Bioequivalence and generic medicinal products: The levothyroxine case

Teresa Torres Moral, Universitat Autònoma de Barcelona

Mentor: Nuria Maria Vivas Sabido

Introduction

Generic medicinal products are playing a more and more important role in the evolution of the pharmatheutical market.

In Spain, the first law related to this type of products came in 1996 .«Ley 13/1996 de 30 de diciembre de Medidas Fiscales, Administrativas y de Orden Social.»[1]. It was the start of the EFGs (Generic Equivalent Pharmaceutical), a start which coincided in time with other countries of Europe (Portugal, Greece, France). In many countries in centre and north Europe, generic products were introduced a decade before, in the 80s, which explains why the use of these drugs is more strongly consolidated there. However, consumption figures have greatly increased in Spain in recent years, as can be seen in figure 1.

The objective of this essay is to study the concept of bioequivalence, seeing if the concept is fully standardized, which tests are applied to drugs to be considered bioequievalent, how reliable they are and the real significance of all this. A more detailed study of levothyroxine is carried out, as an example of a concrete case.[2]

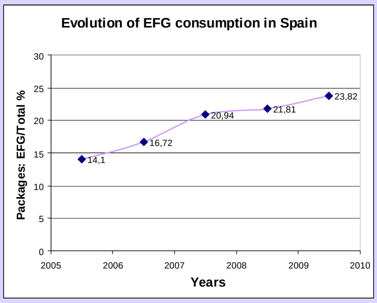

Figure 1. Data from: Cuesta Terán MT. Medicamentos genéricos: una visión global. Información terapéutica del Sistema Nacional de Salud. 2010; 34. [2]

Definitions:

BIOEQUIVALENCE

«Two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects with respect to both, efficiency and safety, will be essentially the same. Alternatively to classical bioavailability studies using pharmacokinetic end points to assess bioequivalence, other types of studies can be envisaged, e.g. human studies with clinical or pharmacodynamic end points, studies using animal models or in vitro studies as long as they are appropriately justified and/or validated»[6]

GENERIC MEDICINAL PRODUCT

«Medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. In such cases, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorised active substance must be supplied by the applicant. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form.»[6]

Bioequivalence studies

Bioequivalence studies vary depending on the type of drugs, and on some occasions they are not neccessary. However, most of them have the following characteristics.

CHARACTERISTICS

Randomized block: They use a systematic and replicable procedure, in which the participants are distributed randomly in different treatment groups.[3]

Crossover: Both, the treatment and the control are administered to the patient in randomly successive periods, which allows each participant his own control.[3]

In two periods: Two doses are taken, separating the two periods.[3]

Double blind: Both, the patient and the researcher ignore whether the patient is having the treatment or the control.[3]

PARAMETERS

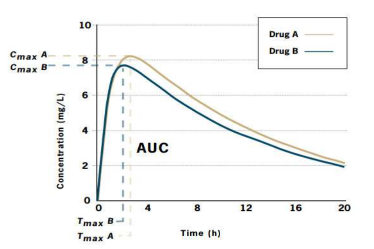

Figure 2. Image from: Birkett, DJ. Generics-equal or not?. Australian Prescriber. 2003; 26 (4): 85-86 [4]

AUC

It's the area under the curve in the graph of drug concentration versus time. This gives information about the total quantity of active substances that reaches the bloodstream, that is, the absortion rate.

Cmax.

It's the highest concentration in blood acquired. It gives information about velocity and absorption rate.

Tmax.

It's the time needed to reach Cmax. It gives information about absorption velocity.

ANALYSIS OF RESULTS

The values of each patient are logarithmically transformed so as to compare the average values of generic and reference drugs. The quotient between these medicines must be within the limits 80-125%, because they have been logarithmically transformed, and with these percentatges they are within a range of symmetric acceptance in logarithmic scale.[5]

Levothyroxine

Levothyroxine is a levoisomer of the thyroid hormone thyroxine, prescribed in many cases of hypotiroidism. It is metabolized in thyroxine when ingested and has the same effects as the endogenous hormone. Thyroxine (also konwn as T4) is syntetized in the thyroid gland and becames triiodothyronine (also known as T3) when leaving the glands. T3 is a molecule with a shorter average life but with more biological activity. This hormone is governed by the hypothalic-pituitary-thyroid system and its syntesis inhibits other hormones as TSH and TRH [7]. The regulation is represented in figure 3.

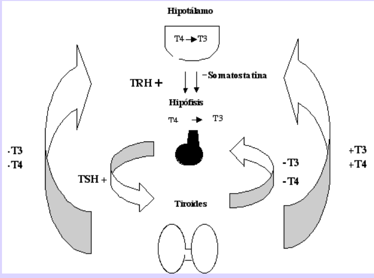

Figure 3. Image of: hypotalamic-pituitary-thyroid system regulation Information and images from Edna Mancilla. Curso Salud y desarrollo del adolescente.[8]

INTERCHEANGEABILITY OF LEVOTYROXINE

Non interchangeable drugs in Spain
Biological drugs (insulin, blood products, vaccines, biotechnological medecines) whose active substance can't be proved identical due to the characteristics of their raw materials or the manufacturing process.
Drugs that contain some of the active substances within the Narrow Therapeutic Index (NTI), unless they are administered intravenously: acenocoumarol, carbamazepine, cyclosporine, digoxin, phenitoin, levothyroxine, lithium, methyldigoxin, tacrolimus, theofiline and warfarin. In case of these drugs, a small variation in bioavailability could cause levels outside theraputic range.
Drugs that contain active substances subjet to special medical control or the ones that require specific follow-up actions for safety reasons: derivates of A vitamins (isotretinoin, acitretin), with systemic administration, acetohidroxamic acid, thalidomide, clozapine, pergolide, cabergolina, vigabatrin, and sertindiol. Patients must be subjected to special supervision and is not appropriate to be controlled by different persons.
Drugs for respiratory tract administered via inhalation, as the instructions for use of different devices change, and correct usage is vital for a correct dosage, in addition to the fact that studies of those devices have been carried out wirh insensitive pharmacodynamic variables.

Table 1. Non interchangeable drugs in Spain . Information from: Ley de garantías y uso racional de los medicamentos y productos sanitarios. Orden SCO/2874/2007 de 28 de septiembre. Boletín Oficial del Estado, nº 239, (5-10-2007).[9]

CAUSES THAT HINDER THE STUDY OF BIOEQUIVALENCE

1. Drug with a narrow therapeutic index (NTI)

By legislation, NTIs have to meet stricter parameters of bioequivalence. [10]

2. Difficult distinction between administered and endogenous hormone

FDA's accepted method consists in taking 3 measures of endogenous hormone before the dose, and substract them from the final concentration of the hormone. A study with high quantities of exogenous hormone is also performed to reduce the effect of endogenous hormone as much as possible.[10]

3. Carryover effect

It means that because the dose is high, the results of the next period are not only caused by the intake of that dose, but also by the effects caused by the high first dose. It hasn't been proved that this has resulted in therapeutical problems. [10]

AND MORE ABOUT LEVOTHYROXINE…

- As it is a non interchangeable drug, the pharmacist cannot supply a drug different to the prescribed one, although its bioequivalence has been proved.

- In spite of the difficulties, there have been cases in which bioequivalence has been proved following the present legislation.

- New ways to study bioequivalence in levothyroxine are being investigated, but they are not universally accepted. [11] [12]

Conclusions

1. There is a well defined, unambiguous concept of biodisponibility, bioequivalence and generic medicinal product. These concepts are commonly shared by all official entities in Spain, Europe and the rest of the world.

2. The studies which determine bioequivalence are standardized and there are clear instructions for them. However, acceptance parameters vary slightly between countries, specially in the cases of drugs with complex characteristics.

3. The fact that two medicinal products are bioequivalent does not always imply that they can be legally interchanged. This is stipulated by each country, and there are differences between different countries.

4. Legislation on EFG is clear and safe, although there are people who distrust this type of drugs, possibly because of ignorance or the fact that they are cheaper. In my opinion, both, more research and better information campaigns are needed to consolidate the industry of generic medicinal product.

Selected bibliography

1. Ley 13/1996 de Medidas Fiscales, Administrativas y del Orden Social. Boletín Oficial del Estado, nº 315, de 31 de diciembre de 1996
2. Cuesta Terán MT. Medicamentos genéricos: una visión global. Información terapéutica del Sistema Nacional de Salud. 2010; 34 (2).
3. IMIM: Institut Hospital del Mar d'Investigacions Mèdiques. Términos de Ensayos Clínicos . Disponible en: http://www.imim.es/media/upload/arxius/terminologia.pdf.
4. Birkett, DJ. Generics-equal or not?. Australian Prescriber. 2003; 26 (4): 85-86
5. García Arieta, A., Hernández García C, and Avendaño Solá C. Regulación de los medicamentos genéricos: evidencias y mitos. Información Terapéutica del Sistema Nacional de Salud. 2010; 34 (3): 71-82.
6. Guideline on the Investigation of Bioequivalence. CPMP/EWP/QWP/1401/98 Rev.1/Corr **. EMEA (20-01-2010).
7. Scanlon MF, Toft AD. Regulation of thyrotropin secretion. Werner & Ingbar's The Thyroid: A Fundamental and Clinica. 2008; 9
8. Edna Mancilla. CursoSalud y desarrollo del adolescente. Pontificia Universidad Católica de Chile: Departamento de Pediatría. Disponible en: http://escuela.med.puc.cl/paginas/ops/curso/lecciones/leccion08/m3l8leccion.html.
9. Orden SCO/2874/2007, de 28 de septiembre, por la que se establecen los medicamentos que constituyen excepción a la posible sustitución por el farmacéutico con arreglo al artículo 86.4 de la Ley 29/2006, de 26 de julio, de garantías y uso racional de los medicamentos y productos sanitarios. Boletín Oficial del Estado, nº 239, de 5 de octubre de 2007.
10. Bolton, S. Bioequivalence studies for levothyroxine. The AAPS journal. 2005; 7 (1): E47-E53.
11. Blakesley VA. Current methodology to assess bioequivalence of levothyroxine sodium products is inadequate. The AAPS journal. 2005; 7 (1): E42-E46.
12. Eisenberg M, and J. Distefano III J. TSH-based protocol, tablet instability, and absorption effects on L-T4 bioequivalence. Thyroid. 1996; 19 (2): 103-110.