Comparative Effectiveness and Safety of Original Gabapentin and Generic Gabapentin in Treating Patients with Neuropathic Pain at Siriraj Hospital, Bangkok, Thailand

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ABSTRACT

Background: Neuropathic pain (NP) develops as a consequence of a lesion or disease affecting the somatosensory system. Patients with severe NP usually suffer from pain and may need many treatment options. Drugs frequently prescribed for treatment of NP include amitriptyline, carbamazepine, gabapentin, and pregabalin.

Objective: To compare the effectiveness and safety between original gabapentin (Neurontin®) and generic gabapentin (Gabapentin Sandoz®) in treating patients with NP at Siriraj Hospital.

Methods: The study was a non-inferiority retrospective study. The medical records of the eligible patients who received gabapentin for NP were retrieved and all relevant data were extracted and recorded. Effectiveness and safety of both formulations of gabapentin were analyzed.

Results: There were 356 NP patients who received original gabapentin and 356 NP patients who received generic gabapentin in which 105 patients received only generic gabapentin and 251 patients had received original gabapentin prior to receiving generic gabapentin. Demographic and underlying conditions of the patients leading to receiving gabapentin were not significantly different. Favorable clinical responses were observed in 91.0% (95% CI: 87.6, 93.6) and 95.2% (95% CI: 92.5, 97.0) of the patients who received original gabapentin and generic gabapentin, respectively. Effectiveness of generic gabapentin was not inferior to that of original gabapentin. Incidences of adverse events in the patients who received only original gabapentin and generic gabapentin were 29.2% (95% CI: 24.7, 34.1) and 28.6% (95% CI: 20.8, 37.9) respectively (p-value = 0.996).

Conclusion: The effectiveness and safety of generic gabapentin and original gabapentinin for treatment of patients with NP at Siriraj Hospital were comparable.

Keywords: Gabapentin, generic gabapentin, neuropathic pain

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INTRODUCTION

Neuropathic pain (NP) is a kind of pain that develops as a consequence of a lesion or disease affecting the somatosensory system.[1] The prevalence of NP in the general population is approximately 7% to 8%.[2] The known common causes of NP include compressive radiculopathy, diabetic neuropathic pain, nerve trauma, herpes zoster, degeneration of the spine and stroke.[2] Patients with severe NP usually suffer from pain and they need many treatment options including medication, physical therapy, and/or surgery. Drugs frequently prescribed to treat NP are amitriptyline, carbamazepine, gabapentin, or pregabalin.

Gabapentin is structurally related to an inhibitory neurotransmitter named gamma-aminobutyric acid (GABA). Gabapentin has been approved for therapy of NP in adults at a dosage of 900-3,600 mg/d.[3] The exact mechanism of action is unclear.[4] GBP may inhibit NP by binding to the 2 modulatory subunit of the voltage-sensitive calcium channel. There are many reports of the effectiveness and adverse effects of gabapentin in the treatment of NP. Gabapentin reduced the pain score up to 50% in 41.3% of patients with diabetic peripheral neuropathy (DPN) and its effectiveness was significantly more than that in placebo.[5]

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In another report on the therapy of DPN, gabapentin also significantly lowered the pain score when compared with placebo.[6] Gabapentin carried some adverse effects such as dizziness, somnolence, confusion.[6] However, most of the patients tolerated such adverse effects of gabapentin.[5] Gabapentin has been available as the original drug (Neurontin®) since 2002. Nowadays there are many generic gabapentin formulations available in Thailand including Gabapentin Sandoz®. The objective of this study was to compare the effectiveness and safety between original gabapentin (Neurontin®) and generic gabapentin (Gabapentin Sandoz®) in treating patients with NP at Siriraj Hospital.

MATERIALS AND METHODS

The study was approved by the Siriraj Institutional Review Board. It was a retrospective study in reviewing medical records of the patients who received gabapentin for therapy of NP during January 2008 to December 2009. The data on patients' demographics and characteristics, pain treatment, response to treatment and adverse effects were extracted. The effectiveness of gabapentin was assessed after the patient received gabapentin for at least 6 months. Favorable response was defined as relief of pain after receiving gabapentin for at least 6 months. Unfavorable response was defined as persistence or worsening of pain or intolerance to adverse effects after receiving gabapentin for at least 6 months. For the patients who switched from original gabapentin to generic gabapentin, the effectiveness of generic gabapentin was defined as persistence of pain relief or improvement of pain relief while receiving generic gabapentin compared with that while receiving original gabapentin.

The sample size of the study was estimated in order to determine whether the effectiveness of generic gabapentin is non-inferior to original gabapentin. We assumed an α-value of 0.05, power of 95% and the proportion of patients responding to generic gabapentin or original gabapentin was 90% with a non-inferiority margin of 7.5%. Using these assumptions, 347 patients are needed in each group. The sample size was estimated using the nQuery Advisor, Version 5.0.

Descriptive statistics were summarized using mean and standard deviation or median and range for continuous variables. Categorical variables were reported with number and percentage. Chi-square test or Fisher's exact test was used to compare categorical variables between groups. Unpaired t test or Mann-Whitney U test was performed to compare continuous variables, as appropriate. Non-inferiority test and 95% confidence interval for the difference between favorable response rates of the two groups were performed to determine whether the effectiveness of generic gabapentin was inferior to original gabapentin. All statistical analyses were performed using SPSS for windows (SPSS Inc., an IBM, Chicago, Illinois, USA) and statistical software R version 2.13.1 (R Development Core Team, 2011). All statistical tests were two-tailed except when the non-inferiority test was made. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

The medical records of 356 NP patients treated with original gabapentin and 356 NP patients treated with generic gabapentin were eligible for analyses. In the patients who received generic gabapentin, 105 patients received only generic gabapentin whereas 251 patients had received original gabapentin prior to receiving generic gabapentin. Most of the patients were females with the mean age of 61 years. The characteristics of the study patients in both groups were not significantly different as shown in Table 1.

Comparison of NP treatment with generic gabapentin and original gabapentin revealed that the number of concomitant pain medications was similar, whereas, the doses of study medications were significantly different as shown in Table 2. The starting dose and maximum dose of the total generic gabapentin group were significantly higher than those of the original gabapentin group. In contrast, when only 105 patients in the generic gabapentin group who never received prior original gabapentin were compared with all patients in the original gabapentin group, the maximum dose of generic gabapentin group was significantly lower than that in original gabapentin group and the starting dose tended to be lower also as shown in Table 3. The patients in both groups received comparable concomitant treatments with physical therapy and other pain medications. However, non-steroidal anti-inflammatory drugs (NSAIDs) and vitamin B12 were given more in the original gabapentin group whereas anticonvulsant was given more in the generic gabapentin group as shown in

TABLE 1. Characteristics of the patients.

Characteristic	Original gabapentin (n = 356)	Generic gabapentin (n = 356)	p-value
Gender: female	263 (73.9%)	260 (73.0%)	0.865
Age: mean ± SD (y)	61.72 ± 12.43	61.55 ± 13.59	0.864
Causes of NP			
Diabetic neuropathy	22 (6.2%)	13 (3.7%)	0.166
Post herpetic neuralgia	17 (4.8%)	17 (4.8%)	>0.999
Trigeminal neuralgia	11 (3.1%)	16 (4.5%)	0.433
Other peripheral neuropathic pain	50 (14.0%)	38 (10.7%)	0.210
Cervical spondylosis with radiculopathy	64 (18.0%)	52 (14.6%)	0.264
Lumbar spondylosis with radiculopathy	82 (23.0%)	101 (28.4%)	0.123
Spinal stenosis with radiculopathy	52 (14.6%)	51 (14.3%)	>0.999
Carpal tunnel syndrome	20 (5.6%)	22 (6.2%)	0.874
Peripheral nerve injury	2 (0.6%)	2 (0.6%)	>0.999
Herniated nucleus pulposus (HNP)	15 (4.2%)	16 (5.1%)	>0.999
Peripheral neuropathy	13 (3.7%)	21 (5.9%)	0.219
Radicular pain	6 (1.7%)	3 (0.8%)	0.505
Tumor of peripheral nervous system	2 (0.6%)	2 (0.6%)	>0.999

TABLE 2. Comparison of neuropathic pain treatment with original gabapentin and generic gabapentin.

Treatment	Original gabapentin (n = 356)	Generic gabapentin (n = 356)	p-value†
Starting dose of gabapentin (mg) Mean ± SD	302.0 ± 191.7	432.9 ± 347.8	<0.001
Maximum dose of gabapentin (mg) Mean ± SD	419.1 ± 277.0	505.3 ± 394.3	0.034
Number of concomitant pain medications Mean ± SD	4.0 ± 2.1	3.9 ± 2.1	0.816

†Mann-Whitney U test

Table 4. There was no significant association between the effectiveness of study medications with taking NSAIDs, vitamin B12 or anticonvulsant. Patients who received NSAIDs responded to study medication 0.67 times (95% CI: 0.36, 1.26) of those without NSAIDs. Patients who received vitamin B12 responded to study medication 0.81 times (95% CI: 0.38, 1.72) of those without vitamin B12. Patients who received concomitant anticonvulsant responded to study medication 1.06 times (95% CI: 0.32, 3.56) of those without anticonvulsant.

Favorable responses after taking study medications ≥ 6 months are shown in Table 5. The favorable response was observed in 91.0% (95% CI: 87.6, 93.6) in the original gabapentin group and 95.2% (95% CI: 92.5, 97.0) in the generic gabapentin group for all patients and 93.3% (95% CI: 86.9, 96.7) for the patients who had never received original gabapentin. The non-inferiority test of the effectiveness of generic gabapentin compared with original gabapentin revealed that the effectiveness of generic gabapentin was non-inferior to original gabapentin, either in all patients who received generic gabapentin or only the patients who received generic gabapentin and had never received prior original gabapentin (p-values <0.001 and 0.005, respectively) as also shown in Table 5.

The occurrence of adverse effects in the generic gabapentin group, 21.1% (95% CI: 17.2, 25.6), was not significantly different from that in the original gabapentin group, 29.2% (95% CI: 24.7, 34.1), as shown in Table 6. Comparison of occurrence of adverse effects with association category.

DISCUSSION

This study was a retrospective study; therefore, it possibly carried some biases and limitations. In the generic gabapentin group, the majority of them, 251 from 356

TABLE 3. Comparison of neuropathic pain treatment with original gabapentin and generic gabapentin of patients without switching study medication.

Treatment	Original gabapentin (n = 356)	Generic gabapentin (n = 105)	p-value†
Starting dose of gabapentin (mg) Mean ± SD	302.0 ± 191.7	277.1 ± 164.2	0.258
Maximum dose of gabapentin (mg) Mean ± SD	419.1 ± 277.0	349.5 ± 244.2	0.003
Number of concomitant pain medications Mean ± SD	4.0 ± 2.1	3.6 ± 2.2	0.143

†Mann-Whitney U test

TABLE 4. Comparison of concomitant treatments.

Concomitant treatment	Original gabapentin (n = 356)	Generic gabapentin (n = 356)	p-value
Physical therapy	34.4%	35.4%	0.813
Co-medication			
NSAIDs	66.9%	55.1%	0.002
Acetaminophen	49.2%	48.9%	1.000
Tramadol	16.9%	17.4%	0.921
Vitamin B complex	59.8%	64.9%	0.189
Vitamin B12	21.1%	10.1%	<0.001
Tricyclic antidepressant	20.8%	18.5%	0.509
Pregabalin	2.5%	1.7%	0.602
Muscle relaxant	48.0%	49.4%	0.764
Anti-inflammation: Serratiopeptidase Aescin amorphosed	2.0%	1.1%	0.543
Antirheumatism	17.8%	17.4%	1.000
Calcium	26.4%	32.0%	0.117
Vitamin D	5.1%	2.8%	0.177
Bone metabolism drug	5.1%	4.5%	0.860
Tropical analgesic	34.3%	38.8%	0.243
Cerebral activator	4.2%	4.2%	1.000
Anticonvulsant	3.7%	9.3%	0.004
Tranquillizer	9.6%	11.8%	0.396
Steroid	2.8%	1.7%	0.448

TABLE 5. Effectiveness of gabapentin in the treatment of neuropathic pain.

Patients achieving favorable response		Difference (95% CI)	Non-inferiority test (p-value)
Original gabapentin	Generic gabapentin		
91.0% (95%CI: 87.6, 93.6)	95.2% (95%CI: 92.5, 97.0)*	-4.2% (-8.1, -0.5)	<0.001†
91.0% (95%CI: 87.6, 93.6)	93.3% (95%CI: 86.9, 96.7)**	-2.3% (-7.2, 4.6)	0.005‡

*=all patients who received generic gabapentin. **= only patients who had never received original gabapentin
†Testing for non-inferiority between all patients in generic gabapentin group and all patients in original gabapentin group
‡Testing for non-inferiority between patients who had never received original gabapentin and all patients who received original gabapentin

TABLE 6. Comparison of occurrence and management of adverse effects.

Adverse effect	Original gabapentin	Generic gabapentin	p-value
Yes	29.2% (95%CI: 24.7, 34.1)	21.1% (95%CI: 17.2, 25.6)	0.083
No association	31 (8.7%)	20 (5.6%)	
Uncertain association	45 (12.6%)	36 (10.1%)	
Association	28 (7.9%)	19 (5.3%)	

NP patients (70.5%), received original gabapentin prior to receiving generic gabapentin that may contaminate the result of effectiveness. At the study time, generic gabapentin had just been available in Siriraj Hospital for one year. As a result, the study needed to recruit many patients who received original gabapentin prior to generic gabapentin in order to complete the target sample size of 347 NP patients. Since there was a limitation to find out the severity of NP which affected the pain response to study medication as well as the pain score this was not used to evaluate the effectiveness, so the result of this study may carry some errors. Importantly, this study was not randomized and not blinded, so it possibly contained bias. For example, it was possible that the treating clinicians may select original gabapentin with the belief that original gabapentin would be more effective than generic gabapentin. Although there were many potential biases and flaws, by means of considerable sample size and the comparable demographic data, proportion of concurrent diseases and proportion of other medications and physical therapy prior to and during study between the two groups as shown in Table 1, the results of this study could be valuable to practicing clinicians.

On comparison of dose of study medication, the starting dose and maximum dose of the total generic gabapentin group were significantly higher than the original gabapentin group (Table 2). In contrast, in comparing with only 105 patients who never took prior original gabapentin in the generic gabapentin group, the maximum dose of this 105 generic gabapentin group was significantly lower and their starting dose tended to be also lower as shown in Table 3. This diversity may not be clinically significant because the difference was small. As severe NP is difficult to treat and need concomitant pain therapy in some patients, concomitant pain therapy may contaminate the effectiveness of study medication. The starting and maximum dosage of both original and generic gabapentin in this study was not very different, i.e. only about 100-200 mg, which is unusual for neuropathic pain control. This finding may also be due to the effect of concomitant pain medications which might have interfered with the efficacy of gabapentin in this study. In this study, concomitant treatment with physical therapy and other pain medications were found comparable except NSAIDs, vitamin B12 and a particular anticonvulsant (Table 2, 3 and 4). However, there was no significant association between the effectiveness of gabapentin and NSAIDs, vitamin B12 or anticonvulsant. This study demonstrated that generic gabapentin was not inferior to original gabapentin in terms of effectiveness both in all 356 patients who received generic gabapentin or only the 105 patients who took only generic gabapentin and had never received prior original gabapentin (Table 5).

Since it was found that the occurrence of adverse effects and occurrence of adverse effects with association category in both groups were comparable (Table 6), this study; therefore, demonstrated that the safety of generic gabapentin was similar to that of original gabapentin.

CONCLUSION

This retrospective study found that the effectiveness and safety of generic gabapentin for treatment of patients with NP at Siriraj Hospital were comparable to those of original gabapentin.

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SUPPLEMENTARY DATA PART

The proportion of patients with concurrent diseases, number of concurrent diseases, time duration before starting the study medications and proportion of patients having prior NP treatment have been shown in Table A. Only the proportion of patients having prior NP treatment was similar in both groups. The rest of the aforementioned characteristics were significantly higher in the generic gabapentin group. All concurrent diseases of the patients except orthopedic conditions and gastrointestinal disorders were comparable between the two groups as shown in Table B. For prior NP treatments, the proportion of other medications and the proportion of physical therapy were also similar in both groups as shown in Table B. However, the proportion of surgery was higher in the generic gabapentin group and there was no significant association

between the proportion of other orthopedic conditions, gastrointestinal disorders or surgery and effectiveness of study medication. Patients with other orthopedic conditions responded to study medication 1.68 times (95% CI: 0.65, 4.32) of those without other orthopedic conditions. Patients with gastrointestinal disorders responded to study medication 0.48 times (95% CI: 0.22, 1.08) of those without gastrointestinal disorders. Patients with prior treatment with surgery responded to study medication 0.50 times (95% CI: 0.20, 1.23) of those without prior treatment with surgery.

Comparison of the adjustment of study medications by category and adverse event management revealed that all were not significantly different between groups as also shown in Table C. Analysis of occurrence of individual adverse events found that all of them except confusion were not significantly different between the two groups as shown in Table D. When 105 patients in the generic gabapentin group who had never received original gabapentin were compared with those in original gabapentin group, the occurrence of confusion was not significantly different (p-value = 0.359).

TABLE A. Comparison of concurrent diseases, duration of neuropathic pain and proportion of patients having prior neuropathic pain treatments.

Factor	Original gabapentin (n = 356)	Generic gabapentin (n = 356)	p-value
Patients with concurrent diseases (%)	259 (72.8%)	294 (82.6%)	0.002
Number of concurrent diseases Mean ± SD	1.5 ± 1.4	1.9 ± 1.6	0.002
Duration of NP before starting gabapentin (months) Mean ± SD	12.0 ± 22.1*	10.4 ± 19.4**	0.946
Patients having prior NP treatments (%)	195 (54.8%)	218 (61.2%)	0.095

* n=186 **n=64

TABLE B. Comparison of concurrent diseases and prior neuropathic pain treatments.

Factor	Original gabapentin (n = 356)	Generic gabapentin (n = 356)	p-value
Concurrent diseases			
Diabetes mellitus	69 (19.4%)	65 (18.3%)	0.774
Hypertension	147 (41.3%)	160 (44.9%)	0.364
Dyslipidemia	96 (27.0%)	107 (30.1%)	0.406
Psychiatric disorders	10 (2.8%)	15 (4.2%)	0.415
Malignancy	11 (3.1%)	16 (4.5%)	0.433
Cerebrovascular diseases	13 (3.7%)	16 (4.5%)	0.705
Liver diseases	9 (2.5%)	7 (2.0%)	0.800
Renal diseases	8 (2.2%)	13 (3.7%)	0.376
Epilepsy	0 (0.0%)	1 (0.3%)	1.000
Urological conditions	12 (3.4%)	23 (6.5%)	0.083
Osteoarthritis	54 (15.2%)	67 (18.8%)	0.231
Other orthopedic conditions	34 (9.6%)	76 (21.3%)	<0.001
Thyroid diseases	7 (2.0%)	10 (2.8%)	0.623
Heart diseases	25 (7.0%)	40 (11.2%)	0.069
Eye diseases	12 (3.4%)	22 (6.2%)	0.114
Gastrointestinal disorders	24 (6.7%)	41 (11.5%)	0.037
Previous neuropathic pain treatment			
Medications	183 (51.4%)	210 (59.0%)	0.050
Physical therapy	41 (11.5%)	56 (15.7%)	0.126
Surgery	16 (4.5%)	33 (9.3%)	0.018

TABLE C. Comparison of management of adverse effects.

Adverse effect	Original gabapentin	Generic gabapentin	p-value
Adjustment of study medication by category	n = 104	n = 76	0.204
No	68 (65.4%)	59 (77.6%)	
Decrease dose	11 (10.6%)	5 (6.6%)	
Discontinue	25 (24.0%)	12 (15.8%)	
Adverse event management (n)	n = 101	n = 75	0.578
No	21 (20.8%)	22 (29.3%)	
Medication	59 (58.4%)	38 (50.7%)	
Procedure	4 (4.0%)	2 (2.7%)	
Unknown	17 (16.8%)	13 (17.3%)	

TABLE D. Comparison of individual adverse event.

Adverse event	Original gabapentin n = 356	Generic gabapentin n = 356	p-value
Rash 5	(1.4%)	3 (0.8%)	0.725
Dizziness	23 (6.5%)	15 (4.2%)	0.243
Nausea/ vomiting	3 (0.8%)	3 (0.8%)	1.000
Confusion	7 (2.0%)	0 (0.0%)	0.015
Somnolence	14 (3.9%)	11 (3.1%)	0.684
Headache	2 (0.6%)	1 (0.3%)	0.624
GI adverse event			0.131
Diarrhea	1 (0.3%)	0 (0.0%)	
Dyspepsia	10 (2.8%)	3 (0.8%)	
GI hemorrhage	2 (0.6%)	0 (0.0%)	
Other	2 (0.6%)	3 (0.8%)	
Weight change			0.846
Weight gain	1 (0.3%)	2 (0.6%)	
Weight loss	1 (0.3%)	1 (0.3%)	
Infection			0.878
Upper respiratory tract infection	11 (3.1%)	10 (2.8%)	
Acute gastroenteritis	2 (0.6%)	1 (0.3%)	
Urinary tract infection	3 (0.8%)	2 (0.6%)	
Other mild infection	2 (0.6%)	3 (0.8%)	
Other sever infect	0 (0.0%)	1 (0.3%)	
Accident	6 (1.7%)	3 (0.8%)	0.505

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