Epaxal® : Clinical Experience with the Only Aluminium-free Hepatitis A Vaccine

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Hepatitis A

1. The disease

Hepatitis A (or 'travel hepatitis') is an acute, usually self-limiting infection, caused by the hepatitis A virus (HAV), a small RNA virus (25 nm in diameter) surrounded by a protein capsid. It spreads by the faecal-oral route and infections mostly result from consumption of contaminated drinking water or food. All age groups are susceptible, but the disease only tends to manifest itself in older children and adults[1]. Adults over 40 years of age are at significantly greater risk than younger patients of serious complications, including death. While the overall case-fatality rate of hepatitis A is estimated at 0.15 % in the general population, it may exceed 2% in patients over 40 years old[2, 3].

2. Changing epidemiology

In Europe, an increasing proportion of cases of hepatitis A are associated with foreign travel. In areas of high endemicity, such as Africa and parts of Asia and Latin-America, infection with HAV is primarily a childhood disease through which lifelong immunity is achieved (as used to be the case in Europe until the 1950s). However, as a result of improvement in hygiene standards in many countries of high endemicity, the age at which HAV infection occurs has started to rise, leaving increasing numbers of adolescents and adults unprotected (Fig. 1). Therefore, the risk of clinically symptomatic HAV infection exists not only for travellers who visit high endemicity regions but also for increasing numbers of adults living in such areas[4, 5].

3. Prevention strategies

Rising standards of hygiene had started to elimi-

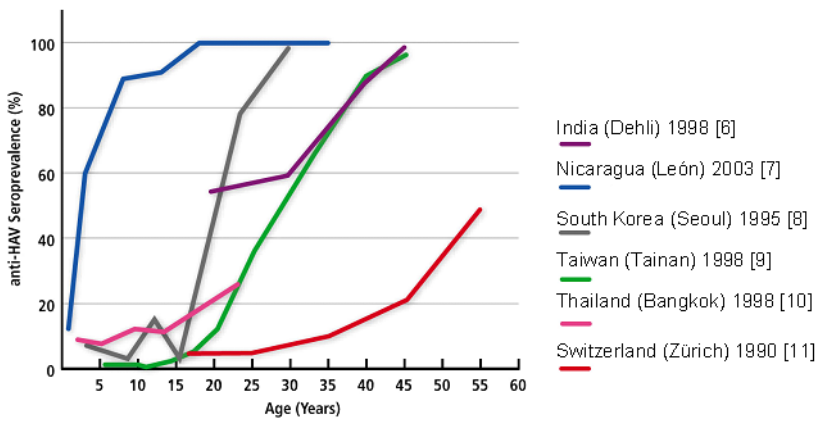

Fig. 1. Seroepidemiology of hepatitis A in selected countries[6~11].

nate HAV infection in industrialised countries decades before the introduction of vaccines. Improvements in hygiene in endemic regions is currently responsible for the shift of infection into older age groups, thereby causing outbreaks and an associated increased disease burden in the adult population[4]. Although the Anti-HAV seroprevalence differs between countries with mixed and low endemicity, the indication for hepatitis A vaccination is today given for both situations :

1) interruption of transmission in mixed endemic areas through universal mass vaccination of young children, as e.g. performed in Israel since 1999[12] and

2) individual prophylaxis of susceptible travellers[13].

Both interventions serve the same purpose, i.e. to prevent potentially serious clinical illness in adolescents and adults.

Passive immunisation with immunoglobulins was used for pre- and postexposure prophylaxis until the late 1990s. This has now been entirely replaced by the use of inactivated HAV vaccines.

Hepatitis A vaccines

A few years after the identification of the virus by Feinstone et al in 1973[14] investigations demonstrated the immunogenicity and protective efficacy of formalin-treated HAV particles in an animal model[15]. The successful *in vitro* propagation of HAV using human-derived cell-line cultures[16, 17] triggered in 1979 the development of inactivated hepatitis A vaccines.

However, it was soon recognised that, like other small virion particles, inactivated HAV alone is not immunogenic enough to elicit an efficient protective antibody response[18]. Therefore, the inactivated HAV were adsorbed to aluminium salts[18, 19], for many decades the only adjuvant method approved by regulatory authorities[20, 21]. The use of such vaccines is, however, often accompanied by local reactions at the site of intramuscular injection.

Aluminium-free hepatitis A vaccine Epaxal

1. Virosomes - mechanism of action

Epaxal® uses a novel immunostimulant principle based on the attachment of the inactivated hepatitis A virions to virosomes. The hepatitis A virus (strain RG-SB) is propagated in MRC-5 human diploid cells and subsequently inactivated with formaldehyde. The inactivated virus particles are then bound to the

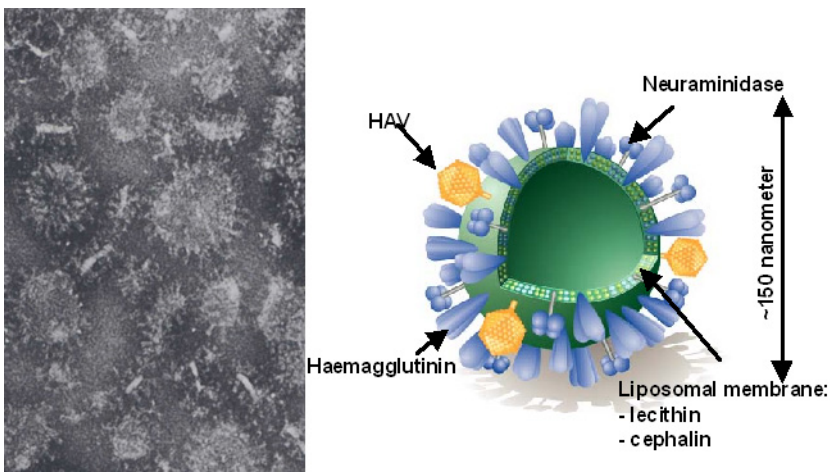

Fig. 2. Virosomal preparation under electron microscope and Epaxal® virosome.

immunoadjuvant virosomes. The virosomes are synthetic, spherical particles which comprise a double membrane, composed of the phospholipids lecithin (phosphatidylcholine) and cephalin (phosphatidylethanolamine) as well as viral phospholipids and surface glycoproteins haemagglutinin (HA) and neuraminidase, both isolated from inactivated influenza virus A/ Singapore/6/86 (H1N1)[22] (Fig. 2).

The proposed mechanism of action of the Epaxal® virosomes is shown in 6 steps in Fig. 3 : It has been shown that the influenza virus HA component of the virosome enables binding to immunocompetent cells such as macrophages[23, 24]. HA-mediated endocytosis (occurs. Exposure to the low pH (≈5) of the cell endosome (causes conformational changes in HA, resulting in fusion (of the virosome and endosome membranes. Within the endosome, the virus antigen is proteolysed (to antigenic peptides. Thereafter, the antigen-containing endosomes join (with vacuoles containing major histocompatibility class II (MHC II) molecules. The resulting MHC II-antigen complex is transported to the surface of the cell (where it initiates either a specific humoral response, and/or a cellular immune response.

2. Properties and Composition

Epaxal is a clear liquid which contains per dose (0.5 mL) ≥24 IU of inactivated hepatitis A antigen (strain RG-SB) as active component, as well as the following excipients : 10 μg influenza haemagglutinin A/Singapore/6/86-like (H1N1), 100 ug phospholipids and sodium chloride (0.9% w/v) ad 0.5 mL. The HA and the phospholipids are the main components of the virosomes (see above) onto which the inactivated HAV are bound by electrostatic forces. The final product is free of preservatives or any traces of antibiotics. The vaccine is provided in ready to use syringes.

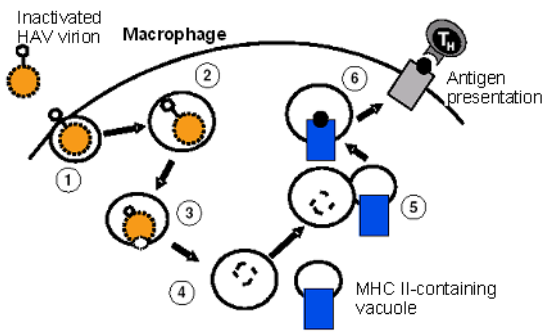

Fig. 3. Mechanism of action of Epaxal® virosomes.

Epaxal : Clinical experience

The aluminium-free, virosome-adjuvanted hepatitis A vaccine, Epaxal®, was first licensed in 1994. Clinical experience in more than 6000 subjects has shown that Epaxal® is highly immunogenic (as measured by ELISA[25]), very well tolerated and confers long-lasting protection against hepatitis A.

Protective efficacy

In Nicaragua, an area of high endemicity of HAV, a double-blind, placebo-controlled field efficacy study has shown that Epaxal® protects against HAV infection[26]. A single dose of Epaxal® protected children as assessed by the detection of raised titres of anti- HAV IgM antibodies. Children aged 1.5 to 6 years received either Epaxal (0.5 mL) or placebo intramuscularly at Day 1 and a booster dose 15 months later.

Epaxal® was shown to confer protection from week 6 to month 15 in all children (100%) who were seronegative at baseline (Table 1). Based on the presence of anti-HAV IgM antibodies, 4 vac-

Table 1. Protective Efficacy of Epaxal® in Children (n=239) in Nicaragua[26]

	Number with infections	% efficacy
Week 0 to week 6		
Vaccine	4	22.5
Placebo	5	not significant
Week 6 to month 15		
Vaccine	0	100
Placebo	17	*P*=0.0001

cinated (n=122) and 22 control children (n=117) were infected. All infections in the vaccinated group occurred within the first 6 weeks after immunisation, i.e. in children incubating hepatitis A at study entry. The serological follow-up data indicate that protection may last for several decades[6].

Immunogenicity in all age groups

1. Infants and children

In 4 studies in Chile (20 toddlers aged 12～16 months and 80 children aged 5～17 years)[27], Lithuania (30 infants aged 6～8 months and 30 children aged 5～7 years)[28], Thailand (children aged 3～11 years)[7] and Nicaragua (137 children aged 1.5～6 years)[26], approx. 400 children received a single intramuscular dose of Epaxal® (0.5 mL) at baseline and a booster dose at 12～15 months. Seroprotection was 94～100% after 4 weeks this continued for up to 12 months. Following the booster dose a strong antibody response was seen in all children. Epaxal® was well tolerated in all age groups and there were no serious adverse events.

2. Adults

In several open, uncontrolled studies enrolling over 700 adults aged ≥18 years, a single dose of Epaxal® elicited good antibody responses with seroprotection rates of 96～100% and 91～100% after 1 and 12 months, respectively, always followed by a 20- to 30-fold rise in GMT and 100% seroprotection after the booster dose one year later[29～37]. Epaxal® was well tolerated with no serious adverse events reported.

In two controlled studies, Epaxal® was shown to be comparable in immunogenicity to an aluminium-adsorbed vaccine but far better tolerated regarding local reactogenicity[36, 37].

3. Elderly

The limited data available on the effect of hepatitis A vaccination in subjects aged >40 years show a lower antibody response compared with younger age groups[38, 39]. In an open, uncontrolled study, 31 seronegative subjects aged >50 years responded to a primary dose of Epaxal® with a relatively low antibody titre (GMT : 64 mIU/mL) and a seroprotection rate (≥20 mIU/mL) of 65% after one month. Following the booster dose one-year later, these subjects, however, showed a typical booster response with a GMT of 1,226 mIU/mL and 98% seroprotection, comparable to results obtained with a control group of 59 younger adults aged 18～45 years run in parallel. This study showed that Epaxal® can successfully prime the ageing, potentially senescent immune system[35].

Excellent local tolerability

In two clinical studies comparison of Epaxal® with an aluminium-adsorbed vaccine has shown superior local tolerability of the virosome-formulated, aluminium-free vaccine. Only 12～24% of vaccinees receiving Epaxal® reported injection site pain/soreness in comparison to 63～64% for those receiving the aluminium-based vaccine ($P<0.0001$)[36, 37]. These findings have recently been confirmed in a large post-marketing safety study in the U.K. with 2.7 times more injection site pain ($P<0.001$) for the alum-adsorbed as compared to the virosome-adjuvanted vaccine (Fig. 4)[40].

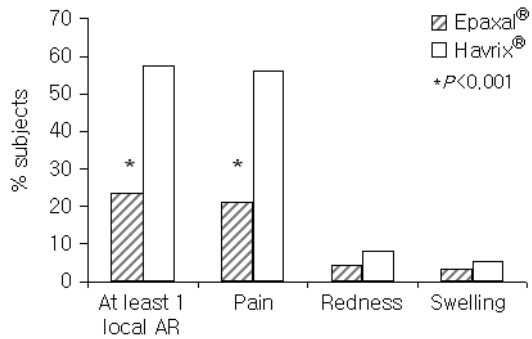

Fig. 4. Incidence (%) of solicited local adverse reactions (AR) Epaxal vs. Havrix[40].

Rapid protection

The results of a clinical study by Ambrosch et al. indicated early protection - within 14 days[32]. The excellent correlation found between the antibody concentration and the neutralising activity of the sera showed that the vaccine-induced antibodies produced as early as 2 weeks after immunisation were protective. After one dose of vaccine was administered at day 1, seroconversion was demonstrated in 97.3 %, 99.1%, 98.8% and 98.9% at day 15, day 29, month 6 and month 12, respectively.

Subsequent work has demonstrated that seroprotection can be achieved even earlier[33]. Antibody levels measured by ELISA started to rise shortly after administration of Epaxal®, and were detectable by day 7 after the primary vaccination. Neutralising anti-HAV antibody levels increased from days 7～9 onwards, and by day 11 all subjects had achieved levels of 10 mIU/mL or greater (Fig. 5). The incubation period of hepatitis A is with 2～7 weeks generally longer than the time for seroconversion after vaccination and, therefore, one has to assume that vaccination with Epaxal confers immediate protection against hepatitis A.

Long-term protection

Mathematical modelling of clinical trials of Epaxal® initiated between 1992 and 1994, in which subjects were followed for several years after a booster vaccination one year after primary vaccination, has indicated an extensive period of protection provided by Epaxal®. The estimated median duration of protection is 46.8 years. After 21.5 years, 95% of the vaccinees will have a projected titre above the minimum protective level (defined as 20 mIU/mL)[41]. Based on these results, Epaxal® is registered to be protective for at least 20 years.

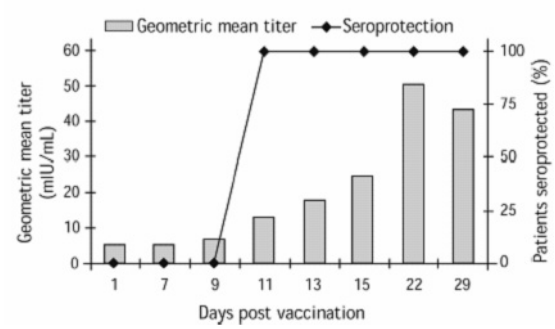

Fig. 5. Neutralising anti-HAV antibody tititers (mIU/mL) following priming and booster vaccination[33].

Booster interval

In order to obtain long-lasting protection against hepatitis A, it is recommended that two doses of Epaxal® are given. Many travellers, however, do not return in time for the second dose. It is therefore important to know for how long the booster vaccination can be delayed and still produce a satisfactory immune response. Travellers at the Swiss Tropical Institute were therefore given a booster dose of Epaxal® at 18 to 54 months after the primary intramuscular vaccination[42]. The response to the booster vaccination was not influenced by the time since primary vaccination. One month after the booster vaccination, the antibody titres had risen by a factor of 48～73, while achieving 100% seroprotection. The booster dose can, therefore, be delayed for 4～5 years and still produce a very satisfactory immune response.

Interchangeability

It may not always be possible to give a booster vaccination with the same hepatitis A vaccine as the one used for the primary vaccination. Therefore, a crossover study has been performed with Epaxal® and a current aluminium based vaccine.

Subjects received either Epaxal® or aluminium hydroxide-adsorbed hepatitis A vaccine for primary vaccination and then received a booster dose of

either vaccine 12 months later (i.e. subjects could receive the same or the alternative vaccine for the booster vaccination)[37]. There was a good booster effect of each vaccine after priming with either Epaxal® or aluminium hydroxide-adsorbed hepatitis A vaccine : a 20- to 39-fold increase in anti-HAV GMTs in response to the booster vaccination was seen, irrespective of the type of primary/booster vaccination.

Administration of Epaxal® to healthy travellers after basic immunisation with an aluminium adsorbed HAV vaccine also demonstrated a successful booster response, confirming the results of the other study[43]. These studies show that Epaxal® and aluminium-adsorbed hepatitis A vaccines are interchangeable.

Co-administration with other vaccines and treatments

Travellers to regions in which hepatitis A is endemic frequently have to receive other vaccinations or other prophylactic treatment against other diseases (e.g. malaria chemoprophylaxis).

In some of the studies of Epaxal®, volunteers were enrolled from a travel medicine clinic and received other vaccinations with Epaxal®, including immunoglobulin or antimalarials in various combinations. There was no apparent adverse influence of simultaneous immune prophylaxis with yellow fever vaccine or antimalarials on the immune response and seroprotection rate after hepatitis A vaccination[44].

Co-administration with hepatitis A immunoglobulin

The use of immunoglobulins can adversely influence the immune response of a concomitantly administered vaccine. In a comparative study, subjects received either Epaxal® alone or were given 200 IU hepatitis A antibodies in addition. Seroprotection was achieved at 28 days in 98% after active immunisation and in 100% after passive-active immunisation, and in 100% at 1 year for both groups[25].

Alternative Routes of administration

In addition to the intramuscular administration of Epaxal® the aluminium free, virosomal hepatitis A vaccine can be given subcutaneously in subjects needing this route of administration (e.g. anticoagulation) with good local tolerability and no significant loss of immunogenicity[34].

In clinical trials Epaxal® was also given intradermally; it was well tolerated and offered a good immune response. In a study of 30 healthy adult volunteers a single dose of 0.1 mL i.d. resulted in an antibody titre of 72 mIU/mL (GMT) and 97% seroprotection ($\geq$20 mIU/ml) at day 29. An i.d. dose of 0.1 mL given one year later resulted in a strong booster response[45]. Similar good immune response and no difference in local tolerability in comparison to intramuscular administration has been seen in a second trial in 8～12 year old children[46].

For aluminium-adsorbed hepatitis A vaccines a poor immune response has been reported following i.d. administration of 0.1 mL volumes[47]. In addition, as for all aluminium-adsorbed vaccines, i.d. administration is bound to cause extensive local irritation.

Marketing status

The aluminium-free, virosome-adjuvanted hepatitis A vaccine is manufactured by Bena Biotech using a patented technology. It was first licensed in 1994 in Switzerland under the brand name Epaxal® and is currently licensed worldwide in more than 40 countries.

Conclusions

Epaxal® is the only aluminium-free hepatitis A

vaccine; it is based on a novel technology - the virosome. Due to the purity and the good tolerability profile of the virosomal vaccine, Epaxal® is an excellent choice to protect against hepatitis A, particularly in infants and children.

Why use Epaxal®

- It is a biodegradable and pure vaccine : it does not contain aluminium, antibiotics nor thiomersal
- It has an excellent local tolerability profile
- It has a fast onset of protection
- It offers long-term protection after booster (minimum 20 years)
- It is indicated for all age groups (adults and children over 1 year of age)
- It needs a small injection volume of 0.5 mL; the same dosage can be administered to children, adolescents and adults
- It can be given simultaneously with other vaccines
- It can be administered intramuscularly and subcutaneously
- It can be used as booster vaccination after priming with aluminium-adsorbed vaccines
- It booster can be delayed up to 5 years after primary vaccination

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