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RAPID COMMUNICATION

Effect of oral naltrexone on pruritus in cholestatic patients

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Abstract

AIM: To determine the efficacy and potential complications of oral naltrexone used in the treatment of pruritus in cholestatic patients and to compare them with other studies.

METHODS: Thirty-four enrolled cholestatic patients complaining of pruritus were studied. In the initial phase, pruritus scores during day and night were evaluated. Subsequently, patients were given a placebo for one week followed by naltrexone for one week. In each therapeutic course (placebo or naltrexone) day and night pruritus scores were distinguished by a visual analogue scale (VAS) system and recorded in patients' questionnaires.

RESULTS: Both naltrexone *and* placebo decreased VAS scores significantly. Naltrexone was more effective than placebo in decreasing VAS scores. Both day and night scores of pruritus decreased by half of the value prior to therapy in thirteen patients (38%). Daytime pruritus improved completely in two patients (5.9%), but no improvement in the nighttime values was observed in any patient.

Sixteen patients (47%) suffered from naltrexone complications, eleven (32%) of them were related to its withdrawal. Complications were often mild. In the case of withdrawal, the complication was transient (within the first 24-28 h of therapy) and self-limited. We had to cease the drug in two cases (5.9%) because of severe withdrawal symptoms.

CONCLUSION: Naltrexone can be used in the treatment of pruritus in cholestatic patients and is a safe drug showing few, mild and self-limited complications.

Key words: Cholestasis; Pruritus; Naltrexone

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INTRODUCTION

Pruritus is one of the most annoying symptoms in cholestatic hepatic diseases[1-3]. Several therapeutic methods with varying degrees of success have been used in its treatment. However, although we can not ignore the positive effects of cholestyramine[4], urodeoxy colic acid[5-7], rifampin[8-12] and antihistaminic agents on pruritus, many patients do not show unequivocal response to any of these therapeutic options. Even liver transplantation has been indicated in patients with refractory pruritus[13-15]. The classic explanation for pruritus during cholestasis is the accumulation of bile acids[16, 17]. However, recent studies show that endogenous opioids in the central nervous system have a role in creating the feeling of pruritus in these patients[18-20]. Plasma levels of endogenouse opioids including enkephalin increase in patients with chronic cholestasis[21]. Pruritus can be controlled by opioid antagonists such as naloxone[22, 23]. Injection of cholestatic patient's serum to monkey's medulla can cause pruritus that is controlled by naloxone[24]. Several recent studies indicate that opioid antagonists such as naloxone and nalmefene are effective in reducing pruritus in patients with primary biliary cirrhosis[18, 25-27]. Unfortunately, these drugs have some limitations in use. Naloxone has a short half-life and low bioavailability. Therefore, the only way to use it is by injection[27, 28]. Furthermore, these opioid antagonists frequently cause severe withdrawal reactions in patients[29-31].

Naltrexone is an oral opiate antagonist that is commonly used in reducing alcohol dependence and opioid addiction[28, 32, 33]. It has been used more recently for rapid opiate detoxification[34]. Acute naltrexone withdrawal reactions have also been reported[35]. Its half-life and bioavailability are between naloxone and nalmefene and it has a considerable first pass effect (95%). Naltrexone clearance from serum is mostly in kidneys[28, 36, 37]. We performed this study to evaluate the effects of naltrexone on cholestatic pruritus and its complications.

MATERIALS AND METHODS

Thirty-four patients (age range: 32-72 years; average age: 54 ± 11.34 years) with cholestatic pruritus were selected for study. These patients had different types of cholestatic diseases including primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC), cirrhosis (in compensated stage), overlap syndrome, choledocholithiasis, cholangiocarcinoma, periampullary tumors and pancreatic head carcinoma. The duration of pruritus ranged from eight days to thirteen months. Criteria for exclusion of patients from the study included age less than 15 years, serum creatinine >1.5 mg/dL, pregnancy, use of opioids, and cirrhosis with B or C Child Paugh score. The study was performed between April 2003 and June 2004 in the Imam Hospital in Tehran, Iran. We conducted the study on admitted patients with the approval of the Ethics Committee of Tehran University of Medical Sciences. All enrolled patients gave their informed consent.

The study was carried out using a single blind, self-controlled trial method. After the day and night pruritus scores were obtained, patients were given a placebo for one week and then the scores were recorded. Subsequently, a naltrexone therapy (50 mg daily) for one week, was begun. Pruritus scores were characterized by a VAS system between 0 and 10. Daytime pruritus was considered as pruritus occurring before sleep and nighttime implied pruritus after waking from nocturnal sleep. A score of zero signified no pruritus while 10 meant sleep or work-disturbing pruritus or of such severity that skin damage occurred.

Scoring was performed in the middle and at the end of the therapeutic course of treatment (placebo or naltrexone) and the mean of the scores was used. Laboratory tests including total and direct bilirubin, alkaline phosphatase (ALP), aminotransferases (AST, ALT) and creatinine were performed for all patients before therapy and recorded in the questionnaires. The mean scores of day and night pruritus were compared before therapy and after placebo and naltrexone courses by Wilcoxon rank test with SPSS10.0.5 software. $P < 0.05$ was considered statistically significant.

RESULTS

The numbers of patients with PBC, PSC, cirrhosis, overlap syndrome, choledocholithiasis, cholangiocarcinoma, periampulary tumors and pancreatic head carcinoma were 4, 6, 11, 7, 1, 2, 2, and 1, respectively.

Naltrexone effect on pruritus

Table 1 Characteristics of patients before therapy ($n = 34$)

Characteristics	Range	Mean ± SD
Age (yr)	32-72	53.97 ± 11.93
ALP	190-1150	657.76 ± 266.36
Total bilirubin	5.8-37.00	16.60 ± 9.03
Direct bilirubin	4-32.5	13.14 ± 8.05
ALT	32-145	66.03 ± 27.13
AST	35-110	60.47 ± 19.73
Creat.	0.7-1.3	1.01 ± 0.14
Pruritus in day before therapy	6-10	8.30 ± 1.07
Pruritus in night before therapy	8-10	9.13 ± 0.78

The characteristics of patients before therapy are summarized in Table 1. In both cases of therapy with placebo or naltrexone, the mean scores of daytime and nighttime pruritus decreased significantly (Table 2). Naltrexone significantly decreased the pruritus score compared to the placebo (Table 2).

In this investigation, two of the thirty-four patients were forced to withdraw from the study because of drug complications. Thirteen patients (38%) showed at least 50% decrease in their pruritus scores and two (5.9%) became completely free of pruritus. Three (8.8%) showed no change in their scores during the therapy and the score even increased in one case.

The onset of naltrexone therapeutic effects was within the first 48 h of therapy. The decrease in pruritus gradually slowed down and returned to some extent in three patients. There was no obvious change in biochemical parameters after therapy. The bilirubin and ALP levels did not significantly differ before or after therapy (without considering the result of therapy).

Complications

Sixteen patients (47%) suffered from naltrexone complications which were generally mild and improved without additional treatment in the first 2-3 d of therapy. The most common complication was a withdrawal reaction in eleven patients (32.4%). The general and gastrointestinal complications (including dizziness, nausea, vomiting, headache, abdominal cramps, lethargy, weakness, irritability, dry oral mucous membrane and insomnia) were seen in other patients and one patient had also dermatologic complications. Two patients did not finish their therapeutic course because of severe withdrawal reactions. However, pruritus decreased relatively to its initial condition in one of the two patients. Except for the withdrawal reactions, other complications were not sufficiently severe to cause drug cessation.

DISCUSSION

The results of this study indicate that oral naltrexone, an opioid antagonist, can reduce or improve cholestatic pruritus. The results agree with the other reports[38-41]. Some researchers believe that the VAS system for evaluating pruritus severity is not reliable and prefer to use a mechanical instrument attached to fingers to show and record patients' pruritus[25]. Although such instruments may be helpful

Table 2 Comparison of pruritus scores in patients before and after placebo and naltrexone therapy (mean ± SD)

Patients (n = 34)	1 Before therapy	2 After placebo	3 After therapy	1 and 2 Significance	1 and 3 Significance	2 and 3 Significance
Pruritus in day	8.30 ± 1.07	7.54 ± 1.38	4.91 ± 2.56	P < 0.001	P < 0.001	P < 0.001
Pruritus in night	9.13 ± 0.78	8.29 ± 1.02	5.54 ± 2.51	P < 0.001	P < 0.001	P < 0.001

in evaluating pruritus objectively, their use has some difficulties. On the other hand, the VAS system can control pruritus quite well[4, 8-12, 42]. It was reported that the pruritus index is significantly correlated with the pruritus score obtained by the VAS system[25, 26]. It has been shown that decreased pruritus index and its perception are similar[43].

In three patients of the present study, the rate of pruritus score decrease was lower after a few days of therapy. The reason is unclear though it may be due to secondary adaptation to opioid or drug resistance (tachyphylaxis). This effect has already been reported in earlier studies on nalmefene[27, 38, 39, 44].

Some researchers believe that cessation of drug therapy for two days during a week ("drug holidays") can reduce drug adaptation effects in such patients[38]. However, others consider that this method is ineffective[40]. Increasing the naltrexone dose to 100 mg/day may be effective in such circumstances. Although side effects were relatively common (47%), most of them were mild, self-limited and transient, requiring no additional therapy in our study. On the other hand, in the placebo group 26% of patients had drug complications. Two patients had to stop the therapy because of severe opioid withdrawal effects. Both of them had a positive opioid addiction history but they were not addicted to it at the time of the study. In comparison with nalmefene, naltrexone leads to fewer and milder complications[18-27].

To decrease naltrexone complications, synchronous prescription of clonidine[18] or naltrexone at a low dose, at least for the first few days of therapy[27], is recommended. Also we can divide the total dose into 25 mg BD instead of decreasing it during the first few days of therapy[38, 39]. Examples of naltrexone hepatotoxicity have been reported[45], but there is no report on the hepatotoxity at the low dose of naltrexone in normal people or patients with hepatic diseases[38, 39, 46].

Endogenous opioids play a role in producing cholestatic pruritus, but opioid antagonists cannot improve pruritus completely[27, 38, 39, 47, 48]. Studies indicate that naltrexone is a drug that can be well tolerated by patients and its complications are often mild and transient not requiring additional therapy[41, 49, 50]. Naltrexone can also be used in treatment of severe and intractable pruritus of varying origins[41].

In conclusion, naltrexone can be used in the treatment of pruritus in cholestatic patients.

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