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Annals of Public Health & Epidemiology
Iris Publishers

Mini Review

Generic Substitution in Patients Whose Illness Has a Narrow Therapeutic Index, Such as Epilepsy

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Received Date: January 21, 2021

Published Date: February 25, 2021

Abstract

Introduction: Generic substitution is championed, claiming health economic benefits, based upon lower costs and therapeutic bioequivalences. This ignores the potential that a change in the salt or excipient may effectively change the availability of the active ingredient. This has relevance when treating conditions with a narrow therapeutic index, as seen in the management of patients with epilepsy (PWE).

What is meant by generic equivalence: This paper specifically addresses generic medications as those compounds produced by other than the innovative research based pharmaceutical company and recognises that these need to satisfy bioequivalence parameters of being within 80-125% of the parent compound at the 90% confidence level. Different generic compounds are not tested against each other but only against the parent medication.

Narrow therapeutic index: Some conditions have a narrow therapeutic index, comparing the 50% efficacy (E50) and lethal doses (L50) and considered narrow if ≤ 2. The European Medicines Association reduced acceptable bioequivalence to 90-111% (12) for treatment with a narrow therapeutic index. It is acknowledged that each formulation may have altered absorption characteristics and solubility properties, leading to possible differences in efficacy and safety. Bioequivalence studies do not account for batch-to-batch potential variations nor possible drug interactions.

Relevance to the treatment of epilepsy: Antiseizure medications (ASM) only achieve of the order of 2/3 seizure freedom, indicative of suboptimal management and need for finesse requiring stability once seizure control is achieved. This can be affected by generic substitution, recognizing that the generic medication may not be identical and respect the narrow therapeutic index. There may be many generic formulations and problems may arise when substituting one generic compound for another, especially if one is at 80% and the other is at 125% bioequivalence, thereby effectively either doubling or halving the effective dosage. While prescribing physicians, in Australia, have the option of refusing the right to substitute brands, by ticking the appropriate box on the prescription, this is not always adhered to by the dispensing pharmacist.

Specific examples in epilepsy management: Noting elevated lamotrigine blood levels in PWE who were taking the innovator, parent compound, Lamictal®, with some necessitating intervention due to toxicity, it was discovered that the pharmaceutical company had changed manufacturers thereby marketing an generic as the parent compound, claiming Good Manufacturing Practices, confirming the suspicion that the excipient caused the elevated levels. A patient, admitted to hospital for an unrelated condition, was given a generic equivalent of Keppra®, resulting in halving the blood level thereof and facilitating breakthrough seizure.

Conclusions: Generic substitution, advocated on the basis of health economic benefits, may not realize same due to inherent risks when treating PWE. There is the risk of either toxicity or breakthrough seizures with foreseeable risk of harm and resultant potential litigation. Prescribing, using proprietary trade names, may obviate risk of substitution, even of one generic for another, if indicating that brand substitution is denied, although not all pharmacists respect this directive.

Introduction

Generic substitution is advocated on the basis of health economics [1]. The claim is reduction of the cost of health care, claiming bioequivalence between the generic substitute and the parent compound, upon which it is based [2]. This need not be the case, considering that a change in the salt that may be used [3] or the so-called 'inate' excipient, included in the generic, may affect the bioavailability of the active ingredient contained within the generic substitute [4]. This is of particular importance in illnesses with a narrow therapeutic index. Such conditions, typified by epilepsy, have a restricted range of therapeutic benefit in which therapy provides efficacy without resultant and unacceptable adverse effects [5]. Patients with epilepsy (PWE) are treated with anti-seizure medications (ASM), known to have a narrow therapeutic index requiring close monitoring. Control of seizures is the hallmark of acceptable treatment, without which there may be serious consequences, but this should not be at the cost of unacceptable, adverse events [6,7]. The paper to follow examines generic substitution for PWE.

What is Meant by Generic Equivalence?

A 'generic medication' may be a therapeutic agent marketed under its non-proprietary, approved 'trade' name, or it may be a medication, marketed with a different brand (proprietary) trade name [7] produced by another company, other than the innovator (research-based) manufacturer, claiming bio-equivalence to the parent compound upon which it is based [8]. The concept of "generic", for the purpose of this review, will be to denote a supposed bioequivalent medication, not necessarily the product of an innovative research-based pharmaceutical company but rather one designed to capitalize upon such innovation, towards the end of its patient protection, the purpose being to directly and financially benefit from such innovation and to essentially "copy" a successful therapy with a similar formulation, with identical active ingredient but different excipient or salt content. Generic equivalents can enter the market and be produced at potentially much cheaper cost, estimated to be 20-90% cheaper [9]. Some innovative pharmaceutical companies also market their original, innovative medication, identified with a different 'proprietary' trade name, as a generic equivalent, the purpose being that of financial expedience, designed to maintain market share [10].

Such generic compounds, unlike the original innovator, previously tested both in health volunteers and extensively trailed in phase I – III studies, need only show bioequivalence in a limited sample of health volunteers [11,12] possibly < 30 people but definitely < 100. Efficacy and safety, of the generic compound, should be within defined boundaries and demonstrate that the identical amount of active ingredient(s), delivered in identical dosage, via the same route of administration, achieves the same, or comparable, standards of drug availability [8]. Bioequivalence testing requires≤ 100 healthy volunteers to receive both the generic and parent medication, in a randomized sequence, with appropriate washout period between them [13]. Both before and after such administration, plasma concentrations are evaluated at regular, predetermined intervals. The identical active moiety, in both the generic and innovator, parent compound, must be compared in the same individual, making each subject his/her own control [13].

Demonstrating such bioequivalence relies upon parameters, such as peak plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC), confirming equivalence of the rate and extent of absorption of the active ingredient [13,8]. The FDA accepts bioequivalence if, at the 90% confidence interval, the ratio of AUC generic to AUC branded and Cmax-generic to Cmax-branded, for the average of the sample of participants lies between 0.80 – 1.25, namely the generic is between 80 –125% of the innovator, at the 90% confidence level for AUC and Cmax [13,8]. The inherent interpretation of this prerequisite, assuming there exists more than a single generic equivalent to the parent compound, is that the generic at 80% bioequivalence is also bioequivalent to that testing at 125%, despite there being >56% variation between the two equivalence interpretations. One generic compound is not tested against other generic medications based on the same innovator, parent compound.

Narrow Therapeutic Index

Medications used to treat some patients, such as patients with epilepsy (PWE), have a 'narrow therapeutic index'. This concept is calculated from the 50% efficacy dose (E50), compared with the 50% lethal dose (L50), and is considered to be narrow if found to be ≤ 2, emphasizing the necessity for true bioequivalence [14]. Recognizing same, the European Medicines Association limited the acceptable variation of bioequivalence to 90–111% [12] for those with a narrow therapeutic index which still reflects >23% variation.

While the maximal accepted variation is set at 80 – 125%, there are reports that the true variation may be as great as ~70 – 140% (namely 74 – 142%), equivalent to either 50 or 100% variation when comparing alternative generic formulations [15,16]. While the active ingredients, in the generic medication, may be identical to that within the innovative parent compound, it may be constituted in a different form (referred to, by the FDA, as pharmaceutical alternatives [17]). This may be represented by a different salt or ester of the complex of the active moiety or alternatively different dosages or strengths (such as salt with amlodipine may be besylate or camsylate, ferrous sulfate or gluconate) [17]. Each formulation may have altered absorption characteristics and solubility properties, leading to possible differences in efficacy and safety [17]. Bioequivalence studies do not account for batch-to-batch variability nor country-to-country variations. In complex diseases, such as Parkinson's Disease, patients may absorb the first daily dose more slowly, consequent to delayed gastric motility, and are often on multiple medications, including dopamine agonists, anticholinergic, monoamine oxidase inhibitors and antipsychotics,

which may have direct relevance when being treated with either a generic or innovator parent medication [18]. Drug interactions have not been adequately addressed by simple bioequivalence studies [18].

Relevance to the Treatment of Epilepsy

When treating PWE, appropriate ASM are reported to stop seizures in approximately two thirds of patients [19], indicative that available ASM remain suboptimal mandating a degree of finesse in management [20]and a need to respect appropriate dosing, with maintenance of a stable regime, without fluctuations, once stability is achieved. It follows that once there has been established seizure freedom, it is ill advised to modify the available dosages. Generic substitution need not equate to identical bioavailability to that of the 'parent medication' but rather should have efficacy demonstrated to be within minus 20% to plus 25% of the parent compound, upon which the generic medication is based [6,7]. Epilepsy, with its narrow therapeutic index relevant to the use of ASM, affects approximately 2% of the population [21]and there may be more than 10 generic substitutes for a given innovative parent compound, as is the case with lamotrigine.

'MIMS', a local listing of available medications in Australia, records 12 different formulations of the lamotrigine (APO Lamotrigine; Lamictal; Lamidus; Lamitan; Lamotigine GH; Lamortigine Sandoz; Lamotrust; Logem; Noumed Lamotrigine; Reedos; Sandoz Lamotrigine; and Tolemo DT) of which Lamictal is the parent compound. A similar situation applies to other ASMs, such as levetiracetam (MIMS cites: Levactam; Levecetam; Levetiracetam; Levetiracetam SZ; Levetiracetam AFT; Levetiracetam GH; Levi; and Keppra – the parent compound). The problem arises when one replaces one generic formulation for another. Assuming the first medication was minus 20% and the alternative was plus 25%, as demonstrated above, that amounts to almost doubling, or halving, the effective dosage, without deliberately changing the prescribed amount of ASM. This may have serious consequences for the unsuspecting patient who is totally reliant on his/her treating doctor who has prescribed the ASM or the pharmacist, a learned intermediary, who dispenses the medication.

Proprietary trade names, of the various agents, may be very similar, as per lamotrigine, for which five include "lamotrigine" within the registered trade name. Patients can be forgiven for assuming that they are identical to each other, a situation often reinforced by the dispensing pharmacist. Dispensing pharmacists, in Australia, have been accused of advocating generic substitution on the basis of direct financial gain, rather than specific consideration of the patient's needs [22]. There was a change in the Pharmaceutic Benefits Scheme which encourage the substitution of innovative parent compounds with generic alternatives [23]. From December 1994, pharmacists were given the option of generic substitution as part of their dispensing services [24], a situation raising some concerns within the Australian Medical Association [24]. It behaves the treating doctor who does not want such substitution to indicate that intension. In Australia, the government issued prescription pad, includes the option for the prescribing physician to nominate "Brand substitution (is) not permitted". The expectation follows that, once this box has been identified as pertinent, the dispensing pharmacist would respect and accommodate the doctor's wish to retain the prescribed brand name, irrespective of whether that be the innovative parent medication or a generic substitute, as stipulated on the prescription. This is far from universal [25], with some pharmacists totally ignoring this directive from the treating/prescribing doctor [25]. Such substitution has the potential to disrupt patient care for PWE as it may result in significant alteration in the bioavailability of what has, thus far, been an effective regimen. The direction, not to substitute, does not preclude the use of generic compounds but rather it should prevent the substitution of one generic medication for another, thereby obviating the identified risk of disrupting patient care by possibly 'doubling' or 'halving' the effective dosage, once the patient has been stabilized on the ASM being prescribed. This consideration would be enhanced if prescribing doctors adopted the approach of only prescribing medications using the proprietary trade names of the chosen medication(s), identifying these as specifically nominated generic ASM or the parent compound.

Specific Examples in Epilepsy Management

Lamotrigine (Lamictal®) blood levels were noted to be universally climbing, without the treating doctor having changed anything in the patients' regimen, with some patients, previously stable and well controlled, showing evidence of medication toxicity [26]. After confirming that the pharmacists had not substituted a generic alternative, the patients asked to produce their medication packaging, and the evaluative laboratory confirming there had been no change in measurement methodology, the responsible pharmaceutical company confirmed that it had changed the manufacturer which resulted in the inadvertent substitution of a generic compound, marketed as the parent medication, resulting in the increase in blood levels of the ASM, without any change in dosage or therapeutic regimen [26]. The pharmaceutical company insisted that the new manufacturer had totally complied with Good Manufacturing Practice (GMP) which demonstrates that the observed changes in blood levels, with some patients experiencing medication toxicity, was most probably not as a consequence of faulty manufacturing but rather as a direct result of altered bioavailability, consequent to inadvertent generic substitution with an altered excipient, despite maintaining equality of the active ingredient contained within the parent compound (Lamictal®) [26].

The take home message from this report was twofold: it underwrote the direct value of monitoring ASM blood level without which this observation may have gone unnoticed; and it further underwrote the need to take changes, as observed in this sample

of cases, very seriously and to pursue any unexpected results to determine the underlying cause. There was report of a PWE who was well controlled until being admitted to hospital where the formulary only included a generic of levetiracetam [7] and the patient, while in hospital, was treated with that generic and discharged from hospital on it without, advising the patient of the generic substitution [7]. She experienced a breakthrough seizure with her blood levels of levetiracetam being halved, resulting in her being accused of non-compliance. Neither she, nor her treating physician, were aware of the brand substitution with the hospital discharge summary only referring to the generic name of the medication and indicating that there had been no change in treatment, while the patient was in hospital for an unrelated problem, citing the same generic name both prior to and subsequent to hospital admission. It was only once the patient left the doctor and examined her medications that she realized what had occurred and brought it to the doctor's attention [7].

It is far from clear that generic medications interact identically with other preparations, prescribed for unrelated diagnoses. Some ASM are known to interact as may be the case with hormone replacement for which interactions have been reported, especially with lamotrigine [27]. This raises additional unanswered questions, when contemplating generic substitution, especially for PWE, but it definitely is not restricted to PWE. These considerations apply to any condition in which there is a narrow therapeutic index for which epilepsy is but one example.

Should untoward consequences follow the introduction of a generic substitute, this has the potential to also undermine any economic rationale that was anticipated by such substitution. Patients may experience loss of income, following loss of employment consequent to a seizure, resulting in a domino effect with serious social sequelae. Litigation is also a costly proposition if there should be related unwanted consequences directly caused, as a result of the generic substitution, and such consequences may result in cause for action in negligence should serious issues arise, such as death or injury, which might directly be caused by changes in the therapeutic regimen as a result of generic substitution.

Conclusion

Generic substitution, advocated on the basis of improved health economics, may not realize same, particularly for patients with illnesses for which there is a narrow therapeutic index, such as PWE. There is the risk of potential harm with patients experiencing either toxicity or breakthrough seizures which may initiate a domino cascade of serious consequences. Despite the option to nominate that brand substitution is not permitted, some pharmacists have ignored this directive, placing patients at risk. It behoves prescribing physicians to use proprietary trade names, when writing prescription, to further protect against brand substitution, be it from the innovator or between various forms of generic alternatives of which there may be many.

Acknowledgement

None.

Conflict of Interest

No conflict of interest.

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