Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense*)
Lat. Am. J. Pharm. **41** (7): 1295-9 (2022)

Received: March 21, 2022
Accepted: May 26, 2022

CYP2C19 Mediates the Inhibitory Effect of Sinomenine on Cyclophosphamide Pharmacokinetics in Rats

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SUMMARY. **To evaluate the potential of sinomenine-cyclophosphamide interaction and to reveal the mechanism, male Sprague-Dawley rats were treated with the single administration of sinomenine or cyclophosphamide or the co-administration of two drugs with six of each. The pharmacokinetics and corresponding parameters were analyzed to evaluate the pharmacokinetic interaction between sinomenine and cyclophosphamide. *In vitro* assessment was conducted in rat liver microsomes, which estimated the metabolic stability and CYP2C19 activity. Sinomenine significantly increased the AUC (13.93 ± 2.17 vs. 6.10 ± 2.63 μg×h/mL), C_{max} (2.20 ± 0.23 vs. 1.23 ± 0.17 μg/mL), and $t_{1/2}$ (10.01 ± 1.31 vs. 2.87 ± 0.49 h) and reduced clearance rate (1.26 ± 0.20 vs. 4.22 ± 2.78 L/h/kg) of cyclophosphamide. No significant changes were observed in sinomenine after co-administration. Additionally, sinomenine could improve cyclophosphamide metabolic stability and suppress the activity of CYP2C19. The co-administration of sinomenine and cyclophosphamide increased systemic exposure of cyclophosphamide through inhibiting CYP2C19.**

RESUMEN. Para evaluar el potencial de la interacción sinomenina-ciclofosfamida y revelar el mecanismo se trataron ratas macho Sprague-Dawley con la administración única de sinomenina o ciclofosfamida o la coadministración de dos fármacos con seis de cada uno. Se analizaron la farmacocinética y los parámetros correspondientes para evaluar la interacción farmacocinética entre sinomenina y ciclofosfamida. Se realizó una evaluación *in vitro* en microsomas de hígado de rata, que estimó la estabilidad metabólica y la actividad de CYP2C19. La sinomenina aumentó significativamente el AUC (13,93 ± 2,17 frente a 6,10 ± 2,63 μg×h/mL), Cmax (2,20 ± 0,23 frente a 1,23 ± 0,17 μg/mL) y $t_{1/2}$ (10,01 ± 1,31 frente a 2,87 ± 0,49 h) y tasa de eliminación reducida (1,26 ± 0,20 frente a 4,22 ± 2,78 L/h/kg) de ciclofosfamida. No se observaron cambios significativos en la sinomenina después de la administración conjunta. Además, la sinomenina podría mejorar la estabilidad metabólica de la ciclofosfamida y suprimir la actividad de CYP2C19. La administración conjunta de sinomenina y ciclofosfamida aumentó la exposición sistémica de ciclofosfamida mediante la inhibición de CYP2C19.

KEY WORDS: cyclophosphamide, CYP2C19, pharmacokinetics, sinomenine.

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ISSN 0326 2383 (printed ed.)
ISSN 2362-3853 (on line ed.)