SELECTED SUMMARIES

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Treatment of Chronic Hepatitis B - A Long Way to Go


Several antiviral agents like adonine arabinoside, adenosine arabinoside monophosphate and acyclovir have been used in the treatment of chronic hepatitis B, but the results have not been very satisfactory. In the present study, the authors evaluated the therapeutic efficacy of recombinant human α-interferon in patients with chronic hepatitis B in a randomized controlled fashion. Only adult patients (aged 18-65 yr) who were known to have raised serum aminotransferase levels and were positive for hepatitis B surface antigen (HBsAg) for at least 1 yr were eligible for the trial. In addition, they had detectable levels of hepatitis B e antigen (HBeAg), hepatitis B virus (HBV) DNA and DNA polymerase activity in serum on at least three determinations during the previous 3-6 months. Patients with decompensated liver disease with serum total bilirubin > 4 mg/dL, prothrombin time prolonged > 3 sec, or history of ascites, variceal hemorrhage or hepatic encephalopathy were excluded. Patients were divided into three well-matched groups in a randomized sequence: group A (16 patients) received α-interferon in a dose of 5 million units (MU)/day for 16 wk; group B (15 patients) received interferon in a dose of 10 MU every other day for 16 wk; and group C (14 patients) received no therapy and served as a control group. Clinical and laboratory evaluation (complete blood count, routine serum biochemical tests and HBV serology) of treated patients was done at 1-2 wk intervals during therapy and once a month thereafter. Control patients were followed up at monthly intervals. All patients were followed up for one year when a repeat medical evaluation and liver biopsy were done. Most patients were men (93%) and more than half of them were homosexuals (60%). Twenty seven percent of patients had antibodies to human immunodeficiency virus (anti-HIV). The results at four months showed that 10 of 31 (32%) treated patients became persistently negative for HBV DNA and DNA polymerase and they were designated as responders. In seven patients, the disappearance of HBV DNA was accompanied by a transient flare in the underlying hepatitis as shown by sudden increase in serum aminotransferase levels. During this period, one control subject (7%) also became negative for HBV DNA and DNA polymerase. The difference in response between the treated and control groups at four months was statistically not significant. During further follow up (4 to 12 months after randomization), all the responders (treatment group) had a marked improvement in serum aminotransferase activities and lost HBsAg from the serum. One of them became negative for HBsAg and developed anti-HBs. Nine patients showed improvement in liver histology. During this period, two more treated patients and one control subject became negative for HBV DNA. These patients were considered as late responders. Thus, at 1 year after randomization, response to α-interferon occurred in 12 of 31 (39%) treated patients compared with two of 14 (14%) controls; this difference was not statistically significant. Further analysis showed that the responders were more likely to be females with more active and severe underlying liver disease. Patients who underwent lymphorrhesis to obtain cells for study of the effects of interferon on the immune system had lower response (6%) than those who did not undergo this procedure (48%). Factors that did not correlate with response included male homosexuality, anti-HIV status and regimen of interferon given. Side effects of the drug were minor but it is three patients the therapy had to be discontinued. The authors conclude that recombinant α-interferon is of clinical benefit to patients with chronic hepatitis B. A four month course can induce remission in disease in approximately one-third of patients.

Comment: With 200 million people worldwide chronically infected by hepatitis B virus (Prag Med Virol 1978; 24: 469-469) and subject to its attendant risks of cirrhosis and hepatocellular carcinoma (Am J Med 1984; 101: 613-615), few will dispute the need for effective antiviral therapy. Several drugs have been tried in the past, but none has been found to be satisfactory. Further, some of these agents produced significant side effects. Hence, the study of a promising new agent is very welcome.

Of the several agents tested in chronic hepatitis B, adenine arabinoside (Gastroenterology 1984; 86: 106-106) and adenine arabinoside monophosphate (Gastroenterology 1984; 86: 106-106) have not been found to be effective. Further, many patients on drug treatment developed significant side effects like neuromuscular pain syndrome and severe urosepsis. Similarly, rozigolone benefits have been noted with acyclovir therapy (Br Med J 1986; 292: 915-7).

Interferons are small proteins that are produced by mononuclear cells as a first defence against viral infections (Lancet 1985; ii: 335-335). They have both immunomodulatory and antiviral effects (Lancet 1986; 137: 517-521). Adequate amounts of highly purified human interferons are available now due to advances in recombinant DNA techniques. Relatively low doses of this agent inhibit hepatitis B virus replication and the treatment is generally well tolerated as compared to that with adenine arabinoside monophosphate (Hepatology 1985; 5: 1132-1136). In recent
review of 14 independent studies involving more than 150 patients with chronic hepatitis B (Hepatology 1986; 6:1038-41), a response was seen in 10% to 20% of the patients. A permanent response occurred in 11% of the patients treated for 1 to 6 months. However, it is not possible to compare these studies with one another because of differences in the dosage/day (0-6 months), dosage (500 to 10 mg units per day) and the type of interferon used (α or β). Further, most of these studies involved very small number of patients.

The present study was conducted in a randomized controlled manner, (b) two dosage schedules of interferon were compared, and (c) the interferon therapy was given for a reasonably long period (16 weeks). However, this was not blind nor was the control group evaluated in a manner comparable to the treatment group. Patients in the treatment group were seen at 1-2 week intervals, while the control group was seen at a longer schedule (1 month intervals). The improvement rates in the treatment and control groups in this study were not significantly different. Though the response rates of 32% in this study compares well with earlier studies, these could be compared for the lower than expected response rate. Firstly, 12 of the 45 patients admitted to this trial had subclinical HIV infection. HIV-infected patients have higher levels of hepatitis B virus replication and depression of the immune system (Ann Intern Med 1988; 108: 383-93). Moreover, homosexual men with and HIV respond less frequently to interferon (Hepatology 1987; 7:190) though this was not seen in this present study and others (Hepatology 1985; 5:756-9, Lancet 1987; 1:66-8). A second factor possibly affecting the results was lymphopenia which is known to decrease mononuclear cells from circulation, thus affecting the immune function. The lack of statistical significance among the treated patients and the control could be explained by a type II error inherent in small clinical trials.

The results of this study are discouraging, but should not be used as evidence for interferon therapy. Higher efficacy of treatment is possible with active or severe liver disease and lower efficacy in patients undergoing lymphopenia. In patients undergoing lymphopenia, it is suggested that patients who exhibit an active immune response to chronic viral infection may respond better to interferon therapy. Similar observations were made in an earlier trial (Gastroenterology 1986; 90: 150-7). Immunosupression stimulation of the host e.g. by a short course of steroids and then withdrawing it prior to interferon therapy may lead to better results. Indeed, this has been proved in a recent controlled trial (Ann Intern Med 1987; 107: 25-30). A 6 week tapered regimen of prednisone, followed by 90 days of treatment with recombinant α-interferon, resulted in a response rate of 50% in the treated patients, compared with 14% in the controls, a difference that was statistically significant. Similar results have been achieved in a trial involving prednisone withdrawal followed by adenine arabinoside monophosphate (Gastroenterology 1985; 88: 760). Further, a combination of interferon with other antiviral agents like adenine arabinoside monophosphate (Ann Intern Med 1987; 107: 278-85) or acyclovir (Lancet 1985; ii: 330-9) may prove better than interferon alone.

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Small Bowel Dysfunction in Irritable Bowel Syndrome


Although the exact pathophysiology of irritable bowel syndrome (IBS) is not understood, altered myoelectrical activity of the colon is believed to be an important factor. Recently, motor dysfunction of the small bowel has also been described in these patients. In order to further explore the role of the small bowel, the authors of the present study investigated the effect of various stimuli on the motility of the jejunum and ileum in patients with IBS. Sixteen patients with IBS (10 females, mean age 34 yrs, range 24-49) and eight age and sex matched healthy controls were studied. All patients complained of abdominal pain and altered bowel habits in the form of diarrhea (n = 8) or constipation (n = 8). Fasting motility was recorded overnight and the effect of various stimuli was noted on the next day. Intraluminal pressures were recorded using a low compliance pneumohydraulic catheter and two synchronized multichannel recorders. Pressure ports were then placed in the ileum, jejunum and/or ascending colon. Motility indices were measured during a 60 min control period of intravenous saline infusion followed by 180 min recording during which sequentially increasing doses (2-4 to 75-6 pmol/kg/min) of cholecystokinin octapeptide (CCK-OP) were infused. After the return of interdigestive motility pattern, a liquid test meal (300 ml, 395 KCal) was infused over a 40 min period and intestinal motility was recorded. Ultrasound means of the gall bladder were obtained before, during and after these provocative infusions. Intraluminal and gall bladder responses to CCK-OP and test meal were recorded as relative motility index (RMI) which was the log of the stimulated motility index minus the median basal (log) MI, divided by the median basal (log) MI. After test meal stimulation, motility indices were recorded in response to nociceptive stimulation and luminal distension was carried out with stepwise graded volumes. The basal motility indices were not different among the IBS and control subjects. However, in response to CCK-OP, normal subjects showed a significant increase in motility. Intestinal contractions (PPC) accompanied by spontaneous pain were recorded in IBS patients and two control subjects. Even in the absence of high pressure waves, abdominal symptoms like distension were experienced by all subjects during infusion of higher doses of CCK-OP. These symptoms appeared earlier in the constipation group than in the diarrhea or control groups. For all dosage levels of CCK-OP, RMI, both in the jejunum and ileum, were greater in IBS patients with diarrhea and lesser in the constipation group as compared with the control subjects. Patients with diarrhea always displayed greater responses to CCK-OP. The small bowel motor activity was the same in different groups in response to test meal but RMI were increased in the small bowel in IBS while these remained the same in normal controls. In response to nociceptive, discrete clustered contractions were seen in the jejunum in eight IBS patients and only one control subject, while in the ileum prolonged pressure waves were seen in 12 IBS patients and five normal subjects. In response to luminal distension, a higher proportion of IBS patients experienced pain than normal controls. The authors conclude that (i) IBS patients responded excessively to stimulation by CCK-OP, fatty meal and test distension, (ii) response was more marked in patients with diarrhea than those with constipation, (iii) motor abnormalities of the small bowel were often accompanied by abdominal symptoms suggesting that small bowel dysfunction may contribute to the symptoms of IBS.

Comments: IBS is essentially a disorder of gastrointestinal
morbidity. Since the colon is generally believed to be the principal site of involvement and also because the small intestine is not easily accessible to manometric and electrical studies, most investigators have focused attention on the colon. However, it is likely that morbidity of other organs, notably the small intestine, may be abnormal and may thus contribute to the symptoms in these patients. In fact, there is evidence of involvement of smooth muscle outside the gut in these patients (Gar 1956; 27; 1014-7.


The present report is the second report by these authors on small bowel dysfunction in patients with IBS. In the previous study on the basis of the small bowel manometry in patients with IBS, patients commonly showed prolonged peristaltic contractions (PPCs) and discrete clustered contractions (DCCs). Both were associated with abdominal symptoms. The study involved the presence of PPCs in patients with various clinical conditions. The results of this study confirm the occurrence of morbidities of other organs, notably the small intestine, may be abnormal and may thus contribute to the symptoms in these patients. In fact, there is evidence of involvement of smooth muscle outside the gut in these patients (Gar 1956; 27; 1014-7.


The present report is the second report by these authors on small bowel dysfunction in patients with IBS. In the previous study on the basis of the small bowel manometry in patients with IBS, patients commonly showed prolonged peristaltic contractions (PPCs) and discrete clustered contractions (DCCs). Both were associated with abdominal symptoms. The study involved the presence of PPCs in various subgroups of IBS. In the present study, however, the diarrhea group seemed to respond more than the constipated group. Similarly, differences in gastrointestinal responses to CCK-OP have also been reported between IBS patients and controls (Am J Physiol 1987; 253: 650-53).

On stimulation with fatty meal, IBS patients showed augmented motility in the small intestine. The change in motility was more marked in patients presenting with diarrhea. What factors resulted in this non-peristaltic motility change? Most likely this was due to CCK released in response to fatty meal stimulation, although the role of other hormonal or neural factors cannot be totally ruled out.

On nonstimulation stimulation, motility was increased in all groups and there was significant difference between IBS and control subjects. Previously, nonstimulation has been shown to increase intestinal transit time in patients with constipation (Am J Dig Dis 1977; 22: 881-7) and this effect was more marked in IBS patients (Gastroenterology, 1981; 86: 99-99). However, there are no other studies on its effect on ileal motility in man. The occurrence of PPCs on nonstimulation stimulation in all the subgroups suggests that their production is mediated by cholinergic mechanisms. Mild distension was another stimulus to which these patients responded more sensitively. Colonic (Gar 1983: 6; 103-12) and rectal (Dig Dis Sci 1988: 25; 404-11) responses have previously been reported to produce abdominal discomfort in IBS. This study, for the first time, has shown increased sensitivity in these patients to mild distension. All these observations suggest that non-peristaltic motility of the small intestine may be partly responsible for the symptoms in patients with IBS.

Percutaneous Aspiration of Hydatid Cyst

Bret PM, Fournier A, Brantoffonel M, et al. (Department of Radiology, Montreal General Hospital, Quebec, Canada, and Hospital Edouard Herriot, University of Lyon, France). Percutaneous aspiration and drainage of hydatid cysts in the liver. Radiology 1988; 168; 617-20.

Echinococcosis is a frequently encountered problem in certain countries and the liver is one of the commonly involved organs. The diagnosis of hepatic hydatid cyst is usually made on routine X-ray or ultrasound (US) examination. However, at times, it is not easy to ascertain the etiological nature of the cyst(s) in the liver with these investigations. Although specific diagnosis is most accomplished by histologic examination, aspiration is not advised because of the fear of anaphylactic reaction. Percutaneous aspiration of hydatid cysts in patients with hepatic cysts is a major diagnostic procedure in patients with type I cysts. In patients with type I cysts, the diagnostic yield was enhanced by immunoelectrophoresis of the aspirate. Both type I and type IV lesions are usually treated with simple cysts or tumoral lesions of the liver.
(Radiology 1981; 139: 459-63). Only one of the 13 patients in the present study had US features characteristic of hydatid disease.

But how safe is it to aspirate hepatic hydatid cysts? Brett et al encountered complications in two (14%) of their 13 patients in the form of urticaria and pruritus. Only one patient required therapy with corticosteroids. The evidence from the literature is not helpful as it neither supports nor confers aspiration. The exact frequency and severity of anaphylactic shock from rupture of a hydatid cyst are not clearly known (Ann Surg 1968; 167: 337-41; JAMA 1966; 195: 158-60). At the same time, there are documented cases of intentional or inadvertent puncture or hydatid cysts without any complication (AJR 1984; 143: 133-6; Radiology 1985; 155: 627-8). It would thus seem that in certain situations, a guarded diagnostic aspiration may be carried out in patients with hepatic hydatidosis if radiology and serological testing are equivocal.

The other aspect of the paper covers therapeutic drainage in such patients. The standard treatment of hepatic hydatid cysts remains surgical (Ann Surg 1984; 199: 412-7) though medical therapy with mebendazole (Am J Trop Med Hyg 1984; 33: 332-7) and albendazole (Clin Radiol 1984; 35: 297-300) has been tried. Percutaneous placement of a drainage catheter entails the risk of spillage of hydatid fluid but it offers an opportunity to instill scolicidal agents. The authors were successful in all three of their patients. In a previous report, long term catheter drainage was successfully used in a patient in whom the cyst was communicating with the biliary tree (Radiology 1985; 155: 627-8). Percutaneous radiologic catheter drainage of fluid collection in the abdomen is now a well-established and safe alternative to surgery (AJR 1979; 133: 1-8; Radiology 1984; 121: 343-7). Applying the same principle, percutaneous drainage and irrigation with a scolicidal agent may serve as an alternative form of therapy for patients who are not candidates for surgery. This may also hold true for patients having a communication between the hydatid cyst and the biliary tree or those who have an infected cyst.

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