ABSTRACT
Objective: To develop strategies and to monitor patient’s adherence to the follow up of the experimental treatment of secondary cholestasis in its isolate chronic form with portal hypertension. Methods: Experimental study made with 11 patients. Ursodeoxycholic acid was administered in the dosage of 15 mg/kg/day twice a day for 45 days. Evaluation of adherence was performed using pill count strategy and interviews. Results: The variation during pill count had no influence on the patient’s laboratory results. Serum activity of $\gamma$GT normalized during treatment, returning to increased levels after interruption of medication. Conclusions: The strategies developed were effective presenting a significant laboratory result regarding the decrease of $\gamma$GT serum activity.

Keywords: Patient compliance; Schistosomiasis; Health education; Ursodeoxycholic acid/administration & dosage

INTRODUCTION
Patient’s knowledge about their disease is part of the treatment. To successfully provide correct information on drugs is a challenging task, and Healthcare teams have to use strategies to encourage the patient’s compliance to the treatment. The correct use of drugs is also essential for clinical trials, because the evaluation of the drug efficacy depends on it.

Some studies showed that the intervention of education enhanced patient’s knowledge and, potentially, the treatment results. In this regard, Ribeiro et al. developed and applied an education program on schistosomiasis directed to lower cultural and socioeconomic brackets, with the use of simple language and supported by interactive classes and exchange of experiences; the program also included specific instructive materials, full of illustrations. The authors concluded that such action not only helped patients to learn and understand important aspects of the disease, but also had a positive influence on the patient’s compliance to follow-up outpatient’s visits.

The abovementioned program, which is available on the Web at <www.unifesp.br/dmed/gastro/dgastro.htm>, has been used by Healthcare institutions in Brazil that work in schistosomiasis endemic regions(1).

Schistosomiasis mansoni is a severe public Health problem. It is endemic in 74 countries and affects more than 200 million people in rural agricultural areas and urban outskirts from tropical and subtropical regions. Out of these individuals, 20 million suffer from the most severe forms of the disease, and 120 million are symptomatic. Schistosomiasis is included among the
21 main causes of mortality, and accounts for 200,000 deaths/year.

Hepatic changes comprise the most important manifestations of schistosomiasis, and, despite the fact that this disease is not characterized by the presence of cholestasis stricto sensu, increased serum levels of cholestatic enzymes have already been described in patients who suffer from the hepatosplenic or hepatointestinal forms. This mechanism has not been explained yet.

There are many factors that can be associated with compliance to treatment: the misunderstanding of its need, the educational level, socioeconomic difficulties, the Healthcare professional-patient relationship, among others. The difficulty is even greater when some individuals do not feel sick (asymptomatic individuals)\textsuperscript{(2-4)}. It all contribute to the mortality rate of this disease.

Studies on this topic can contribute to developing actions and strategies that enable reaching higher rates of compliance to treatment within the asymptomatic and low cultural and socioeconomic level population.

OBJECTIVE
In this study the proposition was to develop and evaluate strategies pointed toward controlling compliance to an experimental treatment on an asymptomatic and low cultural and socioeconomic level population.

METHODS
The experimental study chosen was the new indication for ursodeoxycholic acid, which has been used for long-term treatment of predominantly cholestatic liver diseases with no significant complications, including the use during pregnancy\textsuperscript{(5-8)}. Therefore, it is possible to characterize non-icteric cholestasis on schistosomiasis patients, as well as to assess if it is a potential risk factor in the progression of the disease.

It is an observational, prospective cohort study carried out at the Gastroenterology Service, Department of Medicine, at the Universidade Federal de São Paulo (UNIFESP), which provides multidisciplinary outpatient's care to adult suffering from this condition.

The inclusion criteria were: both genders, age range 18-60 years, individuals suffering from the pure chronic form of schistosomiasis with portal hypertension, with serum \( \gamma \)GT levels twice the upper normal limit, in good general conditions, non-alcoholic, individuals who have not used drugs that are predictably hepatotoxic or capable of interfering in hemostasia, presenting negative serology for hepatitis B and C virus, and with no other chronic diseases besides schistosomiasis.

Furthermore, they all must have attended the education program on schistosomiasis.

The exclusion criteria included body mass index \(< 20 \text{ or } > 30 \text{ kg/m}^2\), intra or extra-hepatic obstruction of bile ducts on images of ultrasonography, and increased aminotransferase levels higher than twice the reference value.

Sample size: due to the number of inclusion criteria, the sample consisted of 11 patients and the data was gathered after approval of the project by the Research Ethics Committee from Universidade Federal de São Paulo. The study procedures complied with the requirements of the Brazilian Resolution Conselho Nacional de Saúde 196 and 251.

For all the individuals that participated on the research, the medical prescription was ursodeoxycholic acid 15 mg/kg/day, twice a day, and the number of pills prescribed varied according to their body weight.

Strategies chosen to control compliance
1. Education program on schistosomiasis during which the patients carriers were informed for they were all asymptomatic.
2. Information given to the participants about the experimental treatment to be carried out: indication, dosing schedule and drug distribution free of charge. They were also informed that ursodeoxycholic acid can be used for a long period in other cholestatic diseases with no undesired effects, even during pregnancy\textsuperscript{(5-7)}.
3. Weekly follow-up at outpatient’s clinic conducted by the main researcher, who is a registered nurse. The follow-up consisted of assessing patients’ understanding about the treatment offered (correct use of the drug), identifying any adverse effects presented by patients (according to the assessment tools), individualized education intervention (according to the needs identified) during the period in which the drug was used. It also consisted of applying compliance tests (pill count and interviews) that guided the education interventions.

Compliance assessment by pill count
When patients were included in the study, the data on medical prescription were registered on the structured form, the packages were identified, and the participants were instructed to bring them to the follow-up visit. No participant was informed that during the follow-up visits the pills remaining in the packages would be counted. After the visit with the nurse, the amount of pills was registered once again on the form for the next pill count.
Evaluation of reported compliance

The form to evaluate the reported compliance was prepared according to the ACTG Baseline Adherence Questionnaire and ACTG Adherence Follow-up Questionnaire (9) models, suggested by Chesney et al., and adjusted to the disease and patients studied (9-10). The interview to assess compliance was conducted every seven days during the entire period in which the drug was used. Data regarding the use of ursodeoxycholic acid was gathered on seven days prior to the visit, including factors that could influence compliance, use of drugs and alcohol, and side effects.

Statistical data analysis

Two proportions comparison test was used to analyze the sample schooling. The t-Student test was used to compare the means of enzyme levels during the period the drug was used. The Friedman, Mann Whitney and Wilcoxon tests were also used to compare enzyme levels, drug use period, and compliance test through pill count.

RESULTS

The proportion of men was significantly higher than women (p = 0.003). The patients reported a family income between US$100 to 300.

Most patients had less than eight years of schooling (54.6%) and of those, 18.2% were illiterate (Table 1).

Table 1. Schooling level of patients with schistosomiasis mansoni, São Paulo, 2006

<table>
<thead>
<tr>
<th>Schooling</th>
<th>n* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illiterate</td>
<td>2 (18.2)</td>
</tr>
<tr>
<td>Incomplete junior school</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Complete junior school</td>
<td>4 (36.4)</td>
</tr>
<tr>
<td>Complete high school</td>
<td>1 (9.1)</td>
</tr>
</tbody>
</table>

n = number of patients; * two proportion z-test

Table 2 describes the pill count test; the number preceded by the minus sign indicates less pills than expected during the follow-up count; The number preceded by the plus sign means that there were more pills than expected; the zero shows the expected amount of pills during the follow-up. The test showed that the highest variation in drug use was during the first week, being this variation decreased during treatment/weekly follow-up at outpatient’s clinic. Such variation was not significant and did not influence the γGT levels, which decreased significantly during all treatment periods. After completing the therapy, that is, that the drug was withdrawn, the γGT levels increased again, returning to baseline levels. These results were reported (11).

The drug use proportion was similar on both tests (count = 98.3%; reported = 99.7%).

<table>
<thead>
<tr>
<th>Period of treatment</th>
<th>P1</th>
<th>P2</th>
<th>P3</th>
<th>P4</th>
<th>P5</th>
<th>P6</th>
<th>P7</th>
<th>P8</th>
<th>P9</th>
<th>P10</th>
<th>P11</th>
</tr>
</thead>
<tbody>
<tr>
<td>D7</td>
<td>-2</td>
<td>+6</td>
<td>F</td>
<td>0</td>
<td>-8</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+14</td>
<td>-3</td>
</tr>
<tr>
<td>D14</td>
<td>0</td>
<td>+6</td>
<td>-2</td>
<td>0</td>
<td>+7</td>
<td>0</td>
<td>+4</td>
<td>-2</td>
<td>+3</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>D28</td>
<td>+1</td>
<td>+1</td>
<td>-3</td>
<td>+2</td>
<td>0</td>
<td>-2</td>
<td>+2</td>
<td>0</td>
<td>+1</td>
<td>-2</td>
<td>0</td>
</tr>
<tr>
<td>D42</td>
<td>0</td>
<td>+1</td>
<td>-3</td>
<td>-1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

P = patient; D0 = before treatment; D14 = 14 days of treatment; D28 = 28 days of treatment; D42 = 42 days of treatment

DISCUSSION

In this study, the individuals that participated were adults, predominantly men. For chronic diseases, in general, there is no described association between gender and compliance (12). All patients had similar social status, with a monthly income varying from US$100 to 300. Such fact did not influence in compliance, since the costs related to transportation were paid for and the drug was supplied free of charge. Studies on compliance to antiretroviral drug use in AIDS reported association between low socioeconomic bracket and non-compliance, especially on poverty extremes (12-13). A recent study verified the existence of association between the socioeconomic level and the success in preventing secondary coronary disease (14).

Despite the patients’ low schooling level, it was verified that, with the development of intervention strategies it was possible to reach high compliance rates. We found a study in the literature that relates low schooling with non-compliance (15).

The use of alcohol during treatment was not frequent and did not influence in the final results. The habit of drinking alcohol is among the prognostic factors for the unfavorable outcome of treating tuberculosis (16-17).

The patient’s previous knowledge of the disease was important to guide the education interventions. During the study, despite being asymptomatic, the patients were aware of the possible complications of the disease, such as ascites, hematemesis and melena, and four of them had already undergone splenectomy. Some authors estimate that 30 to 60% of patients do not follow the prescribed treatment plan correctly, and this percentage is even higher in asymptomatic individuals (5-4).

During the first week on the drug, with the beginning of the intervention strategy actions, we identified the patients who were using it incorrectly (lower dosage than the prescribed) and we intervened in a way that did not compromise the drug effect assessment. According to Loanzon et al., the contact between nurses and patients is greater than that with physicians, hence nurses are
usually the first to notice any alteration/complication that can interfere in the study. The weekly follow-up at outpatient’s clinic by the nurse contributed to rigorous control of treatment and diagnosis of problems/risk factors for non-compliance, in addition to strengthening the bond between the Healthcare professional and patient.

CONCLUSIONS

The set of strategies used in this study to monitor compliance to an experimental treatment on an asymptomatic and low cultural and socioeconomic level population was efficient considering the compliance rates: 98.3% (pill count) and 99.7% (reported). Moreover, it was effective in laboratory parameters, for the serum activity of γGT decreased.

REFERENCES