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Treatment of Pruritus of Primary Biliary Cirrhosis with Rifampin

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Pruritus can be a debilitating symptom in patients with chronic cholestasis. Based on previous reports of its efficacy, we evaluated the impact of rifampin on the pruritus associated with primary biliary cirrhosis. Fourteen patients were included in a randomized, crossover study. After a 15-day washout period, subjects were followed for three weeks. During the first and third week, patients received 600 mg of rifampin or placebo; no treatment was administered during the second week. Pruritus was subjectively scored on a scale from 0 to 100. With rifampin, pruritus disappeared in 11 patients and partially improved in three; with placebo, only two had a partial response ($P < 0.001$). Six patients with a prior poor or no response to cholestyramine improved with rifampin. No changes in biochemical tests or side effects were observed during this period. We conclude that short-term administration of rifampin relieves pruritus in primary biliary cirrhosis. When administered over a period of eight months in an open study, the relief of pruritus was maintained, while one individual developed an allergic reaction. Rifampin appears to be a safe drug in the management of the pruritus of primary biliary cirrhosis.

KEY WORDS: pruritus; primary biliary cirrhosis; treatment; rifampin.

Pruritus associated with cholestasis can be a debilitating symptom that interferes with daily activities and sleep. Although its cause remains controversial (1), several therapeutic agents are used with variable success. These include drugs such as cholestyramine, androgenic steroids, phenobarbital, and H_1-histamine blockers (2–5) or procedures such as plasmapheresis and phototherapy (6, 7).

Recent studies from Ghent and Carruthers (8) and Bachs et al (9) have indicated that rifampin, a widely used antibiotic, relieved pruritus in patients with primary biliary cirrhosis. An improvement on hepatic function and a reduction of the severity of cholestasis also was observed after two weeks of treatment (9). Therefore, we designed a randomized clinical trial to confirm the efficacy of short-term rifampin for the treatment of pruritus of primary biliary cirrhosis. We also evaluated in an open study the persistence of antipruritic effect and safety of rifampin over an eight-month period.

MATERIALS AND METHODS

Fourteen patients with primary biliary cirrhosis, followed at the Hospital Nacional de Gastroenterologia "Dr. Carlos B. Udaondo" and the Hospital Italiano de Buenos Aires, were included in this study. The diagnosis was made based on clinical, biochemical, immunological, and histological criteria (10). The characteristics of patients at entry are summarized in Table 1. Histologically (10), two patients were classified as stage I, three as stage II, four as stage III, and five as stage IV. Nine patients were receiving cholestyramine, with a poor or no re-

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TABLE 1. CLINICAL AND LABORATORY FEATURES OF 14 PATIENTS AT ENTRY*

Age (years)	43	(32–72)
Sex (M/F)	1/13	
Jaundice (bilirubin >2 mg/100 ml)	9	(64%)
Pruritus (months)	25	(12–120)
Cirrhosis	5	(36%)
On cholestyramine	9	(64%)
Bilirubin (mg/100 ml)	5.2	(0.4–15.9)
Alkaline phosphatase (40–190 units/liter)	1149	(95–3519)
Aspartate aminotransferase (0–12 units/liter)	49	(8–151)
Alanine aminotransferase (0–12 units/liter)	50	(8–184)
Antimitocondrial antibody (+)	13/14	

*Data expressed as mean (range). A patient with normal alkaline phosphatase and another with negative antimitocondrial antibody had hepatic histological appearances compatible with primary biliary cirrhosis.

sponse in six subjects; the remaining patients did not receive this therapy because of its high cost.

Patients stopped treatment 15 days prior to entry to the trial. A clinical and biochemical evaluation was done weekly until the study was completed. After oral informed consent was obtained, patients were randomized to receive either rifampin 300 mg twice a day or an identical appearing placebo. Most patients taking rifampin develop a red–orange coloration of the urine, thus allowing them to identify the experimental period, and eliminating the double-blind nature of this study. However, this effect could be negligible in patients with high bilirubin and only two patients commented about darkening of the urine during the study. Vials containing a one-week supply of drug or placebo were prepared by an independent observer and randomization made with the toss of a coin. After seven days had elapsed, the treatment was stopped, a one-week washout period ensued, and the subjects were crossed over to the other therapy for an additional seven days.

The severity of pruritus was evaluated 15 days before and daily (between 8 and 12 AM, 12–8 PM, and 8–8 AM) during treatment. A scale of 0 to 100 was used and noted in an individual log book. Criteria for maximal scoring (100) were pruritus that interfered with sleep, altered daily activities, or resulted in self-inflicted skin breakdown. A full response to treatment was defined as the complete lack of pruritus and a partial response as a 50% reduction in the pruritus score. The pruritus score reported corresponds to the mean of the last two days of each period. Time to relief or to reappearance of pruritus also was recorded. Compliance was assessed during the weekly encounters with pill counts.

In an open study, rifampin (300 mg twice a day) was administered during 8.2 ± 4.2 (mean ± SD) (range 3–15) months to 18 patients with pruritus and primary biliary cirrhosis. Twelve patients of the short-term treatment and six additional individuals were included. All patients were studied as outpatients at monthly intervals for eight months. Severity of pruritus was evaluated using the same scoring system as for the short-term treatment. Patients were advised to stop medication if any side effects became troublesome.

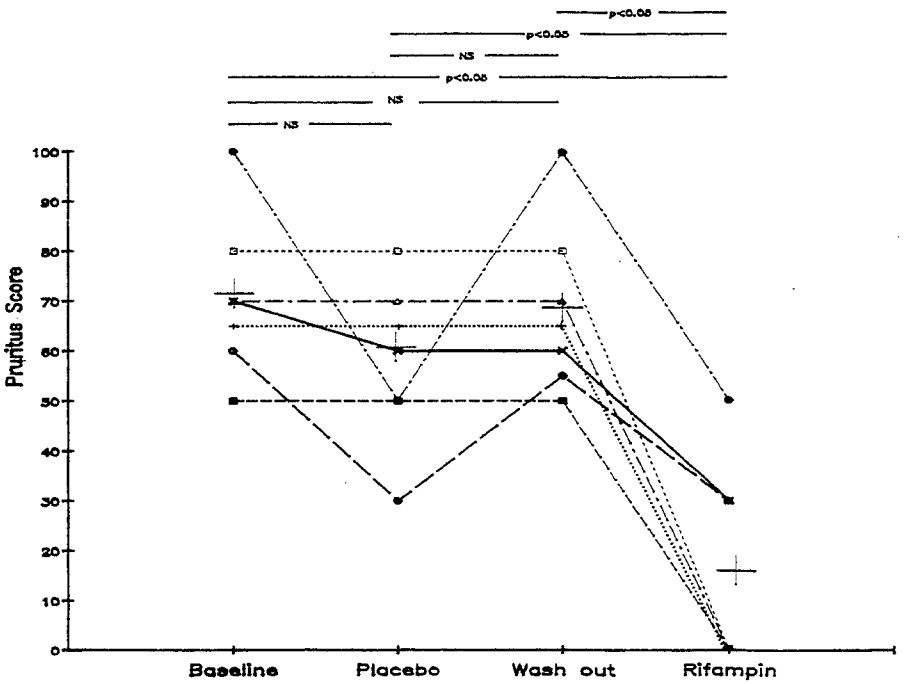

Fig 1. Mean pruritus score in seven patients who started the study with placebo. Each score averages the last two days of each period for each patient. No differences in pruritus score were seen during baseline, placebo administration, and washout. Rifampin significantly decreased pruritus ($P < 0.05$) compared to all three other periods.

TABLE 2. EFFECT OF RIFAMPIN ON PRURITUS*

	Response		
Group	*Complete*	*Partial*	*Negative*
Rifampin	11 (79%)	3 (21%)	0
Placebo	0	2 (14%)	12 (86%)

*Difference: $P < 0.001$.

Overall response to treatment was assessed with the chi-square test. Hepatic chemistries were compared before and after treatment with the Wilcoxon rank test. When groups were analyzed according to the sequence of administration; Friedman's test and Wilcoxon signed rank test were used for paired samples. One-way ANOVA was used for multiple comparisons. This study was performed following the guidelines of the Declaration of Helsinki for protection of human subjects during clinical research.

RESULTS

All patients complied with the study design, as assessed by pill counts. In the crossover design, baseline pruritus score was similar in the two groups: 72 ± 19 and 76 ± 15 (mean ± SD). After administration of rifampin, pruritus completely disappeared in 11 patients; a partial response was observed in three. In the placebo group, only two subjects had a partial response, a highly significant difference when compared to the rifampin group ($P < 0.001$) (Table 2). The response was not influenced by the order of administration of the drug (Figures 1 and 2); although the partial responders receiving rifampin were in the group that received placebo first (Figure 2), two of such individuals also experienced a similar response with placebo. Mean time for onset of beneficial effects was two days, while a progressive reappearance of symptoms occurred during the seven-day washout period. Five patients, who, prior to this study, had been receiving up to 24 g/day of cholestyramine without relief of their pruritus, had total disappearance of this symptom during rifampin treatment.

No relation could be observed between plasma bilirubin at admission and subsequent response to rifampin. There was no significant difference in alkaline phosphatase levels between basal (1149 ± 786 units/liter) and rifampin (1057 ± 545 units/liter) periods (Figure 3). Serum bilirubin (from 5.2 ± 4.7 to 5.4 ± 4.4 mg/100 ml), AST (from 49 ± 38 to 39 ± 24 units/liter) and ALT (from 50 ± 53 to 41 ± 43 units/liter) were not affected by the treatment; no side effects were elicited.

In the 18 patients patients with pruritus and primary biliary cirrhosis included in the open study, rifampin administration caused a complete relief of symptoms in 17 patients; a partial response was observed in one. This beneficial effect was observed

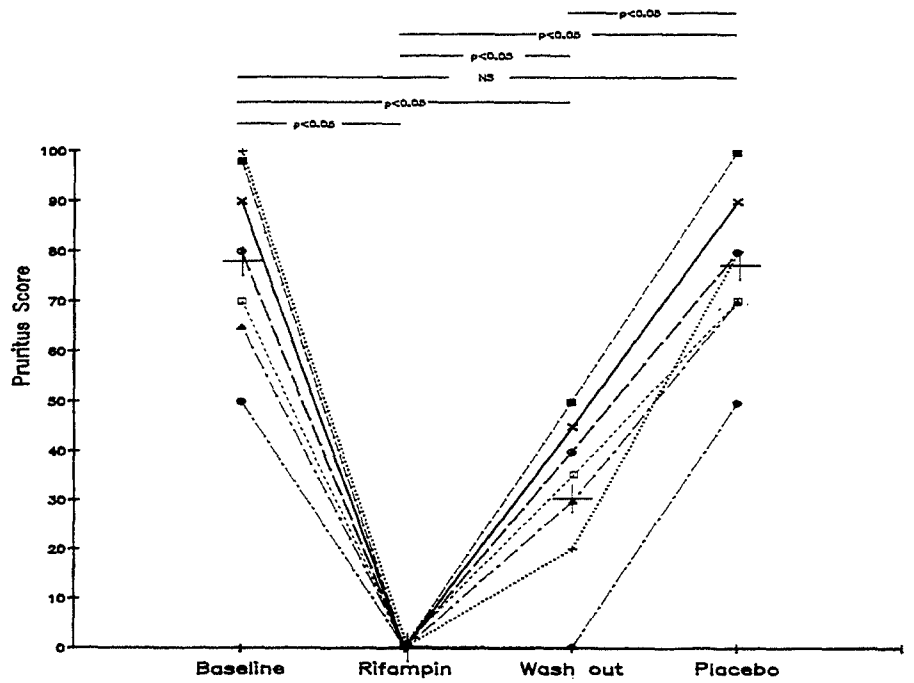

Fig 2. Mean pruritus score in seven patients that began the study with rifampin. A significant decrease in score ($P < 0.05$) was seen when compared to each of the three periods.

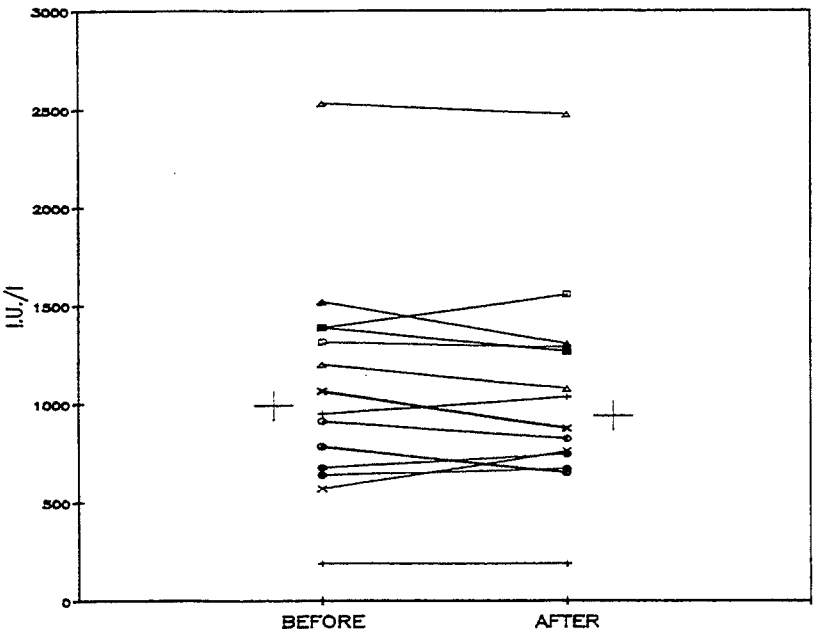

Fig 3. Serum alkaline phosphatase levels before and after rifampin treatment. There was no significant difference between basal and rifampin periods.

within the first days of treatment and was maintained over an eight-month period. All but one have tolerated chronic rifampin administration well. One patient developed an allergic reaction after three months of therapy and had to be withdrawn from the study. The allergic reaction was characterized by eosinophilia, cutaneous rash, and facial edema. Discontinuation of rifampin administration has resulted in its resolution. At present, the patient still suffers from intense pruritus despite cholestyramine administration. Plasma bilirubin (from 5.5 ± 4.5 to 5.2 ± 5.9 mg/100 ml, NS) and AST (from 48 ± 38 to 58 ± 30 units/liter, NS) levels were unchanged by the treatment. A moderate but not significant decrease in alkaline phosphatase (from 1246 ± 780 to 863 ± 289 units/liter, NS) levels was observed after eight months of rifampin administration.

DISCUSSION

Our results confirm that short-term administration of rifampin is an effective therapy for relieving pruritus in patients with primary biliary cirrhosis. This beneficial effect also was maintained over an eight-month period. Moreover, rifampin was not associated with changes in hepatic tests or significant side effects over a short and long treatment period.

The pathogenesis of pruritus in chronic cholestatic disorders is still uncertain, with controversy surrounding a role for retained bile acids on nervous terminals in the skin (1, 7). Recently, Ghent postulated that high concentrations of bile salts in the liver could cause membrane disruption via detergent effects, which would result in the release of a pruritogenic compound(s) from the liver itself (1). If this hypothesis were true, substances that compete for hepatic uptake with bile acids, such as rifampin (8), could provide relief from pruritus.

In the work of Ghent and Carruthers (8), cholestyramine was not discontinued during the period of testing with rifampin, in spite of its reported lack of efficacy or poor tolerance. In this study, we have chosen to administer rifampin alone in order to avoid any possible interference with our results. In this regard, cholestyramine administration could be modified rifampin pharmacokinetic. On the other hand, in studies where two different drugs are administered simultaneously, it is difficult to define the contribution made to the outcome by each drug. Our findings clearly indicated a beneficial effect of rifampin. Pruritus score at baseline was similar in the two groups; while relief of pruritus in the group that started with rifampin was complete (7/7, Figure 1), it was complete in four and partial in three of those to whom rifampin was administered for the first time during the third week (Figure 2). Although this could represent an effect of the crossover design, two of the partial responders also had

experienced a similar improvement with placebo. Thus, we conclude that a one-week treatment with rifampin resulted in complete elimination of pruritus in 11/14 individuals.

Recently, Bachs et al (9) have shown that short-term rifampin administration is more effective than phenobarbitone for relieving pruritus in patients with primary biliary cirrhosis. Also, an improvement on hepatic function tests and a reduction of the severity of cholestasis was observed after two weeks of treatment (9). In this latter study, rifampin administration was associated with a severe hemolytic anemia and renal failure in one patient (9).

In our study, no significant changes in hepatic tests and clinical side effects could be detected during rifampin. Although Girling and Hitze (11) indicated that hepatitis occurs in 1% of rifampin-treated individuals, this estimate was based on hepatic chemistries rather than histology. Up to 5% of individuals may have a moderate increase in transaminases, alkaline phosphatase, and bilirubin that normalize even in the presence of continued treatment (12). An isolated increase of unconjugated bilirubin during the first weeks of treatment may reflect competition for uptake at the sinusoidal membrane (13). Other effects include an increase in biliary cholesterol saturation and a reduction of serum 25-OH cholecalciferol. Clinical and humoral monitoring is recommended for patients with underlying hepatic disease in whom this drug is administered (14).

Rifampin may rarely cause serious idiosyncratic hypersensitivity reactions, such as hemolytic anemia, renal failure, and thrombocytopenic purpura (9, 15–18). They occur after prolonged or intermittent courses of therapy, may be seen after readministration, and are reversible upon discontinuation of the drug.

Finally, chronic rifampin administration was effective for relieving pruritus in patients with primary biliary cirrhosis. This beneficial effect was maintained over an eight-month period. Also, in accordance with our previous data, chronic rifampin administration was not associated with hepatic test changes; therapy was discontinued in one patient because of allergic reaction.

The results of the present study indicate that short-term administration of rifampin is an effective therapy for pruritus in primary biliary cirrhosis; its beneficial effect was maintained over an eight-month period. Moreover, its safety was evidenced by a low number of clinical side effects observed. However, further clinical studies will be required to confirm the efficacy and safety of rifampin during a long time period.

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