

World Congress on **Infectious Diseases**

August 10-12, 2015 London, UK

The influence of NAT-1 genotype on *Para*-aminosalicylic acid (PAS) pharmacokinetics and intolerance following once daily or twice daily PAS dosing

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Para-aminosalicylic acid (PAS) is still used for extensively- or multidrug- resistant tuberculosis (TB) (XDR or MDR). Despite relatively good survival (81% 5-years) when used with streptomycin, current XDR TB mortality using PAS with remaining drugs is poor (30%-90%).

We reviewed PAS literature concluding that PAS accompanied by weak drugs should be dosed 20 g daily; intolerance did not increase with once daily-dosing. Early bactericidal activity studies found PAS moderately bactericidal.

We studied pharmacokinetics and tolerance over 8-days post-administration of granular slow-release PAS (PASER) 8 g once daily or 2x4 g in 32 patients with MDR or XDR TB using a randomized, two-period, cross-over design; NAT1 and NAT2 genotypes were determined and tolerability assessed by visual-analog scales.

Median C_{max} following PAS once daily and twice daily was 80 and 61 $\mu\text{g/mL}$ and AUC_{0-12} 652 and 428 $\mu\text{g.h/mL}$ respectively ($p < 0.001$ for both comparisons). The commonest NAT1 genotype was *4/*10 found in 45% of patients. The *14A allele was present in two patients (6.3%) and NAT1*3 in one patient all three had higher PAS C_{max} ($p = 0.007$).

Intolerance was similar between regimens; VAS scores for intolerance were low and more than 50% of scores were 0. Neither C_{max} nor AUC was associated with intolerance; occurrence of intolerance differed little between regimens. Women had higher C_{max} ($p = 0.003$), but less intolerance.

PAS could be dosed once daily without increased intolerance; this might improve efficacy. The slow acetylator status of NAT1*4/*10 genotypes is confirmed and for the first time the NAT1*3 allele associated with high PAS concentrations.

Biography

Peter Donald is emeritus professor in The Department of Paediatrics and Child Health, Stellenbosch University, South Africa. His main research interest is the assessment of antituberculosis drugs in adults and children and tuberculosis in childhood. He is author or co-author of more than 200 papers listed in PubMed the majority dealing with tuberculosis and in 2010 he was awarded the gold medal of the International Union against tuberculosis and Lung Disease for his contribution to improving lung health in children.

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