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A two-dose schedule for combined hepatitis A and B vaccination in children aged 6–15 years

Zafer Kurugöl*, Fatma Mutlubaş, Tijen Özacar

Department of Paediatrics, Ege University Faculty of Medicine, İzmir, Turkey

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Abstract

A combined hepatitis A and B vaccine, Twinrix, in a paediatric formulation for ages 1–15 years and in an adult formulation for those ages 16 years and older, became commercially available in Turkey as well as in many countries. It is administered according to a three-dose schedule (0, 1 and 6 months). A reduction in the number of doses would improve the compliance rate and reduce administration costs. Therefore, we planned a trial evaluation of the immunogenicity, safety and reactogenicity profile of a high-dose combined hepatitis A and B vaccine, administered in two doses, compared with the profile of a paediatric-dose combined vaccine, administered in three doses, in healthy children aged 6–15 years. One hundred children were randomly attributed to the two study groups. The first group (paediatric-dose vaccine group) received the licensed Twinrix Paediatric, at months 0, 1 and 6; the second group (high-dose vaccine group) received the high-dose vaccine, following a 0, 6 months schedule. The reactogenicity was assessed after each vaccine dose. The immunogenicity was evaluated by testing for anti-HBs and anti-HAV antibodies. Seroconversion rates and geometric mean titres (GMTs) were compared. Both formulations of the combined vaccine were well tolerated. The high-dose combined vaccine administered in two doses, elicits satisfactory immunogenicity profiles, similar to those elicited by the paediatric vaccine administered in three doses. On completion of the vaccination schedule in the two groups all children were protected against hepatitis B and immune for hepatitis A. Anti-HAV GMTs after completion of the vaccination schedule were 7163 ml U/ml in the paediatric-dose group, 8241 ml U/ml in the high-dose group; anti-HBs GMTs were 8679 and 4583 ml U/ml, respectively. These results indicate that a two-dose schedule, compared with the standard three-dose schedule, offers fewer injections for satisfactory protection against the two infections. This means fewer clinic visits, lower administration costs, better compliance, and higher coverage rate. Therefore, this two-dose schedule can be considered an appropriate regimen for the immunization of children and adolescents against hepatitis A and B infection, in the context of school-based immunization programmes.

Keywords: Combined hepatitis A and B vaccine; Two-dose schedule; School children

1. Introduction

Hepatitis A and B infections still constitute an important public health problem in Turkey. Although the seroprevalence of hepatitis A and B are variable between geographic regions, Turkey is classified as areas of intermediate endemicity for both HAV and HBV. In 1997, 15,419 cases of hepatitis A and 4343 cases of hepatitis B were reported to the Ministry of Health [1]. The actual number of hepatitis cases is certainly much higher, since the diseases are significantly underreported. Seroepidemiological studies reported from different region of Turkey demonstrate shifting patterns in the prevalence of anti-HAV, with a corresponding increase in the age of exposure from childhood to early adulthood [2,3]. The infection is more frequently seen in young adolescents. A recent epidemiological study has shown that outbreaks occur when a sufficient number of sensitive people are reached and hepatitis A vaccination plays an important role in preventing these outbreaks [4]. However, a vaccination programme against hepatitis A has not been initiated in Turkey yet.

* Corresponding author. Fax: +90 232 3426990.
E-mail address: kurugol@med.ege.edu.tr (Z. Kurugöl).

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Since 1998, universal hepatitis B immunization programme has been introduced in Turkey for all infants. However, 5 years after the start of the immunization programme, i.e. in 2003, the coverage rate for hepatitis B vaccination reached only 68% in infants. Moreover, most of the population, i.e. children who were born before 1998 (>6 years of age) and adolescents, are not protected against hepatitis B, since this population has not been vaccinated against hepatitis B by Ministry of Health free of charge and no charge for hepatitis B vaccine is paid by Social Insurance Institutions. Thus, this population in Turkey is at imminent risk of HBV transmission, as well as HAV, and should be protected against the two infectious diseases.

The combined hepatitis A and B vaccine facilitates dual protection against both infections with fewer injections. A combined vaccine, Twinrix (SmithKline Beecham Biologicals, Rixensart, Belgium) has been licensed in Turkey since 2001. It is available in a paediatric formulation for ages 1–15 years and in an adult formulation for those ages 16 years and older. The standard primary vaccination schedule for both age groups consists of three-dose administered at 0, 1 and 6 months. Vaccine trials show that both formulations, administered in three doses, is safe, well tolerated and immunogenic in adults, adolescents, and children [5–9]. A further reduction in the number of doses would improve the compliance rate as well as being more convenient for the vaccines [10]. Therefore, we planned an open, randomised study evaluating the immunogenicity, safety and reactogenicity profile of a high-dose (adult formulation) combined hepatitis A and B vaccine, administered in two doses (0, 6 months), compared with the profile of a paediatric-dose combined vaccine, administered in three doses (0, 1 and 6 months), in healthy Turkish children aged 6–15 years.

2. Materials and methods

2.1. Study participants and inclusion/exclusion criteria

Seventy healthy Turkish children aged between 6 and 15 years were enrolled in this trial. Written informed consent had been obtained from the parents or guardians of each vaccinated children prior to enrolment. A physical examination and recording of medical history established eligibility for enrolment into the trials.

Exclusion criteria were: presence of hepatitis B surface antigen (HBsAg), anti-hepatitis B surface (anti-HBs) antibodies, anti-hepatitis B core (anti-HBc) antibodies, or anti-hepatitis A virus (anti-HAV) antibodies at screening; a history of previous vaccination against hepatitis A or B; a history of significant and persisting haematologic, hepatic, renal, cardiac, or respiratory disease; any acute disease at study entry; elevated serum liver enzymes; under chronic drug treatment; a history of allergy against vaccine components; administration of immunoglobulins (6 months before or during the study); and administration of vaccines not foreseen by the protocol (within 1 week of a dose of the study vaccine).

2.2. Study design and vaccines

The 100 children were randomly attributed to the two study groups. The first group received the paediatric-dose combined hepatitis A and B vaccine (Twinrix Paediatric, licensed for children aged 1–15 years), using a 0–1–6-month schedule (paediatric-dose vaccine group). The second group received the high-dose combined vaccine (Twinrix Adult, licensed for subjects aged ≥16 years) using a two-dose schedule at 0 and 6 months (high-dose vaccine group). Both combined vaccines were developed and manufactured by SmithKline Beecham Biologicals, Rixensart, Belgium. The Twinrix Paediatric contained at least 360 ELISA units of inactivated hepatitis A virus and 10 μg of recombinant HBsAg in a 0.5 ml dose. The high-dose vaccine contained at least 720 ELISA units of inactivated hepatitis A and 20 μg of recombinant HBsAg and was administered in a 1 ml dose. Both antigens were adsorbed onto aluminium. Both vaccines were injected intramuscularly in the deltoid muscle with a 25 G (0.5 mm), 25-mm needle.

2.3. Reactogenicity

In order to evaluate reactogenicity, each parents or guardians were asked to record on diary cards solicited local and general adverse experiences, which may occur on the day of each vaccination and the three subsequent days (total of 4 days). Incidence of each solicited symptom was evaluated according to the number of diary cards returned (per-dose analysis).

The local solicited symptoms consisted of pain at injection site, swelling, and redness. The severity of the symptoms was graded differently. Scoring for pain at injection site was: Grade 1, minor discomfort on touch; Grade 2, painful on touch; and Grade 3, preventing normal daily activities. The size of redness and swelling was obtained by measuring their longest diameter in millimetres and was scored as follows: Grade 1, 1 to <10 mm; Grade 2, 10 to <50 mm; and Grade 3, ≥50 mm. The general solicited symptoms were headache, fever, fatigue and gastrointestinal symptoms. The grading for fever was: Grade 1, 37.5–38.0 °C; Grade 2, 38.0–39.0 °C and Grade 3, >39.0 °C (axillary temperature).

Any adverse event that occurred within 30 days after administration of each vaccine dose was recorded. These unsolicited symptoms were reported with date of onset and end date, intensity and outcome. The relationship to the vaccination was assessed as either not related, unlikely, suspected or probable. In addition, serious adverse reactions were recorded during the whole study period.

2.4. Immunogenicity

For measurements of anti-HAV and anti-HBs antibodies blood samples were obtained at months 1, 2 (only