Chronic Pain Treatment With Cannabidiol in Kidney Transplant Patients in Uruguay

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ABSTRACT

Background. Chronic pain is a major therapeutic problem in kidney transplant patients owing to nephrotoxicity associated with nonsteroidal antiiflammatory drugs. Benefits in chronic pain treatment with cannabidiol (CBD) have been reported. This study assesses the effect, safety, and possible drug interactions in kidney transplant patients treated with CBD for chronic pain.

Methods. We assessed patients who asked to receive CBD for pain treatment. Doses were increased from 50 to 150 mg twice a day for 3 weeks. Creatinine, blood count, liver function, liver enzymes, and drug levels were determined every 48 hours the first week and then once a week thereafter.

Results. We assessed 7 patients with a mean age of 64.5 years (range, 58–75 years). CBD initial dose was 100 mg/d, CBD dose reduction to 50 mg/d has been done on day 4 to patient 1 for persistent nausea. Tacrolimus dose reduction in patient 3 was undertaken on days 4, 7, and 21 owing to persisting elevated levels (even before CBD) and itching, and on day 21 in patient 5. Tacrolimus levels decreased in patient 2 but were normal in the control 1 week later. Patients on cyclosporine were stable. Adverse effects were nausea, dry mouth, dizziness, drowsiness, and intermittent episodes of heat. CBD dose decrease was required in 2 patients. Two patients had total pain improvement, 4 had a partial response in the first 15 days, and in 1 there was no change.

Conclusions. During this follow-up, CBD was well-tolerated, and there were no severe adverse effects. Plasma levels of tacrolimus were variable. Therefore, longer follow-up is required.

KIDNEY transplantation is the treatment of choice for patients who develop end-stage chronic renal failure [1]. It has been shown that patients who receive a kidney transplantation have better survival than those who continue dialysis [1,2]. Immunosuppression necessary to avoid rejection of the graft has evolved over the years; however, there have been no major advances since the introduction of cyclosporine in the 1980s [3]. Immune tolerance is the main objective of immunosuppression in solid organ transplantation, and is defined as the state of no response to alloantigens present in the graft, maintaining an adequate immune response to other stimuli. This ideal tolerance state is very difficult to achieve because each patient requires a different level of immunosuppression depending on baseline alert state [4–7]. Renal transplant recipients have a higher incidence of infections and cancer as main complications of immunosuppression [8].

Chronic pain is another common problem in this population, and is related to the underlying disease or other intercurrent diseases [9]. Despite the many groups of drugs used in the treatment of chronic pain, achieving adequate

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analgesia is elusive. Transplant patients must limit the use of nonsteroidal antiinflammatory drugs owing to their nephrotoxicity [10–13]. Recently, there has been shown benefit of the endocannabinoid system modulation in chronic pain treatment [14–21]. Uruguayan law allows the use of cannabis derivates for medical purposes; therefore, patients suffering chronic pain have been asking for this treatment. Our main concern was the potential interactions between cannabinoids and immunosuppressive drugs.

Cannabinoids are substances that usually have a carbocyclic structure with 21 carbons and are generally formed by three rings, cyclohexene, tetrahydropyran and benzene. Cannabidiol (CBD) is a bicyclic compound, because the tetrahydropyran ring is cleaved. CBD has neuroprotective, antioxidant, anticonvulsant, analgesic, and antiinflammatory effects, and has been shown to be safe and well tolerated in adults at doses of up to 1600 mg/d [22,23]. The most common components with potential therapeutic effect extracted from the plant *Cannabis aativa* include delta-9-tetrahydrocannabinol (THC) and CBD. THC is the main psychoactive component found in this plant; CBD does not have psychoactive properties. CBD used in our patients is the main component of a whole plant extract of the variety of *C sativa* Charlotte's Web, in oral solution produced by Stanley Brothers Social Enterprises (Colorado Springs, CO), containing 50 mg/mL with a ratio of CBD to THC of 30:1. Pure CBD is found as a white crystalline solid.

The CBD is fat soluble and its metabolization is carried out by hydroxylation and hepatic oxidation. Although it is known that CYP3A4 and CYP2C19 are mainly responsible for their liver metabolization, CBD is a potent inhibitor of CYP2D6, CYP2C8, CYP2C9, CYP2C19, and CYP2A4. The excretion of CBD is through urine and feces. Plasmatic peaks have significantly interindividual variability, but usually occur between 1 and 2 hours after oral administration. Reported CBD side effects include headaches, dizziness, fatigue, anorexia, oral paresthesia, dry mouth, neck pain, feeling of strangeness, depression, loss or modification of taste, gastrointestinal disturbances, feeling of weakness, falls, shaking, muscular rigidity, strange daydreams, nosebleed, outbursts of heat or cold, heartburn, bradycardia, and dysphagia. These adverse effects have been reported in patients undergoing treatment with initial doses of 1 mg/kg/d up to a dose of 16 mg/kg/d [22–27]. Potential CBD interactions with calcineurin inhibitors are unknown. CBD administered orally has a maximum concentration at 2 hours, a multicompartmental distribution, and a variable elimination half-life [22,28-31].

Calcineurin inhibitors have great intraindividual and interindividual pharmacokinetic variability. There is consensus that clinical and plasma monitoring is necessary throughout the treatment in kidney transplant patients [32]. Tacrolimus is a macrolide antibiotic synthesized by *Streptomyces tsukubaensis* [33], differs from cyclosporine in that it is a more potent molecule to inhibit calcineurin, achieving a greater inhibition of the activation of T lymphocyte. Its safety profile is almost identical to that of the cyclosporine, but it has a higher incidence of posttransplant diabetes and a lower incidence of band interstitial fibrosis. Its oral

Table 1. Baseline Characteristics and Results at Days 1 and 21

	Patient 1		Patient 2		Patient 3		Patient 4		Patient 5		Patient 6		Patient 7	
Day	1	21	1	21	1	21	1	21	1	21	1	21	1	21
Age	75		58		61		60		60		73		65	
Sex	Female		Male		Female		Male		Male		Female		Male	
Pain cause	Fibromyalgia		Osteoarticular		Fibromyalgia		Osteoarticular		Osteoarticular		Osteoarticular		Neuropathic	
Creatinine (mg/dL)	1.10	1.04	1.03	1.12	0.92	0.89	1.14	1.16	1.94	2.8	2.07	1.95	2.39	2.36
Hemoglobin (g/dL)	11.4	10.7	13.4	13.1	12.4	12.9	15	14.3	11	10.2	11.5	10.9	14.7	14.8
Leucocytes (mm^3)	3990	4370	7080	8960	4480	5280	8830	10850	7420	6360	12900	11760	10100	126oo
Platelets (10^3 m^3)	185	174	215	237	182	199	248	245	189	174	306	265	157	213
TGO/TGP (mg/dL)	14/11	14/10	14/18	16/22	20/12	19/12	16/9	12/8	16/11	15/11	25/19	19/16	19/16	16/19
Tacrolimus (ng/mL)	10.1	6.5	7.4	2.8	14.4	16.7	9.7	9.8	7.8	13.8	—	—	—	—
Cyclosporine (ng/mL)											355	332	261	291

Abbreviation: TGO/TGP, glutamic oxaloacetic transaminase/glutamic pyruvic transaminase.

bioavailability is variable. It is extensively metabolized by CYP3A4, which determines important pharmacokinetic interactions.

We sought to evaluate clinically relevant pharmacokinetic interactions between CBD and calcineurin inhibitors. Secondary objectives were to evaluate (1) the CBD safety profile in kidney transplant patients, (2) CBD effect in pain control and (3) CBD tolerability in kidney transplant patients.

METHODS

Clinical follow-up was carried out for 3 weeks. At medical visits, creatinine, blood count, liver function, liver enzymes, and drug levels were determined every 48 hours the first week and once a week thereafter. Each visit included a physical examination, evaluation of adverse effects daily report form, blood count, liver function test, liver enzymes, creatinine, and calcineurin inhibitors plasma determination.

Population

Kidney transplant patients with chronic pain who requested to associate CBD for their analgesic treatment were included. We included patients who were older than 18 years and received a kidney transplant $\geq$1 year before the time of inclusion, who experienced uncontrolled chronic pain. We excluded patients suffering an acute rejection episode, humoral rejection episode, or acute infection within the last 6 months. Safety was assessed through daily report of adverse effects and plasma creatinine, liver function parameters, and hematologic determinations.

RESULTS

We assessed 7 patients with a mean age of 64.5 years (range, 58–75 years), who had asked for CBD pain treatment. Blood count, liver function test, and liver enzymes were determined every 48 hours the first week and on days 7, 14, and 21, and were steady. Baseline characteristics and laboratory results for days 1 and 21 are shown in Table 1.

The initial dose of CBD was 100 mg/d with a progressive increase up to 300 mg/d. CBD dose reduction to 50 mg/d has been done on day 4 in patient 1 owing to persisting nausea. Tacrolimus levels decreased in patient 2, but were normal in the control 1 week later. Tacrolimus dose reduction in patient 3 was been done on days 4, 7, and 21 owing to persistently increased tacrolimus plasma levels and itching. The patient stated that itching started 1 or 2 months before CBD treatment. Adherence problems were detected in this patient because she resisted decreasing the tacrolimus dose owing to a personal belief. We managed to modify the situation and finally the patient adhered to the treatment in an appropriate way. Tacrolimus levels increased in patient 5 on day 21 and were associated with a creatinine increase, which prompted a decrease in the tacrolimus dose. Creatinine and tacrolimus plasma levels normalized 1 week later. Patients on a cyclosporine regime had stable cyclosporine levels and only the female had some dizziness in the second week of treatment. Adverse effects reported were nausea, dry mouth, dizziness, drowsiness, and episodes of intermittent heat; no specific intervention was needed for these effects. No further modifications in CBD treatments were made.

Results in pain control were optimal in 2 patients, 4 had a partial response in the first 15 days, and in 1 there was no change (Table 2). Patients 6 and 7 had optimal pain control response, one having osteoarticular pain and the other neuropathic pain; both patients were treated with cyclosporine in the immunosuppressive regimen. Patients 1, 3, 4, and 5 had a partial improvement in pain control, especially a decreased pain limitation perception. Patient 5 had the best pain control with lower CBD doses; with an increase of the CBD dose, pain increased as well. In this patient, the CBD dose was decreased after day 21.

DISCUSSION

This is not a pharmacokinetic study. We report the feasibility of CBD as analgesia in kidney transplant patients with chronic pain, detecting potential interactions that could determine calcineurin inhibitors dose adjustments and assessing safety.

CBD was well-tolerated. The adverse effects reported were mild and all of them were linked to the nervous or digestive system. This symptom specificity is related to the distribution of cannabinoid receptors in the body. Most adverse effects reported occurred just after increasing the CBD dose. The incidence of adverse effects reported could be explained by the short period between each CBD dose increase. They were all self-limited except in patient 1, in the which CBD dose was decreased owing to persistent nausea, and this measure was enough to control symptoms. It is remarkable that this patient had a previous history of digestive intolerance to several other medications. This

Table 2. Pain Score Index and Limitation Perception

Patient	Week 1	Day 1	Day 2	Day 3	Day 4	Day 7	Day 14	Day
1	6/Moderate	5/Moderate	5/Moderate	5/Mild	2/Mild	2/Mild	2/Mild	3/Mild
2	2/Mild	2/None	2/None	2/None	2/None	2/None	2/None	2/None
3	4/Mild	1/None	1/None	1/None	3/Mild	3/None	4/None	2/None
4	7/Moderate	4/Mild	4/Mild	4/Mild	4/Mild	3/Mild	4/None	3/Mild
5	7/Moderate	6/Moderate	4/Mild	4/Mild	4/Mild	4/Mild	8/Severe	6/Moderate
6	7/Moderate	6/Moderate	3/Mild	2/None	2/None	1/None	1/None	1/None
7	9/Severe	8/Severe	4/Mild	2/Mild	2/None	2/None	2/None	2/None

patient is receiving a tacrolimus and prednisone regimen without mycophenolate mofetil, which had to be discontinued because of digestive intolerance.

Tacrolimus has a very high intraindividual variability, as has been extensively reported. Decreased tacrolimus levels in patient 2 on day 21 could be interpreted as intraindividual variability because the level has returned to normal 1 week later. We identify an increase in tacrolimus levels after CBD treatment in case 5. Variability of pharmacokinetic parameters are increased in this patient owing to diabetic gastroenteropathy. From this case we cannot conclude that the increase in the plasma determination of tacrolimus is due to a pharmacokinetic interaction with CBD. Further follow-up is necessary.

In conclusion, during this follow-up study, we found mild adverse effects reported during CBD use that required the individualization of treatment, especially titration of the optimal dose for each patient. There were no serious adverse effects reported. In general, the CBD was well-tolerated and there was no need to discontinue the treatment. Although a longer follow-up with more patients is required to draw conclusions about clinically relevant pharmacokinetic interactions between CBD and calcineurin inhibitors, we consider that these data are sufficient to recommend a weekly follow-up during the first month and a biweekly or monthly follow-up on a case-by-case basis.

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