Population Pharmacokinetics of Imatinib in Nigerian Patients with Chronic Myeloid Leukaemia: A Need for Dosage Review

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Background: Pharmacokinetic studies on imatinib in patients with chronic myeloid leukaemia (CML) have established inter-individual and inter-population variations in its disposition. However, none of these studies have been performed in African patients; hence this study investigated the disposition of imatinib in Nigerians with CML, established a valid population pharmacokinetic model and examined the involvement of genetic factors in the variability of the drug disposition.

Methodology: A total of 250 plasma concentrations from 126 recruited CML patients including 15 imatinib-naive patients were quantified for imatinib using a validated HPLC-DAD method. Population pharmacokinetic models were fitted to the data using NONMEM VII software. Covariate analyses were performed to estimate the effect of age, neutrophils, sex, tribe, packed cell volume, platelet count, weight, white blood count (WBC) and genetic polymorphism corresponding to CYP3A5*3 and ABCB1 3434C>T on clearance.

Results: The mean population-derived apparent steady state clearance, $t_{\beta 1/2,}$ AUC_{24} and V_d were 17.2±1.8L/h., 12.05±2.1h, 23.26 ±0.6μg•h/mL and 299±20.4L, respectively. WBC ($P<0.001$,df2), tribe ($P<0.05$,df1), CYP3A5*3 ($P<0.001$,df2), and ABCB1 C3435T ($P<0.001$,df2), were found to have significant influence on apparent clearance. The inter-individual variability in clearance and inter-occasion variability in bioavailability were 17.4% and 20.4% respectively. There was higher apparent clearance and lower AUC_{24} in this population was linked to influence of genetic polymorphism in CYP3A5*3 and ABCB1 C3435Ton the disposition of imatinib.

Conclusion: This study suggests the need for a review of dosage and dosage regimen in this population and possible need for therapeutic drug monitoring-guided dose individualization.