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Pregabalin Efficacy and Tolerability: A Clinical Point of View

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Abstract

Objectives

Antiepileptic drugs have been used in pain management since the 1960s. Pregabalin is a recently developed antiepileptic drug also used in management of chronic neuropathic pain conditions. The aim of this observational prospective study was to assess the analgesic efficacy and associated adverse events of pregabalin in treated patients with neuropathic pain. The source of medication was the free samples that have been provided by the company for evaluation.

Methods

Neurologists and Endocrinologists at king Hussein Medical Center prescribed Pregabalin for selected patients (no. =50) who were diagnosed to have neuropathic pain according to pre-formulated questionnaire that was developed by researchers. The majority of patients received Pregabalin 150mg as a starting dose, 300 mg as a maintenance dose for three months. then the magnitude of pain was assessed first after one week of treatment, if the patient had pain relief after one week and maintained on treatment further assessment was performed at intervals of one, two and three months. Then for each patient the average score of pain relief was calculated (0=worst value, 10=best value).patients were also encouraged to report any adverse effect during treatment period.

Results

A total of 50 patients with neuropathic pain were included. During the course of the study 17 patients terminated treatment during the first week (but were replaced by other 15 patients) either due to lack of efficacy (12%, n=6) or due to intolerable adverse effects (22%, n= 11). For the remaining patients the average score of pain relief was 2.8 ±1.2. The average score of pain reduction was higher among patients with diabetic neuropathy (3.4) than with other types of neuropathic pain (2.2). The most frequently reported adverse effects were dizziness, fatigue, somnolence, and gastrointestinal disturbances.

Conclusion

Pregabalin is effective in reducing diabetic neuropathy and to a lesser extent than other types of neuropathic pain. (But) However intolerable adverse effects still face a problem. Further studies comparing its efficacy and tolerability with other neuropathic treatment choices are needed.

Keywords: Pregabalin, neuropathic pain, diabetic neuropathy, postherpetic neuralgia

Introduction

Neuropathic pain, caused by a lesion of the nervous system is especially problematic. [1,2] because; it is often experienced in parts of the body that otherwise appear normal, it is generally chronic, severe and resistant to over-the-counter analgesics, and it is further aggravated by allodynia (touch-evoked pain).[3,4, 5] It may result from various causes that affect the brain, spinal cord and peripheral nerves, including cervical or lumbar radiculopathy, diabetic neuropathy, cancer-related neuropathic pain, postherpetic neuralgia, HIV-related neuropathy, spinal cord injury, trigeminal neuralgia and complex regional pain syndrome type II. [6] The epidemiology of neuropathic pain has not been adequately studied, partly because of the diversity of the associated conditions. Current pooled estimates suggest that neuropathic pain may affect as much as 3% of the population. [7–13]

Characterization of Neuropathic Pain

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Symptoms described by patients with neuropathic pain are numerous, representing a variety of possible nerve injuries implicated in causation. [14] Neuropathic pain sufferers complain of numbness, burning, or tingling,or a combination; they describe electric shock–like, prickly, or pins and needles sensations. Patients completing the McGill Pain Questionnaire [15] described their pain using terms such as "punishing-cruel" and "tiring-exhausting." In 1990, Boureau et al [16] identified six adjectives used substantially more frequently to describe neuropathic pain; *electric shock, burning*, and *tingling* were most commonly used (53%, 54%, and 48%, respectively), in addition to *cold, pricking*, and *itching*.These terms should suggest a neuropathic etiology for pain. Table 1 defines the sensory symptoms and signs associated with neuropathic pain.[1]

Table 1: Sensory Symptoms and Signs Associated With Neuropathic Pain

Symptom or Sign	Description
Allodynia	Pain due to non-noxious stimuli (clothing, light touch) when applied to the affected area. May be mechanical (e.g., caused by light pressure), dynamic (caused by non painful movement of a stimulus), or thermal (caused by non painful warm, or cool stimulus).
Anesthesia	Loss of normal sensation to the affected region.
Dysesthesia	Spontaneous or evoked unpleasant abnormal sensations.
Hyperalgesia	Reduction of normal sensation to the affected region.
Paresthesias	Non painful spontaneous abnormal sensations.
Phantom	Pain from a specific site that no longer exists (e.g., amputated limb) or where there is no current injury.
Referred Pain	Occurs in a region remote from the source.

Assessing Neuropathic Pain

Recently, pain researchers have focused attention on a theory that accurate measurement of pain quality could provide insight into treatment effects too subtle to be noticed when global measures are similar. [18] This accuracy is especially important for neuropathic pain, because specific sensory characteristics (e.g., burning, tingling) may spotlight pathophysiologic mechanisms of such pain and give clues to those types of intervention most likely to result in palliation. Pain scales provide useful, standardized, and validated tools for charting an individual's response to a pain-control intervention. In addition, detailed documentation utilizing accepted pain scales to assess a patient's level of discomfort provides protection from legal challenges regarding any prescribed pharmacotherapy. [17]

Neuropathic pain medications

Medications used to treat neuropathic pain include over-the-counter analgesics,

anticonvulsants, tricyclic antidepressants (TCAs), and selective serotonin-norepinephrine reuptake inhibitors (SSNRIs), topical anesthetic agents, nonsteroidal anti-inflammatory drugs (NSAIDs), antiarrhythmics, non-narcotic analgesics, and opioids. [14, 19, 20] All of which are reflective of not only the heterogeneity of the patient population, but also the varying underlying pathophysiologies of neuropathic pain.

Sufficient evidence indicates that neuropathic pain impairs patients' mood, quality of life, activities of daily living and performance at work. People with the condition have been found to generate 3-fold higher health care costs compared with matched controls. [21] Relative resistance to conventional treatment is

found in a high percentage of patients with neuropathic pain. Treatment failure may be due to insufficient analgesic efficacy or early side effects that prevent administration of effective dose levels.

For these reasons new drug alternatives that may be more efficacious and better tolerated are desirable.

Pregabalin

Pregabalin is a structural analog of -aminobutyric acid (GABA), which shows analgesic, anticonvulsant, and anxiolytic effects. In many countries, it is approved for the treatment of neuropathic pain. Mechanism of action for pregabalin appears to be the same as that for gabapentin; it binds with high affinity to alpha- 2 -gamma subunits of voltage activated calcium channels, blocks Ca2+ influx into nerve terminals, and decreases transmitter release producing inhibitory modulation of "over-excited" neurons and returning them to a "normal" state [(22)]

Pregabalin has been investigated in diabetic neuropathy (DPN) and postherpetic neuralgia (PHN) in few placebo-controlled studies, but data from routine clinical practice are not yet sufficient.

The aim of this observational prospective study was to assess the analgesic efficacy and associated adverse events of pregabalin administrated to patients with neuropathic pain. The source of medication was the free samples that have been provided by the company for evaluation in the Royal Medical Services (RMS), Jordan.

Methodology

The present study was conducted from March 2011 to August 2011 as a prospective observational study. Neurologists and Endocrinologists at king Hussein Medical Center prescribed Pregabalin for selected patients (no. =50) who were diagnosed to have neuropathic pain according to pre-formulated questionnaire that was developed by researchers.

The majority of patients received Pregabalin at the dose of 150mg – 300 mg administered in two or three individual doses for three months. then the magnitude of pain relief was assessed first after one week of treatment, if the patient had pain relief after one week and maintained on treatment further assessment was performed at intervals of four, eight and twelve weeks. Then for each patient the average score of pain relief was calculated (0=worst value, 10=best value). Patients were also encouraged to report any adverse effect during treatment period.

Inclusion criteria:

Adult patients with NP from different etiologies (mainly diabetic neuropathy, inter-vertebral disk, postherpetic neuralgia) either newly diagnosed or failed to respond to other medications.

Exclusion criteria:

Patient who did not have pain relief after one week of treatment was excluded and replaced by another patient.

The questionnaire

Was developed by researchers and included four parts:

Part 1: demographic, medical and drug history data

Part 2: Yes or No questions related to the nature of patient's pain

Part 3: a numeric rating scale (0-10), that measures patient's extent of pain relief at each assessment period; 0=no pain relief, 10=full pain relief

Part 4: detailed adverse events record (nature, time of onset, duration)

Data Analysis

Quantitative values were calculated as mean value and standard deviation. Frequency and percentage were calculated and presented. Data from observation were analyzed descriptively

Results

A total of 50 patients with neuropathic pain were included (table 2). During the course of the study 17 patients terminated treatment during the first week either due to lack of efficacy (12%, n=6) or due to intolerable adverse effects (22%, n= 11).

The excluded patients were replaced by another 15 patients. So the total number of patients who were evaluated for pregabalin efficacy was 48,

while the side effects of pregabalin were evaluated in 65 patients.

Table 2: Characteristics of Patients Who Participated in the Study

Characteristic	**(n=65)**
Age (mean ± SD))(range) (yrs)	56 ± 13.3
Male (n [%])	38 (58)
Etiology of Neuropathic Pain	
Diabetic polyneuropathy (n [%])	44 (68)
Inter-vertebral disk (n [%])	8(12)
Postherpetic neuralgia (n [%])	7(11)
Neuropathy of other etiology (n [%])	6(9)
Previous analgesic treatments	
NSAIDS and paracetamol(n [%])	8 (12)
Other Anticonvulsants	6 (9)

Dose delivered during Treatment

Pregabalin was prescribed for 12 weeks on an average. Overall 22% stayed on 150mg/day for the duration of the study and 78% had their dose stepped up to 300mg/day.

Efficacy

The average score of pain relief was 2.8 ±1.2. The pain relief score after one, four, eight, and twelve weeks of treatment were 1.6, 2.4, 4, and 3.2 respectively (Figure 1).The average score of pain reduction was higher among patients with diabetic neuropathy (3.4) compared to the (than with) other types of postherptic neuralgia, Inter-vertebral disk neuropathic pain, and neuropathy of other etiologies which was (3), (2.6) and (2.2) respectively (Figure 2).

Adverse Effects

During the course of the study 22%, n= 11 patients terminated treatment due to intolerable adverse effects (dizziness 46% n=5, fatigue 27% n=3, somnolence 18% n=2, peripheral edema 9% n=1).

(In the) The remained patients (18.7% n=9) reported mild to moderate adverse effects. The most frequently reported adverse effects were dizziness, fatigue, somnolence, and gastrointestinal disturbances

Discussion

In this prospective observational study Pregabalin was evaluated in routine clinical practice for its efficacy and tolerability in the treatment of neuropathic pain from different

etiologies. The (outcomes) target was (that were) focused on (were) the score of pain relief and the tolerability of the drug. In summary pregabalin showed an acceptable efficacy in the treatment of different types of neuropathic pain. 68% of the evaluated patients suffered from diabetic neuropathy, 12% suffered from neuropathic pain due to inter-vertebral disk, 11% suffered from neuropathic pain due to postherpetic neuralgia, and 9% suffered from neuropathic pain due to other etiologies.

(At week one) the first week of the study there was a high percent of treatment failure in 34% of patients either due to lack of efficacy or due to intolerable adverse effects. Such findings have been reported previously by Arezzo et al. (2008) who found that the (Were) the percentage of discontinuations during (his) their randomized, double-blind, placebo-controlled trial was similar: pregabalin (34%) and placebo (28%). Most of these withdrawals were due to adverse events, with 17% discontinuing pregabalin and 12% discontinuing placebo. During the follow-up of the patients, adverse events were again considered the most common reason for withdrawal, with 9% discontinuing from the pregabalin and 6% discontinuing from the placebo groups. [(23)]

In our study the intolerable adverse effects that led patients to terminate treatment were dizziness 46% n=5, fatigue 27% n=3, somnolence 18% n=2, peripheral edema 9% n=1.

The remained patients (18.7% n=9) reported mild to moderate adverse effects. The most frequently reported adverse effects were dizziness, fatigue, somnolence, and gastrointestinal disturbances. In total 40.7% of our patients that were included for the study of side effects of pregabalin experienced some degree of the drug side effects.

Pregabalin was effective in treating neuropathic pain. The average score of pain relief was 2.8 ±1.2 and it was calculated in a simple way that was suggested by researchers by using a numeric rating scale (0-10) that measures patient's extent of pain relief at each assessment period ; 0=no pain relief, 10=full pain relief. Analgesic effect of pregabalin was observed in patients regardless of etiology, age, or gender. Administration of pregabalin in currently available placebo-controlled studies of peripheral neuropathic
pain compared to placebo resulted in a significant greater change in the mean end point pain score compared to the baseline score . **(24, 25, 26)**

For patients who completed the study (n=48) the extent of pain relief varied between patients, the pain relief differed from neuropathic pain due to different etiologies and during the period of study. Patients with diabetic neuropathy were the most satisfied group of patients; the average score of pain relief in this group was 3.4 out of 10. The efficacy and safety of pregabalin was further reported in a pooled analysis of seven studies over 5–11 weeks in 1346 diabetic patients with painful neuropathy. **(27)** The response rates were 46% (600 mg/day), 39% (300 mg/day), 27% (150 mg/day), and 22% (placebo). The reported pain reduction in this pooled analysis is comparable to our stated (reported) score of pain relief in this group of diabetic patients (3.4 scores out of 10 =34%) in the same range of dose that we used (150-300 mg/day).

In patients with postherptic neuralgia was used in the present study (in the current study) also showed (reported) a clinically acceptable score of pain relief (3 out of 10). In a study done by (were) Cappuzzo et.al(2009) they reviewed the treatment of postherpetic neuralgia with focus on pregabalin remedy concluded that despite positive findings with several drug classes, the very heterogeneous nature of PHN makes successful pain management difficult. Often, trials of more than 1 agent are necessary before adequate pain management is achieved. Pregabalin appears to be an efficacious, a well-tolerated option for the treatment of PHN. The present information (Data) suggest efficacy for relief of pain and sleep disturbance secondary to PHN in affected patients. Although there are no head-to-head comparisons, pregabalin appears comparable to gabapentin and other first-line agents for treating PHN. **(28)**

The role of pregabalin in the treatment neuropathic pain due to other etiologies like inter-vertebral disk is not well established yet although the results of our study showed some clinical efficacy (average score pain reduction 2.6 out of 10) .

Conclusion

Pregabalin is effective in reducing diabetic neuropathy and to a lesser extent other types of neuropathic pain. However intolerable adverse effects and cost may be an issue. Further studies comparing its efficacy and tolerability with other neuropathic treatment choices are needed.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Figure 1: Average score of pain relief

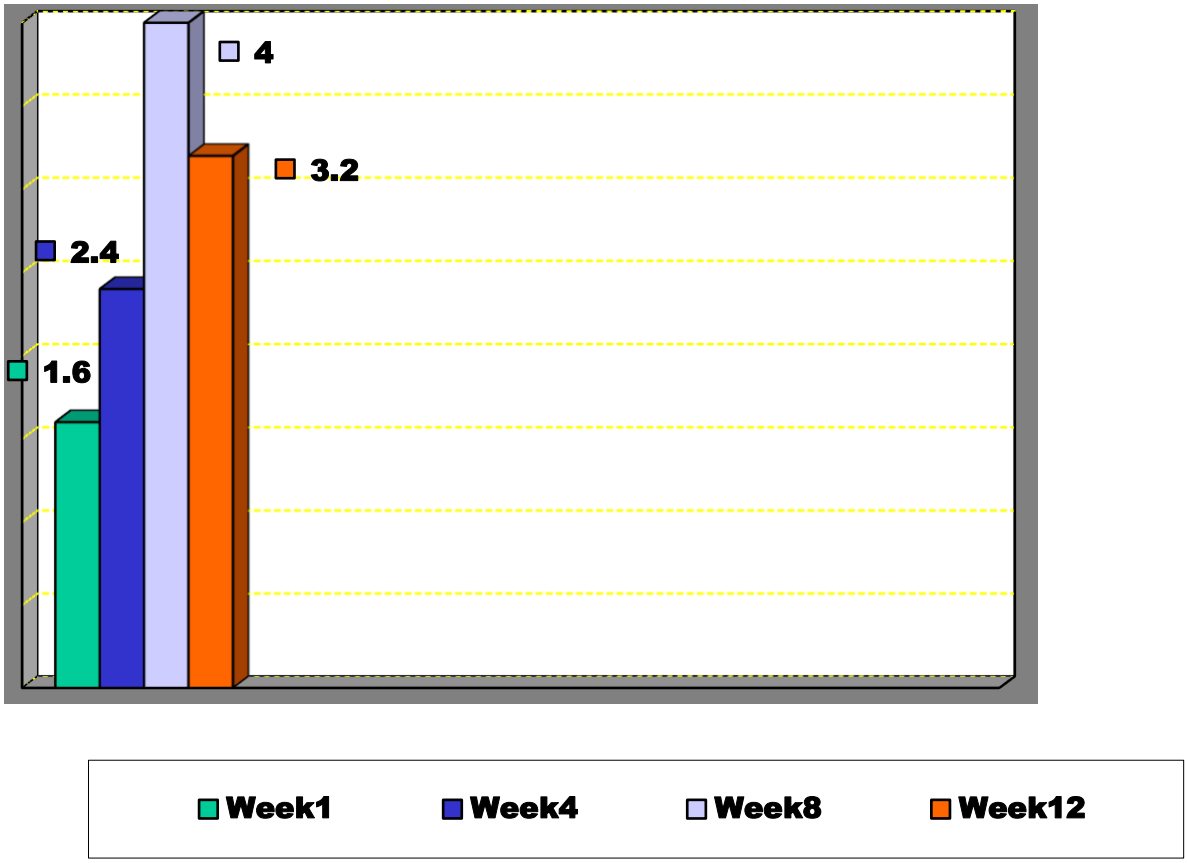

Figure 2: Average Score of Pain Reduction of Neuropathic pain of Different Etiologies
DPN: diabetic neuropathy,PHN: postherpetic neuralgia,IVD: intervertebral disk