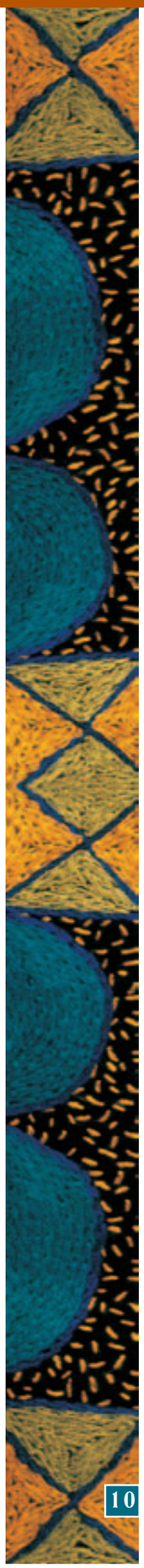

LABORATORY

ANTIRETROVIRAL THERAPEUTIC DRUG MONITORING

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Antiretroviral therapeutic drug monitoring (TDM) is an additional monitoring tool to assist in the management of HIV-infected patients. Antiretroviral TDM is frequently undertaken in Europe, but less often in the USA. This overview will assess the principles, current evidence for, and limitations of TDM. Lastly, the potential role of TDM in southern Africa will be discussed.

GENERAL PRINCIPLES OF TDM

The vast majority of drugs used in clinical practice do not require TDM. It is far easier for clinicians to adopt a 'one size fits all' approach to dosing. Alternatively doses may be modified according to response. However, with some drugs this will result in high rates of toxicity, or suboptimal efficacy.

The characteristics that make drugs suitable for TDM include:

- A narrow therapeutic window
- Good correlation between drug concentration and effect or toxicity
- Variable pharmacokinetics in different individuals
- The availability of a reliable assay.

Digoxin and the first-line anticonvulsants are examples of drugs where TDM plays an important role. However, even when all of these characteristics are present, TDM is seldom done as a routine part of management for every patient. Clinicians typically use TDM if there are clinical concerns such as toxicity, poor efficacy, drug interactions, or special groups at risk of altered levels. This use of TDM is rational and appropriate, as there are very few randomised controlled trials to support the routine use of TDM.

WHICH ANTIRETROVIRALS ARE SUITABLE FOR TDM?

The nucleoside reverse transcriptase inhibitors (NRTIs) are pro-drugs, which require activation by intracellular phosphorylation. There is a poor correlation between plasma NRTI levels and effect. Only a few laboratories are capable of measuring intracellular levels. NRTIs are therefore not suitable for TDM.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) display highly variable pharmacokinetics. The key cytochrome P450 isoenzyme responsible for metabolising efavirenz, CYP2B6, has a polymorphism that results in slower metabolism. This polymorphism occurs much more frequently in African Americans than Caucasians[1] – it is unclear whether this polymorphism will occur commonly in southern Africa. There is a correlation between higher plasma levels and neuropsychiatric adverse effects of efavirenz, and between lower levels and virological failure.[2] A population pharmacokinetic study has shown that Thai and South African patients have lower clearance of nevirapine, resulting in greater exposure, than patients in 'Western countries'.[3] This may account in part for high rates of nevirapine-induced hepatotoxicity, particularly among women with a lower body mass index, reported in a South African study.[4] Higher nevirapine levels are associated with a greater chance of virological success.[5]

The protease inhibitors (PIs) also have highly variable pharmacokinetics. Plasma concentrations of PIs have been shown to correlate with virological success.[6] High levels of certain PIs correlate with adverse drug reactions, notably nephrolithiasis with indinavir[7] and dyslipidaemia with lopinavir/ritonavir.[8]

Therefore both NNRTIs and PIs have many characteristics that make them potentially suitable candidates for TDM.

ARE RELIABLE ANTIRETROVIRAL ASSAYS AVAILABLE?

Currently there are no commercial kits to measure drug levels of antiretrovirals, though a few are in development, so antiretroviral TDM is conducted by laboratories that have developed their own in-house assays. It is therefore essential that laboratories participate in regular quality control to ensure that their assays are reliable. In a recent survey of laboratories conducting TDM, only 12 out of 31 had assays that were in the acceptable range for more than 90% of measurements.[9]

LIMITATIONS OF TDM

A number of randomised controlled trials have been conducted to assess the value of routine TDM. In these studies patients

were randomised to control or TDM arms, where the treating clinician was advised about the antiretroviral level and, if necessary, to adjust the dose. Two of these studies[10,11] showed higher rates of virological suppression in the TDM arms. However, a number of other studies have failed to show a benefit for routine TDM.[12,13] One problem encountered in these randomised trials is that clinicians often did not make the recommended dose adjustments. In some trials the follow-up was very short. Lastly, the trials were under-powered. Until a large trial is conducted to address the weaknesses of the existing studies, there does not appear to be a role for routine TDM for all patients treated with antiretrovirals.

A recent study[14] found that drug levels, particularly for PIs, were very variable in individual patients sampled at different times. This could partly be explained by the variability in the effect of dosing with food, which is important for the PIs studied. In addition, adherence can clearly affect drug levels; indeed, TDM is one tool to detect poor adherence. Controlling for adherence is difficult in clinical practice. This study[14] highlights the importance of not making major clinical decisions on the basis of a single TDM result.

PATIENTS AT HIGHER RISK OF DRUG LEVELS OUTSIDE REFERENCE RANGES

Given that current evidence does not support routine TDM, it makes sense to utilise TDM in patients at particular risk for either suboptimal or toxic levels.

CHILDREN

Several important physiological changes in childhood, particularly early childhood, affect the pharmacokinetics of drugs.[15] Firstly, the volume of distribution is affected as total body water is high in neonates and remains high in young children. Neonates have impaired drug absorption, metabolism and excretion, while in young children these parameters are enhanced compared with adults. Many authorities therefore recommend TDM in young children, especially as there are very limited data available for most antiretrovirals in children.

PREGNANCY

Many physiological changes in pregnancy affect pharmacokinetics:[16]

- Increased GIT motility
- Decreased protein binding
- Increased volume of distribution (fat and water)
- Mild hepatic enzyme induction
- Increased renal excretion.

Up to a third of pregnant epileptics experience an increased frequency of seizures owing to sub-therapeutic anticonvulsant levels, illustrating that these physiological changes of pregnancy are clinically relevant. A recent study showed lower lopinavir levels in pregnant women.[17] Despite this, the women still had good virological suppression. This change in PI levels induced by pregnancy is likely to be relevant when a degree of PI resistance is present – TDM should be considered in this setting.

DRUG INTERACTIONS

Many PIs are substrates of the important drug transporter, P glycoprotein. Their levels can be affected by drugs that inhibit or induce P glycoprotein. PIs and NNRTIs are metabolised by the cytochrome P450 system, and their levels can be affected by drugs that inhibit or induce this system. If a drug known to have such interactions has to be co-administered, TDM should be considered.

LIVER DISEASE

PIs and NNRTIs are metabolised by the cytochrome P450 system, which occurs primarily in the liver. Unlike renal disease, there is no accurate biochemical marker to indicate how much hepatic impairment is present. TDM should therefore be considered for patients with evidence of liver failure, as they may experience toxicity due to high levels.

INTEGRATING TDM AND PI RESISTANCE DATA – WHAT'S THE IQ?

PI resistance can to a certain extent be overcome by increasing the levels. It therefore makes sense to integrate the resistance data and the drug level. This is done using the inhibitory quotient (IQ), which is calculated by dividing the trough level by a factor, depending on the resistance test conducted. This is typically a genotypic test, and the trough level is divided by the number of major PI mutations. This genotypic IQ has been shown to correlate with virological success in PI-experienced patients.[18]

Note that this strategy cannot be used with the NNRTIs, as a single mutation generally confers very high-level resistance, which cannot be overcome by increasing the dose.

A ROLE FOR TDM IN SOUTHERN AFRICA?

Antiretroviral TDM could play an important adjunctive role in our area. Clearly this will be a limited resource, confined to high-risk patients or to those with some degree of PI resistance. There is a danger that laboratories will offer TDM without the necessary quality assurance. Until commercial kits become available, TDM should only be conducted by specialist pharmacology laboratories that participate in regular quality assurance.

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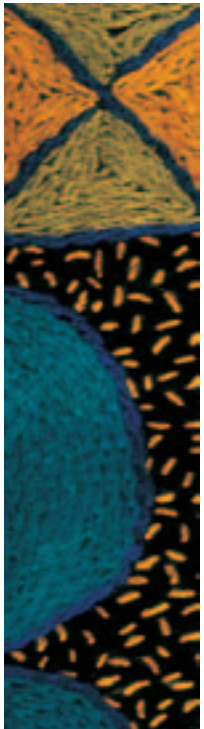

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