Transpl Int (2002) 15: 586–588
DOI 10.1007/s00147-002-0438-5

Costas Fourtounas
Ioannis Kopelias
Despina Kiriaki
Basil Agroyannis

Increased cyclosporine blood levels after nisoldipine administration in a renal transplant recipient

Received: 27 February 2001
Revised: 2 April 2002
Accepted: 27 May 2002
Published online: 27 September 2002

C. Fourtounas (✉) · I. Kopelias
B. Agroyannis
Department of Nephrology,
Aretaieon University Hospital,
Vas Sofias 76, 11528 Athens, Greece
E-mail: cfourt@usa.net
Tel.: +30-1-7226225

D. Kiriaki
Department of Nuclear Medicine,
Laikon General Hospital, Athens, Greece

Dear Editors:

Calcium channel blockers are widely used in renal transplantation. Verapamil, Diltiazem, Nicardipine and Amlodipine, but not Nifedipine, Nitrendipine or Isradipine, can significantly increase cyclosporine whole blood concentrations [2, 3, 4, 5, 6, 7, 8, 9, 10]. However there are no reports of an interaction between Nisoldipine and cyclosporine in the literature. We present the case of a male renal transplant recipient with stable cyclosporine whole blood concentrations that increased after the patient started on Nisoldipine.

A 46-year-old male who had been undergoing chronic maintenance hemodialysis for 10 years secondary to chronic glomerulonephritis, received a cadaveric renal graft in 1995. He had an uneventful post transplant recovery and was on triple immunosuppressive treatment (Prednisolone 7.5 mg, Azathioprine 100 mg and cyclosporine (Neoral: Novartis) 325 mg). As antihypertensive treatment, 2 days post-transplant, the patient was administered 60 mg of Nitrendipine orally b.i.d., and 40 mg of Furosemide orally b.i.d.. He presented adequate control of his blood pressure and excellent renal function (serum creatinine 1.1–1.3 mg/dl). His cyclosporine morning trough levels (12-h troughs without taking the morning dose) were stable, ranging from 100–150 μg/l (Monoclonal Antibodies Whole Blood, Star USA). One year post transplant, he presented with accelerated hypertension that was unresponsive to many antihypertensive drug combinations. Various combinations were attempted, including Atenolol, Metoprolol, Prazosin, Clonidine, Nifedipine and Nitrendipine. The initiation of an ACE inhibitor (4 mg of Perindorpil daily) resulted in moderate control of blood pressure. Finally, the hypertension was found to be caused by a severe common iliac artery stenosis proximal to the graft artery [1]. The stenosis was successfully treated with percutaneous angioplasty; all antihypertensive drugs were stopped, and renal function remained well preserved. Six months later (1.5 years post-transplant) he was admitted to another hospital for coronary angiography and angioplasty for unstable angina, and was started on nisoldipine 5 mg b.i.d.. The patient remained normotensive, and the rest of his regimen remained unchanged. During the following month, an increase of serum creatinine was observed (1.6 mg/dl), and his cyclosporine levels were also elevated (200 μg/l). The patient was taking cyclosporine and Nisoldipine together (08.00 a.m. and 08.00 p.m.). Cyclosporine dosage was decreased gradually from 325 mg to 300- and 250 mg daily, resulting in a drop in serum creatinine- and cyclosporine levels to the previously measured levels (Fig. 1). Six months later, he remains on 250 mg of cyclosporine and 5 mg of Nisoldipine b.i.d with stable renal function (Serum creatinine 1.2 mg/dl). His cyclosporine blood levels remain stable as well.

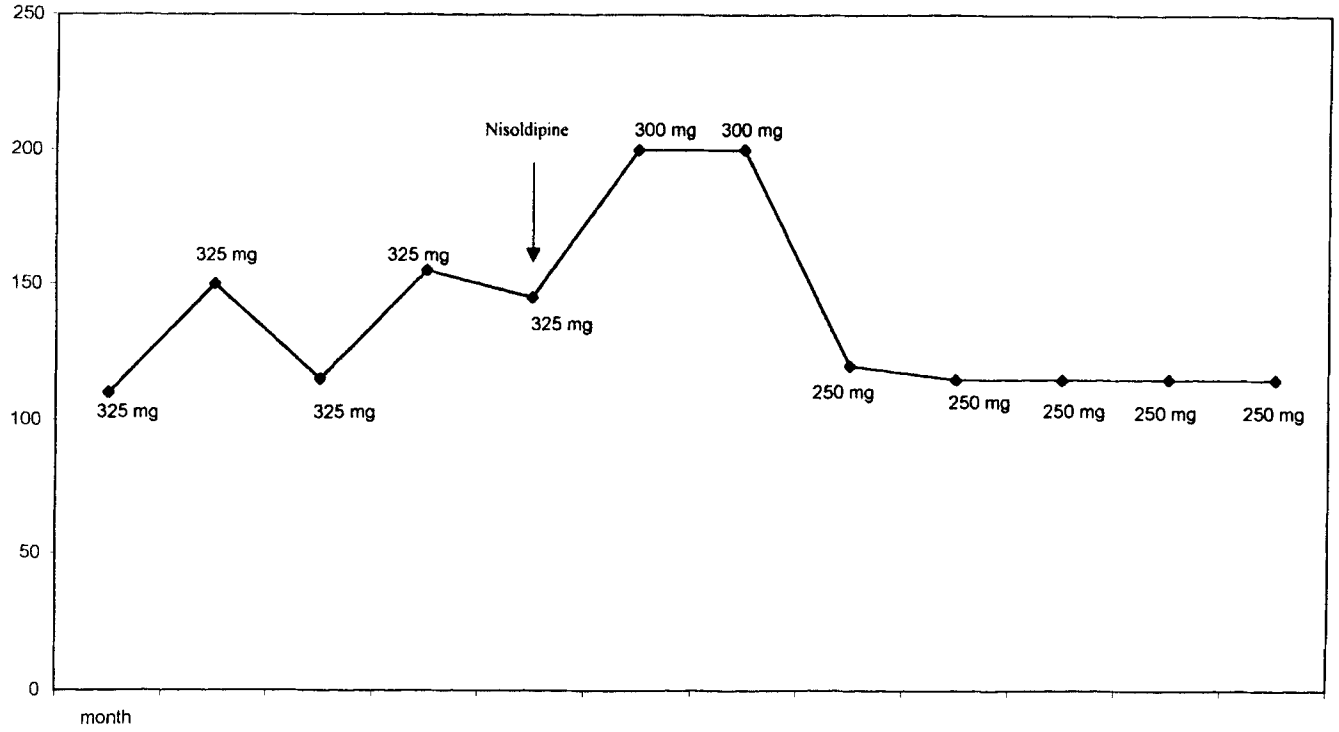

Fig. 1 Evolution of cyclosporine blood levels before and after nisoldipine administration. The reduction of daily dosage from 325 to 250 mg resulted in equal cyclosporine blood levels

(Fig. 1). All blood samples for cyclosporine whole blood concentrations (immediately post- transplant, as an outpatient, pre- and post-angioplasty, during the admission to another hospital and during follow-ups) were morning trough-levels that were measured in the same institution (Laikon Hospital), with the same assay (IncStar).

Cyclosporine undergoes hepatic and intestinal metabolism through the cytochrome P450 (CYP) subfamily CYP 3A, and, more specifically, by the isoform CYP3A4 [6, 7, 11]. Nisoldipine is also a substrate for this enzyme system. In our patient, a 100% increase (from 100–200 μg/l) in cyclosporine levels was observed. The increases in plasma cyclosporine levels for other calcium channel blockers are, in percentages; Verapamil (300%), Amlodipine (40%), Diltiazem (30%) and Nicardipine (20%) [2, 3, 4, 6, 7, 8, 9, 10]. The dihydropyridine class members Nifedipine, Nitrendipine and Isradipine do not interact with cyclosporine. However, Amlodipine belongs to this class and may alter cyclosporine metabolism. Experiments have demonstrated that Amlodipine binds not only to the dihydropyridine ring, but also interacts with the verapamil- and diltiazem binding site [9]. The same has also been observed for Nicardipine [3]. Our patient had received two other dihydropyridine class members (Nifedipine and Nitrendipine) without any alteration of his cyclosporine blood levels, but the same was not observed for Nisoldipine. These observations indicate that not all dihydropyridine members alter cyclosporine levels in a uniform manner [6] and, according to our observation, Nisoldipine should also be included in the list of the drugs that can increase cyclosporine levels.

This is the first report of a nisoldipine-cyclosporine interaction, and it seems prudent to monitor the concentration of cyclosporine in renal transplant recipients more frequently, especially when a new drug is added. Cyclosporine dosage should also be adjusted appropriately.

References

1. Agroyannis B, Fourtounas C, Mourikis D, Tzanatos H, Kopelias I (1998) Management of claudication and hypertension by stent implantation in a renal transplant recipient. J Hum Hypertens 12:417–418
2. Bourbigot B, Guiserix J, Airaiu J, Bressollette L, Morin JF, Cledes J (1986) Nicardipine increases cyclosporine blood levels. Lancet 1:1447
3. Endersen L, Bergan S, Holdaas H, Pran T, Sinding-Larsen B, Berg KJ (1991) Lack of effect of the calcium antagonist isradipine on cyclosporine pharmacokinetics in renal transplant patients. Ther Drug Monit 13: 490–495
4. Friedel HA, Sorkin EM (1988) Nisoldipine. A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in the treatment of angina pectoris, hypertension and related cardiovascular disorders. Drugs 36:682–731
5. Jadoul M, Pirson Y, van Ypersele de Strihou C (1991) Drugs potentiating cyclosporine nephrotoxicity. Nephron 58:383–384
6. Kronbach T, Fischer V, Mayer U (1988) Cyclosporine metabolism in human liver: identification of a cytochrome P-450 III gene family as the major cyclosporine metabolizing enzyme explains interactions of cyclosporine with other drugs. Clin Pharmacol Ther 43:630–635
7. Lampen A, Christians U, Bader A, Hackbarth I, Sewing KF (1996) Drug interactions and interindividual variability of cyclosporin metabolism in the small intestine. Pharmacology 52: 159–168
8. Lindholm A, Henricsson S (1987) Verapamil inhibits cyclosporine metabolism (letter). Lancet 1: 1962–1963
9. Pesavento TE, Jones PA, Julian BA, Curtis JJ (1996) Amlodipine increases cyclosporine levels in hypertensive renal transplant patients: results of a prospective study. J Am Soc Nephrol 7:831–835
10. Smith CL, Hampton EM, Pederson JA, Pennington LR, Bourne DW (1994) Clinical and medicoeconomic impact of the cyclosporine-diltiazem interaction in renal transplant recipients. Pharmacotherapy 14: 471–481
11. Webber IR, Peters WHM, Back DJ (1992) Cyclosporin metabolism by human gastrointestinal mucosal microsomes. Br J Clin Pharmacol 33:661–664