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Alterations of Liver Function Test in Patients Treated With Antipsychotics

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The prevalence of alterations of liver function tests in patients treated with a wide range of antypsychotics is unknown. The aim of this study was to analyze the effects of antipsychotics on liver function tests in a population of schizophrenic outpatients. Concentrations of AST, ALT, GGT, alkaline phosphatase, albumin, and bilirubin were determined in 54 patients fitting DSM-IV criteria of schizophrenia, and the same number of sex- and age-matched healthy subjects. Assessments included the Clinical Global Impression (CGI) and the Positive and Negative Syndrome Scale (PANSS) in addition to treatment related variables. Transaminases concentrations were slightly elevated in study patients compared to healthy controls, but without statistical significance. Alkaline phosphatase showed higher values in schizophrenic patients. Albumin and bilirubin were lower in study patients. Liver function tests abnormalities were found in about 10% of schizophrenic patients treated with antipsychotics. Treatment with depot phenotiazines induces alteration in these tests more frequently than treatment with other antipsychotics. PANSS negative subscale scores directly correlated with alkaline phosphatase and inversely correlated with albumin. A substantial number of patients in treatment with antipsychotic drugs present alterations of liver function tests. Both pharmacological and clinical factors could be related with these alterations. J. Clin. Lab. Anal. 17:216–218, 2003. © 2003 Wiley-Liss, Inc.

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Severe hepatotoxicity of antipsychotics (neuroleptics) occurs in a small proportion of patients and can be considered idiosyncratic. It has been studied in patients treated with classic neuroleptics (mainly chlorpromazine) and have been found to affect approximately 0.1–1% of patients (1,2). However, asymptomatic liver test abnormalities are reported in more than 20% of patients treated with these drugs (3). Recent reviews (2–4) deal with pathophysiology of antipsychotics induced hepatitis, but the real prevalence of alterations of liver function tests (LFT) in patients treated with a wide range of antypsychotics is unknown. Previous research focused on the effects caused by phenothiazines (chlorpromazine) and, to an extent, effects caused by haloperidol and clozapine. Chlorpromazine has been widely used in the past, but its usage now is unusual. Other classic and newer (atypical) antipsychotics are frequently prescribed today. The implications of treatment with these drugs are enormous. For example, schizophrenia is only one of the disorders treated with these compounds and it affects at least 1% of population.

Our aim was to analyze the effects of antipsychotics on LFT in a population of outpatients suffering from schizophrenia.

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METHODS

All schizophrenic patients on stable treatment from an outpatient practice of a Mental Health Unit in Santander (a city in the North of Spain) were included. This department attends a population of 44,032 people. We selected all patients fitting Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria of schizophrenia (5) assessed with the Item Group Checklist of the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview (6,7). Exclusion criteria included: other concurrent psychiatric disorders (including drug abuse); medical disorder; or drugs treatment (excluding psychotropic drugs). From the 81 patients of the initial sample, 54 fit inclusion criteria and gave informed consent. The same exclusion criteria was applied for 54 healthy controls. The controls were sex- and age-controlled exactly with the study patients to avoid differences attributable to demographic factors (since, for example, alkaline phosphatase has an age dependence).

Clinical information included data from the medical records, the Clinical Global Impression (CGI) (8), and the PANSS (9). Fasting blood specimens were drawn from an antecubital vein between 8:00 and 9:00 a.m. Specimens were centrifuged immediately and serum was stored at -40°C until assayed. Concentrations of AST, ALT, GGT, alkaline phosphatase, albumin, and bilirubin were determined using a Technicon Dax (Technicon Instruments Corp., Tarrytown, NY). Data was analyzed with the statistical package SPSS for Windows 7.0 (SPSS Inc. Chicago, IL). Since some of the variables did not show a normal distribution, nonparamentric (U-Mann-Whitney test, Spearman test) statistics were used.

RESULTS

The values of liver function tests are represented in Table 1. Transaminases concentrations were slightly elevated in study patients compared to healthy controls, but without statistical significance. Alkaline phosphatase showed higher concentrations in schizophrenic patients. Albumin was lower in study patients, and bilirubin showed changes in the same direction.

Patients with *depot* neuroleptic treatment (fluphenazine, a phenotiazine) had higher GGT ($P = 0.005$), and lower concentrations of both serum albumin and bilirubin ($P = 0.054$ and 0.056, respectively) than patients on oral treatment. Typical/atypical antipsychotic treatment and the dosage of neuroleptic treatment (converted to mg of chlorpromazine/day) did not correlate with LFT. When we compared LFT with pharmacological subgroups of antipsychotics, Kruskal-Wallis test did not show significant differences among groups. However, analyzing the two subgroups with biggest samples, we found a trend toward lower concentrations of bilirubin in patients with thienobenzodiazepines (olanzapine) treatment compared to those on butyrophenones (haloperidol) ($P = 0.08$). The rest of the pharmacological groups did not show differences in their LFT. Interestingly, global clinical severity and PANSS negative subscale scores directly correlated with alkaline phosphatase ($P = 0.008$), and inversely with albumin ($P = 0.003$).

DISCUSSION

Our results suggest that depot phenotiazines can produce more alteration in some LFT than other antipsychotics. We cannot, however, exclude the influence of a better treatment adherence because of its depot nature. Our results also suggest that newer antipsychotics (such as olanzapine) can induce changes in the same direction. Previous reports have suggested an induction of some liver function tests (alkaline phosphatase, GGT) by phenothiazines. This could explain our results of increased alkaline phosphatase values in patients (10,11).

The fact that liver function tests had relationships with psychiatric symptoms also suggests that factors related to life habits, feeding, etc. (usually affected as a result of the negative symptoms) could be related to

TABLE 1. Results of liver function test in patients with schizophrenia and healthy controls

	Patients with schizophrenia		Controls			
	Mean	SD	Mean	SD	P[a]	N (%) of patients above-below 2 SD of controls
AST (U/L)	26.0	(18.4)	24.4	(8.6)	0.1	5 (9.3%) above
ALT (U/L)	39.4	(55.7)	25.3	(12.2)	0.9	7 (13.0%) above
GGT (U/L)	25.9	(32.4)	20.6	(12.7)	0.6	4 (7.4%) above
Alkaline Phosphatase (U/L)	63.3	(17.8)	53.9	(15.0)	0.003	7 (13.0%) above
Albumin (g/dL)	4.41	(0.31)	4.73	(0.42)	<0.001	2 (3.7%) below
Bilirubin (mg/dL)	0.53	(0.23)	0.70	(0.33)	0.001	1 (1.9%) above

[a]Mann-Whitney test.

the findings in these patients. Moreover, the relationship between LFT (at least some of them) and psychopathology could be mediated by other factors, such as interleukin-6. We have demonstrated that negative symptoms remained as the main variable affecting interleukin-6 values in a multiple linear regression analysis in the same sample (unpublished). In fact, alkaline phosphatase directly correlated and albumin negatively correlated with interleukin-6 values (Spearman test, $P = 0.006$ and $P = 0.01$, respectively [data not shown, available on request]).

In conclusion, we found liver function test abnormalities in about 10% of schizophrenic patients treated with antipsychotics and significant differences in alkaline phosphatase, albumin, and bilirubin serum concentrations when they were compared to concentrations found in healthy controls. Further studies are needed to assess the role of psychopathology, other biological markers, and life habits over these changes.

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