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Valsartan-Induced Hepatotoxicity in a HBs-Ag-Positive Patient

TO THE EDITOR: Hepatotoxicity caused by angiotensin II receptor blockers is a very rare disorder. We report the first case with acute hepatic injury associated with valsartan, which is an antihypertensive agent.

A 52-yr-old hypertensive woman was admitted to our hospital with complaints of weakness, nausea, jaundice, and right subcostal abdominal pain. Her past medical history was unremarkable except for primary hypertension and hepatitis B surface antigen (HBs-Ag) positivity. She had been followed as a HBs-Ag carrier for 4 yr without clinical and laboratory symptoms and signs of acute or chronic liver disease in our hospital. She had been treated for primary hypertension by valsartan for 1 month. There was no other medication. The patient had manifested pruritic erytematous skin changes 1 wk before this admission. After this complaint, moderate nausea, jaundice, and right subcostal abdominal pain developed.

On admission, her physical examination revealed no abnormality except for painful mild hepatomegaly. Laboratory findings were as follows: complete blood count was normal and eosinophilia was present. Her total and direct bilirubin levels were 3.2 mg/dl and 2.8 mg/dl, respectively, on admission, and peaked 7.8 and 6.9, respectively on the 7th day of admission. Liver enzymes peaked at the 6th day as follows: ALT 780 U/L, AST 1292 U/L, γ-glutamyl transferase 945 U/L, and liver-specific ALP 1840 U/L. Serological tests for hepatitis virus were negative (anti-hepatitis A virus IgM, anti-hepatitis B core IgM and IgG, hepatitis B virus DNA by polymerase chain reaction, hepatitis C virus antibody hepatitis C virus RNA by polymerase chain reaction, anti-Epstein-Barr virus IgM, and anti-cytomegalovirus IgM and IgG), except for HBs-Ag positivity. Markers for toxoplasmosis, herpes simplex virus, and HIV were all negative. International Normalized Ratio (INR) and PT were mildly elevated. Hepatobiliary ultrasonography revealed mild hepatomegaly. Liver biopsy was considered, but the patient refused. Valsartan therapy was discontinued at once. Hepatic failure and related complications were not seen. The complaints of the patient were resolved within 2 wk under conservative management. Liver enzymes and bilirubin levels decreased rapidly within 2 wk and returned to normal limits within 3 months. She has been followed for 6 months asymptomatically.

As far as we know, this is the first case of valsartan-associated hepatotoxicity in a patient with HBs-Ag positivity. There is just one case report of valsartan-associated hepatic injury from Spain (1). There are not a lot of cases of angiotensin II receptor antagonists associated hepatotoxicity, and in this case, presumably this association is a hypersensitivity reaction together with pruritic skin changes. Valsartan is eliminated mainly by hepatic clearance. Headache, dizziness, and fatigue were the most common adverse events in placebo- controlled studies; the incidence of these adverse events was not significantly different between placebo and valsartan recipients (2). Rash and angioedema have been reported with angiotensin II receptor antagonists very rarely (3). Drug-induced hepatic injury associated with losartan was reviewed by Tabak *et al.* (4). The importance of HBs-Ag positivity in this hepatotoxicity remains unknown, and the physicians who recommended these agents should be careful about this complication.

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Traveler's Constipation

TO THE EDITOR: It is frequent for patients (and physicians!) to complain of constipation when traveling. To our knowledge, no study has been conducted to evaluate

whether traveling is truly associated with constipation. Thus, although traveler's diarrhea is very well known (1), "traveler's constipation" is still an unknown entity. Popular logic has attributed the constipation that appears (or worsens) when traveling to changes in diet, different timetable, fussy problems related to public lavatories, etc. Moreover, because brain and gut influence each other in an important way (2), it could be speculated that traveling tiredness, or jet lag, might influence bowel movements through the brain-gut axis. The aim of the present study was to investigate the presence (or not) of constipation in a group of healthy persons traveling by air from Europe to America on a 12-h trip for a 7-day stay. Factors that could be involved in this bowel movement modification, including jet lag, were also analyzed.

Seventy Spanish individuals (40 women, 30 men) with ages ranging from 18 to 67 yr (mean age 50 ± 11 yr) participated in the study. Five subjects were excluded for the following reasons: currently receiving β-adrenergic blockers, or medication for anxiety, depression, or other psychiatric problems, or chronic problems with insomnia.

On November 2000, a 12-h flight from Madrid, Spain, to Buenos Aires, Argentina, took place: departure time was at 22:00 h and arrival at 07:00 h; time difference between both countries is 5 h. The stay in Argentina lasted 7 days.

The following measurements were performed in all subjects: habitual bowel habit during the month before the trip by an 11-item questionnaire (n = 20), day-by-day depositional habit before the trip (basal state) (n = 20) and during the trip (n = 23), feces consistency by the visual Bristol Stool Form Scale (3) before the trip (basal state) (n = 18) and during the trip (n = 21), jet lag caused by the trip by the Columbia Jet Lag Scale questionnaire (4) (n = 19), and colonic transit time (CTT) using radiopaque markers (5) during the basal state (n = 9) and during the trip (n = 28). On the last day of the trip, travelers (n = 65) were asked to evaluate their bowel habit during the previous week, indicating if it had changed.

Thirty (46%) of the 65 subjects evaluated considered their bowel habit to have changed during the trip: 25 (38%) reported to be constipated and five (8%) to have had diarrhea. However, a poor relationship was observed between their subjective opinion and the data obtained from their diaries. Most participants considered that changes in diet (66.7%) and time schedule of defecation (85.7%) were the major factors implicated in their bowel habit change. Interestingly, all but one subject suffered changes in their evacuation timetable.

The average number of bowel movements per day decreased from 0.97 ± 0.07 before the trip to 0.68 ± 0.06 during the trip ($p < 0.05$) (individual data are shown in Fig. 1). No significant changes were observed in the number of episodes of defecatory effort, sensation of incomplete evacuation, or stool consistency, measured according to the Bristol scale.

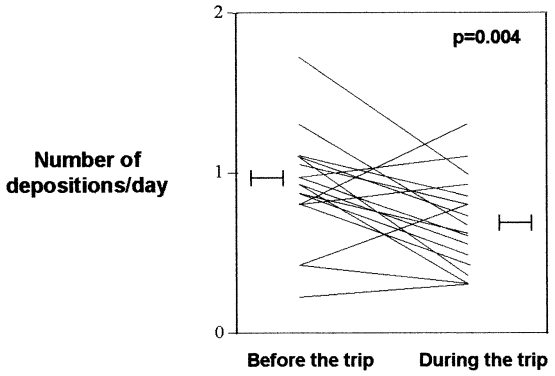

Figure 1. Mean number of depositions per day during the week before the trip and during the week of the trip (⊢⊣ = mean value of the group).

Significant jet lag (score > 10) was present in 52.6%, 10.5%, 10.5%, and 21.1% of the subjects the first 4 days of the trip, respectively. Jet lag correlated with a decreased number of bowel movements during the first day of the trip (Pearson correlation = −0.5; $p = 0.02$). Data are shown in Figure 2.

Total CTT was similar before and during the trip (36.7 ± 4.2 h and 36.2 ± 2.8 h). Segmental CTT (rectal, left colon, and right colon) were also similar. All values were within the normal standards established in healthy Spanish controls (6).

Traveling may induce changes in bowel movements. We found that a considerable number of subjects (almost 40%) complained of having been constipated during this transatlantic trip, whereas less than 10% had diarrhea. The number of bowel movements decreased significantly during the trip week, although total and segmental CTT did not change. Defecatory frequency decrease was related to jet lag, mainly during the first days of the trip. However, taking into account that physical activity and diet changed dramatically the day of the trip, as a normal consequence of flying, this finding should be regarded with caution.

The impact of constipation on health is lower than that of diarrhea, but both can change a supposedly delightful into a disappointing experience. It is our opinion that "traveler's constipation" is an entity to bear in mind.

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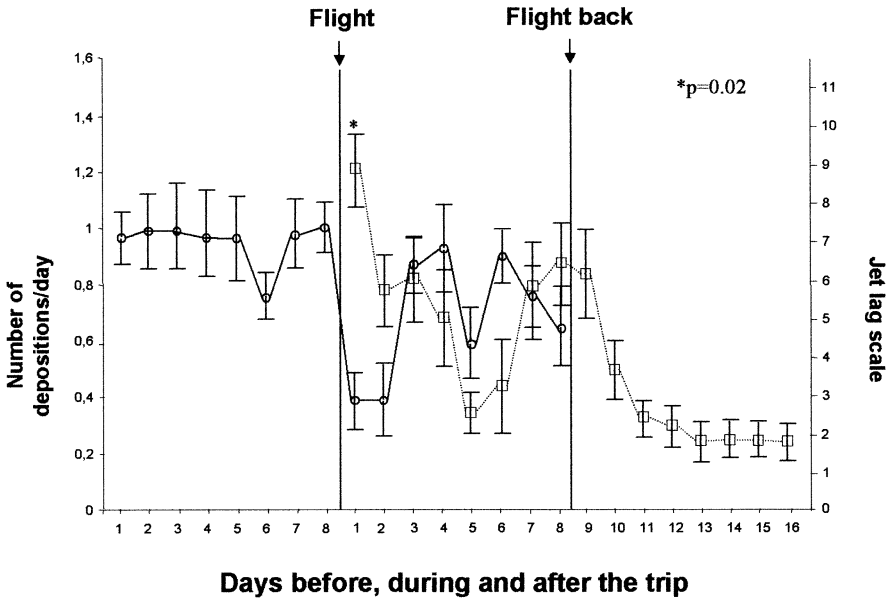

Figure 2. Number of bowel movements per day (solid line) and jet lag values established using the Columbia Jet Lag Scale questionnaire (dotted line) before, during, and after the trip. Statistical correlation was only obtained for the first day after the trip (*). Values are means and SDs.

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Crohn's Disease Involving the Gallbladder: Case Report and Review of the Literature

TO THE EDITOR: Crohn's disease is known to involve the gastrointestinal tract from the oral cavity to the anus. Extraintestinal involvement has also been described, including the hepatobiliary system. We present a case report and review of the literature of acute cholecystitis caused by Crohn's disease of the gallbladder.

A 64-yr-old man presented to the Audie L. Murphy Memorial Veterans Hospital in San Antonio, TX, with complaints of abdominal pain, anorexia, and nausea occurring for approximately 1 wk. The pain was localized to the right upper quadrant and made worse by food ingestion. He denied fevers, chills, melena, hematochezia, scleral icterus, or dark colored urine.

His past medical history included Crohn's disease, which had been diagnosed 5 yr before presentation after being admitted to an outside institution with a clinical picture compatible with a small bowel obstruction. Laparotomy had revealed transmural inflammation involving the distal ileum requiring resection of 20 cm of ileum with 30 cm of colon and an ileotransverse anastomosis. The diagnosis of Crohn's disease was confirmed by pathological examination of the submitted specimen. The patient recovered uneventfully and remained asymptomatic without medications until the time of admission to our hospital years later.

At the time of admission, the patient's vital signs were: temperature 100.8 F, blood pressure 119/78 mm Hg, and pulse 92 beats/min. Physical examination revealed a man in