http://jmscr.igmpublication.org/home/
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossref DOI: https://dx.doi.org/10.18535/jmscr/v13i01.08

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Review Article

Substituting Brands: A Case Study of DEKSEL an "Evidence-based Formulation"

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Abstract
Brand substitution should not be encouraged because of various reasons like drug content, formulation stability, difficulty in establishing bio-equivalence, and above all patient and prescriber familiarity with a specific brand etc., as this all may have a bearing on treatment outcome. A wide range of variation is seen as far as drug content of a formulation is concerned, in the Indian market. This wide variation in drug content might result in either inefficacy or toxicity with the drug/ formulation. In this review we are going to discuss about the necessity of using the prescribed brand and not substituting them with others with some examples.

Keywords: *Brand, Cost, Efficacy, Safety, Substitution, Generic.*

Introduction

Two formulations may not be therapeutically equal even though they are bioequivalent and therefore, should not be freely interchanged.

A substantial part of India's population fulfils its healthcare needs from government run facilities which are free, contributory or highly subsidized. Use of medicines forms a large part of this healthcare set-up. As the number of medicines and brands available in market continue to increase, it is usual for pharmacy to substitute a brand instead of the prescribed brand if the prescribed brand is not available. This type of substitution is known as "brand substitution". The factors which contribute to this practice of substitution include cost of the medicine, belief that the "substitute" is better than "what is prescribed", and a very high number of brands being available in market where it is not possible to stock all in the pharmacy[(1)].

Switching from one brand to another has become a common cost-containment measure. Although this is an important goal for health-care systems around the world, the impact of this practice on patient outcomes must be carefully evaluated[(2)]. A

report on the findings of an extensive study in which generic antiepileptic drug treatment was linked to greater total medical service and direct health care expenses than branded drug use, despite the fact that generic pharmaceuticals were less expensive. The overall annual health care costs for patients receiving therapy with generics were 25.8% higher than for patients treated with brand-name products, because of higher health care costs[3].

Furthermore, it should be noted that though an increased use of cheaper generic prescription drugs as an alternatives to more expensive branded products is encouraged by many including healthcare authorities, unlike the innovator, comprehensive clinical trial evidence does not exist for generic drugs. In fact, there are instances where generic products have been approved by the regulators even without a bioequivalence study. In essence, the bioequivalence of two products is determined by their relative comparability in terms of pharmacokinetics and pharmaceutical equivalence. However, certain limitations apply to the bioequivalence requirements for generic formulations. First, these investigations are carried out on healthy adult volunteers rather than patients with the therapeutic indication for which the medicine is utilized. As a result, the obtained data do not represent any changes caused by disease, gender, or age[4, 5]. Also, there can be differences in formulation as it is not a regulatory requirement that the "inactive" ingredients in two formulations be identical[6]. However, small a difference may be, let's say in terms of impurities in the excipients used, can alter the properties of a medication and lead to unexpected adverse effects on drug absorption, bioavailability, efficacy, and safety[7].

Another restriction of generic substitution is that the substitute's appearance may vary. The changes in shape, size, and colour of the dosage form may cause the patient to assume incorrect dosing and increase the likelihood of noncompliance. Considering the above limitations, this approach should be followed with caution and patients must be advised to seek medical attention sooner in case they sense something amiss about their medication whenever they have been dispensed a substitute[1].

Brands: Are they all equal!

In the majority of patients and for the majority of medications, switching brands is a means to obtain similar therapeutic benefit at considerably lower costs, without any problems. However, several researchers have reported patient concerns related to generic medicines[8]. Many investigations center on the impact of the relative cheapness of generic medications on attitudes toward effectiveness[9], with some reports showing that patients or prescribers did not perceive a generic drug to be as effective, or work at all, in comparison with the original brand prescribed. Generic switching has the potential to interfere with a patient's usual medication regimen and impact adherence, which can affect clinical and safety outcomes, and the total costs of care.[10] Brand substitution should not be permitted because of other various reasons like patient safety, formulation stability, difficulty in establishing bio-equivalence, patient familiarity with a specific brand which might cause adverse effect because of the brand substitution, etc. With the intention to make our point clearer, let us consider the example of DEKSEL Nano Syrup here.

DEKSEL: Correction of Vitamin D status

A vitamin D3 nano-delivery system designed utilizing AQUEOL™ Technology, developed and patented by Pulse Pharmaceuticals Pvt. Ltd., Hyderabad with a brand name of DEKSEL is developed as a suitable delivery system for appropriate and accurate delivery of Vitamin D3. It differs from other existing vitamin D3 formulations in being an "evidence-based formulation" as it has undergone extensive

research in subjects of all age-groups and both gender, whether healthy or otherwise, and with multiple dosing schedules.

In few of the studies, carried out and reported by various investigators, the drug plasma concentration of 25(OH)D was found to be higher in case of DEKSEL than that of other marketed products of Vitamin D such as, syrups, tablets, capsules, granules, orally disintegrating strips and injections. Associated with this higher level was a significant improvement in the therapeutic outcome in the DEKSEL group including reduction in pain intensity, disability and others [11-14].

In an unpublished work undertaken by Tripathi et al, the rise in vitamin D levels with DEKSEL as compared to granules and soft-gel capsules was 30% and 35% higher, respectively[15]. The data has been shown in Table 1.

Table 1 Impact of Three Vitamin D3 Formulations on Change in 25(OH)D levels over a period of 12 weeks [15]

Group	Formulation	25(OH)D levels (Mean ± SEM ng/ml)							
		Baseline		4 week		8 week		12 week	
I	Syrup	11.79±0.55		34.99±1.54		44.16±1.47		49.05±1.38	
II	Capsule	12.67±0.70		28.19±1.27		35.24±1.20		38.04±0.95	
III	Granule	12.11±0.62		27.42±1.41		33.57±1.24		36.58±1.13	
		Compared group	P	Compared group	P	Compared group	P	Compared group	P
ANOVA with Post Hoc Bonferroni test		1 vs 2	0.973	1 vs 2	**0.003**	1 vs 2	**0.000**	1 vs 2	**0.00**
		1 vs 3	1.0	1 vs 3	**0.001**	1 vs 3	**0.000**	1 vs 3	**0.00**
		2 vs 3	1.0	2 vs 3	1.0	2 vs 3	1.0	2 vs 3	1.00

Impact of the Formulation

The greater rise in vitamin D level is desired, to have a more cost-effective and less frequent therapy. Furthermore, the extra-skeletal benefit of vitamin D like positive impact on neuro-endocrine or inflammatory diseases warrant a much higher level than what is required for skeletal benefits[16]. These later aspects assume significance in light of the fact that vitamin D today is not considered a "mere vitamin" but a hormone with a positive impact in diseases of kidneys, skin, brain, heart and blood vessels[17].

The AQUEOL™ Technology which has been used in the development of DEKSEL involves creating nano-particles of lipids entrapping/ encapsulating vitamin D3. The surface of these nano-particles is decorated with ligands which not only impart stability in the varying gastro-intestinal pH and to the lytic enzymes, and but, also to degradation by environmental factors like heat, humidity and oxidation. Also, at the same time accurate and complete dose delivery is ensured by the negative zeta potential imparted to the surface of nano-particles. These formulation characteristics ensure consistency and predictability of outcomes with DEKSEL, making it a truly "evidence-based formulation".

When it comes to other generic formulations, the drug content is seen to vary widely. In a study conducted by Khadgawat, et al, they measured cholecalciferol (Vitamin D3) content of 14 commercial preparations available in Indian market by high-performance liquid chromatography and found only 4 (28.57%) to be within the acceptable ranges of 90% to 125% of drug content as defined by Indian Pharmacopia, while rest had higher or lower content than the label claim. The observed percentage variation in cholecalciferol content varied from -91% to +65%. This variation has many clinical

implications as it may lead to either under treatment or vitamin D toxicity[18].

Legal Consequences Attached to Brand Substitution

Patients who receive a generic substitute without being informed of the possible risks and suffer grave repercussions may file a lawsuit for negligence in medicine. This obligation falls on the institution, physician, or pharmacist who fail to warn. Professional misconduct may also occur when a pharmacist disregards a doctor's advice. Internationally, litigation against manufacturers was unsuccessful in the USA, but it is still feasible to sue prescribers or dispensers. US physicians have the right to refuse brand substitution, even while generic substitutes are preferred. Other jurisdictions support generics as well; some even mandate them, although the majority give consumers the choice to decline brand substitution [19].

In India presently, the governing document in the context of prescribing of all forms of medicines, the Drug and Cosmetics Act 1945 and Rules as amended makes no mention of generic or therapeutic substitution[20]. The website of Pharmacy Council of India hosting the Pharmacy Practice Regulations, 2015 considers substitutions (of any kind) without the consent of Registered Medical Practitioner as malpractice and liable for disciplinary action[21]. As a consequence, any substitution in India, whether necessary owing to the non-availability of the recommended brand or medicine, should only be made with the agreement of the prescribing physician.

Conclusion

There have been cases highlighting the potential of a brand to alter patient's disease management, without changing the amount of active medication present in the formulation. This is generally due to the use of a generic formulation utilizing different excipients. Brand substitution is certainly not advisable when dealing with patients on hormones, anticonvulsants, anticoagulants, asthma medications, cardiovascular agents, psychiatric drugs especially mood-stabilizers and antipsychotics, to name a few.

The musculoskeletal effects of vitamin D are well-established. Today we know there are several tissues that have vitamin D receptors but do not participate in calcium or phosphorous metabolism. Pleiotropic effects of vitamin D include regulation of hormone secretion, cell proliferation and differentiation, and immune function[22]. Debates on the non-calcemic and the extra-skeletal actions of vitamin D appears to be non-ending, and revolves around serum vitamin D level, study designs, and negative results. In addition, meta-analyses of vitamin D supplementation trials have failed to show clear improvements in various clinical conditions, thus suggesting that the link between vitamin D deficiencies and for example, cardiovascular disease may be an epiphenomenon. The controversy has a relation with the level of serum vitamin D required to reduce the incidence of or to treat extra-skeletal conditions. The adequacy of vitamin D levels are arrived at from the levels required for promoting calcium absorption from intestines and to reduce bone resorption. The prolonged and severe deficiency, vitamin D levels of <20nmol/L, increases the risks of osteomalacia, levels well above these are required for addressing extra-skeletal issues. In response to a given dose of vitamin D supplement, the increase in vitamin D concentration has been reported to differ between individuals[23]. This could be because of wide inter-individual variations in the population. Workers have shown the importance of body weight for the dose-response relationship with circulating vitamin D levels. They have demonstrated a 34.5% of variation in the circulating vitamin D can be explained by body weight, type of supplement, age, calcium intake and basal concentrations, leaving approximately 50% of the variations to unknown factors[23].

The unknown factors apart from daily sun exposure may also be formulation-related, and for one may include need to consume supplement with fat-rich food or milk for better absorption and bioavailability. In addition, the stability of formulation during the shelf-life may affect the amount of vitamin D delivered vis-à-vis label claim of the brand/ formulation. With the huge variability in vitamin D content of various marketed formulations during the shelf-life[18, 24], the reproducibility of benefits with supplements become suspect, and therefore, the evidence becomes equivocal. Hence, we firmly believe brands should not be substituted as the expected outcome of treatment may get compromised.

Following the Indian Prime Minister's statement that physicians should be prescribing generic medications, the Indian Medical Association has reaffirmed their backing of the initiative. However, they have rightly stressed the need for government to ensure the quality of medication. Though the affordability of the prescribed medication is a desirable attribute yet it cannot be the sole measure determining prescription.

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