



# REVISTA DE GASTROENTEROLOGÍA DE MÉXICO

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## EDITORIAL

### Fecal concentration of intravenous vancomycin preparation after oral administration: Preclinical data supporting unmet clinical needs<sup>☆, ☆☆</sup>



### Concentración fecal de la preparación de vancomicina intravenosa posterior a administración oral: datos preclínicos que sustentan necesidades clínicas no satisfechas

Antimicrobial resistance is one of the biggest global health threats in our time, according to the World Health Organization. Therefore, efforts to optimize the use of antimicrobial medicines and develop sustainable innovation are part of the objectives of worldwide actions<sup>1</sup>. In low and medium-income countries, such as those in Latin America, we may see the coexistence of insufficient access to antibiotics and excessive consumption, making distribution and regulation a difficult challenge<sup>2</sup>. Thus, it is important to provide scientific evidence, at all levels, on the correct use of those drugs.

One example is the oral administration of vancomycin (either by off-label use of the parenteral presentation or by specific oral formulations), given that its use has increased in the treatment and prevention of active *Clostridioides difficile* infection (CDI). Although typically used in severe forms of CDI, vancomycin usually supersedes metronidazole, especially for mild-to-moderate disease<sup>3</sup>. A rationale behind said substitution is that almost 25% of patients have disease recurrence after initial treatment, and a second recurrence is reported in 35% of patients<sup>4</sup>. In addition, metronidazole

resistance in CDI has been reported from 0 to 18.3% and can be unstable, inducible, and heterogeneous<sup>5</sup>. Moreover, vancomycin has good water solubility, protease stability, and lacks metabolism<sup>6</sup>, and its poor absorption from the gastrointestinal tract results in high intracolonic drug levels<sup>7</sup>. This is clearly an advantage when CDI is confined to the colon, long-term therapy is needed, and systemic adverse events may complicate baseline health conditions.

A low-dose regimen of oral vancomycin, using the intravenous formulation (i.e., 125 mg every 6 h) has demonstrated no detectable drug in the serum of patients with different levels of renal function<sup>7</sup>. Other reports suggest that higher doses (500 mg of vancomycin capsules), severe CDI (with increased intestinal permeability), and renal compromise (supportive dialysis) are risk factors for systemic vancomycin absorption after oral administration<sup>3</sup>. Effects of assay detection limits, associated morbidities, concomitant drugs, and dosage regimens make the findings on the non-absorbable property of oral administration of vancomycin inconclusive. Nonetheless, the risk-benefit balance is positive, compared with the known systemic effects of intravenous vancomycin (ototoxicity, nephrotoxicity).

It is important to remember that the most feared adverse event for vancomycin, the “red man syndrome”, has been reported with both intravenous and oral administration, given that it is not related to systemic drug concentration<sup>3</sup>.

Despite the available information, switching vancomycin to noninvasive administration routes to increase patient quality of life and reduce direct and indirect costs, as well as systemic adverse events, is still an incomplete task. In that context, the original article by Ramos-García et al. that is published in the current issue of the *Revista de Gastroenterología de México*, “Fecal concentration of intravenous vancomycin preparation after oral administration

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<sup>☆☆</sup> See related content at

<https://doi.org/10.1016/j.rgmex.2022.03.005>, Ramos-García J, Robles-Rivera F, Chávez-Soto M, et Al. Fecal concentration of intravenous vancomycin preparation after oral administration in an experimental model: preclinical assay. *Rev Gastroenterol Mex*. 2023;88:85–90.

in an experimental model: preclinical assay'' is an important contribution because it provides preclinical evidence that corroborates the important excretion of intravenously designed vancomycin in stools after oral dosing, using a murine model.

Several significant messages can be highlighted: first, the confirmation that stool concentration is dose-dependent (mouse dosing equivalent to 125 mg and 500 mg in humans); second, that vancomycin showed important concentration as fast as 2 h post dose; and third, that at 6 h, the low-dose regimen showed a decrease in stool concentration of vancomycin (below the 2 h data), confirming the need for an administration schedule of every 6 h.

Some of the concerns regarding the discussion presented in the manuscript should be addressed in future work. Alongside the ones identified by the authors, others are proposed. For example, the safety of the oral administration of vancomycin in their experimental study cannot be properly analyzed, because no specific details on mouse necropsy (if any) were provided. Moreover, the study design was meant for acute exposure only (single dosing). In the clinical setting, oral vancomycin can be needed for at least one week, and tapering is preferred to the traditional loading dose regimens. The fact that vancomycin is a concentration-independent antibiotic and that higher peak concentrations do not reflect clinical efficacy should be kept in mind<sup>8</sup>.

Further experiments must properly address systemic effects of long-term exposure. In addition, extrapolating vancomycin's stool concentration to the minimum inhibitory concentration or to the minimum bactericidal concentration (MBC<sub>90</sub>) is risky, given that there are other factors to consider. For example, the total quantity of water drunk, if different between groups, could have misrepresented the vancomycin concentration in stool, unless dry weight or other harmonization strategies were put in place. Furthermore, even though the doses tested resemble the current availability of vancomycin for humans, the suggestion to use the 500 mg dosing regimen as the starting dose in CDI is not in line with the current clinical recommendations. At present, tapering doses, instead of loading them, is recommended for mild CDI and moderate CDI.

In conclusion, the study by Ramos-García et al. and the projects derived from it will contribute to further evaluating the oral administration of intravenous-intended vancomycin as a novel approach to improve CDI treatment in our clinical setting. Clinical efficacy, safety, costs, and quality of life in those patients are the main outcomes to be addressed in future projects.

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## Conflict of interest

The author has been an academic and researcher at public and private institutions. He works for Takeda México S.A. de C. V. in the area of pharmacovigilance. The text solely and exclusively reflects his professional experience in the area of pharmacology and is not related to his current position.

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