

Safety and efficacy of generic drugs with respect to brand formulation

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ABSTRACT

Generic drugs are equivalent to the brand formulation if they have the same active substance, the same pharmaceutical form and the same therapeutic indications and a similar bioequivalence respect to the reference medicinal product. The use of generic drugs is indicated from many countries in order to reduce medication price. However some points, such as bioequivalence and the role of excipients, may be clarified regarding the clinical efficacy and safety during the switch from brand to generic formulations. In conclusion, the use of generic drugs could be related with an increased days of disease (time to relapse) or might lead to a therapeutic failure; on the other hand, a higher drug concentration might expose patients to an increased risk of dose-dependent side-effects.

Key words: Antibiotics, bioequivalence, brand, clinical efficacy, generic, safety

INTRODUCTION

In the last years, several generic drugs have been introduced in Italy in agreement with the Finance Law of 1996 (Law n. 549/1995 in G.U. n. 302 of 29.12.1995) and in several other countries in order to reduce the medication prices and reduce the economic burden on national health systems. In fact, following the entry of a generic drug, a branded drug loses about 50% of its market share after 3 months and 80% after 1 year.^[1]

As legally defined in Italy, generic drugs are equivalent to the brand formulation if they have the same active substance (with a difference of $\pm 5\%$), the same pharmaceutical form, the same therapeutic indications and a similar bioequivalence ($\pm 20\%$) relatively to the reference medicinal product (Law n. 425/1996 in G.U. n. 208 of 05.09.1996. Legislative Decree no. 219/06).^[2]

In this contest, at least at a physiological level, generic medicines behave very similarly to their originator counterparts; therefore, theoretically, they may show a similar efficacy. In fact, an interesting study comparing 2070 single-dose clinical bioequivalence studies of orally administered generic medicine products approved by the Food and Drug Administration (FDA), from 1996 to 2007, demonstrated that the products did not significantly differ.^[3]

In agreement, other authors documented that treatment with generic drugs or the switch from brand to generic formulation

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.120972

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is not related to significant clinical failure or development of adverse drug reactions.^[4-6]

On the other hand, while generic drugs are tested for bioequivalence within a certain range compared to innovator drugs, safety and efficacy testing is not required; therefore, generic drugs are not necessarily therapeutically equivalent to branded drugs.^[7]

In particular, in agreement with the above reported law, bioequivalence study is not necessary in the presence of injectable formulations. Moreover, in the presence of drugs with sustained release or narrow therapeutic index, clinical studies performed in 12 young health volunteers (from 18 to 55-year-old) are necessary. However, these studies evaluate the bioequivalence of these formulations, performing a pharmacokinetic and not a pharmacodynamic evaluation. Therefore, no data concerning the efficacy and safety are recorded. In fact, other authors documented the development of side-effects or clinical failure after the switch from brand to generic formulation.^[8-14]

In particular, it has been estimated that brand-generic switch is related with a clinical improvement in 30% of the treated patients, but 30% did not experience any improvement, 10% experienced side effects and 30% discontinued treatment for clinical inefficacy or due to side-effects.^[15]

In this case-review, we report the lack of efficacy during treatment with generic formulations of fluoroquinolones and discuss the relative reasons also considering the limitations of this legal approach.

CASE REPORTS

Case 1

A 70-year-old woman presented with a history of recurrent urinary infections was admitted on July 10, 2012, to her general practitioner (GP) for the development of painful burning sensation when urinating. History revealed the presence of blood hypertension treated with calcium blockers (amlodipine, 10 mg/day) and a previous history of skin reaction after amoxicillin treatment. Clinical evaluation revealed discomfort in the lower abdomen and pain in the pelvic area. Laboratory findings of urinary samples documented the presence of leucocytes and blood, with an acid pH [Table 1]. Moreover, urine had a strong smell and appeared cloudy.

On July 12, 2012, a diagnosis of acute cystitis was performed and a 7 days treatment with ciprofloxacin (Ciproxin, Bayer® 750 mg once daily) was prescribed; on 13 July microbiological evaluation of urine samples revealed the presence of *Escherichia coli* (2×10^5 colony forming units [CFU]/mL),

Table 1: Laboratory findings in urinary samples for case 1

Diagnostic tests	July 10 th	July 20 th	July 30 th
<i>E. coli</i> CFU/mL	2×10^5 CFU	5×10^5 CFU	1×10^2 CFU
Leukocytes	>10 μ L	>10/ μ L	<10/ μ L
Nitrite	Positive	Positive	Negative
Haematuria	Positive	Positive	Negative

E. coli=*Escherichia coli*; CFU=Colony forming units

with a good sensibility to both ciprofloxacin (Minimum inhibitory concentrations [MIC]: 4.9 mcg/mL; range: 0.06-8) and amoxycillin-clavulanate (3.96 mcg/mL; range: 1-16).

During the follow-up performed on 20 July, the persistence of cystitis induced a new microbiological evaluation that revealed, 3 days later, an infection sustained from *E. coli* (5×10^5 CFU/mL) still ciprofloxacin-sensitive (MIC: 4.9 mcg/mL; range: 0.06-8).

Pharmacological evaluation revealed that the patient took the generic ciprofloxacin (Mylan Generics® 750 mg once daily) instead of the prescribed drug; therefore, the brand formulation of ciprofloxacin (Ciproxin, Bayer®; 750 mg once daily) was prescribed with an improvement of clinical symptoms and laboratory values [Table 1] and without the development of side-effects.

Case 2

A 72-year-old woman has been brought to her GP's attention for the development of an acute bacterial bronchitis. History revealed the presence of blood hypertension in treatment with calcium blocker (amlodipine 10 mg daily) and a beta-blocker (atenolol 100 mg/day).

On examination, blood pressure was 120/85 mm Hg, body temperature was 38.6°C and no lymphadenomegaly/lymphadenopathy was observed. Cardiovascular and abdominal relieves were normal.

Clinical evaluation documented the presence of wheezing, coughing with green mucus and shortness of breath. Therefore, paracetamol (500 mg as need) and levofloxacin (Tavanic, sanofi-aventis® 500 mg tablet once daily for 10 days) were prescribed, but 4 days later the patient returned to the GP for the persistence of symptoms. A detailed pharmacological evaluation revealed that the patient was taking generic levofloxacin (Ranbaxy®, 500 mg once daily) instead of the branded ones because in agreement with Italian law, the pharmacist advised that a bioequivalent drug with a lower price was available.

Generic levofloxacin was changed to Tavanic® with a complete improvement of symptoms in 2 days and without the development of side-effects.

Case 3

A 49-year-old woman, without a history of other systemic diseases presented to her GP's for a fever (38°C) that appeared 2 days before accompanied by coughing with mucus and shortness of breath. A diagnosis of acute bronchitis was postulated and a treatment with paracetamol (500 mg as need) and levofloxacin (Tavanic, sanofi-aventis® 500 mg tablet once daily for 10 days) was prescribed. Six days later, patient returned to the GP for the worsening of symptoms (fever 39.5°C and green mucus). History revealed the use of generic levofloxacin (Ranbaxy®, 500 mg once daily) instead of the branded ones; therefore, generic levofloxacin was changed to Tavanic® with a complete resolution of symptoms in 7 days. No side-effects appeared during drug treatment.

Case 4

A 41-year-old man with 4 days of pain, tenderness, swelling and pressure around the eyes presented to his medical practitioner for clinical evaluation. Examination revealed the presence of fever (37.9°C), reduced sense of smell and taste and the patient lamented nasal obstruction with a yellow discharge from the nose.

Acute sinusitis was diagnosed and due his allergy to betalactam drugs, a treatment with levofloxacin (Tavanic, Sanofi-aventis® 500 mg tablet once daily for 14 days) with beclomethasone (Bentelan, biofutura pharma S.p.A® 1 mg tablet every 8 h for 3 days) was prescribed and patient was asked to return after 3 days for clinical evaluation. During the follow-up, 3 days later, clinical evaluation revealed the persistence of symptoms with a worsening of the fever (38.5°C) and the patient referred that he was using a generic formulation of levofloxacin (Ranbaxy®, 500 mg once daily). The change from generic to brand formulation induced a complete resolution of symptoms in about 10 days.

Comments

In these cases, it is important to underline that:

- The switch from brand drug to generic formulation has been suggested by the pharmacist. Pharmacist can recommend and sell generic drugs instead of a brand name medication in agreement with the Italian law (number 149-July 26, 2005) if the doctor, as in this case, doesn't specifically prohibit the generic substitution on the prescription.
- All factors related to the lack of efficacy, e.g., dispensing error, diseases, drug interactions, resistance to quinolones,^[16-29] were excluded. The development of resistance may be excluded because in the first case microbiological evaluation revealed a high sensibility of bacteria to antibiotic; however, in all patients treatment with brand formulations induced an improvement in both clinical and laboratory findings without the development of side effects.

- With the exception of the first case, in all other cases reported, the lack of effects cannot be completely confirmed since the patients continued with the same drug; so, it could be argued that also continuing with the generic drug a therapeutic effect might have been observed. In any case, the lack of an early efficacy during treatment is controversial and further studies are warranted.

Therefore, in these cases a lack of efficacy during treatment with generic formulations may be hypothesized.

Several mechanisms could be involved in both lack of efficacy and development of side-effects:

Difference of $\pm 20\%$ of bioequivalence between generic and brand

This difference could play a role in the effectiveness of drugs and it is very relevant during treatment with antibiotic drugs. In particular, ciprofloxacin undergoes hepatic metabolism for about 60% with a bioavailability of 50-65% and shown a half-life of 3-5 h. It is excreted by active tubular secretion. Levofloxacin has a very high bioavailability (about 100%), a hepatic metabolism and a half-life of 6-8 h. The efficacy of fluoroquinolones in bacterial infections is determined by the possibility to obtain appropriate values of pharmacokinetic and pharmacodynamic indexes: Area under the inhibitory time curve = area under the concentration (AUC)₍₀₋₂₄₎/MIC (the AUC-time curve over 24 h divided by the MIC) and C_{max}/MIC (the peak level divided by the MIC).^[30] Therefore a reduction in bioequivalence between generic and brand could induce a decrease in the clinical efficacy, particularly in patients with a cytochrome P450 polymorphism.^[31,32]

Moreover, it is important to underline that in agreement with current law the difference of 20% in bioequivalence is between brand drug and its generic formulation, but it is not possible to define the bioequivalence during the switch between generic formulations.

Difference in excipients

Previous study suggested that a possible explanation in clinical difference between brand formulation and a generic one might be represented by the difference in excipients.^[33]

In Italy, the actual law (Legislative Decree 219/2006 in G.U. n. 142 of 21.06.2006) does not consider as relevant for drug response the differences in excipients.

In fact, the presence of excipients that could influence "gastrointestinal transit (e.g., sorbitol, mannitol, etc.), absorption (e.g., surfactants or excipients that may affect transport proteins), *in vivo* solubility (e.g., co-solvents) or *in vivo* stability of the active substance" is also indicated in the EMA guideline for bioequivalence.^[34]

Moreover, several studies documented that a difference in excipients is related with the loss of response during treatment with the generic formulations.^[9,35]

Other studies reported the development of an allergic reaction to croscarmellose sodium used as excipient in a generic furosemide preparation in a patient who had previously been taking branded furosemide.^[36] Similarly, a lactose-intolerant patient with an arrhythmia who was switched from one formulation of antiarrhythmic drug (e.g., Isoptin 120 mg[®] or Rytmonorm 300 mg[®]) to another that contains a lactose-based excipient (e.g., Verapamil e.g.[®] or Propafenone Sandoz[®]) may experience gastrointestinal disturbances, which in turn, could affect gut transport time and overall drug absorption, thereby affecting systemic levels of the drug. Moreover, Reiffel^[37] reported associations between arrhythmia recurrence, proarrhythmia and death in patients with cardiac arrhythmias after the formulations' switch.

Difference in excipients [Tables 2 and 3] could be involved in the lack of efficacy reported in our case series.

Impurity of pharmaceutical preparation

Several studies are shown that generics formulations had a total impurity rate superior to the 3% in comparison to brand formulation. This factor has been previously reported to affect the bioavailability of the drug and therefore, its therapeutic efficacy.^[38]

In this light, the switch from brand to generic formulation might not always be considered favourable according to cost-effectiveness.

Table 2: Differences in excipients between brand (Tavanic[®]) and generic (Ranbaxy[®]) formulation of levofloxacin 500 mg

Excipients	Tavanic (500 mg)	Ranbaxy (500 mg)
Tablet core		
Crospovidone	+	+
Hypromellose	+	–
Hydroxypropyl cellulose	–	+
Magnesium stearate	–	+
Microcrystalline cellulose	+	+
Sodium stearyl fumarate	+	–
Tablet coating		
Hypromellose	+	+
Titanium dioxide (E171)	+	+
Talc	+	–
Macrogol	+	+
Yellow ferric oxide	+	+
Red ferric oxide	+	+
Indigotin (E132)	–	+
Sunset yellow orange (E110)	–	+

Table 3: Differences in excipients between brand (Ciproxin[®]) and generic (Mylan[®]) formulation of ciprofloxacin 750 mg

Excipients	Ciproxin (750 mg)	Mylan generics (750 mg)
Microcrystalline cellulose	+	+
Cornstarch	+	+
Crospovidone	+	+
Pre-gelatinized starch	–	+
Colloidal anhydrous silica	+	+
Magnesium stearate	+	+
Hypromellose	+	+
Titanium dioxide (E171)	+	+
Polydextrose	–	+
Glycerol triacetate	–	+
Macrogol 8000	+	+

In fact, a retrospective study, that evaluated the effect of generics on price and consumption of ciprofloxacin in primary health-care, has demonstrated a significant increase in the total consumption of oral ciprofloxacin and an increased resistance of *E. coli* obtained from urine isolates.^[39]

Moreover, in October 2012, the Drugs Italian Agency (Agenzia Italiana del Farmaco), suggested, for antiepileptic drugs (e.g., levetiracetam and topiramate), to maintain chronically treated patients under the same formulation avoiding switch from a manufacturer to another. In other words, newly diagnosed epileptic patients starting an anticonvulsant treatment with a specific formulation should be maintained on the same identical drug.

CONCLUSION

In conclusion, the use of generic drugs could be related with an increased days of disease (time to relapse) or might lead to a therapeutic failure; on the other hand, a higher drug concentration might expose patients to an increased risk of dose-dependent side-effects. Overall, it is advisable to well evaluate the effects of generic formulations during the therapeutic treatment.

In agreement with Manning and Smith,^[41] it is necessary to underline the importance that clinician's change their attitude toward pharmacovigilance and post-marketing surveillance systems, which can help to identify the lack of efficacy during the treatment with generic formulations.

ACKNOWLEDGMENTS

The Italian Drug Agency (Agenzia Italiana del Farmaco) is kindly acknowledged for its financial and technical support.

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How to cite this article: Gallelli L, Palleria C, De Vuono A, Mumoli L, Vasapollo P, Piro B, Russo E. Safety and efficacy of generic drugs with respect to brand formulation. *J Pharmacol Pharmacother* 2013;4:110-4.

Source of Support: Nil. **Conflict of Interest:** Nil.