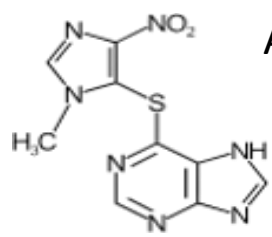


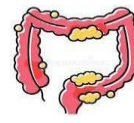
Laura López Guerra, Eva Aguilar Duque, Manuel Ángel Torrecilla Abril, Adrián Domínguez García, Silvia Peña Caba, Benito García Díaz.
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BACKGROUND AND IMPORTANCE



AZATHIOPRINE:

- Non-specific immunosuppressor
- Narrow therapeutic range (0.157-0.3mg/L)
- Inflammatory bowel disease



Metabolism: enzymes as **TPMT** and **NUDT15**, which polymorphisms can diminish its clearance. A 30–80% dose reduction is recommended in patients with heterozygous mutant genotype.

AIM AND OBJECTIVES



To perform population-based simulations using an azathioprine pharmacokinetic model to narrow down the dose adjustment in patients with TPMT or NUDT15 polymorphisms.

MATERIALS AND METHODS



LITERATURE SEARCH

Population pharmacokinetics of azathioprine active metabolite in patients with inflammatory bowel disease and dosage regimens optimisation

Rongfang Lin¹, Weiwei Lin¹, Changlian Wang¹, Jiashan Dong¹, Weiwei Zheng², Dayong Zeng¹, Yiwei Liu¹, Cuihong Lin¹, Zheng Jiao³, Pinfang Huang¹

N=100

Covariates that influenced clearance:

- Body weight
- TPMT heterozygous variant
- Concomitant mesalazine treatment

MONOCOMPARTMENTAL PHARMACOKINETIC MODEL WITH FIRST-ORDER KINETICS, INTERINDIVIDUAL VARIABILITY 0.342 AND RESIDUAL VARIABILITY 0.054 → ADAPTED BY ADDING THE ABSORPTION PHASE ($K_a = 7.12 \text{ h}^{-1}$)

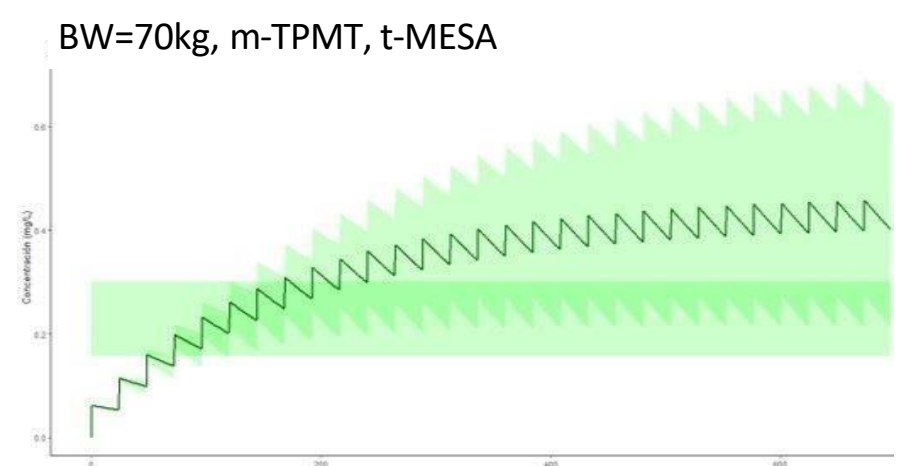
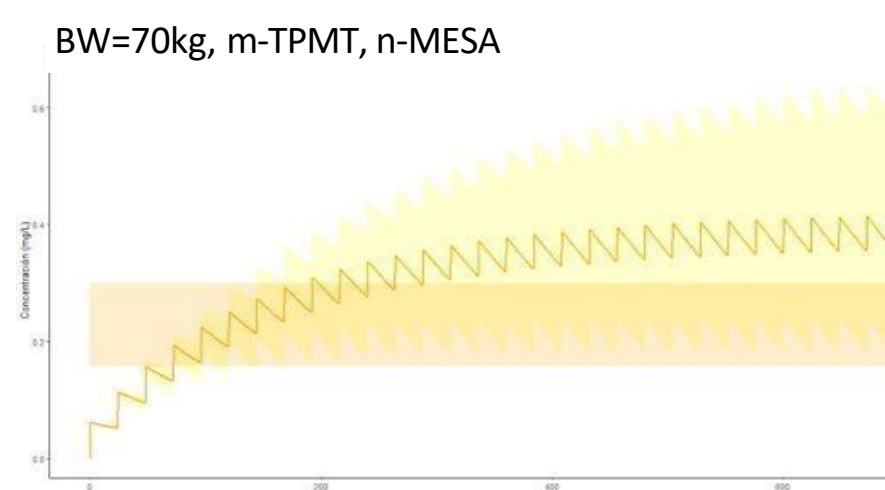
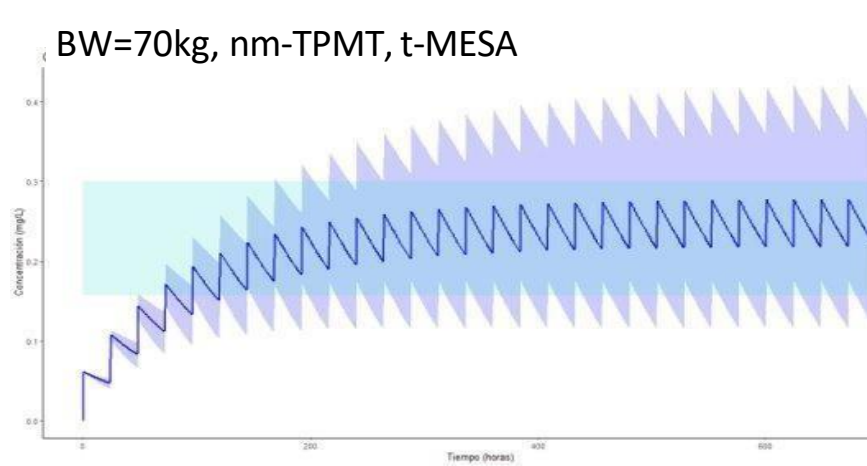
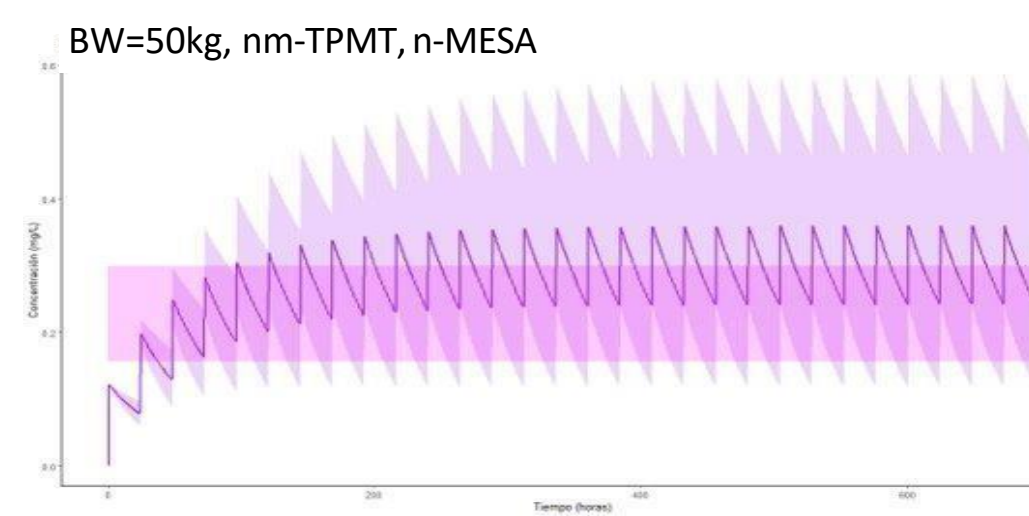
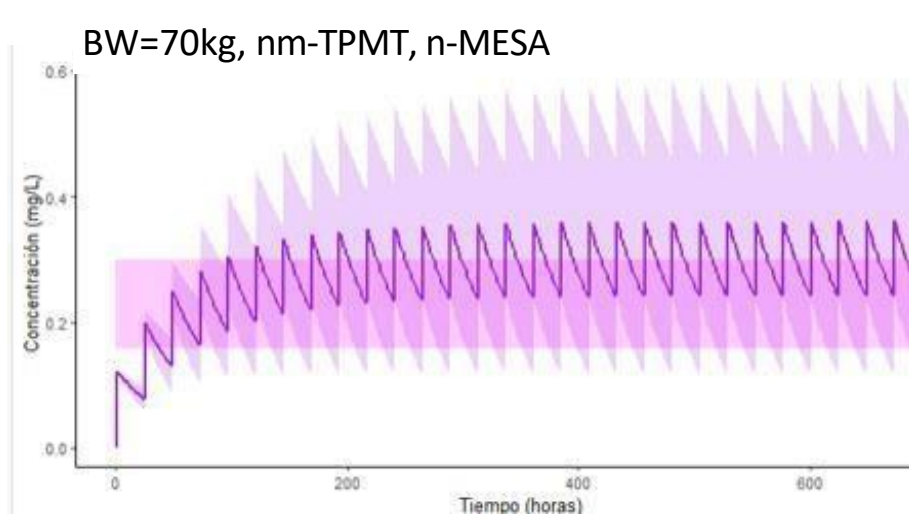
- Population-based Monte Carlo simulations were performed for 100 patients, and a dose of 50mg of azathioprine every 24h, obtaining mean plasma concentrations and 5th-95th percentiles.
- R was used for performing the simulations, with *mrgsolve* language package and *ggplot* to create the graphics representing azathioprine plasma levels versus time.
- A shiny app was also created.

RESULTS

WE OBTAINED A BICOMPARTMENTAL PHARMACOKINETIC MODEL WITH FIRST-ORDER PHARMACOKINETICS, WITH THE DIFFERENTIAL EQUATION:

$$Dxdt_{Cp} = 7.12 \text{ h}^{-1} \times C_{gut} - \left[\frac{11.6 \times \left(\frac{BW}{70}\right)^{0.625} \times \theta_{TPMT} \times \theta_{MESALAZINE} \times e^{-\gamma CL}}{809(V)} \right] \times Cp$$

Non-mutated TPMT (nm-TPMT) = 1, mutated (m-TPMT) = 0.515, no mesalazine treatment (n-MESA) = 1 and treated with mesalazine (t-MESA) = 0.802. Simulations results are expressed as mean trough concentration in steady state (m-TCSS), (5th-95th percentiles).



CONCLUSION AND RELEVANCE

- ✓ The mean concentrations obtained with the adapted model can provide a more accurate estimate of the starting dose of azathioprine for patients according to body weight, TPMT polymorphism, and treatment with mesalazine than previous recommendations.
- ✓ Interindividual variability is substantial, and further studies are required to confirm it.
- ✓ Azathioprine might be considered for pharmacokinetic monitoring given its narrow therapeutic range.

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