what is bioequivalence?

Bioequivalence is defined as the absence of a significant difference in the rate and extent of absorption into the systemic circulation, of two pharmaceutically equivalent medicines, when administered in the same dose under similar conditions. Therapeutic effect (in terms of efficacy and safety) of bioequivalent medicines is considered to be essentially the same.[1]

The rate and extent of absorption of an active ingredient in a medicine is defined as its ***bioavailability***.[2] Pharmacological response is related to the concentration of an active ingredient at the site of action (receptor site). Drug concentrations cannot usually be measured at the site of action so it is assumed that the drug concentration at the receptor site is in equilibrium with that in the blood. Most bioavailability studies therefore measure the drug concentration in blood. The bioavailability of the active ingredient is what determines a product's clinical efficacy.[3]

Bioavailability is measured using three main parameters – the area under the plasma drug concentration versus time curve (AUC), the maximum plasma concentration (C_{max}) and the time to reach maximum concentration (T_{max}).

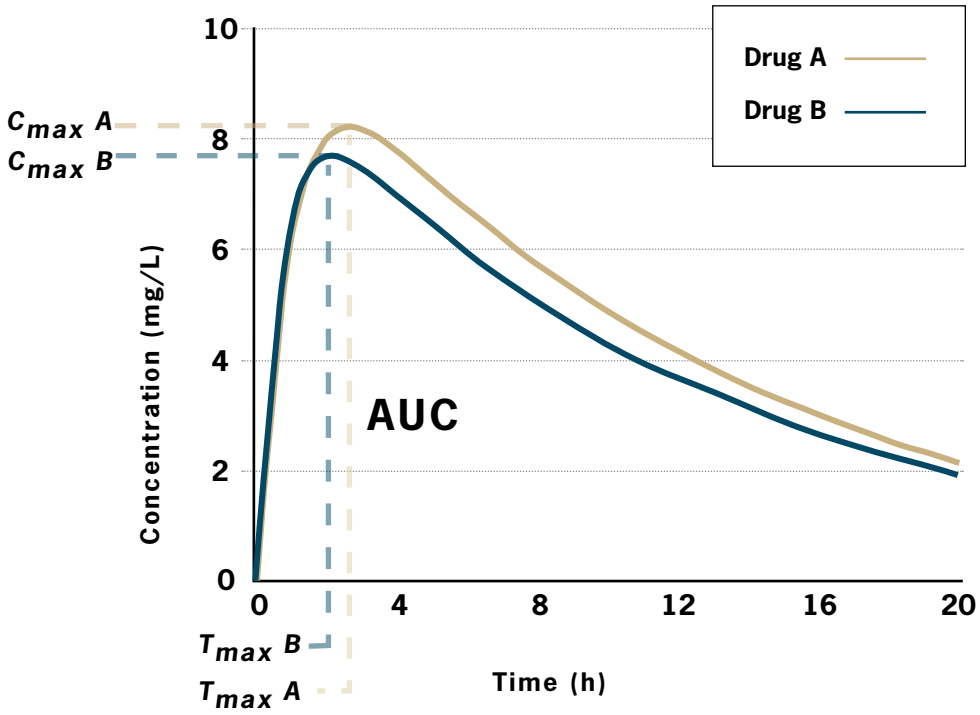
Bioequivalence can be determined by a comparison of the bioavailability of two formulations of the same drug given at the same dose. The generic (or new brand) is always compared with the innovator (or reference) product. Wherever possible, both products are tested in the same group of subjects in a randomised cross-over study. The two medicines may be said to be bioequivalent if the 90% confidence intervals for the ratios of the geometric means (generic:innovator) of the AUC and C_{max} fall between 0.8 and 1.25 (80% and 125%). The T_{max} of the generic and innovator version of the drug must also be similar and there should not be a marked difference in inter-subject variability.[2]

In practice, the generic company tries to achieve a ratio of bioavailability (AUC,C_{max}) close to 1. If the ratio is closer to 0.8 or 1.25, then the data would have to be very uniform for the 90% confidence intervals of the ratios to lie in the 0.8 to 1.25 range and therefore achieve bioequivalence.[2]

According to FDA guidelines for bioequivalence, a generic copy of a drug must contain identical amounts of the active ingredient in the same dose formulation and route of administration. Some inactive ingredients (excipients) are allowed to differ but must occur in a similar ratio to the active ingredient as that observed in the innovator drug.[4]

Simulation of a drug concentration versus time curve for two drug products

Adapted from Birkett D, 2003



C_{max} *maximum plasma drug concentration,* T_{max} *time required to achieve a maximal concentration,*

AUC *total area under the plasma drug concentration-time curve*

Drug A is the innovator product and Drug B is the generic product.

Drug A: C_{max} = 8.1 mg/L; T_{max} = 2.6 h; AUC = 124.9 mg.h/L

Drug B: C_{max} = 7.6 mg/L; T_{max} = 2.1 h; AUC = 112.4 mg.h/L

The ratio of areas (generic:innovator), and therefore the relative bioavailability, is 0.9. To be accepted as bioequivalent, the 90% confidence intervals for the area ratio would need to fall within the range 0.8–1.25.

How is bioequivalence regulated in NZ?

Adapted from Medsafe Bioequivalence Guidelines.[1]

In New Zealand, Medsafe is responsible for determining that a generic copy of a drug is bioequivalent to the innovator version, before it is released onto the market. Medsafe bases bioequivalence testing guidelines on overseas regulations and on what they regard as best current international practice.

Guidelines from the following regulatory authorities are currently used by Medsafe:

- European Commission Rules Governing Medicinal Products in the European Community Volume III and CPMP Notes for Guidance
- United States Food and Drug Administration (FDA)
- Australian Therapeutic Goods Administration (TGA)
- Therapeutic Products Directorate, Health Product and Food Branch, Health Canada
- World Health Organisation (WHO)

Any company wishing to manufacture or distribute a generic version of an innovator drug in New Zealand must submit a Comparative Bioavailability Study report, in compliance with international standards, to be considered by Medsafe.

Variables included in a bioequivalence study

Ideally the bioavailability of systemic medicines should be measured using blood plasma or serum concentration of the active ingredient. Where this is not possible, the quantity of the active ingredient or its metabolites excreted in urine, or pharmacodynamic variables (e.g. heart rate) may be measured. However this results in a less accurate measure of bioavailability.

Single dose studies are appropriate in most cases. A steady-state study may be used in certain circumstances including; medicines with a long terminal elimination half-life, highly toxic medicines, modified release products, medicines which induce their own metabolism, enteric coated preparations (if coating is innovative), combination products, medicines that exhibit non-linear pharmacokinetics and medicines which are likely to systemically accumulate.

Bioavailability studies are usually carried out in healthy adult human volunteers of both genders (where appropriate), of average weight and between eighteen and sixty years of age. The number of subjects needed should be based on the number required to reach statistical significance. The acceptable number of subjects is usually greater than twelve and less than forty.

Experimental conditions should be standardised including gastrointestinal conditions, posture, physical activity and timing of samples. The test formulation of tablets or capsules should originate from a batch of at least 10% of full production scale or 100 000 units (whichever is greater) and should be manufactured using full production scale equipment. The mean potencies (actual drug content) of the generic and innovator product should not differ by more than 5%.

What are the main issues with the validity of bioequivalence?

The introduction to the market of a generic drug, especially when replacing the innovator counterpart, is often met with suspicion and concern by health care providers and patients. Concerns mainly surround the issue of bioequivalence and whether use of the generic drug will result in unforeseen effects. Generic drugs are often perceived as being inferior due to their lower cost and the lesser extent of development that goes into manufacturing these drugs compared to the innovator version.[5]

The measure of bioequivalence

There has been some criticism of the use of the 80–125% reference range for bioequivalence in drugs which have a narrow therapeutic range such as carbamazepine, phenytoin and digoxin.[6] A relatively small change in systemic concentration of these drugs can lead to a markedly different therapeutic response or even toxicity. Warfarin also has a narrow therapeutic range and bioequivalence has not been established between the two main brands of this drug. Therefore the two variants are not considered interchangeable.[2] Similarly, concerns have been raised over using this reference range for drugs with a wide therapeutic range, for example antibiotics and antihistamines.[5]

Testing bioequivalence in a "normal and healthy" population

When an innovator drug is developed, evidence is required of its pharmacokinetics, efficacy and tolerability in volunteer study subjects as well as the target population. However the development of a generic equivalent requires only evidence of its bioequivalence with the innovator drug in the study subjects. This leaves some doubt as to whether the generic drug would perform differently in a patient population, taking into consideration factors such as co-morbidities, concurrent prescriptions and physiological factors such as differences in first pass metabolism, gastric pH and bacterial flora.[5]

Older patients may also experience unique difficulties with a switch to a generic drug. Many suffer from multiple medical conditions and receive multiple drugs which may affect pharmacokinetic properties. Physiological changes associated with ageing may also affect drug absorption, distribution, metabolism and excretion.[7] Bioequivalence is generally tested in healthy subjects under the age of sixty.

Use of single-dose studies and the potential effect of excipients

Bioequivalence studies most often involve single doses of a drug.[1] In clinical practice, most drugs are administered in multiple doses and require maintenance of a steady-state. The maximum drug concentration attained at a steady state is often higher than that achieved after a single dose.[5] It is possible that excipients used in the generic formulation (preservatives, pH adjusters, thickening agents etc) could affect the absorption, and metabolism at steady state without producing these differences from a single dose.[8] Excipients can not always be considered inactive or inert.[3] Some patients could have individual reactions or sensitivity to a change in excipient.[2] The potential effects of drug accumulation may also not be seen with a single dose study.

Has the validity of bioequivalence been tested in NZ?

Adapted from Medsafe Media Release.[9]

In 2002 a drug company brought a challenge to the High Court against Medsafe's procedures in evaluating the safety and efficacy of a generic version of the drug, paroxetine mesylate. The company claimed that Medsafe had not followed its own procedures for assessing the generic drug and that clinical trials may be required to confirm that paroxetine mesylate was safe and effective.

The court case reviewed Medsafe's handling of the process for approval of the generic drug. This was supported by chemical, pharmaceutical and bioequivalence data which established the product's quality, safety and efficacy. The data showed that the generic version of paroxetine did not solely rely upon pre-existing toxicological data for the innovator product. The data also demonstrated bioequivalence between the generic and innovator product, with respect to the same amount of active substance being absorbed to the same extent.

The High Court rejected all grounds of challenge by the drug company and found in favour of Medsafe. It was ruled that the evaluation process for the generic drug was robust and followed correctly and that Medsafe properly considered all information about the drug.

The outcome of this challenge can provide reassurance that Medsafe applies rigorous procedures to evaluate the safety and quality of medicines before they are made available to the public.

So what does this mean?

There is no recent documented evidence of proven failure of a generic formulation of a drug, due to issues of bioequivalence. There are some reports of therapeutic inequivalence, however most of these cases were determined to likely be the result of progression of disease rather than lack of bioequivalence of a generic and innovator formulation of a drug.[10]

Given the fact that distributors of generic drugs in New Zealand must provide scientific evidence of bioequivalence in accordance with Medsafe's guidelines, it can be assumed that if a generic drug is on the market, it can be considered therapeutically equivalent to the innovator counterpart, unless classified as non-interchangeable.

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