Clinical Pharmacology
& Biopharmaceutics

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& L W D W L R Q Vázquez M P, Alvariza S, Ibarra M, Maldonado C, et al. (2014) Skin Reactions Associated to Phenytoin Administration: Multifactorial Cause. Clin Pharmacol Biopharm 3: 125. doi:

the reaction mix, for the EPHX1 and EPHX2 genotyping protocol, and between 50 and 100 ng, for the COMT genotyping protocol. To determine the genotype of EPHX1 and EPHX2 a real time-PCR (Polymerase chain reaction) protocol was used, TaqMan Drug Metabolism Genotyping Assay (Applied Biosystems kits), for rs1051740 and rs2234922 performed in StepOne (Applied Biosystems). To determine COMT activity, a conventional PCR was performed, the PCR product was veri ed by gel electrophoresis in polyacrylamide 6%, 5 L of the PCR product was puri ed and sequenced with specially designed primers and BigDye® Terminator v3.1 Cycle Sequencing Kit, then the product was puri ed with Big Dye X-Terminator Puri cation kit and a capillary electrophoresis in ABI3500 sequencer was performed.

Pharmacokinetic analysis

e area under the steady-state plasma concentration versus time curve ($AUC_{ss\ 0\text{-}T}$) was calculated using the trapezoidal rule until the end of the interval of administration (T). Beta ( ), the rst order elimination rate constant, was calculated from the slope of the terminal log-linear concentration-time regression in Treatment A. In Treatment B, was estimated once the drug was discontinued (from day 15). Steady state average concentration ($C_{mean\ ss}$) was determined as $AUC_{ss0\text{-}T}$

7 PtW D O 0 H Q : R P H Q (S D Q X W L Q Subjects633Age (years)21 (19-23)21 (19-23)21 (20-23)Weight (kg)70.1 (53.7-86m8)80

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in increased amounts of o-quinone metabolites. Hence, an increased production and/or decreased detoxi cation of arene oxide metabolites seemed to be the cause in triggering the immune response. Genetic

a compensation of the amount of arene oxide and p-HPPH formed so once again a defective EPHX activity seems to be one of the main genetic causes responsible for the cutaneous adverse event. In addition, the metabolite p-HPPH can follow two routes: glucuronidation and PHT catechol formation. e latter involves CYP2C enzymes and arene oxide formation as well. Five out of the six volunteers that experienced rash had a higher p-HPPH concentration (mean ± SD, 0.121 mg/L ± 0.018) and a decreased EPHX activity. Subject E1, despite a decreased EPHX activity, did not experience the cutaneous reaction. is subject had a lower p-HPPH concentration (0.064 mg/L), and therea er the subsequent arene oxide of pHPPH might also be reduced.

Conclusions

According to our observations, arene oxide metabolite seems to be the responsible for the immune response observed. In our study population, the genesis of the cutaneous response a er PHT administration appears to be multifactorial: to have genetic disposition leading to a defective EPHX activity; to be a woman in the fertile life period, or with contraceptive therapy; to have a higher formation rate of the arene oxide due to a rapid input of the drug (rapid infusion or the formulation itself), or due to a faster PHT metabolism.

Con ict of Interests

ere is no con ict of interests regarding the publication of this paper.

$ F N Q R Z O H G J H P H Q W V

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