Case Report

Two cases of delayed cyclosporin absorption leading to CsA exposure higher than that predicted by C2 monitoring alone

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Introduction

Cyclosporin administration designed to achieve target peak, rather than trough, concentrations is now routine practice for many transplant programmes. The peak cyclosporin concentration exhibits some degree of inter-subject variability. However, the concentration attained 2 h following the administration of cyclosporin micro-emulsion (CsA-ME), referred to as C2, is the most consistent peak [1]. Recent trial data have demonstrated the effectiveness of CsA-ME dose adjustment according to C2 targets, achieving excellent tolerability, safety and freedom from rejection after kidney [2] and liver transplantation [3].

Reliance upon C2 as the sole guide to CSA-ME dosing for an individual patient assumes that the peak CsA concentration consistently occurs at \( C_{24} \) following ingestion for that individual. Significant intra-patient variability in time to CsA peak concentration may theoretically reduce the reliability of C2 monitoring as a surrogate for overall CsA exposure, and hence for clinical outcomes. We present two illustrative cases where time to peak CsA concentration was delayed by intercurrent clinical events, temporarily rendering C2 an underestimate of overall CsA exposure.

Case 1

A 39-year-old Caucasian female with spina bifida and end-stage renal failure secondary to reflux nephropathy underwent spousal donor kidney transplantation. Immunosuppression consisted of basiliximab 20 mg on days 0 and 4, prednisone 30 mg daily, mycophenolate sodium 720 mg b.d. and CsA-ME 300 mg b.d. (Neoral). All CsA concentrations in our centre are assayed by the fluorescent polarization immunoassay technique using the Abbott Axsym system.

At day 8 post-transplant, the patient was well and serum creatinine of 137 \( \mu \text{mol/l} \) indicated good allograft function. C2 (1289 ng/ml) was slightly below target (1600–2000 ng/ml); however, the dose was not changed due to the presence of moderate tremor thought to be due to a cyclosporin effect.

On day 12, the patient presented with a presumed viral illness characterized by fever and nausea, with no clear focus or infective organism identified. The patient denied vomiting or diarrhoea and remained compliant with all prescribed medications. Serum creatinine had increased to 200 \( \mu \text{mol/l} \), C0 increased to 501 ng/ml and C2 fell to 544 ng/ml. Following intravenous re-hydration and observation in hospital, symptoms and fever abated and serum creatinine returned to baseline. No alteration to CsA-ME dose was made and a CsA concentration profile performed after full recovery on day 15 had normalized: C0 361 ng/ml, C2 1367 ng/ml and C4 933 ng/ml.

On day 46, fever and malaise developed and an Escherichia coli urinary tract infection was confirmed. Nausea but no vomiting was reported and all medications had been taken. However, C2 was unusually low at 724 ng/ml even though there had been no alteration in CsA-ME dosage. The following day, a CsA profile demonstrated clear evidence of delayed absorption: C0 388 ng/ml, C2 851 ng/ml, and C4 1852 ng/ml. CsA-ME dose was reduced on the basis of this markedly elevated C4. Three days later, with improvement in symptoms, a more typical pattern of cyclosporin absorption was evident with C0 439 ng/ml, C2 1136 ng/ml and C4 788 ng/ml.

A further febrile illness on day 106 again resulted in delayed absorption of CsA-ME: C2 of 930 ng/ml and C4 1030 ng/ml, which normalized following resolution of fever.

The patient did not receive any medication suspected of contributing to altered absorption or metabolism of CsA-ME. Each episode of delayed absorption...
coincided with a systemic illness and resolved quickly once this resolved. We hypothesize that in this patient, transient systemic illness led to episodes of delayed gastric emptying and drug absorption, resulting in a delay in peak CsA concentration.

Case 2

A 47-year-old Caucasian male with end-stage renal disease caused by glomerulonephritis underwent deceased-donor kidney transplantation. Immunosuppression consisted of prednisone 30 mg daily, mycophenolate mofetil (Cellcept) 1 g b.d. and CsA-ME (Neoral) 350 mg b.d.

The initial course was complicated by a partial torsion of the allograft vein, detected by duplex scanning and managed by emergency re-operation. Immediate graft function was achieved, with a serum creatinine fall from 1272 to 673 μmol/l by day 3. On day 3, cyclosporin concentrations were C0 181 ng/ml and C2 957 ng/ml and no CsA-ME dose adjustment was made.

Hypertension developed and felodipine was commenced on the evening of day 3. On day 10, acceptable kidney function and cyclosporin exposure were documented: creatinine plateaued at 246 μmol/l, C0 464 ng/ml, C2 of 1612 ng/ml and a C4 of 923 ng/ml. The CsA-ME was subsequently reduced to 250 mg b.d. in anticipation of increasing exposure. An ultrasound performed on day 13 demonstrated a large lymphocele causing compression of the allograft. Surgical drainage was performed on day 14 and again on day 17 because of re-accumulation. Cyclosporin concentrations measured on day 15 revealed a C0 that was inappropriately high at 490 ng/ml and a C2 which was unusually low at 786 ng/ml. Subsequent cyclosporin profiles on day 21 (C2 856 ng/ml and C4 1018 ng/ml), day 24 (C0 363 ng/ml, C2 950 ng/ml and C4 1070 ng/ml) and day 28 (C0 417 ng/ml, C2 1041 ng/ml and C4 1071 ng/ml) confirmed a pattern of delayed absorption. During this period, despite multiple episodes of intra-abdominal surgery, the patient showed no clinical evidence of an ileus and was not systemically unwell.

Felodipine was discontinued on day 29 to test the hypothesis that this dihyropyridine might be contributing to delayed CsA-ME absorption or delayed CsA clearance. After cessation of felodipine, the cyclosporin absorption profile returned to a normal pattern: C0 336 ng/ml, C2 1293 ng/ml and C4 856 ng/ml. No further evidence of delayed absorption of CsA-ME has been observed.

Discussion

Overall CsA exposure appears to be the key determinant of both rejection (underexposure) and nephrotoxicity (overexposure) for transplant recipients receiving CsA-ME-based immunosuppression [4,5]. C2 approaches the peak concentration for the majority of patients taking CSA-ME and is therefore a clinically useful surrogate measure of the area under the time–concentration curve and thereby total CsA exposure [1]. However, patients who exhibit delayed absorption of CsA-ME experience a peak concentration significantly beyond 2 h after ingestion. In this instance, reliance upon C2 measurement will provide an underestimate of total CSA exposure, and dose adjustments made to achieve C2 targets may lead to overexposure and drug toxicity. The two cases presented highlight this potential pitfall of sole reliance on C2 monitoring.

In theory, systemic infection (as per case 1), drugs (as per case 2), autonomic neuropathy (particularly diabetic), surgery and other clinical entities may lead to a transient or stable delay in gut transit or drug absorption. The true incidence of delayed absorption of CsA is difficult to ascertain, at least in part because delayed absorption may be transient.

Among patients who fail to achieve satisfactory C2 targets, poor absorption must be distinguished from delayed absorption. Performing a CsA absorption profile will reveal C4 concentrations lower than C2 in cases of poor absorption, whereas C4 concentration will exceed C2 among delayed absorbers. This distinction is clinically significant as poor absorbers are likely to benefit from an increase in CsA-ME dose in order to prevent acute rejection, whereas those with delayed absorption may experience toxicity if CsA-ME dose is increased. Thus, measuring C4 may guide therapy in cases of low C2.

C4 monitoring is by no means routine. Clinical trials rely primarily on C2, and the generally excellent outcomes achieved attest to the suitability of this approach for the majority of patients receiving CsA-ME [2,3]. Published practice guidelines [6] recommend that CsA concentration be sampled further at a point in time significantly later than 2 h post-ingestion (e.g. C4 or C6) when C2 is lower than expected in order to differentiate between delayed (C4 and or C6 higher than C2) absorbers and poor (C4 and or C6 lower than C2) CsA-ME absorbers.

Our experience in the two cases presented leads us to suggest that C4 measurement should be entertained for all patients at one stage soon after the commencement of CsA-ME therapy and for those who experience a decrease in C2 in the setting of intercurrent illness or new medication.

Conflict of interest statement. Steven Chadban has received speaker fees from Novartis, the manufacturer of Neoral. All other authors declare no conflict of interest.

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