Tolerability of Compulsory Generic Switching from Originator to Generic Levetiracetam in the Outpatient Epilepsy Clinic of a Tertiary Hospital in Kedah

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Abstract

Introduction: Procurement of certain medications in the Ministry of Health Malaysia (MOH) is bound to the central government contracts with designated manufacturers. Thus, generic switching of levetiracetam had occurred in MOH facilities despite mixed evidence on the safety and tolerability of brand switching of anti-seizure medication.

Objective: The objective of this study was to assess the tolerability of generic substitution of Levetiracetam in terms of the occurrence of fit and side effects among epilepsy populations in Hospital Sultanah Bahiyah, Kedah**.**

Methods: This study included patients who were taking originator levetiracetam 500mg tablets (Keppra®) for at least 90 days prior to overnight switch to generic levetiracetam 500mg tablets (Torleva®) and had taken the generic drug for at least 90 days after the switch. The tolerability of levetiracetam and patients' compliance during the 90-day pre-switching period and 90-day post-switching period were compared. Data were collected retrospectively from the clinic visit notes in electronic medical record (e-HIS).

Results: Ninety-seven patients were included in this study. The patients documented with a fit episode increased significantly from 60 (61.9%) to 70 (72.2%) patients post switching to generic Levetiracetam (p=0.031). However, the side effects experienced by patients and patients' compliance pre- and post-switching were not significantly different (p=0.508 and p=0.375 respectively).

Conclusion: This study provided preliminary evidence on the tolerability of brand switching of anti-seizure medication among epilepsy patients.

Key Words: anti-seizure medication, generic substitution, efficacy, tolerability

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Introduction

Epilepsy is one of the most common non-communicable chronic neurological conditions that is characterised by recurrent, unprovoked and epileptic seizures. Epilepsy affects approximately 50 million people worldwide (1). The choice of anti-seizure medication (ASM) must be individualised, taking into consideration the tolerability, long term safety and efficacy of drug. During the past decade, epilepsy guidelines had been emphasising on the issues of generic ASM whereby the use of generic substitutes in epilepsy may not be cost-effective (2). Generic products are equivalent to their originator counterparts in active ingredients, route of administration, strength and dosage form but may differ in some excipients and the specific manufacturing process.

The drug regulatory authorities approve generic drugs based on their bioequivalence to originator counterparts, which requires similar rate and extent of bioavailability of the active ingredient. Such studies generally evaluate the ratio of the generic product's maximum concentration (Cmax) to the originator product's Cmax and the ratio of the generic product's area under the plasma concentration versus time curve (AUC) versus the originator product's AUC in healthy volunteer (3). If the 90% confidence intervals of

the geometric means for these ratios fall within the range of 80% to 125%, the two products compared are deemed bioequivalent (3). Some have argued that this can result in clinically meaningful differences in terms of efficacy and safety between a generic drug and its originator counterpart (3).

The generic ASMs substantially reduces the expenditure of treatment and is therefore encouraged by the health systems (4). Various studies that compared generic and innovator ASMs have been published. Some studies had reported increased seizure events and side effects after ASM generic switching (5,6,7). In addition, most professional societies, including The American Academy of Neurology, Italian League Against Epilepsy, and National Institute for Health and Clinical Excellence had issued statements opposing the generic substitution of ASMs prior to physician's approval (4,8). On the contrary, some organisations such as the US FDA and the American Society of Health System Pharmacists suggested that generic ASM can provide similar efficacy, tolerability and safety to that of the original ASM, thus therapeutically interchangeable (8). Despite conflicting viewpoints regarding generic substitution of ASM, there are also emerging data supporting the use of generic ASMs (8). In recent years, the National Pharmaceutical Regulatory Agency, Ministry of Health Malaysia (MOH) has approved the registration of various generic ASMs which passed the bioequivalence study (2). However, there was a lack of local studies on the real-world response to generic switching of ASMs among our local epileptic population.

Among the ASMs, levetiracetam is one of the common drugs used for the treatment of partial or generalised epilepsy in children and adults due to its broad spectrum of efficacy in different epilepsy syndromes, pharmacokinetic properties, minimal side effects, and safety in pregnancy (8-11). Given the wide use of Levetiracetam in epilepsy, several pharmaceutical companies have manufactured their own generic levetiracetam. In MOH, the procurement of levetiracetam is done via central contract at the national level, in which the contract will be granted to suppliers or manufacturers that offer the most reasonable price. Therefore, when the contract was awarded to a supplier of generic levetiracetam, all MOH facilities will procure the specific brand of generic levetiracetam within the contract period. Thus, generic switching of levetiracetam had occurred. As there were limited studies that explore the efficacy and safety of generic substitution of levetiracetam, and while sometimes the evidence might be conflicting (4,5,6,7,8), this study was conducted to assess the tolerability of generic substitution of levetiracetam in terms of the emergence of fit and occurrence of side effects among the epilepsy patients in a tertiary care hospital.

Method

This was a retrospective cohort study of patients who were treated with levetiracetam in the outpatient Medical Department in Hospital Sultanah Bahiyah, Kedah, Malaysia. The study period was from November 2018 to February 2019. This study was registered with the National Medical Research Register (NMRR) and was approved by the MOH Medical Research and Ethics Committee (MREC) (NMRR-18-1522-42180).

Before March 2018, levetiracetam 500mg tablets used in the MOH was an originator (Keppra®) manufactured by UCB Pharma S.A. Braine-l'Alleud, Belgium. In March 2018, the central contract of levetiracetam 500mg tablets was awarded to a generic brand (Torleva®) manufactured by Torrent Pharmaceuticals, India. MOH patients who were initially taking originator levetiracetam were switched to generic levetiracetam with the new cycle of procurement.

This study included patients from the outpatient epilepsy clinic of the Medical Department in Hospital Sultanah Bahiyah, who were switched from originator levetiracetam 500mg tablets to generic levetiracetam 500mg tablets at the same dose due to the change of procurement contract in March 2018 while the other concomitant anti-seizure medications (ASM) remained unchanged. This study included only patients taking the originator levetiracetam for at least 90 days prior to generic switching, and had taken generic Levetiracetam for at least 90 days after the switch. Paediatric patients taking levetiracetam, patients discharged to other facilities for follow up, patients taking different dosage form of levetiracetam besides tablet and patients having different dose of levetiracetam upon switching were excluded in this study.

The tolerability of generic levetiracetam in the patients were assessed by the absence of fit and levetiracetam-related side effects. Patients were also assessed in terms of emergence of fit, which means presented with new episode of fit after fit free for one year and longer. The data were traced retrospectively from patients' clinic visit notes in the electronic medical record (e-HIS). Data on compliance of treatment was also collected from the e-HIS. Data on compliance of treatment was self-reported by the patients and recorded in patient's case notes in the e-HIS by prescribers. The tolerability of levetiracetam, patients' compliance and emergence of fit during the 90-day pre-switching period (originator levetiracetam 500mg tablets) and 90-day post-switching period (generic levetiracetam 500mg tablets) were compared.

Statistical analysis was performed using SPSS statistical package (version 21.0, SPSS Inc., Chicago, IL, USA). The results were expressed as means and standard deviation (SD) for continuous variables and number (n) with percentage (%) for categorical variables. Comparisons between categorical data were analysed using Pearson chi-square test, whereas continuous variables were analysed using independent t-test. Statistical significance was defined as a p value < 0.05.

Results

A total of 114 patient records were screened for this study. Only 97 patients were eligible after excluding patients who have defaulted, discharged to other hospitals or clinics, and deceased.

Table 1 showed the clinical characteristics of included patients. Patients involved in the study were suffering from generalised seizure (41 patients) and focal seizure (56 patients). Among them, some patients were on levetiracetam tablets as monotherapy (17.5%) while most of the patients (82.5%) were taking as polytherapy in concomitant with one or more other ASMs.

Table 2 compared the tolerability and compliance of patients during the pre- and post-generic switching of levetiracetam. The patients documented with an episode of fit was noted to increase from 60 (61.9%) to 70 (72.2%) patients post switching of generic levetiracetam (p=0.031). Switching of brands neither affect the occurrence of side effects (p=0.508) nor patients' compliance (p=0.375).

Among the 70 patients experiencing fit post-generic switching, 14 patients were categorised as having emergence of new fit, which means they were presented with new episode of fit after being fit free at least one year. In Table 3, we sub-analysed the comparison of factors associated with the emergence of new fit among these 14 patients. The type of seizures, whether generalised or focal, was one of factor significantly associated with the emergence of fit post switching (p=0.017). Gender and age of patients played no role in post switching effect (p=0.536 and p=0.520 respectively).

Table 1: Clinical characteristics of patients who were switched to generic levetiracetam (n=97)

Variables	n (%) / Mean ± SD
Age, years; mean ± SD; range	36.19 ± 12.67; range 16-81
Gender	
Female	49 (50.5%)
Male	48 (49.5%)
Type of seizure	
Generalised	41 (42.3%)
Focal	56 (57.7%)
Daily dose of LEV (mg); mean; range	1972; range 500-3000
Number of AEDs used	
1	17 (17.5%)
2	38 (39.2%)
3	30 (30.9%)
4	9 (9.3%)
5	3 (3.1%)

Table 2: Comparison of outcomes in patients' pre and post switching of generic levetiracetam in terms of tolerability and compliance

Outcome	Pre, n (%)	Post, n (%)	*p*-value [a]
Fit Free (Tolerability)			**0.031**
Yes	37 (38.1%)	27 (27.8%)	
No	60 (61.9%)	70 (72.2%)	
Side Effect* (Tolerability)			0.508
Yes	4 (4.1%)	7 (7.2%)	
No	93 (95.9%)	90 (92.8%)	
Compliance			0.375
Yes	94 (96.9%)	91 (93.8%)	
No	3 (3.1%)	6 (6.2%)	

[a] McNemar Test
* Documented levetiracetam-related side effects reported by patients after change, e.g. mild headache, forgetfulness, etc.

Table 3: Comparison of factors associated with the emergence of new fit episode post generic switching

Outcome	Emergence of new fit episode*		*p*-value
	Yes	No	
Age, years; mean ± SD	38.21 ± 10.47	35.84 ± 13.03	0.520 [a]
Gender, n (%)			0.536 [b]
Female	6 (12.2%)	43 (87.8%)	
Male	8 (16.7%)	40 (83.3%)	
Type of seizure, n (%)			**0.017** [b]
Generalised	10 (24.4%)	31 (75.6%)	
Focal	4 (7.1%)	52 (92.9%)	

* presented with new episode of fit after fit free ≥ 1 year
[a] Independent t-test
[b] Pearson Chi Square test

Discussion

In view of the increasing medical costs in recent years, health care systems have adopted measures to limit expenditures and maximise cost saving by the encouragement for the use of cheaper generic products (9,12). Epilepsy is associated with high treatment cost that affect individuals and society due to the high prevalence of the disease and its long duration of treatment (8). In epileptic patients, reduced efficacy and potential occurrence of side effects after switching from originator name to generic products ASM was reported to be a common phenomenon (4,8). Furthermore, most ASMs have a narrow therapeutic index (12). Thus, generic substitution of ASM raises special concerns regarding their use in the treatment of epilepsy. In recent approved novel chemical analogue of Levetiracetam, Brivaracetam, the average annual cost is higher than other ASM (13,14). This raised the concern in future whether the increase of generic use of levetiracetam or the safety of switching should be prioritised in focal onset seizure.

We reported a retrospective study over a six-month period, which was three months before compulsory switching from originator to generic Levetiracetam and another three months after the switch. Our results showed a significantly higher number of patients experiencing fit post switching. These results are consistent with a few literatures (5,12,16) that demonstrated that generic ASM exhibited reduced efficacy and tolerability compared with their originator counterparts. Also, previous studies showed that patients who showed a high seizure count before switching experienced worsening in clinical response and appearance of side effects when moving from originator to generic ASMs (5,8,12).

Our study result is in contrast with result reported recently in Maria *et al*. (8) and Martina *et al*. (9) where overnight switch from originator levetiracetam to generic levetiracetam was easy and safe in patients with epilepsy. These discordant results may be possibly due to our larger sample size (n= 97) compared to these studies (8,9). Our findings were also at variance with a similar retrospective analysis by Bosak *et al*. that comprised of 90% subjects on epilepsy polytherapy, in which their findings revealed that generic

substitution of Levetiracetam was generally safe (4). Bosak *et al*. refuted the study result by Chaluvadi *et al*. (17) (35.5% of patient on monotherapy) that showed generic substitution of Levetiracetam will lead to loss of seizure control because Bosak *et al*. presumed that patients on monotherapy were more prone to increased seizure frequency as there was only one medication to control seizure (4). However, our current study comprised of 82.5% of patients with polytherapy, yet the findings still showed a significant increase in the occurrence of fit after switching from originator to generic levetiracetam. Thus, polytherapy or monotherapy may not affect the frequency of fit. The American Academy of Neurology advised to avoid switching between originator and generic formulations of ASM (1). The 2017 Consensus Guideline in Management of Epilepsy by Malaysian Society of Neuroscience also suggested that patients with refractory epilepsy and those who are on polytherapy are best maintained on their original ASM to prevent seizure (2). Our study showed that the type of seizures, whether generalised or focal, could be one of the factors affecting the emergence of new fit among stable patients. Based on our findings, the types of seizure may also be used to guide decision on the suitability of brand switching for levetiracetam. Nevertheless, due to observational nature of our study, further confirmatory studies will be needed to verify our findings.

This study was limited by several factors that could have influenced the fit outcome. First of all, this was a retrospective study and therefore the confounding factor affecting seizure threshold was beyond our control. Secondly, the choice of generic levetiracetam was restricted by the government procurement contract and hence we were using a different generic brand of levetiracetam (Torleva®) compared with other similar studies (Epitiram® and Matever®) (9,15). Other factors such as herbal medicines that might trigger fit were not taken into consideration as well. Moreover, the assumptions made in this study was that there were no changes in other ASMs in our patients pre and post brand switching of levetiracetam, except for dose changes in these ASMs. Another limitation of our study was serum levels of levetiracetam were not assessed before and after the generic substitution, limiting the possibility of comparing drug availability (4,15). Finally, the assessment of compliance in our patients were only based on self-reporting as recorded in the e-HIS instead of using any compliance assessment instruments (15).

Conclusion

In summary, our study provided preliminary evidence on the potential influence of levetiracetam brand switching on the tolerability of patients. This warranted more studies to investigate the causal effects of the brand switching on the tolerability. However, given the conflicting evidence on the the safety and effectiveness of generic substitution of ASMs, procurement and brand selection for ASMs in MOH should be more flexible to provide more alternatives for clinicians to optimise the pharmaceutical therapy for seizure patients.

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Conflict of Interest Statement

This study did not receive any funding from public, commercial or non-profit organisations. The authors declared no conflict of interest.

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