Annales Pharmaceutiques Françaises (2014) 72, 178—183

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

ORIGINAL ARTICLE

Generic vancomycin products: Analysis of serum concentrations in patients with acute myeloid leukemia

Génériques de vancomycine : analyse des concentrations sériques chez des patients atteints de leucémie aiguë myéloïde

A. Monnier[a], C. Malbranche[a], P. Fagnoni[a,b], L. Serge Aho[c], P. Guerard[d], C. Sgro[e], M.-H. Guignard[a], D. Croisier-Bertin[f], P. Chavanet[f], M.-L. Chrétien[g], D. Caillot[g], M. Boulin[a,*,b]

[a] *Department of Pharmacy, University Hospital, 14, rue Gaffarel, 21000 Dijon, France*
[b] *University of Burgundy, EA4184, BP 87900, 21079 Dijon, France*
[c] *Department of Epidemiology, University Hospital, 14, rue Gaffarel, 21000 Dijon, France*
[d] *Department of Pharmacology-Toxicology, University Hospital, 2, rue Angélique-Ducoudray, 21000 Dijon, France*
[e] *Department of Pharmacovigilance, University Hospital, 14, rue Gaffarel, 21000 Dijon, France*
[f] *Department of Infectious Diseases and Vivexia, University Hospital, 14, rue Gaffarel, 21000 Dijon, France*
[g] *Department of Hematology, University Hospital, 14, rue Gaffarel, 21000 Dijon, France*

Received 7 August 2013; accepted 19 December 2013
Available online 21 January 2014

KEYWORDS
Vancomycin;
Serum concentration;
Generic product;
Acute myeloid leukemia

Summary Concerns have recently emerged about the quality of generic vancomycin products. Our aim is to analyze serum vancomycin concentrations measured 48 hours after the start of an empirical treatment regimen in patients with acute myeloid leukemia (AML) who received one of the two generic vancomycin products available in France.
Patients and methods. — Seventy-nine AML patients treated with vancomycin during two study periods were included in the study. Our vancomycin dosing regimen was based on the patients' total body weight adjusted for renal clearance.
Results. — A total of 93 serum vancomycin concentrations were collected: 31 in period 1 and 62 in period 2. In bivariate analysis, the mean serum vancomycin concentrations were not significantly different (19.9 ± 11.2 mg/L in period 1 vs 18.9 ± 6.0 mg/L in period 2, $P = 0.64$). In

* Corresponding author.
E-mail address: mathieu.boulin@chu-dijon.fr (M. Boulin).

0003-4509/$ — see front matter
http://dx.doi.org/10.1016/j.pharma.2013.12.010

the final generalized estimating equations model, serum vancomycin concentrations correlated statistically with a positive coefficient for age ($P < 0.001$) and with negative coefficients for male sex ($P = 0.001$) and hemoglobin level ($P = 0.021$).
Conclusion. — Serum vancomycin concentrations measured 48 hours after the start of an empirical treatment were not influenced by the nature of the generic product but correlated with age, sex and hemoglobin level in AML patients.

MOTS CLÉS
Vancomycine ;
Concentration sérique ;
Médicament générique ;
Leucémie aiguë myéloïde

Résumé Des doutes sur la qualité des génériques de vancomycine ont été émis récemment. Notre objectif est d'analyser les concentrations sériques de vancomycine mesurées 48 heures après le début d'un traitement empirique chez des patients atteints de leucémie aiguë myéloïde, ayant reçu l'un ou l'autre des 2 génériques de vancomycine disponibles en France.
Patients et méthodes. — Soixante-dix-neuf patients traités par vancomycine durant 2 périodes correspondant à la disponibilité de chacun des 2 génériques ont été inclus dans l'étude. Notre schéma de traitement de vancomycine était basé sur le poids des patients ajusté à leur fonction rénale.
Résultats. — Quatre-vingt-treize concentrations sériques de vancomycine ont été recueillies : 31 durant la période 1 et 62 durant la période 2. L'analyse univariée n'a pas rapporté de différence significative entre les concentrations sériques moyennes de vancomycine entre les 2 périodes ($19,9 \pm 11,2$ mg/L (période 1) vs $18,9 \pm 6,0$ mg/L (période 2), $p = 0,64$). Dans le modèle linéaire généralisé final, la concentration sérique moyenne de vancomycine était liée avec un coefficient positif à l'âge ($p < 0,001$) et avec des coefficients négatifs au sexe masculin ($p = 0,001$) et au taux d'hémoglobine ($p = 0,021$).
Conclusion. — Les concentrations sériques moyennes de vancomycine mesurées 48 heures après le début d'un traitement empirique n'étaient pas influencées par la nature du générique de la molécule mais étaient corrélées à l'âge, au sexe et au taux d'hémoglobine des patients atteints de leucémie aiguë myéloïde.

For several years, the World Health Organization (WHO), governments and drug-regulatory agencies have encouraged the development of generic products for economic reasons and because they are the sole therapeutic option in countries that lack the innovator product [1]. In 2008, the percentage of generics among all drugs submitted for approval to the ex Agence Française de Sécurité Sanitaire des Produits de Santé and to the European Medicines Agency was 90% and 65%, respectively. According to the WHO, two products are therapeutically equivalent ''if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical, or in vitro studies'' [1]. However, generic parenteral formulations do not have to demonstrate their therapeutic equivalence because it ''may be considered self-evident'' [1].

In 2010, it was demonstrated that 3 generics of vancomycin did not have the same in vivo efficacy as the innovator product (Vancocine®, Lilly; no longer available). The authors showed under different conditions in neutropenic mice infected in the thighs with two wild-type clinical strains of *Staphylococcus aureus*, that the maximal antibacterial effect expressed as E_{max} (log10 CFU/g) was significantly superior for the innovator product than for the 3 generics [2]. The conclusions of this study have to be interpreted with caution since the animal model used was considered not validated for the evaluation of the efficacy of antibacterial agents by a panel of experts [3] and since a recent stringent methicillin-resistant *S. aureus* (MRSA) endocarditis model found no significant differences in the bactericidal activities of six generic vancomycin products [4]. In France, only 2 vancomycin generics are now available.

Therefore, the objective of our study was to analyze, as a parameter that reflects the antibacterial activity of the antibiotic, serum vancomycin concentrations (SVCs) measured 48 hours after the start of treatment in two groups of patients with acute myeloid leukemia (AML) receiving intensive chemotherapy, and empirically treated for febrile neutropenia with one of two vancomycin generics available in France.

Patients and methods

Study design

This was a single-center, retrospective study. All adults (≥ 18 years old) admitted to the Hematology Unit of our teaching hospital, receiving induction or consolidation chemotherapy for AML, and treated with our standard vancomycin empirical treatment regimen were eligible. AML diagnosis was based on the World Health Organization (WHO) criteria [5]. The standard vancomycin empirical treatment regimen in