The Liverpool TDM Registry: Studying influences upon plasma HIV drug exposure

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Background

The treatment of HIV, as for virtually all other infections, depends upon prescribing the same dose of drug to all adults in the expectation that this dose is equally effective in different individuals. For most drugs, the majority of patients will respond as anticipated, some not at all while others develop excessive toxicity even at standard doses. Therapeutic drug monitoring (TDM) has been utilised for over 30 years as a tool to guide clinicians in achieving optimal treatment outcomes for the individual patient, and has most recently been advocated as a tool for optimising HIV therapy, particularly in relation to protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs). HIV treatment guidelines from the USA and across Europe recognise the potential benefit of TDM for optimising anti-retroviral therapy in selected groups of patients e.g. children or pregnant women, or those with drug interactions, liver failure, drug toxicity or receiving unlicensed dosing regimens. Data mining of these registries may be used to estimate effectiveness of therapy (percentage of patients with drug levels which are too low risking failure, or too high risking toxicity) and how this might be affected by gender, ethnicity and body weight. Comparison of drug exposure in specialised groups of patients such as very young children, pregnant mothers, and patients with liver failure (eg through hepatitis co-infection) or renal failure through TDM registries has led to separate dosage recommendations for these patients, which have been reflected in European, US and WHO treatment guidelines. TDM datasets may also be used to screen for unforeseen adverse drug interactions (e.g. between HIV drugs, or with ulcer healing agents, TB drugs and herbal preparations) and more particularly whether with the use of TDM and dose modifications, these interactions may be successfully overcome. Not least, TDM registries may often be the only opportunity to study large surveys of 'real life' data rather than limited interaction data from healthy volunteer or single dose pharmacokinetic studies. The University of Liverpool provided a TDM service for the UK from 1999 to 2006 in which partially anonymised samples were archived along with service request forms containing data such as reason for TDM, concomitant medications, CD4 count, viral load, age, gender, body weight, height, and sample collection details.

Aims

The aim of the study was to create a TDM registry using the existing samples and associated data in order to explore relationships between but not limited to drug exposure and weight, gender, age, co-medications.

The study also aimed to explore the relationship between host genetic polymorphisms and plasma drug concentrations.

Results

The registry was examined for factors influencing plasma concentrations of the NNRTIs, efavirenz and nevirapine. Clear associations between ethnicity and concentrations of both efavirenz and nevirapine were observed. Co-administration of rifampicin showed substantial decreases in concentrations of both efavirenz and nevirapine. Weight, PIs and tenofovir also influenced concentrations.

The registry data was used to evaluate the association of dose, gender, age, weight, ethnicity and concomitant medication on lopinavir and atazanavir plasma concentrations. The analysis showed

that weight, dose and rifabutin influenced lopinavir concentrations whilst dose and efavirenz influenced atazanavir concentrations.

The effect of age on antiretrovirals was found to affect PI plasma exposure but not NNRTI exposure but other clinical parameters showed no significant association.

An investigation into the relationship between atazanavir and pregnane X receptor (PXR) polymorphisms showed that atazanavir concentrations were strongly associated with homozygosity for the PXR 63396T allele resulting in concentrations below the minimum effective concentration.

The PIs but not the NNRTIs were found to be substrates for the drug transporters OATP1A2, OATP1B1 and OATP1B3. The 521T>C polymorphism in SLCO1B1 was significantly associated with higher lopinavir plasma concentrations.

A population analysis was used to quantify the impact of PXR 63396C>T, patient demographics and diurnal variation on atazanavir clearance. The results showed that evening dosing was associated with a higher bioavailability of atazanavir as well as homozygosity for the T allele for PXR 63396.

A population approach was also used to determine the association of CYP3A4*22 with the pharmacokinetics of lopinavir. Patients with the minor allele for CYP3A4*22 had lower clearance of lopinavir. The combined effect of CYP3A4*22 with SLCO1B1 521T>C was also analysed and showed a 9.7 fold higher trough concentration in individuals homozygous for both single nucleotide polymorphisms, compared with noncarriers.

Dissemination

All samples analysed in this study were anonymised so that it was not possible to link the original sample back to any identifiable data therefore, it was not possible to provide formal feedback to individuals. Data generated from the TDM registry has been presented in numerous formats including conference presentations and journal publications. Publications are listed on the University of Liverpool website and can be viewed using the following link https://www.liverpool.ac.uk/translational-medicine/staff/saye-khoo/publications/ with links to a selection of individual published papers below:

https://www.ncbi.nlm.nih.gov/pubmed/18771051
https://www.ncbi.nlm.nih.gov/pubmed/18831695
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