Intracellular Boosting of HIV Protease Inhibitors through inhibition of transport – a novel strategy for potentiating HIV therapy

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Background
The protease inhibitors (PIs) form part of HIV treatment. Following oral administration they are metabolised by cytochrome P450 (CYP P450) enzymes. The PIs are also substrates for transmembrane efflux transporters such as P-gp and MRP-1 and 2. The inhibitory effect of ritonavir (RTV) on CYP3A4 and possibly P-gp allows boosting of plasma concentrations by increasing bioavailability and/or inhibiting hepatic metabolism and excretion. The primary site of action of the PIs is thought to be within the cell. Despite the marked boosting of plasma PI concentrations achieved by RTV, intracellular accumulation has not been observed. In vitro data revealed significant intracellular boosting of lopinavir (LPV) with dipyridamole and furosemide.

Aims
The primary aim of this study was to evaluate the potential of furosemide and dipyridamole on the intracellular accumulation of LPV boosted with RTV in HIV positive subjects. The secondary aims were to evaluate the safety including ECG changes, to evaluate the correlation between any boosting effects of dipyridamole or furosemide and relative expression of drug transporters in peripheral blood mononuclear cells (PBMCs) and to examine the relationship between transporter genotype and intracellular accumulation of the PIs.

There was also a sub-study that aimed to determine raltegravir and maraviroc concentrations in PBMCs.

Results
Of 8 recruited subjects to the main part of the study, data were available for 4 subjects (1 subject excluded due to dynamic non-specific ECG abnormalities at baseline, 1 withdrew consent, 1 unable to sample). There was one screen failure due to low haemoglobin. There were no changes observed in LPV plasma or intracellular concentrations in the presence of either study drug or when co-administered together.

There were no apparent significant differences between LPV intracellular concentrations when furosemide and dipyridamole were administered alone or together. Of note ECG changes were observed in all subjects on addition of study drugs. With small subject numbers statistical analysis was not achievable. With the PIs being associated with PR and QTc prolongation and as no intracellular boosting was observed, this intervention is unlikely to be of benefit in clinical practice.

Five subjects were recruited into the sub-study. PBMCs were isolated and raltegravir intracellular concentrations were determined. Analysis showed that there was no difference between the two different methods to determine intracellular raltegravir concentrations but washing of the PBMCs decreased intracellular concentration.

Dissemination
All publications relating to this trial will be available on our website www.hiv-druginteractions.org. Participants were informed of the website at the time of participation. No other arrangements were

made to feedback to participants. No formal feedback regarding the study results was provided to study participants apart from access to our website.

Results from the sub-study were presented in April 2011 at the 12th International Workshop on Clinical Pharmacology of HIV Therapy. The poster presentation was entitled Investigating variability in reported intracellular raltegravir concentrations: contribution of PBMC isolation methodology.

We are currently preparing an abstract to be submitted to the Third Joint Conference of the British HIV Association (BHIVA) with the British Association for Sexual Health and HIV (BASHH) with the results from the main study.