Effectiveness of Ketotifen in Treating Uremic Pruritus

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Abstract

Introduction Among the commonest distressing complaints in patients with chronic kidney disease, is itching. We conducted a prospective study to assess the efficacy of ketotifen, a putative mast cell stabilizer, in patients with uremic itch refractory to traditional treatment.

Materials and Methods A double-blind randomized trial with a crossover design was applied on 25 patients .In all of these patients,causes of itching other than uremia had been excluded. We divided the patients into two groups A and B ; they received either oral ketotifen, 1 mg, twice a day for 2 week or placebo for the same period . After A one week period of washout, each group was conversely treated. The response was assessed by the patients subjectively by a questionnaire to assess their itching is either totally relieved ,partially relieved, or still the same (no effect).

Results nine patients (36%) reported totally relieved itching with ketotifen and none (0%) with placebo (*P* =.003). Partial relieve was reported in 15 (60%) and 16 (64 %), respectively. One patient (4%) with ketotifen and nine patients (36%) with placebo showed no change in their symptoms . Eleven patients (44%) suffered from drowsiness that decreased spontaeously in all them after average 5 days.

Conclusions in this study,we postulate that ketotifen, a putative mast cell stabilizer, can be employed to relieve pruritus refractory to other traditional therapies in chronic kidney disease patients who were on maintenence hemodialysis. A moderate dose of ketotifen was effective while safe despite its major side effect, drowsiness, which was transient and could be well accepted by uremic subjects.

Keywords. pruritus, ketotifen , chronic kidney disease , hemodialysis, drowsiness.

الخلاصة

المقدمة من بين الشكاوى الأكثر إضرارا لدى المرضى الذين يعانون من مرضى الفشل الكلوى المزمن، هو الحكة.أجرينا دراسة مستقبلية لتقييم فعالية كيتوتيفين,وهو مثبت مفترض للخلية البدينة ، في المرضى الذين يعانون من حكة والغير مستجيبين إلى العلاجات التقليدية.

المواد وطرق العمل تم تطبيق دراسة عشوائية مزدوج التعمية على 25 مريضا. في كل من هؤلاء المرضى، تم استبعاد أسباب الحكة الأخرى فيما عدا الفشل الكلوى المزمن. تم تقسيم المرضى إلى مجموعتين A و B وتم اعطاء إما كيتوتيفن عن طريق الفم، 1 ملغ، مرتين في اليوم لمدة 2 أسبوع أو علاج وهمي لنفس الفترة .بعد فترة أسبوع واحد من سحب العلاج، عولجت كل مجموعة على العكس .تم تقييم الاستجابة من قبل المرضى انفسهم عن طريق الاستبيان كما يلي: هم إما إستجابة تامة، اوجزئية، أو لا تزال الحكة هي نفسها (أي لا يوجد تأثير).

النتائج تسعة مرضى (36٪) ذكروا إستجابة تامة للحكة مع الكيتوتيفين و لا يوجد مريض (0٪) استجاب مع الدواء الوهمي (P = .003).تم تسجيل عن تخفيف جزئي في الحكة 15 (60٪) مع الكيتوتيفين و 16 (64٪) مع الدواء الوهمي تم تسجيل .مريض واحد (4٪) مع كيتوتيفين وتسعة مرضى (36٪) مع العلاج الوهمي لا يظهر أي تغيير في أعراضهم .. أحد عشر مريضا (44٪) عانوا من النعاس الذي انخفض بشكل تلقائي في كل منهم بعد متوسط 5 أيام.

الاستنتاجات في هذه الدراسة، نحن نفترض ان كيتوتيفين,وهو مثبت مفترض للخلية البدينة يمكن استخدامه لتخفيف الحكة الغير مستجيبة إلى العلاجات التقليدية الأخرى في المرضى الذين يعانون من فشل الكلى المزمن الذين يعتمدون على الغسيل الكلوي .جرعة معتدلة من الكيتوتيفين فعالة في حين آمنة على الرغم من تأثيره الجانبي الرئيسي، و هوالنعاس، وهو عابر ويمكن أن يكون مقبول بشكل جيد من قبل مرضى الفشل الكلوي المزمن.

الكلمات المفتاحية الحكة، كيتوتيفن، أمراض الكلى المزمنة، غسيل الكلى، النعاس.

Introduction

Pruritus is an unpleasant sensation stimulates a desire to scratch. In patients with end staged kidney disease, pruritus represents distressing and severe symptom which disturbs their sleep and affects quality of their life (Pisoni *et al*., 2006). Uremic itching is frequently experienced by patients with end staged chronic kidney disease who are on maintenance renal replacement therapy (continuous ambulatory peritoneal dialysis or haemodialysis). the prevalence of uraemic itching has decreased over the years, from 85% in the 1970s and 50–60% in the 1980s to about 22% at the time being (Pauli-Magnus *et al*., 2002). This is in part due to the use of biocompatible haemodialysis membranes and the improving efficacy of haemodialysis. Despite that, it is still a challenging clinical problem for the nephrologist. The exact pathophysiological basis of uraemic itching is unknown and most therapies are not totally effective. Nevertheless, possible etiological factors include histamine, substance P , interleukin-2 (IL-2) and tumor necrosis factor, peripheral neuropathy, hypercalcemia, hyperphsphatemia, hyperparathyroidism, hypermagnesemia, Aluminum abnormalities, derangemet in divalent ion, proteases, inflammatory factors, or some kind combinations of them (Al Shafei *et al*., 2016). Two theories for the possible pathological basis of uremic itching have been suggested, opioid theory and immunogenic theory (Mettang *et al* 2000). uremic itching correlates with markedly impaird health -related lifestyle in many aspects, including well being, quality of sleep, mood and social impacts (Mathur *et al* 2006).

Histamine released from dermal mast cell and basophils, is one of the most studied chemical mediators of itching. Histamine may work directly on the nerve ending or through other mediators. Blood levels of histamine are remarkably high in dialysis patients, and significantly increased levels were reported in patients with severe uremic itching signifying a causal correlation between pruritus severity and Level of histamine (Dugas-Breit *et al*., 2005).

A variety of therapeutics has been tried, with minimal effectiveness. Besides the frequently employed regimen of antihistamines and tranquilizers, naloxone and naltrexone. (Mikus *et al*., 2000, Legroux-Crespel *et al*., 2004) ultraviolet light phototherapy (Ada *et al*., 2005, Ko *et al*., 2011) other medications used to treat pruritus include erythropoietin (Urbonas *et al.,* 2001), serotonin receptor antagonists (Layegh *et al.,* 2007), parathyroidectomy. (Chou *et al*., 2000), all have been used in the treatment of uremic itch. The diversity of this approach in treatment reflects that the pathogenic basis of this disorder is not well defined, and suggests that the commonly employed treatment is not totally effective.

The hypothesis in our study,is that the increased release of mast cell and the subsequent increased plasma level of the pruritogen ,the histamine ,may lead to uremic itch, and that dermal mast cells stabilization by medication might be of benefit(6). Thus, we conduct a double-blind., placebo-controlled., crossover trial in maintenance hemodialysis patients to examine the therapeutic effects of the putative mast cell stabilizer, ketotifen against uremic itching .

Materials and methods

A double-blind randomized study was performed in a cross-over design at Babylon dialysis center / Merjan Medical City/ Babylon/Iraq. The study was conducted during the period from December 2016 to January 2017 .The selection criteria of patients in this study includes: patients on maintenance dialysis with persistent itching, hemo-dialysis, three to four times per week , serum calcium of no more than 11.5 mg/dL, serum phosphate of no more than 6.5 mg/dL, serum parathormone of neither less than 13 pg/mL and nor than 66 pg/mL,

serum magnesium 2.6 mg/dL or more, and hematocrit more than 31%. The excluded patients were those who had received anti-pruritus meditions one week before the study and the patients underwent dialysis for acute renal failure. 25 patients matches the inclusion criteria for this study and informed consent was provided for each one of them. These patients were divided into groups A and B randomly. For a two weeks period, patients in group A were given ketotifen in a dose of 1mg two times/day, and group B patients were given placebo. Afterthat, one week washout period for both groups, was ensued (without ketotifen), then ,group A patients were given placebo and group B patients were given ketotifen in the same previous dose for another two weeks. The managing doctors and patients were blinded to this randomisation. treatment response was recorded on the patients'subjective report according to the visual analogue pruritus scale, as either total relieve or partial relieve or no change in their symptoms .patients were followed for any development of adverse events in each session of hemodialysis.

Ethical Approval

Written & verbal consent agreement were obtained from each subject participated in this work .Moreover, this work was approved by research ethical committee in College of medicine –Babylon University /Iraq.

Statistical Analysis

Data analysis was done by SPSS software (Statistical Package for the Social Sciences,version16, SPSS Inc,) and proportional variables comparison was done using Fisher exact test and chi-square test . A value for P value less than 0.05 was regarded to be significant.

Results

Twenty five chronic kidney disease patients receiving scheduled hemo-dialysis in Babylon dialysis center, met the inclusion criteria of this study.The mean age was 59.92 years (range, 39 to 80 years) ,twelve of the patients were female (48%) and thirteen were male (52%) and their age and gender distributions are shown in tables (1) and (2) which showed insignificant difference between study groups (*p* values=1 for each).

Table (1) Age Distribution for Both Placebo andTreatment Groups

Groups / Age	**Placebo** (n =25)	**Treatment** (n =25)	**p-value**
Years (Mean ± SD)	59.92±11.948	59.92±11.948	1

Table (2) Gender Distribution for Both Placebo and Treatment Groups

Group / Gender	**Placebo** (n =25)	**Treatment** (n =25)	**Total** No. (%)	**p-value**
Males No. (%)	13 (52)	13 (52)	26 (52)	1
Females No. (%)	12 (48)	12 (48)	24 (48)	
Total No. (%)	25 (50)	25 (50)	50 (100)	

tables (3) and (4) shows the readings of blood urea and serum creatinine for treatment and placebo group and no significant difference between the two groups was evident (*p* values=0.501,and 0.468 respectively).

Table (3) Comparison of Blood Urea for Both Placebo and Treatment Groups

Group / Blood urea	**Placebo** (mmol/l)	**Treatment** (mmol/l)	**p-value**
Years (Mean ± SD)	31.01 ± 8.27	29.56 ± 6.78	0.501

Table (4) Comparison of Serum Creatinine for Both Placebo and Treatment Groups

Group / S.Creatinine	Placebo (mmol/l)	Treatment (mmol/l)	**p-value**
Years (Mean ± SD)	520.1 ± 211.9	478.88 ± 186.2	0.468

Table (5) outlines the results of administration of ketotifen compared to placebo as denoted by the study patients. Total relieve with ketotifen was denoted in 36% of the patients which was higher in significant proportion as compared to the relieve gotten from placebo (*P* = **0.003**). partial improvement was achieved in 60 %, and no effect was seen in 4% . Eleven patients (44%) suffered from drowsiness that decreased spontaeously in all them after average 5 days.

Table (5) Responsiveness to Ketotifen Therpy Compared to Placebo in Patients With End-Stage kidney Disease with Itching

Group / Response to Treatment	**Placebo** (n=25)	**ketotifen** (n=25)	**p-value**
Complete improvement No. (%)	0 (0)	9 (36)	**0.003**
Partial improvement No. (%)	16 (64)	15(60)	
No effect No. (%)	9 (36)	1 (4)	

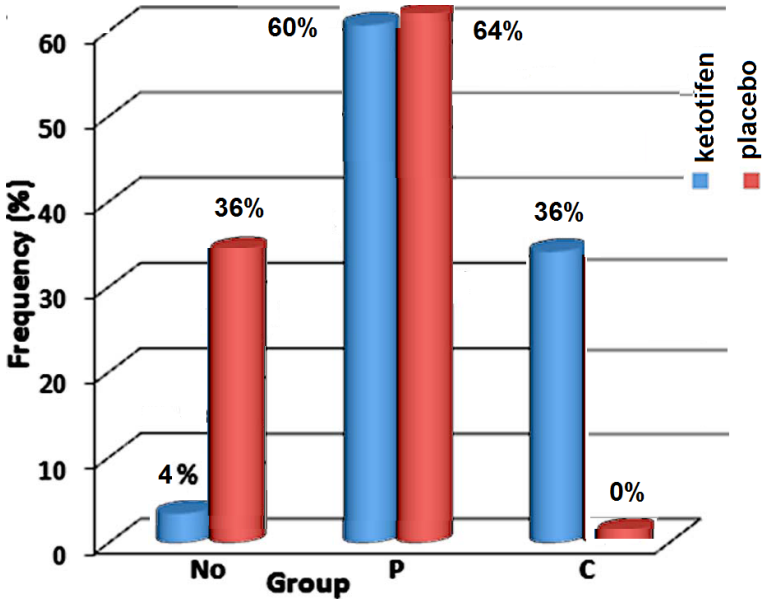

Figure1: Comparing Treatment Responsiveness Between Ketotifen and Placebo for Pruritus in Patients with Chronic Kidney Disease on Regular Hemodialysis .No(No Effect), P (Partial Relieve), and C (Complete Relieve)

Tables (6),(7) and (8) show Previous history of Hypertension ,diabetes mellitus, smoking , and there was statistically insignificant difference between patients and placebo(*p* values=1 for each) .

Table (6) Comparison of Placebo and Treatment Groups Regarding Hypertension

Group / Hypertension	Placebo (n=25)	Treatment (n=25)	Total No. (%)	p-value
Hypertensive No. (%)	18 (72)	18 (72)	36 (72)	1
Non-Hypertensive No. (%)	7 (28)	7 (28)	14 (28)	
Total No. (%)	25 (50)	25 (50)	50 (100)	

Table (7) Comparison of Placebo and Treatment Groups Regarding Diabetes Mellitus

Group / diabetes mellitus	Placebo (n=25)	Treatment (n=25)	Total No. (%)	p-value
Diabetic No. (%)	7 (28)	7 (28)	14 (28)	1
Not diabetic No. (%)	18 (72)	18 (72)	36 (72)	
Total No. (%)	25 (50)	25 (50)	50 (100)	

Table (8) Comparison of Placebo and Treatment Groups Regarding History of Smoking

Group / Smoking	Placebo (n=25)	Treatment (n=25)	Total No. (%)	p-value
Smokers No. (%)	10 (40)	10 (40)	20 (40)	1
nonsmokers No. (%)	15 (60)	15 (60)	30 (60)	
Total No. (%)	25 (50)	25 (50)	50 (100)	

The dose of dialysis for both placebo and treatment groups are showed in table (9) ; and there was statistically insignificant difference between patients and placebo regarding the dose of dialysis for all of them (*p* values=1**).**

Table (9) Comparison of Placebo and Treatment Groups Regarding The Dose of Dialysis

Groups / Dialysis	Placebo (n=25)	Treatment (n=25)	Total No. (%)	*p*-value
Two times weekly No. (%)	11 (44)	11 (44)	22(44)	1
Three times weekly No. (%)	13 (52)	13 (52)	26 (52)	
Four times weekly No. (%)	1 (4)	1 (4)	2 (4)	
Total No. (%)	25 (50)	25 (50)	50 (100)	

Discussion

Uremic pruritus remains an important concern that negatively affect the quality of life patients on maintenance dialysis. Besides that, intense uremic itching is correlated with adverse outcome in maintenence dialysis patients as it is shown by Narita *et al* (Narita *et al* 2006). In addition, as the pruritus intensity increases, the number of missed HD sessions increase. This frequent missed HD sessions might, explain the increased mortality rates in patients with Uremic pruritus (Shayan Shirazian *et al* 2017).

A number of studies showed increased numbers of mast cells in the dermis of Uremic pruritus patients. As long as histamine, the mast cell mediator, is a well known pruritogenic factor, so we postulated that if increased levels of histamine were evident,downregulation of mast cell degranulation might improve itching (Dugas-Breit *et al* 2005). The antihistamines are one the widely employed antipruritic therapies .They can be sorted into two groups: histamine receptor blockers such as hydroxyzine, loratidine, or cetirizine and inhibitors of histamine release such as the mast cell stabilizers cromolyn sodium and ketotifen. Researches in the evaluation of the anti-itching properties of histamine receptor blockers in general reveals very limited improvement in the uremic pruritus (Kuypers *et al* 2009, Lugon, 2005, Balaskas 2011, Legroux-Crespel et al 2004). Ketotifen is a benzocyl-

coheptathiophene derivative which can inhibits the release of histamine by mast cells. Bsaed on the same principle , It is hypothasized that ketotifen can inhibits histamine release at level of tissues to an extent sufficient to relieve uremic itching (Dugas-Breit *et al* 2005). This principle was supported by the findings previously stated by usage of radio - immunoassay for plasma levels of histamine in which high levels were shown in uremic pruritus patients (Stockenhuber *et al.,* 1987).

In this study we evaluate the therapeutic benefit of ketotifen in treating uremic pruritus . In the patient group there was significant improvement in itching score as compared to placebo after 2 weeks of ketotifen 1mg twice daily. But in regard to adverse effects, a few patients develop drowsiness and dizziness and none had palpitations or tachycardia . the current findings are consistent with the study of Francos *et al,* in which ESKD patients received ketotifen as therapeutic trial for itching . Each patient had a remarkable clinical improvement graded by a subjective pruritus score (Francos *et al.,* 1991). The study of Dimkovic´ *et al,* showed a significant response in patient with uremic itch with usage of ketotifen (Dimkovic´ *et al.,* 1992).

Khalili, *et al.,* in their study , evaluated Pruritus severity before and after 2 weeks ketotifen therapy 1mg BID period with Pruritus Severity Score (PSS) .They found that ,the mean PSS decrement with ketotifen was 4.5% which was statistically significnt(Khalili *et al* 2006).Other researchers had varying results in their studies. Saeid Amirkhanlo, *et al.,* study, concluded that both gabapentin and ketotifen significantly relieved pruritus in maintenance dialysis patients, albeit gabapentin shown slightly higher response than ketotifen (Saeid Amirkhanlo *et al.,* 2016).

In several large scale studies, hypertension, diabetes mellitus, smoking, were found to be associated with enhanced severiy of pruritus (Pisoni *et al* 2006; Kimata *et al* 2014), However in the current study no significant assosciation was found between pruritus and these comorbidities. In our study blood urea and serum creatinine was high for all patient in both treatment and placebo groups with no statistically important correlation between high blood urea and serum creatinine and severity of pruritus.these findings are in harmony with the study of Vahide BAYSAL et al, who showed that no statistically important correlation between high blood level of histamine and severity of pruritus (Vahide BAYSAL *et al.,* 1997).

In summary, chronic kidney disease patients suffering from pruritus possibly have increased plasma levels of histamine . ketotifen, The potent mast cell stabilizer ,produced a remarkable improvement in pruritic symptoms in such patients. Certainly the number of patients in the current study who received ketotifen was not plentiful. A large scale, double blinded study for validating effectiveness of ketotifen in treating uremic itchinin is warranted in the future.

Conclusions and Recommendations

Ketotifen, the putative mast cell stabilizer, is safe and efficacious medication for employment to relieve pruritus refractory to other traditional therapies in chronic kidney disease patients who are on maintenence hemodialysis. A moderate dose of ketotifen is effective while safe despite its major side effect, drowsiness, which is transient and could be well accepted by uremic subjects. However, further studies with bigger sample sizes and comparison of ketotifen with other more efficacious agents are indicated in the future .

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