ECONOMICALLY BENEFICIAL DRUG INTERACTIONS WITH CYCLOSPORIN AND TACROLIUMUS- CLINICAL STUDIES IN RECIPIENTS OF KIDNEY AND LIVER TRANSPLANTS

By

T. E. JONES B.Pharm, Dip. Ed.

Department of Clinical and Experimental Pharmacology

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The work described herein was performed within the departments of Clinical Pharmacology and Pharmacy, The Queen Elizabeth Hospital

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Contents:

Abstract:

The studies contained in this thesis comprise three separate clinical studies in organ transplant recipients, an extension clinical study and two surveys of Australasian transplant units. The overall aims of the studies presented are to examine fundamental questions regarding the clinically and economically important pharmacokinetic interaction between diltiazem and cyclosporin, an interaction widely utilised in organ transplantation.

The first survey demonstrated, that diltiazem is widely employed as a cyclosporin-sparing agent by some transplant physicians but not by others. It also showed that the reasons for using cyclosporin-sparing agents was not based upon hard data but was more likely to be influenced by familiarity with the agents and/or philosophical reasons. The magnitude of the savings afforded by the coprescription of diltiazem approximated AUD $7 million in 1995/6.

The second survey demonstrated that the use of diltiazem provided benefits in the early post transplant period in the form of reduced need for dialysis and immunosuppressive drugs and this data provides a strong argument in favour of the routine coprescription of diltiazem in adult kidney transplant recipients. It also examined the effects of using different blood cyclosporin concentrations on markers of efficacy and adverse effects which allowed recommendations for therapeutic ranges for cyclosporin in kidney transplantation.

ABSTRACT

The first clinical study demonstrated considerable interpatient variability in both magnitude of cyclosporin-sparing effect and the dose of diltiazem needed to produce the effect. Importantly, a significant effect was demonstrated with doses of diltiazem that were lower than those currently employed. The potential for cyclosporin to interact with diltiazem's metabolism was also investigated and three different patterns of diltiazem kinetics were seen in kidney transplant recipients treated with cyclosporin. Although interpatient plasma diltiazem concentrations varied considerably, these appeared to have little bearing on the magnitude of the cyclosporin-sparing effect.

The extension clinical study demonstrated the folly of switching formulations without proof of bioequivalence. The 'controlled diffusion' formulation of diltiazem was shown to interact differently with cyclosporin than conventional release formulation diltiazem in several transplant recipients.

The second clinical study failed to demonstrate an interaction between cyclosporin and diltiazem in a patient who did have a considerable cyclosporin-sparing effect with itraconazole, despite using a higher than usual dose of diltiazem.

The final clinical study examined the potential tacrolimus-sparing effect of diltiazem in kidney and liver transplant recipients. Interestingly, there appeared to be a difference in tacrolimus-sparing effect between these two transplant types where a clinically significant sparing effect was noted in kidney transplant recipients but a less marked effect was observed in liver transplant recipients.

These data should assist the development of soundly based policies that will ensure a benefit exists before a sparing agent is coprescribed and that the lowest effective dose of sparing agent is used.

ABSTRACT

Synopsis

The advent of cyclosporin (CsA) improved organ transplant success rates but increased the costs of maintaining these transplants and introduced a new set of adverse effects (including nephrotoxicity and hypertension). CsA-sparing agents were advocated by the late 1980s primarily as a means of curbing costs, but how widely these were used and what drugs were used, was not known. No formal dose response studies had been performed with any sparing agent and the reliability of the interaction had also not been studied.

A number of drugs had been shown to increase blood CsA concentrations via interactions with the cytochrome P450 isoenzyme CYP3A4 (and/or the P-glycoprotein drug efflux pump). Potentially useful CsA-sparing agents included DTZ, verapamil and ketoconazole (KCZ) while grapefruit juice had also been shown to elevate blood CsA concentrations. In addition to the economic benefits, therapeutic benefits (including reduced nephrotoxicity) had also been demonstrated with some agents in some transplant types.

Much of the literature on interactions with CsA and of the use of CsA-sparing agents was derived from limited data and there was limited data on interpatient variability in sparing effect. No dose-response relationship studies had been conducted and this was presumably the reason for the doses of CsA-sparing agents being the same as those that applied to the approved indications for these drugs. There was no data on the extent of

use of CsA-sparing agents by different Australasian transplant centres, nor whether their use affected therapeutic ranges that were utilised by these centres.

A survey of Australasian transplant physicians demonstrated that CsA-sparing agents (especially DTZ) were widely used (Chapter 2). Considerable variability existed with some centres using CsA-sparing agents routinely in all patients while in other centres, they were not used at all. Different patterns of use were noted, where the majority of heart, lung and kidney transplant recipients were prescribed CsA-sparing agents, but only a minority of liver and pancreas transplant recipients were. The decision to use these agents appeared to be based upon local factors since centres located in close proximity to each other had widely different utilisation rates. Factors affecting the decision included prescriber familiarity (surgeons appeared less likely to use them), consideration of drug regimen complexity and philosophy rather than specific data relating to their use. Several physicians observed that perceived benefits afforded by the use of DTZ needed to be balanced against the potential for adverse outcomes, both direct and indirect e.g. via increased complexity of drug regimen with resulting poor compliance.

The economic benefits resulting from the use of CsA-sparing agents accrued to the funding body (the Commonwealth government when CsA was used for organ transplantation). However, the Commonwealth government did not advocate this use and had not granted approval for any specific drug for a CsA-sparing indication while the respective pharmaceutical manufacturers were either ambivalent or hostile to their use. Hence, individual physicians and transplant units would be the most likely targets for litigation in the event that an adverse outcome resulted from this (non-approved) use.

Interestingly, there was no evidence that the use of CsA-sparing agents affected the therapeutic range for blood CsA concentrations reported by clinicians and, despite comments that assay methodology should affect the range used, this was not evident from the data collected. There was great disparity in therapeutic ranges quoted which was evident not only across organ transplant types (which may reflect the life-threatening consequences of rejection of transplanted hearts and livers versus the less disastrous effects of rejecting a kidney) but also within the same organ transplant type.

In Chapter 3, data from almost the entire Australasian cadaver kidney transplant population was analysed to assess the clinical sequelae of using different therapeutic ranges for CsA and also of using DTZ. Earlier findings that DTZ use reduced the need for dialysis in the first week and month post transplantation were confirmed. DTZ use appeared not to reduce the frequency of rejection episodes post transplant, but this may be because the marker used (methylprednisolone use) was insensitive. DTZ use was associated with a reduced muromonab use, suggesting that the severity of rejection episodes was reduced in this period. Importantly, these therapeutic benefits did not occur as a consequence of higher blood CsA concentrations induced by DTZ.

No association was found between blood CsA concentration and either the need for dialysis or the likelihood that serum creatinine concentrations would fall sooner in the post transplant period. This may be a type II error, but it is consistent with earlier findings in similar patient populations (Nankivell BJ, et al. 1994. Mahalati K, et al. 1999) and is one of the reasons for the current interest in sparse sampling AUC monitoring.

DTZ use was associated with a reduced need for additional antihypertensive agent use at 3, 6 and 12 months post transplantation. This accords with the approved indication for DTZ but is contrary to earlier findings from a prospective study in an Australian kidney transplant population. The reduced need for additional antihypertensive therapy was confirmed when drug doses were taken into account by way of a scaling system.

Serum creatinine concentration was used as a marker of nephrotoxicity, one of the more ironic adverse effects of CsA. Creatinine concentration was also used as a marker of efficacy since rejection reduces functioning kidney mass. It was perhaps not surprising therefore that no relationship was found between this marker (serum creatinine concentration) and blood CsA concentration at 3, 6 and 12 months post transplantation (Chapter 3).

When data from virtually the entire adult Australasian kidney transplant population was examined for evidence of benefit or harm resulting from either high or low blood CsA concentrations, there was little to find that would assist the fine-tuning of current therapeutic ranges. A range of 100-225µg/L for the early post transplant period and 100-200µg/L for the later post transplant period reflects current practice and is recommended for trough blood CsA concentration in the medium to long term.

The study reported in Chapter 4 provides the basic dose-response relationship on the interaction between CsA and DTZ in adult kidney transplant recipients. There was considerable interpatient variation in response to DTZ with respect to elevation of blood CsA concentrations. Mean CsA AUC(0-24h) increased even after the lowest dose of

DTZ used (10mg/day). The mean rate of increase slowed after 30-60mg/day but continued up to the maximum dose tested (180mg/day). Interestingly, morning only doses of DTZ (≤60mg/day) affected both morning (0-12h) and evening (12-24h) CsA AUCs equally. This proves the interaction between DTZ and CYP3A4 (and/or P-gp) persists after DTZ is removed from plasma.

This data shows that a CsA-sparing effect occurs with lower DTZ doses than those currently used for many patients (60mg thrice daily). Lower DTZ doses should reduce the frequency of adverse effects and allow its use as a CsA-sparing agent where conventional doses might be contraindicated. Because of the considerable interpatient variability observed, a CsA-sparing effect must be demonstrated in each patient (via blood CsA concentration monitoring both before and after the introduction of DTZ). One caveat is that therapeutic benefits demonstrated for DTZ have occurred following the use of 'conventional' doses (≥180mg/day) and these may not occur at lower doses.

It was shown in Chapter 2 that many centres switched from conventional release DTZ to the 'controlled diffusion' (CD) formulation in the absence of evidence of bioequivalence with respect to CsA-sparing effect. The folly of this switch was shown in Chapter 5 when patients were given 180mg CD formulation DTZ and the CsA-sparing effect compared to 90mg (conventional release) given twice daily. Group data showed no significant difference, but there were individual falls in CsA AUC(0-12) between 30-60% in 3 of the 8 patients while one experienced an increase of 36%. Interestingly, one patient had unusually low plasma DTZ concentrations following the use of conventional release DTZ followed by a surprising increase when the CD formulation was given.

Notwithstanding this increase in plasma DTZ concentrations, the CsA-sparing effect was largely unaffected and there was no evidence of increased therapeutic effect. The CD formulation appeared not to perform according to the manufacturer's specifications since mean DTZ AUC(0-24) fell by >30% and the anticipated am:pm ratio of 0.67 was not observed. This failure to perform may have affected the CsA-sparing activity and conversely, may have been caused by the coprescription of CsA to the study participants. Patients might be better served by changing the dosing regimen (to once or twice daily) of conventional release DTZ (which simplifies the dosage regimen), rather than switching to CD formulation DTZ.

In Chapter 6, the relative potencies of two CsA-sparing agents, DTZ and the antifungal agent itraconazole (ICZ), was studied in a patient with a single lung transplant. CsA AUC(0-24) increased significantly when ICZ was co-prescribed (compared to when no CsA-sparing agents were given) but no increase was apparent when DTZ was co-prescribed with CsA. Despite widespread use as a CsA-sparing agent, this shows that DTZ does not always increase CsA concentrations, despite the higher than usual dose being used in this study (240mg/day). It is therefore recommended that, where DTZ is prescribed for its economic benefit, the interaction should be proven and not assumed, in every case.

In Chapter 7, DTZ kinetics were reported in adult kidney transplant recipients taking routine CsA. Three different kinetic patterns were observed. One patient had a 'subnormal' AUC for DTZ and all its metabolites which was consistent with poor bioavailability while the other patient had a 'normal' AUC for parent DTZ and primary

metabolites (DMDTZ and DADTZ) but a higher AUC for the secondary metabolite DMDADTZ which suggests a different metabolic pathway. Both patients demonstrated a significant CsA-sparing activity across the DTZ dose range studied however and, combined with the strong statistical association with parent DTZ (compared to metabolites), this suggests that DTZ is the interacting moiety. DTZ dose was as good a predictor of CsA-sparing effect as either Cmax or AUC and hence there was no point in monitoring DTZ kinetics.

In Chapter 8, the interaction between tacrolimus (TRM) and DTZ was studied in recipients of kidney (n=2) and liver transplants (n=2). This study was undertaken because the literature was equivocal regarding this interaction and it was considered important to define the nature of the interaction before DTZ was advocated as a TRM-sparing agent. DTZ exerted a clinically significant TRM-sparing effect in some organ transplant recipients. The increase in AUC(0-24) for TRM was more marked in the 2 kidney transplant recipients than the liver transplant recipients. The magnitude of the increase determined by trough (C_0) concentrations was similar to that demonstrated by AUC(0-24). Whether the difference was due to functional differences in the liver (the organ transplanted) or whether this is a manifestation of wider interpatient variability in the transplant population remains to be determined.

These data will assist the formulation of rationally based policies for CsA (and TRM) sparing agents which will reduce unnecessary exposure to potentially toxic drugs and help simplify drug regimen design such that any effect on compliance is minimised.