Generic Medicines - How confident should we be?

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Introduction

The scientific and clinical robustness of bioequivalence is frequently challenged by health professionals, patients, media and sections of the pharmaceutical industry. Generic medicines rely on being bioequivalent to gain a share of the market once a branded product reaches the end of its patent life. In all countries, the lower prices of generic products provide an important opportunity to reduce the costs of healthcare without reducing quality. In countries such as Fiji with an essential medicines list, the products that are sourced are frequently generic brands. It is therefore essential that health professionals, governments and the broader community are confident in the quality and clinical effectiveness of generic medicines.

Bioavailability and bioequivalence

The concept of bioavailability and bioequivalence is based on biopharmaceutic and pharmacokinetic principles. Relative bioavailability can be determined for an oral, intramuscular or subcutaneous formulation compared with its IV availability, using Cmax (the maxiumum concentration achieved in plasma) and AUC (area under the concentration-time curve) to quantify overall exposure to both preparations. If the log-transformed 90% confidence interval (90% CI) of these two parameters fall within the range 0.8 to 1.20 (80 to 120%) then the two products are considered to be bioequivalent.

Bioequivalence is more difficult to establish if there is large variation in bioavailability within the same individual on different occasions or between individuals. Those who discredit the validity of bioequivalence often interpret the 90% CI limits as implying 80-120% bioavailability and subsequently question the clinical relevance of the measure. This is scientifically incorrect and in fact in order for Cmax and AUC to fall within the 90% CI means that the relative difference in bioavailability can be no more than approximately ± 5%.[1]

Generics

The World Health Organisation (WHO) describes a generic medicine as a pharmaceutical product, usually intended to be interchangeable with an innovator product, that is manufactured without a licence from the innovator company and marketed after the expiry date of the patent or other exclusive rights.

Registered generics of small molecule drugs are bioequivalent with the appropriate innovator product, implying that the rate and extent of absorption will be similar. If it can be assumed that the systemic drug concentration is the determinant of the drug concentration at the drug's site of action then the generic product should yield the same profile of positive and adverse effect. This is the basis of registration for generic products in Australia and many other developed countries. Countries with fewer resources may use the The WHO Certification Scheme, an international voluntary scheme devised to enable countries with limited regulatory

capacity to obtain partial assurance from exporting countries concerning the safety, quality and efficacy of the products they plan to import. This provides confidence that Good Manufacturing Practice (GMP) standards are met. Additional information is required to address bioequivalence, typically a requirement that the product is registered in a country with the regulatory capacity to assess this.

Studies to establish bioequivalence for the purpose of registration of a generic may have additional local country-specific requirements. In Australia, for example, the regulator (TGA) generally requires the comparator (innovator) product to be sourced from Australia unless the comparator from overseas is similar in composition to a local product. Other considerations include whether the drug formulation is not complex in a biopharmaceutic sense (for example, if the product is a spontaneous release dose form or if absorption is dissolution-rate limited).

Generics are much cheaper to market as they do not require the same level of research investment as a new innovator product. This makes generics attractive to many governments and third party payers. The generics industry is a profitable sector of the global pharmaceutical industry, prompting some innovator companies to acquire their own generics business to limit competition from the 'true' generic companies. There have also been concerns about innovator companies attempting to extend patent lives of their products, via 'evergreening'. On the other hand, the generics industry is accused of discounts to monopoly buyers such as governments that limit the influence of normal market forces.

Switching/substitution

Switching from an innovator to a generic product, where that product has been shown to be bioequivalent is a therapeutically sound decision. Not all prescribers are convinced that generics are equally effective and may often influence the extent of switching or substitution, particularly in the private sector. This may mean that patients are incurring considerably more expense for no greater benefit.

Innovator companies would like to minimise switching to maximise prescribing of their innovator products, while generics manufacturers encourage higher rates of switching, and governments prefer generic substitution to drive down drug costs. Thus innovator companies have been known to place advertorials for drugs like anti-epileptics[2] to warn of 'dangers' of switching for conditions which may be inherently clinically challenging to manage. Prescribers sometimes become advocates for not switching. All this creates suspicion in the minds of patients about the use of generics which may be seen as inferior alternatives.

There are other genuine issues to consider when deciding to switch to a generic alternative. For example switching may create confusion for the patient and lead to reduced compliance or a period of unpredictable management in a patient already stabilised on a particular product. This arises because of issues with different size and colour, labelling that does not accentuate the active ingredient and patient information leaflets for the same active ingredient that are seemingly unrelated. It is essential for clinicians to give these issues equal weight to bioequivalence considerations when recommending the switch to a generic product.

The future

Doctors, other prescribers, pharmacists, innovator and generic companies and governments need to provide objective advice on bioequivalence and substitution by generics. Only then will patients accept recommendations knowing that these are based on scientific principles and on rational

References

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Solomon Islands graduates with Dr Rodgers and Dr Pikacha
Fiji School of Medicine Graduation 2004

(Source: Fiji School of Medicine Library)