

CASE REPORTS

Preliminary Observation With Dronabinol in Patients With Intractable Pruritus Secondary to Cholestatic Liver Disease

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ABSTRACT

Pruritus due to cholestatic liver disease can be particularly difficult to manage and frequently is intractable to a variety of medical therapies. The aim of our study is to evaluate the efficacy of Δ -9-tetrahydrocannabinol (Δ -9-THC) for intractable cholestatic related pruritus (ICRP) that has failed conventional (and unconventional) remedies. Three patients were evaluated for plasmapheresis because of ICRP. All 3 patients had previously been extensively treated with standard therapies for ICRP including: diphenhydramine, chlorpheniramine, cholestyramine, rifampicin, phenobarbital, doxepin, naltrexone, UV therapy, and topical lotions. Even multiple courses of plasmapheresis were performed without any benefit for the intractable pruritus. All patients reported significant decreases in their quality of life, including lack of sleep, depression, inability to work, and suicidal ideations. All patients were started on 5 mg of Δ -9-THC (Marinol) at bedtime. All 3 patients reported a decrease in pruritus, marked improvement in sleep, and eventually were able to return to work. Resolution of depression occurred in two of three. Side effects related to the drug include one patient experiencing a disturbance in coordination. Marinol dosage was decreased to 2.5 mg in this patient with resolution of symptoms. The duration of antipruritic effect is approximately 4–6 hrs in all three patients suggesting the need for more frequent dosing. Δ -9-tetrahydrocannabinol may be an effective alternative in patients with intractable cholestatic pruritus. (*Am J Gastroenterol* 2002;97:2117–2119. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

Patients with cholestatic liver disease can suffer from pruritus. Although often a trivial symptom, occasionally it can be severe. The clinical course of cholestasis-related pruritus is variable. Some patients can be treated with simple measures, such as cholestyramine or antihistamines. Pruritus that is intractable and distressful may require more aggressive pharmacological therapy, invasive treatments including

plasmapheresis, charcoal hemoperfusion, or orthotopic liver transplantation.

The active substance in dronabinol (Marinol, Unimed Pharmaceuticals, Deerfield, IL) is Δ -9-tetrahydrocannabinol, a cannabinoid designated chemically as (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo(b,d)pyran-1-ol. Dronabinol, the *p.o.* form of Δ -9-tetrahydrocannabinol, has been synthesized and comes in a capsular form that contains the following inactive ingredients: sesame oil, gelatin, glycerin, methylparaben, propylparaben, and titanium dioxide (1). Dronabinol is approved in the United States for only two indications: treatment of anorexia associated with weight loss in patients with AIDS, and in the therapy of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.

A patient not included in our cohort reported relief of her pruritus after the inhalation of marijuana. With this observation in mind, we evaluated and treated three patients with dronabinol. All of these patients had failed multiple pharmacological interventions and plasmapheresis for severe and disabling pruritus due to cholestatic liver disease. Using dronabinol, all three patients experienced dramatic relief of pruritus.

CASE 1

A 22-yr-old white female presented with 8 months of intractable pruritus, which interrupted her daily lifestyle, forcing her to work part-time, and led to serious sleep deprivation. Her medical history was significant for systemic lupus erythematosus and glomerulonephritis. She had a positive anticardiolipin antibody and developed deep vein thrombosis when placed on birth control pills. The birth control pills were stopped and she was started on medroxyprogesterone acetate *i.m.*, as an alternative form of birth control. Three months after starting medroxyprogesterone acetate therapy, she developed jaundice, followed by pruritus, and fatigue. Medroxyprogesterone acetate was discontinued. Further investigations included a normal ultrasonography and CT of

Table 1. Patient Characteristics and Response to Dronabinol

Patient	Laboratory Results				
	AST/ALT (IU/L)	ALP (IU/L)	Total Bilirubin (mg/dl)	Dronabinol	Duration of Relief
1	370/390	200	6.0	5 mg <i>t.i.d.</i>	>3 h, complete night sleep
2	150/220	125	2.5	5 mg <i>t.i.d.</i>	2 h
3	140/120	1212	2.5	2.5 mg at bedtime	4–5 h

the abdomen. ERCP was normal. Liver biopsy showed intact hepatic architecture and no significant inflammation or proliferation of bile ducts. She was given diphenhydramine HCl (25 mg *q.i.d.*) and the pruritus persisted. Cholestyramine (4 g *q.i.d.*) was the next agent started. Again, she had no relief of the symptoms and was given hydroxyzine HCl (100 mg *q.i.d.*). The pruritus remained unchanged, and phenobarbital (50 mg *b.i.d.*) was added to the regimen but did not help. She then started rifampin (600 mg/day) for 1 month with minimal improvement. We finally initiated a trial of ursodeoxycholic acid (15 mg/kg/day) that resulted in no improvement.

She was given three courses of plasmapheresis that resulted in very little relief. A liver biopsy was repeated, and it demonstrated cholestasis with ductopenia consistent with drug-induced vanishing bile duct syndrome. Over the next month she received another triple course of plasmapheresis and once again there was no improvement in pruritus. Two weeks after completing the second course of plasmapheresis, we gave her the first dose of dronabinol (5 mg). She experienced complete relief of her pruritus. The relief from pruritus lasted approximately 4–6 h. She was started on dronabinol (5 mg every 8 h) and was discharged home free of pruritus for the first time in 7 months since starting medroxyprogesterone.

She returned to work within the month on a full-time basis and her depression resolved. Her abnormal hepatic biochemical profile slowly resolved (Table 1). The dronabinol was discontinued after 2 months, without recurrent pruritus or additional requirements of dronabinol.

CASE 2

A 31-yr-old African American female with cholestatic liver disease induced by medroxyprogesterone presented with fatigue and extreme pruritus for 8 months. Her treatment history for pruritus included diphenhydramine HCl (25 mg *q.i.d.*), cholestyramine (4 g *q.i.d.*), ursodeoxycholic acid (900 mg/day), doxepin hydrochloride (50 mg *t.i.d.*), phenobarbital (50 mg *b.i.d.*), and rifampin (600 mg/day). She was unable to tolerate the diphenhydramine because of drowsiness. All other remedies were discontinued because of a lack of efficacy. In addition phototherapy, topical ointments, and steroid creams were tried without success. She continued to suffer from intractable pruritus, affecting her quality of life and resulting in absence from work, insomnia, and finally severe depression.

She was admitted for a triple course of plasmapheresis, and received no relief. Our previous experience with dronabinol in case 1 prompted us to try dronabinol (5 mg *t.i.d.*). The pruritus resolved, allowing relief of pruritus for 2–3 h after each dose of dronabinol. Her energy level and depression were markedly improved, and she was able to return to work. However, her cholestatic liver disease continued to worsen and she was listed for orthotopic liver transplantation. She eventually received a living related (left lobe) liver transplant from her brother. She remained on dronabinol until the time of transplantation and did not require further therapy postoperatively.

CASE 3

A 57-yr-old white female with stage 3 primary biliary cirrhosis presented with intractable pruritus of 3 yr duration. She had been treated with ursodeoxycholic acid (900 mg/day) for several years, but discontinued it because of lack of benefit. Cholestyramine (4 g *q.i.d.*) was prescribed, but was again discontinued because of constipation and lack of benefit. Diphenhydramine (25–50 mg *t.i.d.*) also resulted in no benefit and the patient discontinued it because of drowsiness. Rifampin (600 mg/day) produced minimal relief and was stopped by the patient. Naltrexone hydrochloride (50 mg *t.i.d.*), hydroxyzine hydrochloride (50 mg *q.i.d.*), aquaphor ointment, loxopine hydrochloride (10 mg *t.i.d.*), and prednisone (10 mg/day) all failed to provide relief. She was then given fluoxetine hydrochloride for depression.

Her primary complaints were fatigue, depression with suicidal ideations, insomnia, and loss of employment because of intractable pruritus. Liver histology demonstrated a cholestatic pattern with ductopenia suggestive of stage III primary biliary cirrhosis.

Three courses of plasmapheresis were given and the pruritus did not improve. We started her on dronabinol (5 mg every 8 h). She reported that the pruritus resolved for approximately 4–6 h. Her family noted a marked improvement in affect, and she stated an ability to sleep throughout the night without “itching.” Adjustments in dronabinol to 2.5 mg at bedtime were made as the side effect of “light-headedness” developed during the day. She remained on dronabinol until she eventually received a transplant. Postoperatively she required no further treatment for pruritus.

DISCUSSION

The pathogenesis of pruritus, in general, is not clearly elucidated. Lewis (2) was the first to demonstrate the induction of pruritus by intradermal injection of "H substances." This H substance was later defined as histamine and subclassified into histamine-1 and histamine-2 receptors. Histamine-1 receptors may act directly on unmyelinated free nerve endings within the epidermis and therefore be a source for the sensation of pruritus. Mast cells store and release histamines in the skin and are activated by complement C5a and tachykinins, including neuropeptides and substance P. Further, an increased concentration of prostaglandin E₂ has been found in the inflamed skin of patients with psoriasis or contact allergic dermatitis and those who had ultraviolet B-light treatment. Although, prostaglandin E₂ does not cause pruritus itself, it may lower the threshold for pruritus by histamines (3). Therefore, agents that block the release of histamines have been used in pruritus of atopic eczema, although with minimal success (4, 5).

The mechanism of pruritus in cholestatic liver diseases may be different and is thus far unknown. Bile acids have been implicated as the mediators of pruritus in cholestasis. These substances accumulate in plasma and tissues of patients with cholestasis. Experimental administration of bile salts into skin of human beings has been reported to be associated with pruritus. However, the absence of pruritus in many cholestatic patients with high serum bile acid concentrations, the spontaneous relief of pruritus in patients in whom the degree of cholestasis remains unchanged, and the disappearance of pruritus as liver failure develops, in the face of marked elevations of bile acids, argue against a strong role for bile acids in mediating pruritus associated with cholestasis.

Cholestasis is associated with an increased opioidergic tone. It has been proposed that this altered neurotransmission mediates, at least in part, the pruritus of cholestasis by a central mechanism (6). This concept is supported by the relief of pruritus that chronic liver disease patients report after the administration of opiate antagonists, as documented in controlled studies (7, 8). The results of clinical studies of opiate antagonists for the treatment of the pruritus of cholestasis have shifted the attention to the central nervous system and to neurotransmitters/neuromodulators as the mediators of pruritus in cholestasis. Therefore, of relevance to the observed amelioration of pruritus by dronabinol are the close interactions between opioid receptors and cannabinoid receptors in the central nervous system.

Cannabis plants have been used in many societies for their medicinal and psychoactive properties. The smoke from cannabis contains many chemicals, including cannabinoids. Of these, Δ -9-tetrahydrocannabinol produces many of the characteristic pharmacological effects. Inhaled preparations of cannabis are 3–4 times more potent than oral forms. The medicinal use of cannabinoids is currently limited to patients receiving chemotherapy for cancer and ex-

periencing nausea and vomiting, and immunocompromised patients suffering from anorexia and weight loss.

Meng *et al.* (9) demonstrated similar analgesia pathways for cannabinoids and morphine. The regulation and suppression of pain are mediated through the pathway of the rostral ventromedial medulla onto the dorsal horn of the spinal cord. There appears to be a downregulation of cells in the rostral ventromedial medulla that contribute to the cannabinoid-induced antinociception. Do the pain neuropathway and the pruritus neuropathway interchange and share receptors? Or is there an elevated threshold for pruritus mediated by cannabinoids, such as with antiepileptic medicines? The exact mechanism and neuropathway remain unknown.

Our experience in successfully treating patients with extreme cases of cholestasis-associated chronic and disabling pruritus is dismal. Many patients eventually develop depression that can lead to suicidal ideations. We treated all three patients in this report with the *p.o.* form of cannabinoids for chronic intractable pruritus. All three patients showed resolution of insomnia, relief of depression, and, most importantly, relief from pruritus. Although, we expect the addictive potential for dronabinol to exist, none of our patients experienced withdrawal symptoms or requested additional prescriptions. These preliminary observations are dramatic and clearly require further investigation in randomized controlled clinical trials.

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