SAFETY AND EFFECTIVENESS OF THE NEW INACTIVATED HEPATITIS A VIRUS VACCINE

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Purpose: To examine the evidence concerning the safety and effectiveness of the inactivated hepatitis A virus vaccine recently licensed for use in Canada.

Data sources: The main source of information were papers presented at the International Symposium on Active Immunization against Hepatitis A, held in Vienna, Austria, Jan. 27–29, 1992. The bibliographies of these papers were searched for additional references. Recent articles describing the new vaccine and the epidemiologic aspects of infection with hepatitis A virus (HAV) were also reviewed.

Study selection: Peer-reviewed reports of trials approved by a government regulatory agency on the safety, immunogenic properties and efficacy of the vaccine.

Data extraction: The authors assembled key reports on adverse reactions, protection from disease and serologic assessment of immune response in vaccine recipients; data from these reports were tabulated and analysed.

Results of data synthesis: The new vaccine contains the HM175 strain of HAV, which is adapted to grow in tissue culture. The virus is purified, inactivated with the use of formaldehyde and adsorbed onto aluminum hydroxide. The recommended dose for adults is 720 enzyme-linked immunosorbent assay (ELISA) units in a 1.0-mL dose and for children 360 ELISA units in a 0.5-mL dose, injected intramuscularly. The usual schedule is three serial doses, the second given 1 month and the third 6 to 12 months after the initial dose. Reported side effects are infrequent and minor. In healthy persons who have received two doses, the seroconversion rate is almost 100%. Protective efficacy after two doses is estimated to be 94%. However, the persistence of protective antibodies has been studied only over the short term (3 years).

Conclusions: The new HAV vaccine is safe, effective and best suited to pre-exposure prophylaxis in people with an increased risk of infection for an extended period, such as travellers to areas where the disease is endemic. Further studies are needed to determine whether infants respond well to the vaccine and whether the vaccine protects recipients from subclinical infection and associated fecal shedding of HAV. Controlled trials to determine the duration of protection beyond 3 years and the effects of more rapid dosage schedules are also needed.

Objectif : Examiner les preuves relatives à la sécurité et à l'efficacité du vaccin au virus de l'hépatite A inactivé dont l'utilisation a été autorisée récemment au Canada.

Sources de données : Des communications présentées au Symposium international sur l'immunisation active contre l'hépatite A, qui a eu lieu à Vienne, en Autriche, du 27 au 29 janvier 1992, ont constitué la principale source d'information. On a recherché des références supplémentaires dans les bibliographies de ces communications. On a examiné aussi des articles récents décrivant le nouveau vaccin et les aspects épidémiologiques de l'infection au virus de l'hépatite A (VHA).

Sélection d'études : Rapports critiqués par des pairs sur des essais approuvés par un organisme gouvernemental de réglementation, et portant surtout sur la sécurité, les propriétés immunogènes et l'efficacité du vaccin.

Extraction de données : Les auteurs ont réuni des rapports clés sur les réactions indésirables, la protection contre la maladie et l'évaluation sérologique de la réaction immunitaire des sujets vaccinés; ils ont analysé les données tirées de ces rapports après les avoir compilées.

Résultats de la synthèse des données : Le nouveau vaccin contient la souche HM175 du VHA, adaptée pour se reproduire dans des cultures tissulaires. Le virus est purifié, inactivé à l'aide de formaldéhyde et adsorbé

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*The National Advisory Committee on Immunization has published a statement on the prevention of hepatitis A infections (*Can Commun Dis Rep *1994; 20: 133–143), which provides further information of interest to readers concerned with hepatitis A.*

← For prescribing information see page 396

sur de l'hydroxyde d'aluminium. La dose recommandée pour les adultes est de 720 unités ELISA (technique de titrage avec immunoadsorbant lié à une enzyme) dans une dose de 1,0 mL et, pour les enfants, de 360 unités ELISA dans une dose de 0,5 mL, injectée par voie intramusculaire. La posologie habituelle comporte trois doses en série, la deuxième étant administrée 1 mois après la dose initiale, et la troisième, de 6 à 12 mois après la dose initiale. Les effets secondaires signalés sont peu fréquents et mineurs. Chez les sujets en bonne santé qui ont reçu deux doses, le taux de séroconversion atteint presque 100 %. On estime à 94 % l'efficacité de la protection après deux doses. La persistance des anticorps protecteurs n'a toutefois été étudiée qu'à court terme seulement (3 ans).

Conclusions : Le nouveau vaccin au VHA est sûr, efficace et convient idéalement à une prophylaxie préexposition chez les sujets à risque accru d'infection pendant une période prolongée, comme les voyageurs qui se rendent dans des régions où la maladie est endémique. Il faudra effectuer d'autres études pour déterminer si les nouveau-nés réagissent bien au vaccin et si le vaccin protège les sujets vaccinés contre l'infection subclinique et l'élimination fécale connexe du VHA. Il faudra procéder aussi à des essais contrôlés afin de déterminer la durée de la protection après 3 ans et les effets de posologies plus rapprochées.

The purpose of this review is to inform physicians and health care workers about the recent advances in research into the hepatitis A virus that have resulted in the development of a new inactivated virus vaccine. This review assesses critically the results of clinical studies to ascertain the safety and effectiveness of the vaccine, which has recently been licensed for use in Canada.[1]

The main source of information are papers presented at the International Symposium on Active Immunization against Hepatitis A, held in Vienna, Austria, on Jan. 27 to 29, 1992. The bibliographies of papers from the symposium were searched for additional references. As a criterion for inclusion in our review, studies had to be premarketing trials approved by a government regulatory agency. The studies included case series to determine side effects of the vaccine and antibody response, and randomized controlled trials of the efficacy of the vaccine.

Hepatitis A infection

Type A hepatitis is usually a self-limited inflammation of the liver resulting from infection with hepatitis A virus (HAV). Infection usually causes illness in adults and school-aged children, but it is often asymptomatic in younger children.[2] Typical symptoms are malaise, fatigue, nausea, fever, chills, headache and abdominal discomfort. In about two thirds of cases these symptoms are accompanied by jaundice.[2] Recovery often takes 4 to 6 weeks. Persistent infection and chronic hepatitis have not been documented. Severe fulminant hepatitis A infection leading to death is rare: case fatality rates are less than 1% among adults with the disease admitted to hospital.[3]

HAV is shed in the feces of an infected person starting early in the incubation period, which is usually 3 to 4 weeks, and reaching a maximum level just as symptoms develop.[2] Hence, the virus is efficiently transmitted in poor hygienic conditions. Reduction of water and food contamination, which interrupts the fecal–oral spread of the virus, along with improvements in personal hygiene, has markedly reduced the incidence of HAV infection.[2]

Epidemiologic features

Hepatitis A is one of the oldest diseases known to humankind. It was especially common in military campaigns, earning the early designation "campaign jaundice." In 1912 Cockayne first used the term "infectious hepatitis" to describe this contagious form of jaundice.[4] In 1947 McCallum[5] introduced the designations hepatitis A and B to distinguish these two types of the disease.

Canada, like most industrialized countries, has a relatively low incidence of hepatitis A. From 1000 to 3000 cases are reported annually.[6] Since 1987, the reported incidence rates have ranged from 4.4 to 11.2 cases per 100 000 population.[6] Hepatitis A accounts for 20% to 40% of sporadic cases of acute viral hepatitis reported in adults (Dr. Donna Holton, Laboratory Centre for Disease Control, Health Canada, Ottawa: personal communication, 1994). Virtually all epidemics of hepatitis are attributable to HAV; however, epidemics account for less than 15% of reported hepatitis A cases.[2]

Risk factors for HAV infection in Canada and the United States include residence in certain communities in rural or remote areas[7] or in certain institutions, including prisons[8] and institutions for mentally disabled people;[9] employment or attendance at day-care centres for infants and toddlers;[10] injection or oral administration of illicit drugs;[11] homosexual behaviour among men involving anal contact;[12] and travel or temporary residence in countries with inadequate sanitation.[11] Infection in returning travellers accounts for 10% to 15% of reported cases in the United States.[11] The risk of acquiring infection for travellers to developing countries is estimated at 3 to 6 per 1000 people per month[13] and higher for those who eat or drink in places with poor hygienic conditions. The most commonly identified risk factor for HAV infection is exposure to an infected person.[2,11] In many cases no specific risk factor can be identified.

Infection with HAV usually results in lifelong immunity.[2] Only one serotype of HAV exists; infection with HAV provides no protection from other hepatitis viruses.[14] Immunity is mediated by antibody to HAV, particularly virus-neutralizing antibody. The minimum anti-

HAV serum concentration required for protection is not known with certainty,[15] but a serum level of 10 to 20 mIU/mL or greater is believed to be protective.

Hepatitis A virus

Many attempts to isolate HAV in tissue cultures were made in the 1950s and 1960s; however, the virus was not identified until 1973, when it was found by immune electron-microscopic examination of fecal specimens from patients with the disease.[16] By 1979 Provost and Hilleman[17] had successfully cultivated HAV and achieved serial passage of the virus in cell culture, opening the door to a vaccine.

HAV is a member of the picornavirus family; it is distinct enough to constitute a new genus with the suggested name of heparna (for Hep-A-RNA virus).[14] HAV has no envelope, making it relatively resistant to drying and detergents. It is also relatively heat resistant, able to withstand a temperature of 60°C for 1 hour. The relative resistance of HAV to disinfectants means that extra precautions must be taken when caring for patients with the disease and handling their body fluids.

Inactivated virus vaccine

Inactivated HAV vaccine became possible once enough HAV for commercial production could be propagated in cell cultures. Such vaccines must meet stringent regulatory requirements. The virus must be grown in approved cell cultures and then be thoroughly inactivated. The final vaccine must have a high degree of purity with almost complete absence of contaminating nonviral proteins and nucleic acids.[18]

The vaccine recently licensed in Canada (Havrix, SmithKline Beecham Biologicals, Rixensart, Belgium) is manufactured from the HM175 virus strain, which is adapted to grow in MRC5 human diploid cells.[1,19] Cell cultures inoculated with the virus are incubated for at least 3 weeks, harvested and disrupted by freeze-thawing to release intracellular virions. The virions are then purified by ultrafiltration and chromatography, and inactivated by treatment with formaldehyde. The virions are then adsorbed onto aluminum hydroxide adjuvant and suspended in isotonic buffered saline solution containing 0.5% phenoxyethanol as a preservative. The final vaccine contains traces of bovine albumin and formalin.

Between December 1988, when the first study was started with a pilot lot of vaccine, and January 1992, when the vaccine was first licensed for use in Europe, 67 studies were initiated in 18 countries.[20] A total of 47 145 subjects, including 20 586 control subjects, participated in these studies. More than 55 000 doses of HAV vaccine were administered to study participants. The results of these clinical studies are summarized in Table 1.

Studies of immunogenicity

Subjects recruited for the various studies were healthy adults who had given informed consent or healthy children for whom consent was obtained from parents or guardians. All study protocols were approved by independent ethical review boards. In small studies, subjects were screened for serum antibodies against HAV, and only seronegative subjects were vaccinated. In large field studies of the protective efficacy of the vaccine, subjects were vaccinated without prior antibody screening.

The optimal level of antigens per dose of the vaccine was determined in a dose-range study[29] that compared the sero-

Table 1: Results of clinical studies of Havrix hepatitis A virus vaccine (results shown after two or three doses)

Study	No. of participants: Vaccine group	No. of participants: Control group	Type of study	Age of participants, yr	Adverse reactions, % of participants*	Seroconversion rate, %
Ambrosh et al[21]	55	55	Case series	18–35	5.4	100.0
André et al[20]†	4 869	0	Case series	Adults	11.3	NM
	1 281	0	Case series	Adults	NM	99.8
Delem et al[22]	79	0	Case series	18–47	NM	100.0
Green et al[23]	27	43	Case series	19–44	Minimal	93.0
Horng et al[24]	103	0	Case series	< 1–6	4.9	100.0
Innis et al[25]	19 037	19 120	Double-blind, controlled trial	1–16	9‡	NM§
Jilg et al[26]	90	0	Case series	Young adults	NM	100.0
Scheifele et al[27]	64	0	Case series	40–61	41–44‖	100.0
Wiedermann et al[28]	69	23	Case series	Adults	NM	100.0

*NM = not measured.
†This was a compilation of 15 case series.
‡This is the rate of adverse reactions observed among the participants given hepatitis A vaccine; the rate was 13.2% among participants in the control group, who were given hepatitis B vaccine.
§In this study the outcome measured was protection from hepatitis A; 94% of participants were protected.
‖Rate of local reactions after two or three doses.

conversion rates and geometric mean serum antibody titres in adult subjects after the administration of vaccines containing 180, 360 or 720 ELISA units of antigen. The results showed a direct relation between antigen dose and the immunogenicity of the vaccine: a single dose of 720 ELISA units resulted in 100% seroconversion 1 month after administration. This dose, contained in 1.0 mL of vaccine, was chosen for immunization of adults, and 360 ELISA units in 0.5 mL of vaccine was chosen for children.[29] In most studies the vaccination schedule consisted of a two-dose primary series administered 1 month apart, followed by a booster dose 6 or 12 months after the initial dose. Results of 15 clinical studies involving 2900 adults, summarized by André and associates,[20] showed a seroconversion rate of 95.7% (1225/1280) 1 month after the first dose. A second dose, given 1 month after the first, resulted in an overall seroconversion rate of 99.8% (1278/1281).[20] The geometric mean serum concentration of antibodies increased from 304 mIU/mL to 517 mIU/mL, and decreased little in the following 6 to 12 months. A booster dose at 6 or 12 months induced a large increase in serum antibody concentrations.[22]

Hepatitis A vaccine can be given at the same time as hepatitis B vaccine[21] or certain other vaccines, provided that separate injection sites are used for each vaccine. A vaccine containing both hepatitis A and hepatitis B components is being developed.[30]

For people who need to obtain protection more rapidly, the initial doses can be given 2 weeks apart. Simultaneous injection of the initial doses (one in each arm) is being assessed but is not yet recommended for routine use.[26] One recent trial of a shorter immunization schedule (with the first two doses administered 2 months apart and a booster dose 4 months after the initial dose) found that it produced adequate antibody levels.[30] However, this alternative schedule is not recommended by the manufacturer.

Another means of obtaining prompt protection if time is limited is to administer HAV vaccine and immune globulin concurrently at separate injection sites; this measure does not substantially impair response to the vaccine.[23,32]

Studies of protective efficacy

The ultimate test of an HAV vaccine, once it is shown to be highly immunogenic in small-scale studies, is to determine its efficacy in protecting recipients from symptomatic infection with HAV. To obtain statistically significant results, studies of protective efficacy must involve several hundreds or thousands of participants in communities where HAV is highly endemic. Such a large, randomized, double-blind controlled study was conducted in Thailand.[25] It involved 40 199 children 1 to 16 years of age, of whom 38 157 entered surveillance after vaccination and 33 586 completed 18 months of surveillance. After two doses, the vaccine was 94% effective in preventing symptomatic illness associated with elevated serum levels of alanine aminotransferase (ALT) and positive IgM antibodies to HAV. Of 6976 episodes of illness in participants during the controlled trial, there were 40 cases of hepatitis A; 38 were in the control group and 2 in vaccine recipients. These recipients fell ill 257 and 267 days respectively after having received only one dose of vaccine. They appeared to have been partially protected, since their illnesses were brief and were associated with only slight increases in serum ALT levels. This study also showed that two doses protected recipients from hepatitis A for at least 1 year. It is assumed that vaccination provides similar protection for healthy adult vaccinees, since their antibody response patterns resemble those of children.[20,22,24]

Follow-up studies showed that vaccinated children continued to be protected for at least 3 years.[31] The persistence of vaccine-induced antibodies is believed to be related to the duration of protection. In passive immunization against HAV with the use of hyperimmune globulin in travellers, a serum level of hepatitis A antibodies of 10 mIU/mL, measured by ELISA, was the minimal antibody concentration that provided protection.[28] Studies of antibodies to HAV have shown that the annual rate of decrease in serum levels after vaccination is about 43%.[28] On the basis of these observations the mean persistence of vaccine-induced antibodies is estimated to be 10 to 11 years after the booster dose and 6 to 7 years if only the two primary doses are administered.[28]

Studies of adverse reactions

Side effects to HAV vaccine have been infrequent and minor, in keeping with the nonreactive nature of the killed virions.[20] The most frequent reaction, reported in about one third of adult vaccinees, is mild soreness at the injection site that usually lasts about a day. This soreness is likely caused by the aluminum adjuvant.[20] Local induration, erythema or swelling occur infrequently. Local reactions do not become more severe with successive doses. General symptoms such as headache, malaise and fatigue are reported by less than 10% of recipients.[20,27] HAV vaccine does not cause elevation of serum ALT levels. In the large study conducted in Thailand, which involved the administration of more than 109 000 doses of vaccine to children, no serious side effects such as anaphylaxis were reported; however, not all of the children were followed.[29] Most studies of adverse reactions were case series. Randomized controlled studies, which would have controlled for "background symptoms" not caused by the administration of the vaccine, would have been preferable.

HAV vaccine is contraindicated in patients who are allergic to any of its constituents, including bovine albumin and aluminum. Safety in pregnant women has not been assessed. Response to the vaccine in immunocompromised patients may be suboptimal.

Studies of a similar product

An inactivated vaccine similar to Havrix, being developed by Merck Sharp and Dohme, is based on an attenuated seed virus (the F′ variant of the CR-326F strain).[34] This

product has not yet been licensed in Canada. Like Havrix, the virus in this product is grown in MRC5 cell cultures, purified, inactivated with formaldehyde and adsorbed to aluminum adjuvant. The vaccine contains thimerosal as a preservative. This vaccine is also minimally reactogenic. One study of the vaccine's effectiveness showed that, in healthy young adults, a single dose of 25 ng of viral protein resulted in 100% seroconversion.[34] Results of a double-blind, placebo-controlled study showed that a single dose of HAV vaccine protected 100% of 519 children in the vaccine group, whereas hepatitis A developed in 7% (34/518) of the children in the control group.[35] The usual immunization schedule for this product is two doses 6 months apart.

Who should receive HAV vaccine?

Havrix, the licensed hepatitis A vaccine, is currently recommended only for pre-exposure prophylaxis.[1] It will be of greatest benefit to people who have an increased risk of infection for an extended period; use of the vaccine will spare such recipients repeated or large-volume injections of immune globulin.[15]

This vaccine is currently licensed for use in adults only, and no specific pediatric formulation is available. However, excellent protection was achieved with no significant side effects in school-aged children in Thailand through vaccination with half the dose given to adults (360 ELISA units in a 0.5-mL dose).[25] No appreciable differences in adverse reactions or seroconversion rates between children and adult recipients have been reported.[20,22,25]

The National Advisory Committee on Immunization has identified people who have an increased risk of HAV infection[1] and are therefore candidates for vaccination.[36]

1. Residents of communities with high endemic rates of hepatitis A or recurrent outbreaks of the disease. In Canada, such communities are typically located in remote areas. Effective community-based vaccination programs would need to include children and adults.[1]
2. Missionaries,[37] diplomats, engineers and other people planning to live for extended periods in developing countries.
3. Members of the armed forces or emergency-relief organizations and other people who could be posted at short notice to areas with high rates of HAV infection.[1]
4. Travellers to developing countries, especially those who plan to stay in areas with rural or primitive conditions.[38]
5. Residents and staff of institutions for the mentally disabled.

HAV vaccination could be considered for patients with a high risk of infection as a result of behaviour, such as homosexual men or users of illicit drugs; for inmates of prisons in which control measures have been ineffective in preventing continuing problems with HAV infection; for workers involved in research on HAV or vaccine production; and for patients with hemophilia A or B who receive plasma-derived coagulation factors.[1]

Other indications for vaccination may emerge as a result of further study of the epidemiologic aspects of hepatitis A in Canada. At present, vaccination of health care workers,[39] sewage workers,[40] food handlers or child day-care staff and students is not clearly warranted. Although child day-care centres have been the focus of numerous outbreaks in the United States, such events have been infrequently reported in Canada.[10]

Targeted vaccination of people with a high risk of hepatitis A is unlikely to affect the epidemiologic features of this disease in North America significantly.[41] Since the incidence of HAV in Canada appears to be very low and hepatitis A is a self-limited illness that does not lead to chronic liver disease, universal childhood vaccination is not currently recommended in Canada.

Other preventive measures

Vaccination cannot be expected to be 100% effective. Sensible precautions concerning beverage and food quality in areas where hepatitis A is endemic remain critical to avoiding HAV infection. For health care workers, the principal way to prevent hepatitis A is through the adoption of good aseptic technique, including scrupulous hand washing and gowning and gloving when needed, in order to protect workers from exposure to body fluids or feces.[39]

Conclusions

1. The new hepatitis A vaccine is safe and effective in children and adults. Side effects have been infrequent and minor. A seroconversion rate of almost 100% is observed in healthy people after the administration of two doses 1 month apart. From the results of a randomized, double-blind controlled trial of the vaccine in children, protective efficacy is estimated at 94% after two doses. On the basis of seroresponse, similar protection is assumed to exist in adults.
2. The recommended vaccination schedule is three doses, the first two given 1 month apart, and the third given 6 to 12 months after the first.
3. The vaccine is recommended for pre-exposure prophylaxis in people with an increased risk of infection for an extended period, such as travellers, in order to spare them from repeated or large-volume injections of immune globulin.
4. Future studies are needed to determine the following:
   - response to the vaccine in infants,
   - protection from subclinical infection and associated fecal shedding of HAV,
   - duration of protection beyond 3 years,
   - rapid dosage schedules,
   - responses of immunocompromised patients and those with long-term illnesses,
   - effectiveness and side effects of combination vaccines that contain HAV vaccine, and any impairment of immune response to other vaccine components in such combination vaccines.

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