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Is generic rifaximin still a poorly absorbed antibiotic? A comparison of branded and generic formulations in healthy volunteers

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ABSTRACT

Rifaximin is an antibiotic, locally acting in the gastrointestinal tract, which may exist in different crystal as well as amorphous forms. The branded rifaximin formulation contains the polymorph rifaximin-α, whose systemic bioavailability is very limited. This study was performed to compare the pharmacokinetics of this formulation with that of a generic product, whose composition in terms of solid state forms of the active pharmaceutical ingredient was found to be different. Two tablets (2 × 200 mg) of branded and generic formulations were given to 24 healthy volunteers of either sex, according to a single-blind, randomized, two-treatment, single-dose, two-period, cross-over design. Plasma and urinary samples were collected at preset times (for 24 h or 48 h, respectively) after dosing, and assayed for rifaximin concentrations by high-performance liquid chromatography–mass spectrometry. Rifaximin plasma and urine concentration–time profiles showed relevant differences when generic and branded rifaximin were compared. Most pharmacokinetic parameters were significantly higher after administration of generic rifaximin than after rifaximin-α. In particular, the differences for C_{max}, AUC and cumulative urinary excretion between the generic formulation and the branded product ranged from 165% to 345%. The few adverse events recorded were not serious and not related to study medications. The results of the present investigation demonstrate different systemic bioavailability of generic and branded formulations of rifaximin. As a consequence, the therapeutic results obtained with rifaximin-α should not be translated *sic et simpliciter* to the generic formulations of rifaximin, which do not claim containing only rifaximin-α and will display significantly higher systemic absorption in both health and disease.

Introduction

Generic medicinal products are 'copies' of patented drugs and can be marketed following patent expiration of the brand product [1]. Accordingly, regulatory authorities have issued guidelines dictating the terms and conditions under which generic drugs can be recognized as therapeutically equivalent to their branded counterparts [2–4].

Bioequivalence studies, consisting of single-dose pharmacokinetic (PK) evaluations, are required for registration of most generic formulations of systemically acting drugs, including antibacterial compounds, for which the therapeutic activity depends significantly on PK parameters [5,6]. For generic formulations of systemic antibiotics, differences in pharmaceutical properties might therefore result in changes of their PK profiles, with consequent alteration of PK/PD (pharmacodynamic) relationships, leading to variations in their clinical efficacy, as compared to the brand-name counterparts.

On the contrary, locally acting antibiotics, such as rifaximin, are medicinal products, which exert their effect at the site of application. In this setting, a systemic action, if any, would be considered as an undesirable effect, which could give rise to adverse events [4,7]. In these medicinal products, a change in formulation or dosage form may influence – through variations in local and/or systemic bioavailability – their efficacy and/or safety profiles.

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Besides formulation, the physico-chemical characteristics of the active ingredient are also relevant to the local and/or systemic bioavailability [8,9]. In this context, crystal polymorphism is extremely important [10–12]. Polymorphism is the ability of a molecule to assemble into more than one crystal structures. Different polymorphs display different atom arrangements within the unit cell, and this can have a remarkable impact on the physico-chemical properties of the crystallized compound [11,12].

Different polymorphic forms of a drug can display different chemical and physical properties, including stability and chemical reactivity, dissolution rate and solubility, which can affect bioavailability, PK and, as a consequence, PD [10,13]. Several examples of polymorphism's impact on bioavailability have been reported [14–18].

Rifaximin (4-deoxy-4′-methylpyrido[1′,2′-1,2]imidazo[5,4-c]rifamycin SV) is a synthetic product designed to modify the parent compound, rifamycin, in order to achieve low gastrointestinal (GI) absorption while retaining good antibacterial activity [19]. Indeed, several studies have shown that rifaximin is a non-systemic antibiotic with a broad spectrum of antibacterial activity [20,21]. According to the European Pharmacopeia, rifaximin shows crystal polymorphism [22] and five distinct crystal forms, namely α, β, γ, δ and ε, have been described [23]. *In vitro* studies have shown different dissolution and solubility rates of these polymorphs, and *in vivo* investigations in dogs found significantly different PK patterns amongst the various crystal forms, with the γ polymorph displaying the highest systemic bioavailability [23].

In addition to crystal polymorphs, an amorphous form of rifaximin can be also prepared. The amorphous form of a drug consists of disordered molecule arrangements and does not display a crystalline lattice [24,25]. Because of this peculiarity, there are significant stability differences between crystalline polymorphs and the amorphous form of a drug. *In vitro* dissolution tests on rifaximin do suggest for the amorphous form a PK behavior similar to that of polymorph-γ, thus implying a higher systemic bioavailability than that of polymorph-α [23]. And indeed, preliminary animal studies showed that this is the case [26].

A previous study [27] on healthy volunteers showed that the PK profile of amorphous rifaximin differs from that of polymorph-α (the crystal form present in the branded formulation), resulting in higher systemic bioavailability. These findings confirm that also in humans different solid-state forms of rifaximin show a different PK behavior.

Since some generic formulations of rifaximin have been marketed, we felt it worthwhile to evaluate their PK profile in comparison to that of the branded product. Indeed, while the summary of product characteristics of the branded rifaximin provides clear information about its specific crystal structure [28], this was not the case for the generic products, whose composition and – as a consequence – systemic absorption is unknown. Provided be it significant, clinical consequences could arise.

The aim of this study was therefore to evaluate the impact of the composition (in terms of crystalline polymorphs and/or amorphous from) of the active ingredient present in the generic formulation on the systemic bioavailability of rifaximin.

Methods

Healthy volunteers

Healthy adult volunteers of either sex (age range: 18–60 years) and Caucasian origin were invited to participate to the study. They were informed of the purpose, methods and potential hazards of the study, and were requested to sign a written informed consent. Clinical evaluations, performed to assess the health condition of volunteers, as well as inclusion and exclusion criteria have been previously described in details [29].

Design of the study

The study was performed in a single center (Institute for Pharmacokinetic and Analytical Studies S.A., Ligornetto, TI, Switzerland), in accordance with a single-blind, randomized, two-treatment, single-dose, two-period, cross-over design, with a wash-out period of 7 days [30]. The study was approved by the Ethics Committee of Canton Ticino and Swissmedic (Switzerland), and was conducted in accordance with ICH guidelines for Good Clinical Practice. The study procedures were performed in compliance with the Declaration of Helsinki.

Subjects were randomized to receive a 400-mg single-dose (2 × 200-mg tablets) of the generic rifaximin or branded formulation (rifaximin polymorph-α; Normix®). The tablets were administered with 250 ml of water at 08:00 AM, under fasting conditions. About 4, 8 and 12 h after drug intake, a lunch (1200 kcal), a snack (150 kcal) and a dinner (900 kcal) were served. After drug intake, subjects were requested to drink water as follows: 500 ml every hour of plain mineral water during each of the 4-h intervals from drug administration till 12 h after dosing; then, at will, until the end of urine collection (*i.e.* 48 h post-dosing).

Venous blood samples of 10 ml were collected into tubes (containing sodium heparin) kept on ice, at pre-set time intervals of 0 (pre-dosing) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 h post-dosing. Plasma was separated from blood within 20 min by centrifugation at 2000 × *g* (10 min at 4 °C). Each plasma sample was split into two aliquots and stored at −20 ± 5 °C. Urine was collected pre-dosing and at intervals of 0–4, 4–8, 8–12, 12–24, 24–48 h post-dosing into refrigerated flasks. The weight of each urine fraction was recorded, a sample of approximately 100 mL was split into two aliquots and frozen.

Study medications

The film-coated tablets (200 mg) of generic rifaximin (Sandoz Biopharmaceuticals SpA) and those of branded rifaximin (Alfa Wassermann SpA) were from the same batch, which was n. 00307 and n. 8278 for generic formulation and Normix™, respectively. The brand of generic rifaximin was selected amongst the products available in the Italian market at the time of the study. It is noteworthy that they were all manufactured by the same company (Special Product's Line SpA, Pomezia, Italy) and contained the same active ingredient (Industrias GMB SA, Barcelona, Spain) [31]. Therefore, no specific criteria were needed to select a given generic formulation. The compositions of Normix™ and generic rifaximin are displayed in Table 1.

X-ray power diffraction analysis of the generic formulation showed the presence of both amorphous rifaximin and rifaximin α. Quantitative estimation was not possible, due to interference of tablet excipients in this kind of analysis.

Safety evaluations

Volunteers were enquired about the occurrence of any adverse event after their admission to the clinical unit, both before the administration of study drugs and throughout the study until discharge. Vital signs were monitored.

Rifaximin assay

Rifaximin concentration in plasma and urine samples was measured by liquid chromatography mass spectrometry (LC/MS-MS) as previously described [23], with a lower limit of quantification