Hepatitis A is an acute infectious hepatitis transmitted through fecal-oral route. Some of the risk factors for transmission are low household socioeconomic status, residence in rural areas, and limited access to improved water sources and sanitation facilities. Recent studies have shown that the positivity of hepatitis A virus (HAV) antibodies in children aged between 6 and 10 years and belonging to the higher-income class in urban areas has reduced significantly. However, no such change has been observed in children belonging to the lower-middle income class. Some studies have reported that there is an increase in the symptomatic cases of HAV among elderly people, indicating an epidemiological shift.

Liv.52 drops, syrup, and tablets have been found to be safe and effective in the prevention and treatment of hepatitis in patients of different age groups. The "Clinical review" section of this issue of Liveline highlights the clinical efficacy and safety of Liv.52 in infective hepatitis as validated in a meta-analysis of 50 phase III clinical trials. In the "Expert comments" section, Dr. Pravin Kumar Sudanikar describes the efficacy of Liv.52 syrup and tablets in the treatment and management of hepatitis A. The issue also features various other informative articles on infective hepatitis.

Do write to us with your valuable feedbacks and suggestions. Happy reading!

— Editor

Research update

Hepatitis A

Brundage SC, Fitzpatrick AN

Viral Characteristics and Epidemiology

Hepatitis A is caused by a nonenveloped RNA picornavirus that infects only primates. Lack of a lipid envelope confers resistance to bile lytic. The virus is hardy, surviving on human hands and fomites and requiring temperatures >85°C for inactivation. Hepatitis A virus survives for extended periods in seawater, fresh water, wastewater, and soil. The virus is resistant to freezing, detergents, and acids, but it is inactivated by formalin and chlorine. Infection occurs primarily by oral inoculation of fecally excreted virus either by person-to-person contact (including any form of sexual contact with proximity to feces) or by ingestion of contaminated food or water. Viral particles are replicated only in hepatocytes and gastrointestinal epithelial cells and are released into blood and bile by a mechanism that does not cause cell lysis. Liver cells are destroyed by a cell-mediated immune response.

The incubation period of hepatitis A virus is 15 to 50 days, with an average of 25 to 30 days. Peak infectivity correlates with the greatest viral excretion in the stool during the two weeks before the onset of jaundice or elevation of liver enzyme levels. Viremia occurs soon after infection and persists through the period of liver enzyme elevation. On rare occasions, hepatitis A virus has been transmitted by transfusion of blood products collected during the donor’s viremic phase. The potential for transmission via intravenous drug use is unknown.

Hepatitis A is highly endemic in developing nations with poor sanitation, where infection often occurs in children, who are likely to be asymptomatic. In developed nations, the proportion of symptomatic patients is higher because infection is more likely in adults. The sources of most reported food-borne outbreaks are infected food handlers at the point of sale, fresh produce such as green onions and strawberries, and consumption of shellfish harvested from contaminated waters.

Diagnosis

Differential diagnosis of acute hepatitis includes bacterial, parasitic, and viral infections; autoimmune diseases; and reactions to drugs or toxins (Table 1). Initial diagnostic tests include determination of hepatic enzyme and bilirubin levels with follow-up viral serology for hepatitis A, B, and C. In patients with hepatitis A, serum transaminase levels may be ≥10,000 U/L, but there is little correlation between level and disease severity. The alkaline phosphatase level usually is elevated only minimally. The bilirubin level usually is elevated to about 5 to 10 mg/dL (86 to 171 µmol/L), and prothrombin time usually is 11 to 26 seconds.

The antihepatitis A virus IgM test is the preferred confirmatory test for acute hepatitis A because it has high sensitivity and specificity when used on specimens from persons with typical symptoms. However, its use among persons without symptoms of hepatitis produces a high percentage of false-positive results, which may lead to unnecessary public health investigations. Serum antihepatitis A virus IgM usually can be detected 5 to 10 days before symptom onset, and the level remains elevated for four to six months. The antihepatitis A virus IgG level begins to rise soon after the IgM level and is present throughout the person’s lifetime, conferring immunity. Nucleic acid amplification techniques are used primarily by researchers to detect hepatitis A virus RNA in serum and stool.

Clinical Course

More than 80% of adults with hepatitis A are ill for up to eight weeks and miss about 30 days of work. The preicteric phase lasts 5 to 7 days, with abrupt onset of fever, malaise, anorexia, nausea, vomiting, abdominal pain, and headache. Less common symptoms include chills, myalgia, arthralgia, cough, diarrhea, constipation, pruritus, and urticaria. Physical signs include tender hepatomegaly, splenomegaly, bradycardia, and posterior cervical lymphadenopathy. The icteric phase, which lasts 4 to 30 days, begins with conjugated bilirubinuria followed within a few days by pale, clay-colored stools and jaundice. Chronic infection does not occur.

Complications

A prolonged or relapsing course of illness lasting several months occurs in 10% to 20% of symptomatic patients, with persistent fever, severe pruritus, jaundice, diarrhea, weight loss, and malabsorption. Liver enzyme levels return gradually to normal, but the bilirubin level remains elevated. Patients with a relapse or a prolonged course should be regarded as potentially infectious. Small subsets of patients with hepatitis A develop extrapathic manifestations (Table 2).

A fulminant course of illness is experienced by <1% of patients and is characterized by worsening jaundice and development of encephalopathy. Advanced age and comorbid conditions such as chronic liver disease increase the risk of a fulminant course, which often results in death or an emergent liver transplant. Prognostic indicators supporting the need for a liver transplant are age <10 years or >40 years, jaundice lasting more than seven days before the onset of encephalopathy, increased levels of serum bilirubin (>17 mg/dL [291 µmol/L]), and prolonged prothrombin time (>25 seconds). The overall mortality rate is relatively low (0.5%), but increases to 2% in adults aged >40 years.

Treatment

Treatment is supportive and includes appropriate rest when necessary, balanced nutrition, and avoidance of hepatotoxins such as alcohol and acetaminophen. No specific antiviral therapy is currently available. About 30% of symptomatic patients require hospitalization for dehyerdration, severe prostration, coagulopathy, encephalopathy, or other evidence of hepatic decompensation.

Caregivers should observe strict contact precautions during the infectious period with persons who are đápared or incontinent. Otherwise healthy adult patients are noninfectious by two weeks after the onset of illness, but children and immunocompromised persons may remain infectious for up to six months.
Meta-Analysis of 50 Phase III Clinical Trials to Evaluate the Efficacy and Safety of Liv.52 in Infection Hepatitis

Kholapure SA, Mitra SK


Introduction

The term “hepatitis A” has replaced all previous terms such as type A viral hepatitis, infectious hepatitis, epidemic hepatitis, epidemic jaundice, catarrhal jaundice, infectious icterus, Icterus disease, and MS-1 hepatitis. It is the most common type of viral hepatitis worldwide and occurs in both epidemic and sporadic patterns. Hepatitis A, an acute but benign form of viral hepatitis, is caused by an RNA virus—hepatitis A virus (HAV)—that does not persist in the blood serum. The disease is characterized by a sudden onset of fever, malaise, nausea, anorexia, and abdominal discomfort, followed by jaundice after several days. Onset of the disease is indicated by the presence of dark urine, which precedes jaundice by 2 or 3 days.

Liv.52 tablet and syrup are polyherbal formulations extensively used in the management of hepatitis A. The aim of this study was to meta-analyze the efficacy and short- and long-term safety of Liv.52 in the treatment of hepatitis A.

Materials and Methods

The meta-analysis included 50 clinical trials (double-blind placebo-controlled studies, placebo-controlled studies, open noncomparative studies, and case reports with less than 10 enrolled patients) comprising 4490 patients, including 233 children. Experimental, preclinical, and phase I and II clinical studies were excluded from the meta-analysis. The predefined primary end points were statistically significant symptomatic improvement, renormalization of biochemical parameters, and total duration of clinical recovery. The predefined secondary end points were incidence of adverse events during the study period and overall compliance to the treatment.

Results

Results of the meta-analysis showed a significant reduction in the mean levels of serum bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, and serum alkaline phosphatase and also in the prothrombin time and mean time required for total (symptomatic, clinical, and biochemical) recovery in patients treated with Liv.52 (Figures 1–5). In all the studies, there was a significant increase in the levels of serum albumin and serum globulin, as compared to the pretreatment values (Figures 6 and 7).

Conclusion

No adverse effects were reported or observed during the study period and the overall compliance to the treatment was excellent. Therefore, it can be concluded that Liv.52 tablets and syrup are safe and effective in the management of patients with hepatitis A.

Effect of Liv.52 on Nutrition Parameters in Patients on Hemodialysis


Drug alert

Acute Cholestatic Hepatitis Along with Agranulocytosis: A Rare Side Effect of Carbimazole

Jain K, et al.


Antithyroid drugs have been used for more than 50 years for the management of hyperthyroidism. Most patients tolerate the treatment well but some may develop life-threatening side effects such as agranulocytosis, aplastic anemia, and cholestatic hepatitis. A 45-year-old woman was diagnosed with severe hyperthyroidism. Treatment with carbimazole 30 mg/day was initiated. Within six weeks following the start of therapy, the patient developed potentially life-threatening acute cholestatic hepatitis and agranulocytosis as adverse effects to carbimazole. The patient’s symptoms and laboratory abnormalities resolved following withdrawal of the offending drug. Agranulocytosis along with cholestatic hepatitis is an extremely rare idiosyncratic side effect of carbimazole treatment and is considered to be dose- and age-related. Antithyroid drugs are deceptively easy to use, but because of the variability in the response of patients and the potentially serious side effects, all practitioners who prescribe the drugs need to have a working knowledge of their complex pharmacology.
Co-infecion of Hepatitis B and C Viruses and Risk of Hepatocellular Carcinoma

Chyo Ly, et al. 


A subadditive effect of hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfection is possible because superinfection of one virus tends to inhibit infection of the other virus. However, studies have reported inconsistent findings, and two meta-analyses of studies from various countries (1998) and China (2005) reported a supradditive effect for hepatocellular carcinoma (HCC) risk. Thus, the authors reevaluated HBV/ HCV coinfection and coinfection of HBV/HCV and HBV infection was higher than HBAg infection, whereas anti-HCV vs anti-HCV/HCV RNA was not different. Geographically, HCC risk was significantly higher in nondemic than in HBV or HCV endemic areas. Subadditive effect for HCC risk was presented in recently published studies, cohort studies and studies conducted in HBV/HCV nondemic areas; an additive effect was presented in studies conducted in HBV endemic areas. Results of the present study suggest that HBV/HCV coinfection for HCC risk is not significantly greater than HBV/HCV monoinfection, and HCC risk due to HBV or HCV is higher in nondemic than in endemic areas. The p-heterogeneity was significant for most analyses, except HBV/HCV+ and HBV biomarker analyses. Prevention strategies targeted toward HBV or HCV monoinfected patients are needed. In addition, tailored prevention to reduce infectivity such as HBV markers (HBsAg, HBV DNA) is needed.

Liv.52 in Infective Hepatitis

E x p e r t  c o m m e n t s

Interview with Dr Pawan Kumar Sultania, MBBS, FCPS (Ludhiana), MRSH (London), FICA (US)

Liv.52 is used in Infective Hepatitis

Liv.52 in Hepatitis B Progression

Yang F, et al. 


Chronic hepatitis B (CHB) appears to progress more rapidly in males than in females, and CHB-related hepatic cirrhosis and hepatocellular carcinoma are diseases that tend to occur predominately in men and postmenopausal women. To obtain more insight into the underlying mechanisms of gender disparity of CHB progress, two-dimensional difference gel electrophoresis was employed to compare liver proteome of C57BL/6 and HBV transgenic (HBV-Tg) mice both in male and female groups. The authors identified 8 differently expressed proteins in HBV-Tg mice and 12 in female HBV-Tg mice. Apolipoprotein A-I (Apo A-I) was found to be down-regulated in male and female HBV-Tg mouse liver. It is more interesting that the pattern of liver Apo A-I isoforms was altered in male HBV-Tg mice but not in female HBV-Tg mice. Further results indicated that the basic Apo A-I isoform, based on pl positions from serum two-dimensional Western blotting, increased in male CHB patient sera but not in female CHB patient sera. Finally, it was identified that the oxidative modification Apo A-I mainly reside in basic isoform. This pattern of selectively modified Apo A-I isoforms may be considered as a pathological hallmark that may extend the knowledge of molecular pathogenesis of CHB progression.

Timming of Hepatitis B Virus Immunization Relative to Human Immunodeficiency Virus Diagnosis

Landrum ML, et al. 


To assess associations between the timing of hepatitis B virus (HBV) immunization relative to human immunodeficiency virus (HIV) diagnosis and vaccine effectiveness, US Military HIV Natural History Study cohort participants without HIV infection at the time of HIV diagnosis were grouped by vaccination status, retrospectively followed from HIV diagnosis for incident HBV infection, and compared using Cox proportional hazards models. A positive vaccine response was defined as hepatitis B surface antibody level ≥10 IU/L. Of 1877 participants enrolled between 1989 and 2008, 441 (23%) were vaccinated prior to HIV diagnosis. Eighty percent of those who received vaccine doses only before HIV diagnosis had a positive vaccine response, compared with 66% of those who received doses both before and after HIV and 41% of those who received doses only after HIV (P<0.01 for both compared with persons vaccinated before HIV only). Compared with the unvaccinated, persons vaccinated only before HIV had reduced risk of HBV infection after HIV diagnosis (hazard ratio = 0.38, 95% confidence interval: 0.20-0.75). No reduction in HBV infection risk was observed for other vaccination groups. These data suggest that completion of the vaccine series prior to HIV infection may be the optimal strategy for preventing this significant comorbidity infection in HIV-infected persons.

Herb facts

Effects of Terminalia arjuna Bark Extract on Apoptosis of Human Hepatoma Cell line HepG2

Sivalokanathan S, et al. 


Aim

To investigate the effects of Terminalia arjuna extract on human hepatoma cell line (HepG2) and its possible role in induction of apoptosis.

Methods

Human hepatoma cells were treated with different concentrations of ethanol extract of T. arjuna and its cytotoxicity effect was measured by trypan blue exclusion method and lactate dehydrogenase leakage assay. Apoptosis was analyzed by light and fluorescence microscopic methods, and DNA fragmentation. The mechanism of apoptosis was studied with expression of p53 and caspase-3 proteins. Glutathione (GSH) was also measured in HepG2 cells after T. arjuna treatment.

Results

T. arjuna inhibited proliferation of HepG2 cells in a concentration-dependent manner. Apoptotic morphology was observed in HepG2 cells treated with T. arjuna at concentrations of 60 and 100 mg/L. DNA fragmentation, accumulation of p53, and cleavage of pro-caspase-3 protein were observed in HepG2 cells after treatment with T. arjuna. The depletion of GSH was observed in HepG2 cells treated with T. arjuna.

Conclusion

T. arjuna induced cytotoxicity in HepG2 cells in vitro. Apoptosis of HepG2 cells may be due to DNA damage and expression of apoptotic proteins. Depletion of GSH may be involved in the induction of apoptosis of HepG2 cells.


**Immune Globulin**

Immune globulin administered intramuscularly provides short-term protection (up to three to five months) through passive transfer of hepatitis A virus antibody. The immune globulin is made from pooled human plasma that has been treated to inactivate viruses and that tested negative for human immunodeficiency virus and hepatitis B and C. No transmission of viral infection has been reported, and serious adverse reactions are rare.

Administration of immune globulin is not contraindicated during pregnancy or lactation. Known IgA deficiency is a contraindication because there have been reports of anaphylaxis after repeated intramuscular administration of immune globulin.

Immune globulin administered intramuscularly as prophylaxis within two weeks after exposure to hepatitis A virus is about 69% to 89% effective in preventing symptomatic infection. When infection is not prevented, immune globulin attenuates symptoms and reduces further viral transmission. Effectiveness when administered before exposure is 80% to 85%.

Administration of intramuscular immune globulin should be avoided within two to three weeks after administration of live, attenuated vaccines because it decreases their immunogenicity. Administration of these vaccines should be delayed until three months (for measles, mumps, and rubella vaccinations) or five months (for varicella vaccination) after intramuscular immune globulin administration.

**Vaccine**

Two types of inactivated whole virus vaccines for hepatitis A virus were introduced in the United States in 1995 and 1996. The first dose provides immunity in 37% of persons within two weeks, in 90% of persons within four weeks, and in 100% of persons at 26 weeks. The second dose provides persistent immunity projected to last at least 20 years.

**Prevention Methods**

Prevention methods include sanitation, case investigation with contact postexposure prophylaxis, and primary vaccination. Physicians should instruct patients about thorough hand washing after defecation and diaper changing, and sanitary disposal of wastes. Ensuring careful food-handling practices are public health focuses.

Previously unimmunized contacts of a patient with acute hepatitis A should receive intramuscular immune globulin without a delay for serologic testing. Hepatitis A vaccine may be given simultaneously with intramuscular immune globulin if the vaccine otherwise would be recommended for that person according to his or her risk status. Community-wide vaccination of children has proved effective in controlling localized outbreaks.

Hepatitis A vaccine is recommended for persons who have a higher risk of hepatitis A virus infection (eg, travelers to certain countries, illicit drug users, men who have sex with men, persons receiving clotting factor concentrates). Vaccination is also recommended for persons with chronic liver disease because of the higher risk of mortality. Routine vaccination is not recommended for persons at risk of occupational exposure, but it should be considered in certain situations (eg, research laboratory workers studying hepatitis A virus).

**Laugh lines**

My therapist told me the way to achieve true inner peace is to finish what I start. So far today, I have finished two bags of chips and a chocolate cake. I feel better already.

**Misuse of Anesthesia May Cause Hepatitis Virus Transmission**

Hepatitis B virus (HBV) and hepatitis C virus (HCV) can be transmitted during intraoperative (IV) administration of anesthesia, according to a new study published in Gastroenterology, the official journal of the American Gastroenterological Association Institute. In this study, doctors found that anesthesia contamination, not endoscopy contamination, was the cause of infection.

Doctors investigated an outbreak of acute HBV and HCV infections among patients who received anesthesia during endoscopy procedures from the same anesthesiologist in two different gastroenterology clinics. They identified six cases each of outbreak-associated HCV and HBV infection in one clinic and one outbreak-associated HCV infection in another clinic. All affected patients in both clinics received propofol from this anesthesiologist, who inappropriately used a single-use vial of propofol for multiple patients. Reuse of syringes to redose patients, with resulting contamination of medication vials used for subsequent patients, likely resulted in viral transmission.

The study results increased concerns regarding infection control practices and use of shared medication vials for anesthesia administration, especially in outpatient settings where infection control is limited and procedures such as endoscopies are increasingly performed.

**News flash**

**Use of shared medication vial for anesthesia administration facilitates transmission of hepatitis virus**

EDITED AND PUBLISHED BY D. Prabu Prasad
The Himalaya Drug Company, Bangalore
Published at
Sri Sudhindra Offset Process

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