Decreased Drug Absorption in a Patient with Behçet’s Syndrome

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Observing a lack of response to orally administered drugs in a patient with Behçet’s disease, we studied the absorption of amitriptyline, diazepam, carbamazepine, phenytoin, and acetaminophen in this patient after single and (or) multiple dose administrations. The relative oral/intramuscular bioavailability of amitriptyline was only 13%, and the steady-state concentrations of this drug on four consecutive days were acutely subtherapeutic (i.e., 3.6, 3.7, 3.9, and 3.7 μg/L). The concentrations of diazepam, phenytoin, and acetaminophen in plasma were nonmeasurable. Examination of the gastrointestinal tract by endoscopy and by light and electronic microscopy of a biopsy section revealed inflammatory and vascular changes in the duodenum. In the absence of clinical evidence for malabsorption syndrome, we believe that the decreased drug absorption observed in this patient was caused by inflammatory changes associated with Behçet’s syndrome.

Additional Keyphrases: malabsorption · gastrointestinal inflammation · amitriptyline · diazepam · phenytoin · acetaminophen · pharmacokinetics

Current data concerning the effect of altered body function on drug absorption by the gastrointestinal (GI) tract are still inadequate. Many physiological factors (e.g., gastrointestinal pH, emptying time, blood flow, motility, and the integrity and size of the surface epithelium) are known to influence drug absorption (1). Hence, disease states that affect these factors have an impact on bioavailability of orally administered drugs. The absorption of aspirin (acetylsalicylate) (2) and pentaerythritoltetranicotinate (3) in achlorhydric patients reported differs from that in normal subjects. Hypothyroid patients exhibited an increase in the absorption of riboflavin, presumably because of a decrease in the intestinal motility associated with hypothyroidism (4); on the other hand, patients with diarrhea had decreased absorption of isoniazid, aspirin, and sulfasalazine (5). Also, impaired absorption of digoxin was observed in patients with sprue and pancreatic insufficiency (6). Patients with malaria, which is known to induce morphological changes in intestinal membrane and blood flow, showed impaired absorption of vitamin B12 and xylose (7, 8). Additionally, decreased absorption of ampicillin and nalidixic acid (9) and acetaminophen (10) was observed in patients with shigellosis and pyloric stenosis, respectively. Gastric surgery and gastrectomy reportedly hampered absorption of quinidine, ethambutol, and sulfaphenazole (11) and decreased absorption of folic acid (12).

Behçet’s disease is a chronic inflammatory condition of obscure etiology involving the mucocutaneous membrane, skin, eyes, joints, and blood vessels as well as organ systems (13). Malabsorption syndrome or reduced bioavailability of any drug has not been reported in this disorder. Here, we present a case in which the absorption of several drugs was severely impaired.

Case Report

The patient, a 33-year-old Saudi woman of Turkistani origin, weighs 70 kg and is 167 cm tall. A school teacher, she has been followed at the King Faisal Specialist Hospital and Research Center for about nine years for multiple complaints including oro-genital ulceration, arthralgia, diffuse GI symptoms, chronic constipation, skin lesions, multiple allergies, recurrent symptoms of Raynaud’s phenomenon, and depression. The diagnosis of Behçet’s disease made in this hospital, was confirmed by a team from the Mayo Clinic (Rochester, MN) when the patient was referred there in 1983. She had normal serum concentrations of creatinine, urea nitrogen, uric acid, total bilirubin, alkaline phosphatase, alanine and aspartate aminotransferases, and lactate dehydrogenase. During her psychiatric treatment, the patient was noticed to be refractory to therapy with tricyclic antidepressants and repeated analyses for these drugs yielded "undetectable" results. Even an overdose of 900 mg of doxepin showed no clinical change, and the concentration of this drug in plasma was still subtherapeutic, 69 μg/L. Thus we undertook a study to investigate drug absorption in this patient.

Methods

After consent was obtained from the patient, we performed several tests, including single- and multiple-dose pharmacokinetic studies with different drugs.

Single-dose study. Although the patient is well educated, motivated, and considered reliable, this study was performed while she was hospitalized, to rule out any doubt about her compliance. A 150-mg dose of amitriptyline was administered to the patient orally under the supervision of a nurse, who inspected her mouth for a direct check of compliance. Blood was then sampled via heparin lock into heparinized tubes at various intervals (0.5, 1, 2, 4, 12, 24, and 36 h) after the dose; plasma was harvested after centrifugation at 1118 × g for 10 min, then stored at −18 °C until analysis. After four days with no drugs, a dose equivalent to 50 mg of amitriptyline was administered.

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intramuscularly, and plasma samples were collected as described above.

Multiple-dose study. After a rest of four days, the patient was given 100 mg of amitriptyline thrice daily for eight consecutive days; plasma samples collected at 09:00 h on the fifth, sixth, seventh, and eighth day were treated as described above.

Also, on an outpatient basis, the patient was given 100 mg of phenytoin thrice daily for a week, at the end of which a plasma sample was collected and stored at −18 °C until analysis. Similar studies were performed with diazepam, carbamazepine, and acetaminophen in respective doses equivalent to 10, 200, and 500 mg thrice daily.

The patient was also subjected to a xylose absorption test, lactose and glucose tolerance tests, and an endoscopic GI examination. Finally, duodenal tissue was obtained by biopsy for examination by light and electronic microscopy.

Xylose absorption test. We administered an oral dose of 25 g of xylose to the patient after she had emptied her bladder, and measured its concentration in blood samples collected 1 and 2 h later. We also measured the xylose content in a urine sample collected 3 h after the xylose ingestion.

Lactose tolerance test. After the patient had ingested 50 g of lactose, we measured the concentration of glucose in blood samples collected at 0 (just before, while still fasting), 15, 30, 45, 60, 90, and 120 min after she took the lactose.

Glucose tolerance test. This test was performed by giving the patient 50 g of glucose orally and measuring its concentration in blood samples collected at 0 (fasting), 0.5, 1, 2, 3, and 4 h after ingestion of glucose.

In addition to these tests, the serum concentrations of carotene and vitamin B₁₂ in this patient were measured.

Analysis of drug in plasma. We analyzed the plasma samples obtained from the amitriptyline studies by "high-performance" liquid chromatography (14), measuring the concentrations of amitriptyline and its metabolite nortriptyline simultaneously. We measured the concentrations of phenytoin, carbamazepine, and acetaminophen by fluorescence polarization immunoassays (TD₂; Abbott Laboratories) (15), and of diazepam by enzyme immunoassay.

Results

The results for amitriptyline in plasma, obtained from the single oral and intramuscular studies, were normalized by dividing by the dose received (Figure 1). The relative bioavailability (oral/intramuscular; RB₉₅/₁₅₅) of amitriptyline was estimated according to the following equation:

RB₉₅/₁₅₅ = AUC₉₅/AUC₁₅₅

where AUC₉₅ and AUC₁₅₅ are the area under the curves from 0 to 36 h, computed by trapezoidal rule from the data obtained from the single oral and intramuscular administrations, respectively. We calculated this value to be 13%. Because we did not have adequate post-peak concentration data to estimate the biological half-life and the areas under the curves for 0 → ∞, we based our calculation on the data acquired up to 36 h, the time of collection of the last sample.

The steady-state concentrations obtained from the multiple-dose studies with amitriptyline, phenytoin, diazepam, and acetaminophen are presented in Table 1.

The concentrations of xylose in blood 1 and 2 h after the administration of 25 g of this compound were 1000 and 500 mg/L; the concentration of xylose in urine was 9.7 mg/L. These values indicate a normal absorption of xylose.

The results of the lactose tolerance test showed impaired absorption: the concentrations of glucose in blood at 0 (fasting), 15, 30, 45, 60, 90, and 120 min after ingestion of lactose were 810, 820, 940, 910, 890, 780, and 850 mg/L, respectively. These results agree with those of the glucose tolerance test, the concentrations of glucose in the blood at 0 (fasting), 0.5, 1, 2, 3, and 4 h being 850, 870, 960, 920, 810, and 790 mg/L, respectively. The concentrations of carotene and vitamin B₁₂ were within the normal range: 1.45 and 3.41 mg/L, respectively.

The endoscopic GI evaluation revealed minor inflammatory changes in the stomach and duodenum. The light-microscopic examination of sections of the duodenal biopsy showed duodenal mucosa with normal villous projections. The lining epithelial cells appeared unremarkable. The lamina propria contained many lymphocytes, plasma cells, and some eosinophils. In addition, benign glandular structures were present. The diagnosis was chronic inflammation. No abnormalities were detected by electron microscopy.

Discussion

The data obtained in this study indicate a marked impairment of drug absorption in this patient. Indeed, the steady-state concentrations of phenytoin, diazepam, and acetamino-
ophen in plasma were below the detectable limits, and the concentrations of amitriptyline on four consecutive days were exceedingly small for the dose used. The bioavailability of amitriptyline from single-dose study was only 13%. This cannot be explained on the basis of the first-pass effect this drug undergoes when administered orally, because the oral bioavailability of tricyclic antidepressants exceeds 65%. Moreover, the exceedingly small concentrations of these drugs cannot be ascribed to an abnormally enhanced hepatic metabolism of the drugs by this patient, because results of liver-function tests were all normal.

Although the lactose and glucose tolerance tests showed impaired absorption of these carbohydrates, the patient has no clinical features of malabsorption syndrome (diarrhea, etc.). Furthermore, the absorption of xylose as well as the concentrations of vitamin B₁₂ and carotene in serum appeared to be normal. Therefore, the impaired absorption of the drugs investigated does not appear to be related to any well-defined, specific malabsorption pattern, but may be linked to the inflammatory changes discussed below.

Currently, diagnosis of Behçet's disease is based merely on clinical findings (16). A combination of three or more of the following symptoms is considered adequate for the diagnosis: recurrent oral or genital aphthous ulcers, cutaneous vasculitis, arthritis or arthralgia, uveitis, meningoencephalitis. This patient has the first three. Although there is no evidence that a marked decrease in the oral absorption of drugs is related to Behçet's disease, the observed impairment of drug absorption in this patient is unlikely to be coincidental. As stated above, Behçet's disease may involve the GI tract with fissuring, nonspecific inflammation, and weak collagen fiber reactions. Also, vascular changes in the intestinal blood vessels, especially the arterioles and venules, have been reported in patients with Behçet's syndrome and have seemed to play an important role in aggravating the symptoms of this disease (17). Indeed, microscopic examination of duodenal biopsy and GI evaluation of the patient by endoscopy revealed chronic inflammatory and vascular changes in the stomach and duodenum. There being no evidence to link the impaired absorption of the drugs to malabsorption syndrome, we think the impaired drug absorption may be related to these inflammatory changes in this patient.

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References