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LETTER TO THE EDITOR

Letter

Sirs,

Severe diarrhoea in an HIV-infected patient with chronic hepatitis B treated with imipramine

Several studies in the literature do recommend prescribing, with caution, psychotropic agents to HIV-infected patients, because these latter are more susceptible to develop rare, severe or even paradoxical adverse effects (Ayuso, 1994; Grassi and Scarone, 1994; Grassi *et al.*, 1995a,b). Here, we report a case of intractable diarrhoea in an HIV-infected patient with chronic hepatitis B, who was administered imipramine as treatment for a depressive episode.

LG, a 32-year-old man, was hospitalized in our psychiatric ward from early November 1995 to late December 1995, due to the occurrence of a depressive episode with suicidal intentionality. The patient's clinical history revealed the presence of a Bipolar Disorder (according to the DSM IV criteria) (American Psychiatric Association, 1994); furthermore, the patient was known to be HIV-infected since 1991 and to be affected by chronic hepatitis B since 1982. At the time of the hospitalization the patient was in good physical condition; his T helper lymphocyte number was 624/ml.

Before starting with antidepressant treatment, liver function was assessed by means of both blood laboratory tests and ultrasonography. Blood laboratory tests produced the following impaired results: aspartate aminotransferase (AST) = 162 mg/dl; alanine aminotransferase (ALT) = 84 mg/dl; total bilirubin = 2·91 mg/dl; direct-reacting bilirubin = 2·38 mg/dl; γ-glutamyltranspeptidase (GGT) = 154 mg/dl; serum cholinesterase = 3·65 U/dl. Liver morphology as assessed by ultrasonography was within normal limits.

Antidepressant treatment with imipramine was started: during the first week, daily drug dosage was gradually increased from 25 mg to 75 mg. The patient was not taking any other medication. Among antidepressants imipramine was chosen because the patient had already taken this drug in the course of the last depressive episode (which occurred during May 1995), thus gaining a good recovery from depression without experiencing significant adverse effects.

After 10 days' treatment, the patient started to develop severe diarrhoea (about 7–10 stools a day), in the absence of any other sign or symptom: in particular, fever, abdominal pain, nausea and/or vomiting were never reported. Diarrhoea responded poorly to loperamide and to diphenoxylate treatment.

Diagnostic procedures were performed in order to rule out common causes of diarrhoea. Repeated stool specimens were tested for the presence of the following pathogens: *Salmonella*, *Shigella*, *Cryptosporidium*, *Clostridium difficile*, *Giardia* and other helminthes or protozoa. Stool specimens were not infected. Further, the patient underwent total abdomen ultrasonography and colonoscopy both of which were normal. Blood laboratory tests results concerning liver function were the same as those obtained before starting with imipramine treatment (see above).

Imipramine treatment was maintained at 75 mg daily dosage. After 3 weeks' treatment, the patient's depressive symptomatology was slightly improved but disabling diarrhoea was still present. Imipramine treatment was then interrupted. Two weeks after drug interruption the diarrhoea completely disappeared. Due to the persistence of the depressive episode, antidepressant treatment with desipramine was started at a daily dosage of 50 mg. This drug was well tolerated by the patient, who reported an improvement of depressive symptomatology after 2 weeks; the patient was administered desipramine for 5 weeks and did not report a further occurrence of diarrhoea.

We believe that imipramine was probably responsible for the occurrence of diarrhoea in this patient, based on the following considerations: (1) the exclusion of other causes of diarrhoea in an HIV-infected patient with good immune function

(T helper lymphocyte number = 624/ml); (2) the poor response of diarrhoea to traditional symptomatic pharmacological approaches (i.e. loperamide and diphenoxylate treatment) together with its abrupt disappearance after imipramine interruption; (3) the observation that diarrhoea did not develop during the course of desipramine treatment.

We also recognize that this adverse effect cannot be attributable entirely to imipramine *per se*; chronic liver dysfunction may have contributed to the development of diarrhoea in this patient. Further, several recent studies in the literature do hypothesize the existence in HIV-infected people of some form of enteropathy caused by the infection of the intestinal mucosa by the virus itself; however, this enteropathy seems to affect principally patients with AIDS-related complex or AIDS (Beaugerie, 1993).

Diarrhoea in the course of imipramine treatment was to be considered a paradoxical effect, because this drug is, on the contrary, associated with constipation due to its anticholinergic effect (Gorard *et al*., 1995).

This case report has to be added to the already existing observations in the literature concerning the particular susceptibility of HIV-infected patients to develop rare, severe or even paradoxical adverse effects when administered psychotropic agents, particularly antidepressants (Ayuso, 1994; Grassi and Scarone, 1994; Grassi *et al*., 1995a,b); because depression is a frequent complication of HIV infection (Forstein and Baer, 1991), physicians have to keep in mind these clinical observations in order to adequately take care of these patients.

This susceptibility of HIV-infected subjects to develop adverse effects when they are taking psychotropic agents is supposed to be mostly dependent on central nervous system (CNS) HIV infection, which occurs early after viral blood infection in almost all individuals. CNS infection creates a sort of viral reservoir: once infection is established in the CNS, the CNS itself may act as an important extravascular source of HIV, shedding virus into the cerebrospinal fluid and thence into the blood. It is well known that CNS HIV infection causes several neurological syndromes (AIDS dementia complex, vacuolar myelopathy, aseptic meningitis, pheripheral neuropathies and myopathy) in some HIV-infected subjects, but experimental evidence supports the hypothesis that, even in the absence of neurological signs and/or symptoms, CNS HIV-infection may nonetheless impair neuronal function and this could condition the response of an HIV-infected individual to psychotropic drugs in terms of adverse effects susceptibility. In particular, alterations in neurotransmission, neuronal trophism and cerebral electrical activity have been reported in subjects without clinical neurological impairment (Maj *et al*., 1994; Grassi *et al*., 1996). Furthermore, patients with symptomatic HIV infection generally receive one or more drugs to control some of the systemic clinical complications they exhibit. When one or various psychotropic agents are added, these substances can compete with protein binding and cause a significant rise in the plasma concentrations of psychotropic agents which could be responsible for the increased incidence of adverse effects. These protein binding displacement interactions can be clinically relevant in patients with decreased plasma proteins secondary to liver disease or malnutrition. In addition, multidrug regimens may cause alterations in the metabolism of any of the agents administered.

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