CICLOSPORIN

01. Assay Details

CH Labs Test Reference Guide

02. Therapeutic Range

Transplant Type	LIVER		KIDNEY		HEART		BONE MARROW		AUTOIMMUNE DISEASE	
Time Post Transplant (MONTHS)	C2	C0	C2	C0	C2	C0	C2	C0	C2	C0
1	1000	225-300	1700	150-225	-	250-325	-	95-205	-	150-200
2	1000	225-300	1500	150-225	-	250-325	-	95-205	-	150-200
3	800	100-150	1300	100-150	-	125-175	-	95-205	-	100-150
4-6	800	100-150	1100	100-150	-	125-175	-	95-205	-	100-150
7-12	600	100-150	900	100-150	-	125-175	-	95-205	-	100-150
12+	600	100-150	800	100-150	300-600	125-175	-	95-205	-	100-150

Transplant Type	Induction(< 3 months) (mg/L)	Maintenance (mg/L)
Liver	225-300	100-150
Heart	250-325	125-175
Kidney	150-225	100-150
Bone Marrow	95-205	95-205
Autoimmune Disease	150-200	100-150

How well established:

The stated reference ranges represent a consensus, and exact therapeutic ranges are not well established. They are also confounded by the use of multiple different assays, which have variable specificity for the parent drug compound, resulting in different levels of CsA for a given drug concentration.

Renal and General

The dose of ciclosporin correlates poorly with the trough blood concentration although it is better with Neoral® than the old Sandimmune®. Studies show a variable correlation between trough drug concentrations and either acute rejection or nephrotoxicity. In a review, 23 studies (18 renal, 1 liver, 2 heart, 1 BM, 1 pancreas) showed a correlation between low trough concentration of ciclosporin and acute rejection or GVHD. However, 9 studies (7 renal, 2 heart-lung) showed no correlation. In general it is accepted that low trough concentrations are indicative of subtherapeutic immunosuppression, with resultant risk of rejection.

There is more controversy regarding the relationship between high trough ciclosporin concentrations and acute nephrotoxicity. 12 studies (9 kidney, 1 liver, 1 pancreas,1 heart) showed positive correlations between high ciclosporin trough concentration and nephrotoxicity, but 9

studies showed a lack of correlation. One study showed that the majority of acute rejection (59%) and nephrotoxicity (63%) occurred with ciclosporin concentrations in the therapeutic range of 150-400mg/L (SP mAb I-RIA assay), although the mean cyclosporine concentrations were significantly lower in patients experiencing acute rejection compared with those experiencing acute nephrotoxicity. Concentrations of 150m g/L or less had a specificity of 91% for diagnosing acute rejection, and concentrations >400mg/L had an 89% specificity for predicting cyclosporine nephrotoxicity.

In general, very high or very low concentrations outside the therapeutic range for a specific assay will cause a patient to be at greater risk for developing acute rejection or toxicity, respectively.

Heart
Higher concentrations are generally used because of difficulty replacing organs in the event of rejection.

Bone Marrow
Early studies with CsA as a single agent showed that low troughs were associated with increased GVHD. However in one small study CsA concentrations of 95-205(mRIA) were used in combination with methotrexate, with no increase in GVHD. Higher concentrations of CsA appear to be associated with higher risk of leukaemic relapse.

Absorption Phase Monitoring of Cyclosporine (C2)
Neoral® is the only ciclosporine formulation now used in New Zealand. It exhibits more predictable absorption kinetics, is not dependent on bile salts for absorption and is not affected by food. Studies have shown that the bioavailability is increased as is the Cmax and its absorption exhibits less intrapatient and interpatient variability. Trough concentrations with Neoral® have a closer correlation with outcome than Sandimmune®, but still do not correlate well. The AUC calculated over the first 4 hours has been shown to have a high correlation with drug exposure and clinical outcome in liver, heart and renal transplant patients The AUC (0-4) also shows a high (>/= 0.85) correlation with the peak whole blood levels (Cmax) and a single sample taken 2 hours after ciclosporin dose. This finding has been confirmed in many clinical and pharmacokinetic trials where the correlation with AUC (0-12hr) was highest with C2 and lowest with C0 (0.95 vs 0.12 in one study). Conversion to C2 from C0 in liver, heart and renal transplant patients resulted in lower dosages, lower creatinine and lower toxicity with a decrease in or equivalence in rejection rates.
Currently at Christchurch hospital, C2 is used in the setting of renal transplant recipients who are not already established on trough monitoring. It is not currently used in heart transplantation and tacrolimus has largely replaced ciclosporin in liver transplantation in Canterbury.

03. Pharmacokinetics

F: 0.5 (0.2-0.6)	**Vd** (L/kg): 3.5	**Cl** (L/h/kg): 0.3-0.6	**t½:** 8 hr (5-18)
Fe: < 0.01	**Elimination route:** Hepatic, via hydroxylation / methylation		
CYP: P450 3A		**Protein binding:** 0.9	

F = Bioavailability, Vd = volume of distribution, Cl = clearance, t½ = terminal half-life of elimination, Fe = fraction excreted unchanged in the urine, CYP = cytochrome P450 enzyme/s

Other PK data:

1. t1/2 reduced in burns, children; increased in renal failure.
2. Cl slightly increased in BMT and children, reduced in hepatitis, cirrhosis and the elderly.
3. Neoral® has increased bioavailability compared with Sandimmune® (it does not require bile salts for absorption).
4. Bioavailability is reduced in diabetics with autonomic neuropathy, short bowel syndrome, cystic fibrosis, liver transplant, GVHD of the gut.
5. Bioavailability increases in the immediate post-op period after renal transplant.
6. Vd higher in children < 10yrs of age, decreased in cardiac transplantation.
1. expand* : 04. Indications (1)
1. Solid organ transplantation: prevention/treatment of allograft rejection
2. Bone marrow transplantation: prevention/treatment of allograft rejection and GVHD
3. Autoimmune disease: severe active RhA, atopic dermatitis, psoriasis.
4. Inflammatory Bowel Disease (refractory)
5. Endogenous uveitis
6. Nephrotic syndrome: induction of remission in steroid-dependent and steroid-resistant disease.

05. Loading dose

1. Solid Organ: 15mg/kg/day (po) or 5-6mg/kg/day (iv) for 1-2 weeks, then taper 5% per week to maintenance dose (similar for children except liver 2-4mg/kg iv in divided dose)
2. BMT: 12.5-15mg/kg/day (po) or 3-5mg/kg/day (iv) for up to two weeks iv then change to oral maintenance (children 1.5mg/kg/day Q12h iv, 6.25mg bd po)
3. Endogenous uveitis initially 5mg/kg (up to 7mg/kg in refractory cases for a short time)
4. Nephrotic Syndrome 5mg/kg in adults and 6mg/kg in children to achieve remission then adjust according to efficacy.
5. Rheumatoid arthritis 3mg/kg/day for the first 6 weeks increased if insufficient response.
6. Psoriasis remission induction 2.5mg/kg/day and increase after one month to a max of 5mg/kg/day if no response. Stop if unresponsive after 6 weeks at 5mg/kg/day.
7. Atopic dermatitis 2.5-5mg/kg/day depending on severity and response. Increase to a max 5mg/kg/day if unresponsive at lower doses after 2 weeks.

06. Maintenance dose

Solid organ: 2-6 mg/kg/day

BMT: 12.5mg/kg for 3-6 months and gradually reduce to discontinue by one year after transplantation.
Others treat at the lowest effective level, not exceeding 5mg/kg/day in adults and 6mg/kg/day in children

Autoimmune: generally 2-5mg/kg/dayin adults and up to 6mg/kg/day in children. May be combined with low dose methotrexate in RhA at an initial dose of 2.5mg/kg/day in those refractory to methotrexate monotherapy.

Inflammatory Bowel Disease: 8-10mg/kg/day (children 4-10mg/kg/day)

Note: Neoral® dose should be approx. doubled when transferring from iv to oral to avoid levels below the therapeutic range.

07. Notes on administration

IV: Dilute 1ml CsA in 20-100ml Normal Saline. Prepare in glass containers.

Oral: Avoid grapefruit juice (increases concentration significantly). May dilute in milk or orange juice. Neoral® should be taken in 2 divided doses.

08. When to monitor

1. Trough (C0) samples should be collected at the trough, within 1 hour of the next dose. If changing to Neoral®, should monitor every 4-7 days initially, and also monitor creatinine.
2. Two hour samples should be taken at 2 hours after the last dosage. (+/- 15 minutes is acceptable)

Note: Full 12 hour or partial 4 hour AUC should be used in the initial 2-7 days after transplant as C2 has been shown to be less accurate during this period.

09. Dose Individualisation

Renal Failure: dose reduction is not required.

Cystic Fibrosis: the dose required is approximately double that of controls, but significant variation is noted. Take in 3-4 divided doses per day.

Hypocholesterolaemia: the dose needs to be decreased proportionally to the LDL because of increased risk of side effects.

Obesity: use the ideal body weight to calculate the dose.

Children: increase the dose because of reduced t 1/2.

10. Adverse Effects

>10% (concentration dependent)

CNS: tremor (21-55%)
CVS: hypertension (25-50%)
DERM: cutaneous conditions and infections
ENDO: hyperglycaemia (11%), hyperuricaemia (80%), gout (24%), hyperkalaemia with hyperchloraemic acidosis, dyslipidaemia (increased total cholesterol, LDL; reduced HDL)
RENAL: nephrotoxicity (20-30%)
MISC: gingival hyperplasia and hirsutism (21-45%)

>1-10%

CNS: headache (2-15%), convulsions (associated with hypomagnesaemia & concomitant steroids), paraesthesia, confusion
CVS: flushing, oedema, pericardial effusion (in cardiac transplant)
ENT: sinusitis
GI: hepatotoxicity (cholestatic)
GU: Haemolytic Uremic Syndrome (3-5%)
HAEM: lymphoma (6% in cardiac transplant), anaemia, thrombocytopenia, leukopenia, thromboembolism
MUSC/SKEL: musculoskeletal pain, myopathy, cramps
MISC: fever, hypomagnesaemia, gynaecomastia

<1%

CNS: alterations in mood or personality, anxiety, depression, visual disturbance (including cortical blindness), hearing loss, motor neuropathy, hemi/quadriparesis, coma, delirium, dementia, encephalopathy, speech disorders. These are usually preceded by lethargy and altered mental state, reversible with dose reduction or cessation. Risk factors include hypomagnesaemia, hypocholesterolemia, fever, hypertension, iv administration, rapidly increasing levels.
CVS: Raynaud's syndrome, mesentericischaemia, myocardial infarction
ENDO: night sweats, adrenal suppression, osteopathy
GI: constipation, mouth sores, swallowing difficulty, weight loss, upper GI bleeding
HAEM: lymphoma (1% renal, liver transplants)

11. Drug Interactions

Drugs that may decrease CsA concentration:

Well substantiated: Carbamazepine, phenobarbital, phenytoin, rifampicin, isoniazid.
Reports: cholestyramine (reduced absorption), Go-Lytely, griseofulvin, heparin, metoprolol, naficillin, octreotide, primidone, probucol, rifarutin, sodium valproate, sulfadimidine/sulfamethazine +trimethoprim, sulfamethoxazole+trimethoprim, sulfinpyrazone, ticlopidine, warfarin.

Drugs that may increase CsA concentration:

Well substantiated: Bromocriptine, cisapride, clarithromycin, danazol, diltiazem, erythromycin, fluconazole, itraconazole, ketoconazole, methylprednisolone, methyltestosterone, metoclopramide (increased absorption), nicardipine, verapamil.
Reports: Acetazolamide, allopurinol, amikacin, amiodarone, bile salts, cimetidine, ciprofloxacin, colchicine, digoxin, estradiol, framycetin, glipizide, imipenem/cilastin, josamycin, levonorgestrel & estradiol, methotrexate, metronidazole, miconazole, nifedipine, norethinfrone & norethisterone, norfloxacin, prenylamine, propafenone, pristinamycin, roxithromycin, sulfamethoxazole, sulfamethoxazole & trimethoprim, sulindac, tacrolimus, tobramycin, vancomycin, warfarin.

Nephrotoxins: additive nephrotoxic effect: eg. aciclovir, ganciclovir, aminoglycosides, amphotericin B, apazone, colchicine, NSAIDs, melphalan. ? ACE inhibitors, ciprofloxacin, cotrimoxazole, disopyramide (case reports)

Pharmacodynamic Interactions

- Thiazides - gout
- Potassium-sparing diuretics - hyperkalaemia
- Digoxin - Increased concentration
- Colchicine - increased side effects, GI dysfunction, hepatonephropathy, neuromyopathy
- Antineoplastic drugs: doxorubicin, daunorubicin, etoposide, mitoxantrone - increased concentrations
- HMG-CoA Reductase inhibitors - increased concentration, risk of myositis

12. Factors that may give a false assay result

Nil known.

13. Overdose

TOXINZ

14. Dialysability

Not dialysable (<1% recovered in dialysate). Poorly cleared by charcoal haemoperfusion.

15. Comments

EMIT is more specific for the parent drug than FPIA, and concentrations measured are on average 29% lower than when measured by FPIA. (Christchurch laboratory). mRIA, EMIT, AxSym, CEDIA and mTDx are all comparable assays.
Neoral® is a water-free microemulsion of ciclosporin

16. Key references

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4. TIAFT (The Bulletin of the International Association of Forensic Toxicologists) Vol 26 No 1 Supp: Therapeutic and toxic Drug Concentrations.
5. Levy G, Biodrugs 2001:15(5) pp279-290
6. Neoral® Data Sheet October 2002: Medsafe.govt.nz

17. Last updated

Jan 2003