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The pharmacokinetics of nevirapine when given with isoniazid in South African HIV-infected individuals

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Summary

Isoniazid preventive therapy is recommended in patients on antiretroviral therapy. Isoniazid inhibits CYP3A4, which metabolizes nevirapine. Administration of isoniazid may cause higher nevirapine concentrations and toxicity. We studied the effect of isoniazid on nevirapine concentrations in 21 patients randomized to either placebo (n=13) or isoniazid (n=8) in an ongoing trial of IPT in patients on ART. Isoniazid was associated with a 24% increase in median nevirapine AUC₀₋₁₂, which was not statistically significant (p=0.66).

Keywords

Isoniazid; nevirapine; drug interactions; HIV

Brief report

The World Health Organization (WHO) recommends isoniazid preventive therapy (IPT) in patients taking antiretroviral therapy (ART) based on observational data.[1] Although current data suggests that the combination is relatively safe, data is limited.[2,3] Isoniazid inhibits various cytochrome P450 (CYP) isoforms, including CYP3A4.[4] Nevirapine is metabolized to some extent by the CYP3A isoenzyme and co-administration with isoniazid may alter nevirapine concentrations, which could alter toxicity.[5,6]

We studied the interaction between nevirapine and isoniazid in HIV-infected participants established on a nevirapine-based ART regimen who were enrolled in a pragmatic randomized controlled trial (RCT) of IPT in participants on ART.[7] In the RCT participants

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were randomly assigned to either isoniazid or placebo. Participants who were on nevirapine-based ART were approached to participate in this sub-study during a 3-week enrolment period when they attended their study visits. Participants had to be on placebo or isoniazid for at least 1 month. The RCT investigators had to remain blinded and analysis of isoniazid concentrations concurrently with nevirapine concentrations determined the allocation sequence in this study. The results were only given to the lead investigator (EHD) who was not involved in the RCT. Exclusion criteria were poor adherence to the IPT study protocol; excessive alcohol consumption (in excess of 2 units per day or 14 units per week); chronic hepatic or gastrointestinal disease; taking drugs other than the study drugs known to alter the pharmacokinetics of nevirapine, and pregnancy. The study was approved by the University of Cape Town Human Research Ethics Committee and written informed consent was obtained from each participant.

Participants were admitted overnight and fasted from 22h00. The nevirapine dose taken the evening before pharmacokinetic sampling was observed and taken 12 h before the first pharmacokinetic sample was collected. Blood samples were collected pre-dose in the morning and at 1 h, 2 h, 4 h, 6 h, 8 h and 12 h after the observed morning dose. Standardised meals were given between the 1 h and 2 h, the 4 h and 6 h, and 8 h and 12 h sampling times respectively.

Within 1 hour of sampling, the blood samples were centrifuged, aliquoted and stored at -80°C until determination of drug concentration. We used validated liquid chromatography tandem mass spectrometry (LC/MS-MS) to determine the nevirapine, isoniazid and acetyl-isoniazid concentrations in the plasma samples. Nevirapine was assayed as previously described.[8] The assay range for NVP, isoniazid and acetyl-isoniazid were 0.078 – 15 $\mu\text{g/ml}$, 0.1 – 15 $\mu\text{g/ml}$ and 0.02 – 15 $\mu\text{g/ml}$ respectively. Inter- and intra-day coefficients of variation were below 10%. We calculated the isoniazid phenotype acetylase status by determining the AUC ratio of acetyl-isoniazid:isoniazid ratio as previously described.[9] The laboratory participates in the International Interlaboratory Control Program of Stichting Kwaliteitsbewaking Klinische Geneesmiddelenanalyse en Toxicologie (KKGT; Hague, The Netherlands).

Using previously published local data,[8] we calculated that we required at least 8 participants in each group in order to detect at least a 30% increase in AUC_{0-12} assuming a one-sided increase, 5% significance and 80% power. Stata version 11.0 (Stata Corporation, College Station, Texas) was used to characterize the pharmacokinetic parameters of nevirapine using non-compartmental analyses. The area under the plasma concentration-time curve (AUC_{0-12}) was calculated for the 12 h dosing interval using the linear trapezoidal rule. Numerical data that followed a non-normal distribution were described using median and interquartile range (IQR), and the Wilcoxon signed-rank test was used for hypothesis testing. At the end of the study we recalculated the sample size using this cohort's nevirapine data and we were powered to detect a 53% difference in nevirapine AUC (power of 80%, significance of 5%, one sided, patient ratio of 13:8).

We enrolled 21 black African participants in the study, of whom 20 were female. All participants were established on nevirapine-based ART for at least 6 months. Thirteen

participants were randomly assigned to receive placebo and 8 participants to isoniazid. The median (IQR) of the baseline characteristics in the placebo and isoniazid groups respectively were: age 33 (26.5 – 38) and 33 (31 – 36) years, $p=0.97$; body mass index 26 (22 – 29.8) and 32.1 (29.2 – 33.4), $p=0.08$; and CD4-count 256 (194 – 461) cells/mm³ and 380 (218 – 408) cells/mm³, $p=0.51$. The median (IQR) of the nevirapine pharmacokinetic measures in the placebo and isoniazid groups respectively were: AUC₀₋₁₂ 62.5 (52.9 – 87.8) and 77.8 (56.6 – 85.5) mg·h/liter, $p=0.66$; maximum concentration (C_{max}) 6.5 (5.1 – 8.5) and 7.7 (5.7 – 8.6) mg/liter, $p=0.66$; time to maximum concentration (T_{max}) 2 (1-2) hours in both groups; and half-life ($T_{1/2}$) 38.9 (28.4 – 77.3) and 36.5 (24.3 – 197.7) hours, $p=0.77$ (see figure 1). Two participants receiving isoniazid had a slow phenotype acetylator status; their nevirapine AUC₀₋₁₂ were not outliers. We developed a non-linear mixed effect model accounting for the effect of body size through allometric scaling. We incorporated age, sex, body mass index (BMI), acetylator phenotype status and isoniazid AUC in the model to test the effect on the AUC of nevirapine. None were significant.

We studied the effect of isoniazid on the pharmacokinetics of nevirapine. Isoniazid non-significantly increased the median nevirapine AUC₀₋₁₂ by 24%. Our study has some limitations. Firstly, the study was not powered to detect larger changes in nevirapine concentrations, making it possible that the non-significant increase may be due to chance. Secondly, we were not able to account for intra-individual variability by sampling the same individuals before and after IPT. Thirdly, the isoniazid group had a higher BMI compared with the placebo group (although not statistically significant), potentially leading to higher nevirapine clearance and subsequent lower nevirapine concentrations. Lastly, our sample size is too small to establish the effect of slow and fast isoniazid acetylators on nevirapine as it is possible that the inhibiting effect of isoniazid in slow acetylators may be more pronounced.[10]

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Figure 1. Median and interquartile NVP concentrations over time when administered with (n=8) and without (n=13) INH.