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Safety of pregabalin among hemodialysis patients suffering from uremic pruritus



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Abstract *Objectives:* The aim of this study was to assess the safety and probability of adverse events associated with the use of 75 mg pregabalin post hemodialysis (pHD) among patients with UP. *Methods:* A cross-sectional study done among the hemodialysis patients suffering from uremic pruritus (UP) Aljaber Kidney Center (AJKC), Al-Ahsa, Eastern Province, Saudi Arabia. Assessment for the safety profile of pregabalin was done using Naranjo's algorithm. A predictive model was developed using binary multiple logistic regression to explore association of patients' demographics and risk factors with the occurrence of AEs. Throughout statistical significance level was considered significant at 0.05. *Key findings:* Assessment of safety of pregabalin revealed that somnolence and dizziness were the two frequent adverse events followed by constipation, weight gain and edema. However, it was noticed that female patients aged less than 50 years were found to be at a higher risk in comparison with men. Moreover, those patients having one comorbid complication (i.e. hypertension or diabetes mellitus alone) were at a higher risk of somnolence, weight gain and dry mouth. *Conclusion:* Naranjo's quantification for the possibility and probability of adverse events reflect that all the events were probable. Age, gender and comorbid medical conditions are some of the factors that might have clinical association with the occurrence of the AEs. © 2014 The Authors. Production and hosting by Elsevier B.V. on behalf of King Saud University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

1. Introduction

Uremia pruritus (UP) is one of the most common complications faced by patients with end stage renal disease (ESRD) (Denman, 1986; Goicoechea et al., 1999; Greaves, 2005; Hiroshige and Kuroiwa, 1996; Kfoury and Jurdi, 2012). Due to complex pathophysiology of disease, variety of drugs such as anti-histaminic, opioids agonist, emollients, antidepressants and neuroleptic drugs are tested to provide relief to the ESRD

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suffering through UP (Alomar et al., 2008; Anand, 2013; Andersen et al., 1984; Aramwit et al., 2012; Balaskas et al., 1998; Begum et al., 2004; Breneman et al., 1992; Cho et al., 1997; De Marchi et al., 1992; Lin et al., 2012; Peck et al., 1996; Schmitz et al., 2002). In most of the cases relief from UP was short term and patients have suffered the consequences in the form of relapse to UP. However, recent studies that has tested pregabalin (PG), provided evidence of promising relief to the patients suffering from treatment resistant UP. Shavit et al., (2013) have reported on the therapeutic effectiveness of pregabalin 25–50 mg/day among UP patients showing resistance to antihistamines and emollients (Shavit et al., 2013). In addition other studies have also reported on the effectiveness of pregabalin 25 mg/day among ESRD patients with treatment resistance pruritus (previously tested for emollients, antihistaminic and UV light) (Aperis et al., 2010; Ehrchen and Stander, 2008; Rayner et al., 2012; Shavit et al., 2013; Solak et al., 2012).

Addressing the safety profile of the pregabalin the drug development data reflect the pregabalin safety among health population and till to date there is limited safety data for pregabalin among ESRD patients (Pregabalin, 2009). Recent case studies and case series have reported some adverse events that were found associated with the use of pregabalin among patients with treatment resistant pruritus (Aperis et al., 2010; Ehrchen and Stander, 2008; Rayner et al., 2012; Shavit et al., 2013; Solak et al., 2012). However, the significance and probability of these events is not yet tested using any algorithm that assist in quantifying the significance/probability of these events. Naranjo's algorithm is widely used globally in order to test the probability/significance of a drug related event (Khan et al., 2013; Naranjo et al., 1981; Smyth et al., 2012). For a drug like pregabalin that is renally cleared, it is very essential to estimate its safety profile when it is considered to be used among ESRD patients. Till to date there is a scarcity of any evidence for the safety and efficacy of pregabalin among ESRD patient from Arab region. The current study will address this issue using a cross-sectional study design to observe the severity and probability of adverse events that are associated with the use of pregabalin among hemodialysis (HD) patients suffering from UP.

2. Methodology

This was cross-sectional study done among the hemodialysis patients suffering from UP and receiving HD at Aljaber Kidney Center (AJKC), Al-Ahsa, Eastern Province, Saudi Arabia. AJKC is the only public dialysis center in Al-Ahsa offering medical services to patients with ESRD. It is operated under the directorate of Health Services, Ministry of Health, Saudi Arabia. "Al-Ahsa" is the Arabic word for "oasis," and Al-Ahsa is perhaps the largest oasis in Saudi Arabia. It is known to be the oldest trade route for merchants in the Gulf region and is the only oil-producing province in Saudi Arabia. The majority of the population resides in three main areas: Al-Hufuf, Al-Dammam and Al-Mubarraz. Nearly 70–80% of Al-Ahsa residents are Saudi natives, followed by expatriates from different parts of world. The remaining population is scattered throughout approximately 50 small villages surrounding Al-Hufuf, Al-Dammam and Al-Mubarraz (Al-Hasa, 2013).

2.1. Study population

A total of 314 patients are registered for dialysis at AJKC. These patients are managed in three shifts: morning, afternoon and evening. Of the total number, 173 are male patients and 112 are female patients. Of whom $N = 285$ patients are on HD while the rest are on peritoneal dialysis. On average, about 130 patients are dialyzed on daily basis. Patients visiting for dialysis during the morning shift were assessed for their potential enrollment in this study. The assessment of severity and intensity of UP was done using a validated version of 5D-itching scale (Khan et al., 2013). The first line treatment at AJKC for UP is loratadine 10 mg daily for two month alone or in combination with Vaseline lotion as an emollient. If the UP persists, then the consultant can recommend pregabalin 75 mg to manage the severity of UP. Furthermore, to ensure the patient safety in advance, a safety assessment protocol was developed to rule out the patients that should not be prescribed pregabalin or monitored closed due to a higher risk of adverse events (AEs) (Khan et al., 2014). Upon screening of the records $N = 51$ patients were found taking pregabalin 75 mg post hemodialysis (pHD) throughout the study duration [April 1, 2012, through May 28, 2013].

2.2. Interpretation and analysis of AEs

In order to make the interpretation of AEs more effective and in line with the evidence-based literature, Naranjo's algorithm, known to be a valid measure for reporting and authenticating drug-related events, was applied (Kathleen et al., 2003; Naranjo et al., 1981). Naranjo's algorithm is a ten-item scale with three options ("yes," "no," and "don't know") to express the occurrence of a drug-related incident. Based on these three options, a score is assigned for each item. If the total score is of more than 9, it reflects that the AEs are due to the drug being used by the patient. A probable drug-related AE is assumed if the score is between 5 and 8, and a possible drug-related AE is assumed when the score is between 1 and 4. If the score is 0, it indicates that the AE is not due to the drug in use, but other factors. Details about the items and scoring pattern for the Naranjo's algorithm are shown Table 2. All the patients completing 42 days of pregabalin therapy were questioned about any AEs that they may have experienced after taking pregabalin. The information was collected based on the patients experience and the list of the AEs mentioned in Table 2 (Lyrica, 2013). Naranjo's algorithm was used to estimate the possibility of an association between these events and pregabalin use.

2.3. Data analysis for the interpretation of adverse events

Possible AEs were listed on a separate data collection form and were documented based on patient responses. Physician and nursing staff support were used to interpret patients' experiences in order to assess the incidence of any of the AEs. Descriptive statistics were applied to calculate scores based on Naranjo's algorithm. A standard scoring pattern was adopted to quantify the possible association between the AEs and pregabalin use (Kathleen et al., 2003; Naranjo et al., 1981). Total scores range from -4 to $+13$; if the score is 9 or more than the AE is considered as definite, probable if 5–8, possible if 1–4, and doubtful if 0 or less (Kathleen

et al., 2003; Naranjo et al., 1981). Furthermore, a predictive model was developed using binary multiple logistic regression to explore association of patients' demographics and risk factors with the occurrence of AEs. Overall, six predictive models were built for six AEs, respectively. Throughout statistical significance level was considered significant at 0.05.

2.4. Ethics approval

The study protocol was approved by institutional authorities: the college of clinical pharmacy, deanship of scientific research and Al-Jaber Kidney Dialysis Center (AJKDC)/King Fahad hospital in Al-Ahsa, Saudi Arabia.

3. Results

Upon initial safety screening, fifty one patients were found to be the potential candidates for the pregabalin therapy. Overall, most of the patients that were selected after safety assessment were from the age group 40–70 years [Mean = 55.54 yrs \pm SD 13.29, Median = 55 yrs]. Majority of the patients 36 (70.6%) were male, and 48 (94.1%) were married. In terms of education level most of them having primary education, followed by high school/college and Islamic education. While investigating the occupational status it was revealed that 20 (39.2%) of the patients were government employees and about 17 (33.3%) were jobless (Table 1).

3.1. Assessment for AEs

The assessment for the safety of pregabalin was done using the manufacturer guide for the patients who have taken pregabalin

for the duration of 6 weeks or more. Overall, Dizziness was reported by 47.0% of the patients followed by somnolence 22 (43.1%), constipation 15 (29.4%), blurred vision 10 (19.6%), weight gain 6 (11.8%) and edema 5 (9.8%) dry mouth 3 (5.9%). However, in some cases it was difficult to rule out the associate of an event with the pregabalin use, because some of the patients they reported that they were facing such complication from last two months or more (e.g. dry mouth, edema and headaches). Moreover in some case for example weight gain, it was hard to conclude that either the variations are due to pregabalin or due to the ESRD. Therefore weight gain was only associated with pregabalin in the case when the increase is more than 5.0 kg in comparison with their baseline assessment. In the case where is a risk of doubt, such incidence was ranked as undecided (Table 2).

For the confirmed AEs Naranjo's algorithm was applied to estimate the possibility of an association of the event with pregabalin use. Upon calculation of the score it was revealed that weight gain and edema (score = 4) have a possible association with the administration of pregabalin. While somnolence, blurred vision, dysarthria, and constipation were found to have probable association with the administration of pregabalin (score = 4). Details are shown in Table 3.

Furthermore, to assess the possible association among AEs with the age, gender and comorbidities were assessed using binary multiple logistic regression model. Overall, no statistically significant association was observed. However, it was noticed that female patients aged less than 50 years were found to be at a higher risk in comparison with men. Moreover, those patients having one comorbid complication (i.e. hypertension or diabetes mellitus alone) were at a higher risk of somnolence, weight gain and dry mouth. Details are shown in Table 4.

4. Discussion

Assessment of the AEs is one of the important aspects of drug safety, which is always preferred by the clinician before approving a drug for the patient with lifelong disease conditions or with compromised organ functions. Recent studies exploring the safety of pregabalin reported a variety of AEs among the patients (Zaccara et al., 2011). Perucca et al. (2009) stated that the AEs of pregabalin may reduce the quality of life of patients (Perucca et al., 2009). Overall, the common AEs reported were associated with "cognition/

Table 1 Demographic information of patients.

Demographic variables	N (%)
<i>Gender</i>	
Male	36(70.6%)
Female	15(29.4%)
<i>Education</i>	
Primary	17(33.3%)
Secondary	7(13.7%)
College/high school	15(29.4%)
Islamic education	12(23.5%)
<i>Job status</i>	
Jobless	17(33.3%)
House wife/stay at home	7(13.7%)
Own business	1(2.0%)
Private company job	3(5.9%)
Government job	20(39.2%)
Farm/agriculture job/business	3(5.9%)
<i>Marital status</i>	
Married	48(94.1%)
Single	1(2.0%)
Divorced	1(2.0%)
Widowed	1(2.0%)
<i>Smoking habit</i>	
Active smokers	19(37.3%)
Non-smokers	32(62.7%)

Table 2 Assessment for confirm AEs.

Adverse events (AEs)	Confirm N (%)	Un decided N (%)
Somnolence	22(43.1%)	–
Dizziness	24(47.0%)	–
Dry mouth	3(5.9%)	3(5.9%)
Blurred vision	10(19.6%)	–
Memory disturbances	–	–
Constipation	15(29.4%)	–
Dysarthria	–	–
Weight gain	6(11.8%)	8(15.7%)
Edema	5(9.8%)	4(7.84%)
Impotence	–	–
Headache	–	7(13.7%)
Flu syndrome	–	–
Gynecomastia	–	–

Table 3 Assessment of itching distribution on day forty two.

AEs	Confirm N (%)	Score based on Naranjo's algorithm	AEs assessment based on Naranjo's algorithm
Somnolence	22(43.1%)	7	Probable
Dizziness	24(47.0%)	7	Probable
Blurred vision	10(19.6%)	7	Probable
Dry mouth	3(5.9%)	7	Probable
Constipation	15(29.4%)	7	Probable
Weight gain	6(11.8%)	4	Possible
Edema	5(9.8%)	4	Possible

Table 4 Variables associated with the AEs.

Adverse event	Variables	OR (CI-95%)	p-Value
Somnolence	Age (< 50 years)	0.981[0.941–1.022]	0.349
	Gender (female)	1.656[0.476–5.766]	0.428
	Comorbidities (1 CM)	1.340[0.394–4.561]	0.639
Vision disturbances	Age (< 50 years)	1.025[0.283–3.710]	0.969
	Gender (female)	1.014[0.974–1.056]	0.496
Dry mouth	Age (< 50 years)	0.971[0.908–1.037]	0.381
	Gender (female)	0.842[0.134–5.297]	0.855
	Comorbidities (1 CM)	6.107[0.587–9.592]	0.130
Constipation	Age (< 50 years)	0.956[0.915–0.998]	0.041*
	Gender (female)	0.694[0.194–2.485]	0.574
Weight gain	Age (< 50 years)	0.964[0.900–1.033]	0.298
	Gender (female)	0.710[0.110–4.574]	0.718
	Comorbidities (1 CM)	1.907[0.266–13.669]	0.521
Edema	Age (< 50 years)	0.974[0.908–1.045]	0.458
	Gender (female)	1.207[0.162–8.974]	0.854

Variable(s) entered on step 1: Age, gender and Comorbidities.

CM = Comorbidity.

* p-Value < 0.05

coordination" and severely reduced the quality of life among the patients (Liao et al., 2008; Nakagawasai et al., 2010; Perucca et al., 2009; Zhuchenko et al., 1997). Common AEs that were observed among the pregabalin users were dizziness, vertigo, incoordination, balance disorder, ataxia, tremor, diplopia, blurred vision, euphoria, poor or lack of attention, abnormal thinking, somnolence, confusion, asthenia, fatigue and amblyopia. Ben-Menachem (2004) associated the inhibition of depolarization-dependent influx as the main reason for the decreased neurotransmitter release (Porter et al., 2004; Ben-Menachem, 2004). Therefore, alterations in the normal levels of neurotransmitters in the central nervous system will lead to these AEs, which increase in severity with increased dose (Liao et al., 2008; Porter et al., 2004; Zhuchenko et al., 1997). Moreover, the other AEs, including edema, peripheral edema, dry mouth and constipation, were not found to be associated with increased dose (Zaccara et al., 2011).

However, the study population of the current study was different from the samples of previous studies addressing safety of pregabalin (Liao et al., 2008; Nakagawasai et al., 2010; Perucca et al., 2009; Porter et al., 2004; Zhuchenko et al., 1997). Therefore, the likelihood of the AEs that were dose dependent was less. Randinitis et al. (2003) have shown pharmacokinetic justifications that limit the dose of pregabalin to 75 mg per day for patients with compromised renal function (Randinitis et al., 2003). Most of the recent case reports and

cross-sectional studies that have studied the effect of pregabalin in refractory pruritus among ESRD patients have used a dose of 25–75 mg per day and, in most cases, the effect and safety of pregabalin were observed after 4 weeks (Aperis et al., 2010; Ehrchen and Stander, 2008; Rayner et al., 2012; Shavit et al., 2013; Solak et al., 2012). Among ESRD patients, the common AEs observed were dizziness, somnolence and over-sedation. Similar to the findings of Aperis et al. (2010), Rayner et al. (2012) and Solak et al. (2012), somnolence and dizziness were the frequent adverse event presented by the majority of the patients. Moreover, other AEs were constipation (29.4%), weight gain (11.8%) and edema (9.8%). However, in some cases, some of the AEs were hard to rule out, and were therefore considered "undecided". Certain complications, including weight gain and edema, are also associated with the ESRD itself, and the patients' medical records show frequent variations in the weight and fluid accumulation among the patients (Chamney et al., 2002). Therefore, in the case where patients had frequent variation in weight and fluid accumulation, the benefit of the doubt was given to pregabalin and the incidence of such events was marked as undecided. However, the probability of AEs was not confirmed through the Naranjo algorithm for weight gain (score = 4) and edema (score = 4). Somnolence, dizziness, blurred vision, dysarthria and constipation were found to be probable AEs due to pregabalin use.

In the current sample, it is hard to associate the genetic element with the incidence of AEs observed after pregabalin use. Two main challenges hinder a valid conclusion in this regard: one is the lack of a safety profile of pregabalin among Arabs, and the second is the deficient pharmacokinetic profile among patients with ESRD. Therefore, it is possible that the genetic composition of the current sample is one of the factors that may have augmented the chance of AEs, such as somnolence and dizziness, in the current sample, and perhaps due to this reason, the incidence of these events was double when compared to other studies that investigated the use of pregabalin among UP patients (Aperis et al., 2010; Ehrchen and Stander, 2008; Rayner et al., 2012; Shavit et al., 2013; Solak et al., 2012). Moreover, other AEs including constipation (29.4%), weight gain (11.8%) and edema (9.8%) were only observed in the current sample, and it can be assumed that genetic factors might be one of the influencing factors that provoke the AEs that were not observed by other studies (Aperis et al., 2010; Ehrchen and Stander, 2008; Rayner et al., 2012; Shavit et al., 2013; Solak et al., 2012). Along with the genetic issues, ESRD itself can be one of the reasons for the events such as dizziness, headaches, dry mouth, somatic symptoms and somnolence (Brown and Gower, 1982; NHS, 2013). However, keeping in mind the scarcity of evidence in this regard, the ability of the current study to draw a solid conclusion about the association of genetics with the AEs observed is limited. Future research among ESRD patients and non-ESRD patients will be helpful in providing evidence to determine the association of genetics with the AEs observed with pregabalin use.

Particularly addressing the gastrointestinal (GIT) complications associated with the use of pregabalin, it was noted that about 17 (33.4%) patients were taking lactulose before starting pregabalin therapy. In other words, it can be stated that 33.4% of the patients had GIT symptoms, i.e. constipation before using the pregabalin, which is a common complication faced by most of the ESRD patients that are on HD (Singharetam and Holley, 1996; Wu et al., 2004; Yasuda et al., 2002). Most of HD patients are on oral iron supplementation. Oral iron consumption is reported to be a known reason for the GIT complications, such as constipation, among normal patients and those with ESRD (Suh and Wadhwa, 1992; Van Wyck et al., 2005). Thus concurrent use of iron with ESRD itself has a major role in resulting GIT complications, including constipation. However, based on the Naranjo algorithm, it seems that constipation is associated with the use of pregabalin. Though, in the presence of confounders, including prior episodes of constipation before starting pregabalin and concurrent use of iron during ESRD, it might be clinically difficult to prove a significant associate of constipation with the pregabalin administration.

By exploring the association of other AEs with the demographics and comorbidities using a multiple logistic regression model, it was revealed that visual disturbances were more common among the male patients with odds ratio of 1.014 [95% CI: 0.974–1.056] compared to female ones. Moreover, about 24 (47.1%) of the patients had diabetes mellitus, which is a known cause of visual complications among the patients (Lee et al., 1997; Nakamura et al., 2005). In addition, the majority of the patients in the current sample were aged more than 50 years, which is in line with the increased risk with odds ratio of 1.025 [95% CI: 0.283–3.710] in our predictive model

for the visual complications among the current sample. Furthermore, it is possible that administration of pregabalin might have worsened the visual acuity of the patients. However, it is noteworthy that although the statistical significance was not observed in the current predictive model, our regression-based approach is useful to control for all potential risk factors to obtain better precision.

5. Conclusion

Naranjo's quantification for the possibility and probability of AEs is a beneficial measure to rule out the possibility and probability of AEs. AEs observed in this study were moderate in nature and well tolerated by the patients. Age, gender and comorbid medical conditions are some of the factors that might have clinical association with the occurrence of the AEs.

6. Clinical implications

Overall, the findings of the current study reflect that pregabalin is safe for use among ESRD patients. That is why there were no dropouts, unlike other studies that have used pregabalin to treat UP (Aperis et al., 2010; Ehrchen and Stander, 2008; Rayner et al., 2012; Shavit et al., 2013; Solak et al., 2012). Moreover, an initial safety assessment before starting pregabalin can be an effective measure to monitor the patients that might be at a higher risk of AEs (Khan et al., 2014). Thus, in cases where pregabalin is contraindicated or may complicate the patient's situation, such cases should be identified in advance and monitored closely or considered for alternative treatment options.

7. Limitations of study

The current study was an observational study addressing the safety of Pregabalin among patients with treatment resistant pruritus. Due to the ethical and regulatory reason, it was not possible to allocate a control group for the effective comparison.

8. Recommendations for future research

The time duration of current study was small, assessment for safety was done on day 42 and there was no longitudinal data available to estimate the long term effect of drug. Future studies planning to address the same issue should consider adopting a longitudinal study design to estimate the safety profile of pregabalin in long run.

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