
School	2	4	7	0	13
Day care center	0	0	1	0	1
Wider community	0	3	2	3	8
Total	9	38	43	22	112

seroconverted 15 d after the administration of one dose of vaccine and that 90% seroconverted at 30 days, suggesting that administration of HAV vaccine as PEP is also efficacious in this age group.[36] An Australian retrospective cohort study[37] found an effectiveness of the HAV vaccine in preventing secondary cases of 95% (95% CI 66.1–99.4), very close to that found in the present study: no contact aged > 40 y who received HAV vaccine was subsequently infected with hepatitis A, and the authors suggested that the upper age restriction for HAV vaccine as PEP might be omitted. In our study, of the 80 exposed people aged > 40 years, one dose of HAV vaccine failed to avoid the appearance of a secondary case in only one person, a 43-year-old man.

A retrospective pooled analysis assessing the effect of age on the immunogenicity of the inactivated HAV vaccine in healthy adults according to randomized, double-blind vaccination studies, concluded that the immune response was similar in adults aged >40 y and in those aged 20–30 y one month after the first and second dose, whereas younger subjects had a higher seroconversion rate 15 d after the first dose.[38]

The prevalence of anti-HAV in the population has been decreasing, raising concerns that anti-HAV levels in IG preparations might lessen effective levels. Although there is no standard for antibody levels in IG preparations, reduced anti-HAV titers have been documented in pooled plasma in the United States and Europe.[39] The manufacture of IG from selected antibody-positive donors may need to be considered in order to develop a hyperimmune globlulin for HA prevention, analogous to other agent-specific hyperimmune globulins.

The protection conferred by vaccination is long-term and the safety of the inactivated HAV vaccine has been widely demonstrated (few adverse reactions which are usually very mild).[40-44] Therefore, we suggest the HAV vaccine might be considered as the preferred PEP option in exposed people aged < 50 y. Administration of HAV vaccine to immunosuppressed subjects does not seem to be associated with a greater risk compared with immunocompetent persons.[2,45] The only contraindication to the vaccine is in people with hypersensitivity to any of the vaccine components.[24]

Successful interventions in outbreaks through active immunization requires close coordination between public health surveillance and the intervention system and, most importantly, compliance from the community involved.[46] In addition, because HA cannot be reliably diagnosed by the clinical presentation alone, serological confirmation of HA infection in the index case by IgM anti-HAV testing is essential before PEP is considered.[7]

One limitation of this study is that the effectiveness of both the HAV vaccine and IG was estimated without considering asymptomatic infections, symptomatic cases that do not attend health care services or cases not reported by physicians. However, this possible underdetection may not differ in outbreaks in which PEP used the HAV vaccine and those in which PEP was IG. Likewise, the hepatitis A+B universal vaccination program has been fully introduced in Catalonia since the year 2000 and some individuals considered susceptible might have been vaccinated already. However, it seems unlikely that this would have produced different results in outbreaks in which the vaccine or IG was administered.

In conclusion, administration of the HAV vaccine was effective in avoiding secondary cases after outbreaks and its effectiveness was equivalent to that of IG. The use of the vaccine as PEP should be prioritized because it provides greater long-term protection.

Material and methods

HA outbreaks reported to the Public Health Agency of Catalonia Surveillance System, which covers all Catalonia, a region in the northeast of Spain with a population of 7.5 million, between January 1, 2006 and December 31, 2012, were analyzed.

Data were collected from reports of outbreaks made by ESU throughout Catalonia. In each report, the number of exposed people, setting of the outbreak (family, day-care, school or community) and the number of secondary cases after PEP (IG, HAV vaccine or neither) were recorded.

A clinical case of HA was defined as a discrete onset of any sign or symptom consistent with acute viral hepatitis (fever, malaise, anorexia, vomiting, diarrhea, abdominal pain or arthralgia, jaundice and elevated serum alanine aminotransferase level). A confirmed case was defined as a case meeting the clinical case definition with positive HAV immunoglobulin M (IgM) antibodies or when the case met the clinical case definition and occurred in a person epidemiologically linked to a laboratory-confirmed case.[47]

Table 3. Effectiveness of post-exposure prophylaxis measures in outbreaks studied. Catalonia, 2006–2012.

Post-exposure prophylaxis	Exposed persons	Secondary cases	Rate of secondary cases (%)	Rate Ratio (95% CI)	Effectiveness (95% CI)	p
Any hepatitis A vaccine	2.381	17	0.71	0.024 (0.014–0.038)	97.6 (96.2–98.6)	<0.01
Hepatitis A vaccine	2.316	17	0.73	0.024 (0.014–0.039)	97.6 (96.1–98.6)	<0.01
Hepatitis A+B vaccine	65	0	0	0.00 (0.00–0.154)	100 (84.6–100)	<0.01
Immune globulin	190	1	0.53	0.017 (0.001–0.087)	98.3 (91.3–99.9)	<0.01
No post-exposure prophylaxis	611	184	30.11	Ref.	Ref.	
Total	3.182	202	6.35			

A HA outbreak was defined as ≥ 2 epidemiologically-linked cases, with at least one being laboratory-confirmed (IgM antibody to HAV positive). The index case was defined as a patient who presented symptoms compatible with viral hepatitis, with IgM anti-HAV positive, and was unrelated to a previous case.

A secondary case was defined as a patient who presented symptoms compatible with viral hepatitis and was epidemiologically linked with an index case who initiated clinical symptoms previously.

To assess the association between PEP measures and secondary cases, the relative rate (RR) and its 95% confidence intervals (CI) were calculated using conditional maximum likelihood estimates. The attack rate of secondary cases in exposed people from outbreaks in which no PEP could be adopted was considered the reference category.

The effectiveness of each measure was estimated using the formula 1-RR, where RR is the ratio between the attack rate of secondary cases in exposed people from outbreaks in whom PEP was administered and the attack rate of secondary cases in outbreaks in which no PEP was administered. 95% CI of the RR were calculated using maximum likelihood estimates.[48]

The analysis was made using the SPSS 18 statistical program.

Abbreviations

Anti-HAV	hepatitis A virus antibody
CI	confidence interval
ESU	Epidemiological Surveillance Units
HAV	hepatitis A virus
HA	hepatitis A
IG	immune globulin
IgM	immunoglobulin M
PEP	post-exposure prophylaxis
RR	relative rate

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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