Davi Rumel

Sérgio de Andrade Nishioka

Adélia Aparecida Marçal dos Santos

Comments

Drug interchangeability: clinical approach and consumer's point of view

ABSTRACT

The rational construction of an essential drug list, considering the patient's need, drug safety, availability and the best cost-benefit ratio, is based on drug safety, efficacy and quality. However, in daily practice, the prescriber's decision is mostly influenced by drug effectiveness, following criteria that increase adherence to the treatment, such as relative drug toxicity, convenience, cost and prescriber's experience. In addition, frequent launching of new molecules for the same therapeutic indication, together with wide publicity targeting prescribers, interferes with the decision-making process. Similarly, the bonuses offered by the industry for over-the-counter drug sales interfere with the consumer's choice. The confrontation between known human biological variability and the knowledge that there is no absolute similarity between drugs of the same therapeutic class, or even generic drugs, has an impact on the prescriber's drug list, which should include the concept of first and second choice drugs. Prescribers' unfamiliarity with these subjects is a determinant factor for irrational drug use: a public health issue. The objective was to introduce to drug prescribers information that can help them building up a rational drug list for their patients, based on the National Health Surveillance Agency (Anvisa) experience of drug regulation.

KEYWORDS: Prescriptions, drug. Drug utilization. Drugs, generic. Similar drugs. Physician self-referral, ethics.

Agência Nacional de Vigilância Sanitária. Brasília, DF, Brasil

Correspondence:
Davi Rumel
Agência Nacional de Vigilância Sanitária (Anvisa)
SEPN 515, bloco B, 3º andar, sala 4
70770-502 Brasília, DF, Brasil
E-mail: davi.rumel@anvisa.gov.br

INTRODUCTION

There are thousands of active substances and combinations in the drug market and new options are offered daily to prescribers, what makes it difficult the choice of the most suitable drugs for each patient. To diagnose the patient's therapeutic needs and to identify the best cost-benefit drugs available require skills that are not provided to health providers during their training.

This study aimed at presenting to drug prescribers information that can help them building up a rational drug list for their patients, based on the Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency - Anvisa) experience of drug regulation.

Drug registration is based on drug safety, efficacy and quality. Drugs are classified as: new, similar, generic, phytomedicines, homeopathic, biological and specific. New (synthetic or biological) drugs include those with a mechanism of action and/or therapeutic indication different from other active substances, and those with original active substances with an already existing indication – "me-toos". Generics are copies of new drugs with expired patents (reference drugs) that "borrow" efficacy and safety results from clinical trials of the original product by means of showing pharmaceutical equivalence (in vitro) and bioequivalence (in vivo). Similar drugs are copy drugs available before the Generic Drug Law (1999) that from May 2003 on have to have similar performance to generics in the same drug tests at the time of register renewal. Renewal is made every five years on the same calendar day of its registration. It is important to know these drug characteristics due to potential interchangeability* of products that are therapeutically equivalent.

Therapeutic equivalence can be determined by: 1) a clinical trial showing similar efficacy and safety for test and reference drugs; 2) a clinical trial showing the same measurement of a pharmacodynamic property for both drugs; 3) a relative bioavailability test, in which pharmacokinetic curves of test and reference drugs are compared and bioequivalence is shown; 4) or in vitro tests showing pharmaceutical equivalence and the same pharmacological and technical specifications of test and reference products.

The Pan-American Health Organization (PAHO) and the United States Food and Drug Administration (FDA) have a similar definition for therapeutic equivalents.[2]

Interchangeability includes the choice of a drug between two or more drugs targeted for the same therapeutic or prophylactic purposes. Drugs with similar pharmacodynamic actions are often grouped within the same therapeutic class, which is helpful for learning clinical therapeutics. Drugs in the same therapeutic class do not necessarily ensure the same efficacy and safety but there are many examples that scientifically show otherwise.[11]

Anvisa requires evidence of therapeutic equivalence to all oral prescription drugs by demonstrating their bioequivalence through in vivo relative bioavailability test. For drugs not administered orally and non-prescription drugs therapeutic equivalence is shown by in vitro pharmaceutical equivalence only. Once approved in these tests, products are considered generics, and can be interchanged in pharmacies, unless otherwise clearly stated by the prescriber (physician or dentist).

For rationally prescribing drugs and their interchangeability a method of drug selection, such as that recommended by the World Health Organization (WHO), is required.[15] WHO recommends that prescribers are trained to select a set of drugs needed in their practice and that they stick to this drug list, being completely familiar with their use in their patients.

In addition to this proposal, the Clinical Practice and Therapeutic Guidelines have been widely promoted as a major source for the construction of a prescriber's drug list. It is also pertinent, in the selection process, to be familiar with the essential drug lists recommended by WHO** and the Brazilian Ministry of Health*** developed by specialists who identify low-cost highly effective drugs for high prevalence diseases.

When there are no therapeutic standards, consensus between specialists represents an advance in comparison to individual initiatives, as long as it is not based on pharmaceutical leaflets and package insert information published in commercial therapeutic guides commonly available in Brazil.****

---

*Intercambialidade é um termo usado em engenharia para a troca de um produto original por outro fabricado por um concorrente, desde que atenda às mesmas especificações técnicas e tenha o mesmo desempenho. Em farmacologia a Intercambialidade indica a possibilidade de substituição de um medicamento por outro equivalente terapêutico receitado pelo prescritor.
**Organização Mundial da Saúde. WHO Model List of Essential Medicines. Disponível em http://www.who.int/medicines/publications/essentialmedicines/en/index.html [acesso em set 2005]
***Ministério da Saúde - RENAME, 3° edição, 2002. Disponível em http://www.opas.org.br/medicamentos/docs/rename02.pdf#search=%22RENAME%22 [acesso em set 2006]
****Daisson JT. Influência da propaganda da indústria farmacêutica na prescrição de medicamentos em escolas de medicina: a experiência em Tubarão, Santa Catarina [dissertação de mestrado]. Tubarão: Universidade do Sul de Santa Catarina; 2005.

Drug interchangeability within the same therapeutic class

Specialists estimate that, for each drug, on average 30% of the patients experience benefits, 30% do not experience any major benefit, 10% only experience side effects, and 30% discontinue treatment because they have either no benefits or side effects.[14] The genetic variability of drug receptors and drug metabolizing enzymes partially explains such interpersonal variability.

Interchangeability in the prescribers' decision-making process is affected by effectiveness (results in actual conditions), not by efficacy differences (result under controlled conditions), taking into consideration criteria that increase treatment adherence, like relative toxicity, convenience of the administration route and dose intervals, costs, and experience of use.

For example, statins and angiotensin-converting enzyme (ACE) inhibitors have the same efficacy after achieving the maintenance dose for a stable desired clinical effect.[7] Given their wide range of side effects, only the prescriber who follows up a patient can properly replace a drug. In a recent review comparing two thiazide diuretics,[5] they both have shown the same effect on lowering blood pressure, notwithstanding their different pharmacokinetics and pharmacodynamics. The authors suggest the occurrence of a phenomenon known as "dose equivalence" between drugs of the same therapeutic class.

In the search for information, publication biases highlighting differences between drugs of the same therapeutic class prevent interchangeability.[9] In a study[6] which title suggests lack of interchangeability between two drugs of the same class, it was shown that both drugs were well tolerated and had similar rates of adverse events. Some industries promote products such as sodium diclofenac and potassium diclofenac, virtually the same in terms of pharmacokinetics and pharmacodynamics.

The interchangeability in the prescriber's decision-making process is also influenced by the introduction in the market of new molecules for the same therapeutic indications ("me-too") largely advertised, suggesting that the new product is better than the ones available in the market.

From a regulatory point of view, one can hardly refute that a "me-too" might bring additional benefits to certain patients. This type of drug can make the market more competitive, increase drug access and generate better understanding of a therapeutic drug class and its usefulness in different populations. Only time and drug surveillance could establish the effectiveness and safety profile of each drug. A randomized, double-blind study compared the efficacy of two "me-too" statins in diabetic patients.[3] This study, conducted many years after these statins were marketed, showed that one of them had higher efficacy and lower need for dose adjustments than the other for this subpopulation of diabetics.

Such controversies can be solved by head-to-head clinical trials, which are rarely conducted as they can eventually show that a company's product is inferior to the competition. Pharmacoepidemiological and pharmacoeconomic studies are alternatives as they are aimed at identifying products of the same therapeutic class with lower safety or lower cost-effectiveness to support regulatory agencies or health insurance companies' determination of taking a drug out of the market or replacing it. These studies, usually sponsored by health insurance companies or governmental agencies, require large and reliable databases and are subject to prescription bias – i.e., the association between prescribing a drug and disease severity. That is, if prescribers systematically choose a given drug for more severe patients, this drug will be associated with more severe adverse events. This bias can be partially controlled by multiple logistic regression data analysis. When results of risk-benefit studies comparing drugs are disseminated among physicians, the time less effective drugs are marketed is reduced. An example of a head-to-head trial is The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[1] that included 33,357 participants in 623 health facilities in the United States. As the Clinical Practice Guides recommend starting anti-hypertensive treatment with a diuretic or beta-blocker or ACE inhibitor drug, investigators randomized double-blindly groups of patients for each drug. Eight years later it was found that, for several surrogate endpoints, there was no difference between the groups, but for primary endpoints, the diuretic drug was more effective to prevent deaths due to stroke and congestive heart failure. It is worth highlighting that these three products have different costs and that the one that is longer in the market is the cheapest one. Although this study was published in 2002, clinical practice guides such as those from the Brazilian Medical Association, have not included these recommendations yet.*

However, regulatory agencies worldwide accept pla-

---

*Associação Médica Brasileira; Conselho federal de Medicina. Diretrizes Médicas. Disponível em http://www.projetodiretrizes.org.br/novas_diretrizes.php [acesso em out 2005]

cebo-controlled clinical trials to support new drug registration, requiring no head-to-head comparisons of drugs already available in the market for the same indications, except for severe diseases. Therefore the importance of these comparisons for developing individual drug lists. Information obtained in clinical trials required for registration is not enough for this purpose.

Besides identifying their patients' therapeutic needs and drug interchangeability, the prescriber needs to consider pricing differences. Pricing differences should be publicly controlled and drug pricing schedule is a government responsibility. In Brazil, drug pricing schedules are established by the *Câmara de Regulação do Mercado de Medicamentos* (CMED, Drug Market Regulation Council).* Resolution n. 2 forbids higher prices for new molecules that show no other therapeutic benefits than other drugs already available in the market. This regulation is not retroactive, and does not allow price reduction for *metoos* registered before March 5, 2004. Therefore, despite this initiative for drug price control in Brazil, there are still price differences for drugs with similar effectiveness for the same indications.

Interchangeability between drugs with the same active principle, concentration and formulation

A recent study assessed the behavior of prescribers when they found different clinical responses after interchanging drugs.[18] More than half of the small proportion of prescribers who answered the study questionnaire were unfavorable to generics and to the possibility of replacing the drug they have prescribed. Neurologists whose patients were taking the reference product attributed their adverse events to either the natural history of their disease or non-adherence to the treatment prescribed and did not report them. Among patients who had their generics replaced with the original prescribed product, their adverse events were attributed to the generic drugs and they were reported. Notwithstanding the limitations, it can be concluded based on this example that unauthorized drug replacement is not well accepted by some physicians.

A generic product can be interchangeable most of the times, but there are exceptions only identified in clinical practice. For registering an injectable generic drug, it is required to determine the drug's pharmaceutical equivalence but not its therapeutic equiva-

lence, as usually one leads to the other. There are situations, however, when a different from the expected therapeutic response is obtained. Such cases can be detected by drug surveillance after the drug is widely used. For example, two hypnotics have distinct sleep induction times due to pharmacodynamic differences. One possible explanation is this difference could be the proportion of dextro and levo isomers, making one more potent than the other. The determination of the proportion of isomers is not included in the usual pharmaceutical equivalence tests.

Another example are drugs that, after small dose adjustments, can have their efficacy affected or cause toxicity to the patient. In such cases drug replacement with the same active principle after dose adjustment can lead to under- or overdose. In bioequivalence tests there is an acceptable variability range (20%) for comparison variables of generic and reference drugs.** In the above mentioned cases, such variability, even if small, can change the clinical response, requiring a new period of adaptation and adjustment. Therefore, once a dose is adjusted, it is not recommended to replace the product in use, either reference or generic drug. Hormonal replacement and contraceptive drugs are among them.

Additional examples include studies[13,16] on clinical control of drugs with large intra-and interindividual variability range such as clozapine, used in the treatment of schizophrenia, and warfarin, an oral anticoagulant.

On the other hand, a study of cyclosporin,[8] another drug with narrow therapeutic window, confirmed bioequivalence between reference and generic drugs in the steady state, without significant intra- and interindividual variability, indicating that interchangeability between generic and reference drugs is possible. Aiming at reducing the impact of interindividual variability in bioequivalence tests for drugs with narrow therapeutic window, Health Canada limited the acceptable variability range between comparison variables in bioequivalence tests for these drugs. However, members of the Canadian Society for Pharmaceutical Sciences suggest to test these drugs in clinical conditions (not in young healthy individuals, as it is usually the case for relative bioavailability tests) to more accurately assess pharmacokinetic and pharmacodynamic differences between formulations.[17] This discussion is analogous that involving the epidemiological concepts of statistical and clinical significance.[12]

A product not approved in a relative bioavailability test can be interchangeable if its failure was due to variation of the maximum plasmatic concentration above the statistical limits regulated for a product with wide therapeutic window. In such situation there should be explained that the observed variation has no clinical impact, based on previous studies, or there is the alternative of a new clinical trial for measuring the pharmacodynamic action or clinical effect to show therapeutic equivalence. The approval of a generic drug in a bioequivalence test only demonstrates interchangeability of this generic drug from company X with the reference drug. The same test comparing two generics does not ensure bioequivalence. Thus, interchangeability between two generics cannot be inferred, as they can differ in both their efficacy and the occurrence of adverse events in some patients. Clinicians should be aware to this fact, as prescription by generic drug name does not assure treatment continuity with the same product. Those in charge of procurement in public hospitals, who are compelled to buy drugs at the lowest prices, should communicate the physicians when they change drug suppliers, and keep a strategic stock for chronic patients who have problems that can be attributed to drug replacement (especially relevant in psychiatric hospitals).

In addition to generic drugs, biosimilars or follow-on biologics – copies of biological products with the same molecule, indication, efficacy and safety – can be interchangeable.[7] Examples of these products are hepatitis A, hepatitis B, *Haemophylus influenzae* b, and acellular DTP vaccines. [4,10]

Consumer's point of view

At the time of purchase, interchangeability between branded and non-branded products (generics with specific identification in the label) at dispensation sites is legally acceptable. Similar drugs end up being interchanged with generics or new drugs against prescribers' will and current regulations.

A study conducted in 2004 by *Associação Brasileira das Indústrias de Medicamentos Genéricos* (Brazilian Association of Generic Drug Manufacturing Companies - Pró-Genéricos)* comprising a sample of 900 consumers from four Brazilian capitals identified that 30% of them did not know what similar drugs were, and 78% what reference drugs were. The majority of consumers (88%) buy the cheapest option available, and 76% follow the prescription. Only 19% mentioned generics as their first choice, and 12% followed the pharmacist or pharmacy clerk's advice.

Product marketing based on their generic names only would eliminate the need for advertisement. However, the availability of generic drugs in pharmacies is determined by wholesale distributors and pharmacy chains may favor specific companies. On the other hand, substitution by similar drugs in the pharmacy has to do with clerks and/or pharmacy owners who benefit from selling products of specific companies.

Consumer's search for the cheapest drug option includes replacing an industrialized product by a pharmacy-prepared one. In many countries pharmacy compounding is an activity complementary to that of the drug industry. Products are compounded when there is no industrialized formulation or at a concentration that would be adequate to patients who need non-standard medication. But the same quality control provided by a modern manufacturing company cannot be assured for a drug compounded in a pharmacy. The use of compounded drugs should be an exception, acceptable for clinical and pharmacological and technical reasons.

Pricing difference between industrialized and compounded drugs can be explained by the cost and quality of raw materials; manufacturers' quality control costs; different taxes collected and more difficult to be controlled for retailers; and different expenditures with advertisements. In any sector of the economy it is not expected that manually manufactured products be less expensive than those manufactured in large scale, as large scale economy entails from price negotiation with suppliers to packaging manufacturing and quality control.

Interchangeability by a compounded product is not limited to the consumer's search for better prices. The easy marketing of manually compounded products with no scientifically tested properties, and direct advertisement to health professionals favor the prescription of compounded drugs, particularly when the prescriber does not have adequate pharmacological and technical knowledge.

To the consumer, price is the main reason for interchangeability. Thus, prescribers should be familiar with their drug list prices to prevent patients from replacing drugs and subsequent unexpected therapeutic outcomes.

FINAL CONSIDERATIONS

Evidence of therapeutic equivalence in in-vitro tests and clinical trials allows that copy products take as

---

*Associação Brasileira das Indústrias de Medicamentos Genéricos. Pró-genéricos. Disponível em http://www.progenericos.org.br/jornal/coletiva.pdf [acesso em set 2005]

their own results of reference product studies to support their own efficacy and safety after reference drug patents are expired. The link between the concepts of therapeutic equivalence and interchangeability has no impact on most consumers who choose the cheapest drug available with the same active substance, even if they are not therapeutically equivalent. Interchangeability negatively affects prescribers as the drug prescribed by them is replaced without their approval. On the other hand, it positively affects public health decision makers, as generics increase access to good quality drugs.

In Brazil, nowadays, a generic drug, when registered at Anvisa, means a copy product of proven quality. Similar drugs have not yet be subject to the same strict quality control but all drugs manufactured starting from November 2009 will go through (in vitro) pharmaceutical equivalence tests, and oral antibiotics, anticancer and antiretroviral drugs will go through (in vivo) relative bioavailability tests. It is expected that by October 2014 all the remaining therapeutic classes for oral use will go through the same tests.

After defining their individual drug lists, physicians and dentists should prescribe generics and require Anvisa to have an effective drug quality control. Quality deviation can occur for both reference and generic drugs. Drug interchangeability is legally approved, by Law No. 9787, from February 10th 1999, establishing that a generic drug can replace a brand name drug, except when otherwise indicated by the prescriber. For drugs with narrow therapeutic window and high interindividual variability and/or requiring dose adjustment, treatment could start either with a generic or a reference drug, whatever is the cheapest one, and the prescriber should clearly indicate in the prescription that no replacement is acceptable subsequently.

To make it easier developing individual drug a database should be created with entries by therapeutic indication, identification of first and second choice active substances, access to reviews on clinical evidence, prices and data on antimicrobial resistance for antibiotics. In Brazil, Anvisa is leading this initiative. There are websites of academic and governmental sources that allow searches by therapeutic indications.*

Due to the large biological variability among humans and non-absolute similarity between drugs in the same therapeutic class or even generics, the differences between these drugs' effects will be established empirically. Individual drug lists should include the concepts of first and second choice drugs to take into consideration their biological variability.

Prescribers should be familiar with pharmacological and technical aspects, pharmacokinetics, pharmacodynamics, and pharmacogenetics and understand the differences between innovator, generic, similar and compounded drugs to prevent mistakes and increase the likelihood of curing their patients.

The Brazilian Health System is in the right track in shifting from emergency to primary care, as without an adequate follow-up of patients it is not possible to achieve rational drug use.

REFERENCES

1. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker versus diuretic. *JAMA.* 2002:288:2981-97.

2. Arias TD. Glosario de medicamentos: desarollo, evaluacion y uso. Washington (DC): Organización Panamericana de la Salud; 1999.

3. Berne C, Siewert-Delle A, URANUS study investigators. Comparison of rosuvastatin and atorvastatin for lipid lowering in patients with type 2 diabetes mellitus: results from the URANUS study. *Cardiovasc diabetol.* 2005;4:7.

4. Bovier PA, Farinelli T, Loutan L. Intercgangeability and tolerability of a virosomal and an aluminium-absrbed hepatitis A vaccine. *Vaccine.* 2005;23:2424-9.

5. Carter BL, Ernst ME, Cohen JD. Hydroclorothiazide versus chlorthalidone, evidence supporting their interchangerability. *Hypertension.* 2004;43:4-9.

6. Chong PH. Lack of therapeutic interchangeability of HMG-CoA reductase inhibitors. *Ann Pharmacother.* 2002;36:1907-17.

7. Crommelin D, Bermejo T, Bissig M, Damiaans J, Kramer I, Rambourg P, et al. Biosimilar, generic versions of the first generation of therapeutic proteins: do they exist? *Contrib Nephrol.* 2005;149:287-94.

*National Health Services. National Electronic Library for Medicines. Disponível em http://www.druginfozone.nhs.uk/home/default.aspx [acesso em set 2005]

8. David-Neto E, Kakehashi E, Alves CF, Pereira LM, Castro MCR, Mattos RM, et al. Bioequivalence of a new cyclosporine A formulation to Neoral. *Ther Drug Monit.* 2004;26:53-7.

9. Devlin JW, Welage LS, Olsen KM. Proton pump inhibitor formulary considerations in the acutely ill: pharmacology, pharmacodynamics and available formulations. *Ann Pharmacother.* 2005;39:1667-77.

10. Feldman S. Interchangeability of vaccines. *Pediatr Infect Dis J.* 2001;20(11 Suppl):S23-9.

11. Furberg CD, Herrington DM, Psaty BM. Are drugs within a class interchangeable? *Lancet.* 1999;354(9185):1202-4.

12. Hennekens CH, Buring JE. Issues in interpreting results of tests of statistical significance. In: Hennekens CH, Buring JE. Epidemiology in medicine. Boston (MA): Little, Brown; 1987. p. 257-8.

13. Lam YWF, Ereshefsky L, Toney GB, Gonzales C. Branded versus generic clozapine: bioavailability comparisos and interchangeability issues. *J Clin Psychiatry.* 2001;62 Suppl 5:18-22.

14. Maitland-van der Zee AH, Boer A, Leufkens HGM. The interface between pharmacoepidemiology and pharmacogenetics. *Eur J Pharmacol.* 2000;410(2-3):121-30.

15. Organização Mundial da Saúde. Guia para a boa prescrição médica. Porto Alegre: Artmed; 1988.

16. Palylyk-Colwell E, Jamali F, Dryden W, Friesen E, Koven S, Mohamed I, et al. Bioequivalence and interchangeability of narrow therapeutic range drugs: Canadian Society for Pharmaceutical Sciences discussion. *J Pharm Pharm Sci.* 1998;1:2-7.

17. Vercaigne LM, Zhanel GG. Clinical significance of bioequivalence and interchangeability of narrow therapeutic range drugs: focus on wafarins. *J Pharm Pharm Sci.* 1998;1(3):92-4.

18. Wilner AN. Therapeutic equivalency of generic antiepileptic drugs: results of a survey. *Epilepsy Behav.* 2004;5:995-8.