



HAL
open science

High serum concentrations of ciclosporin related to administration of tigecycline

Anita N. Stumpf, Christian Schmidt, Wolfgang Hiddemann, Armin Gerbitz

► **To cite this version:**

Anita N. Stumpf, Christian Schmidt, Wolfgang Hiddemann, Armin Gerbitz. High serum concentrations of ciclosporin related to administration of tigecycline. *European Journal of Clinical Pharmacology*, 2008, 65 (1), pp.101-103. 10.1007/s00228-008-0557-8 . hal-00486503

HAL Id: hal-00486503

<https://hal.science/hal-00486503>

Submitted on 26 May 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

High serum concentrations of ciclosporin related to administration of tigecycline

Anita N. Stumpf · Christian Schmidt ·
Wolfgang Hiddemann · Armin Gerbitz

Received: 18 August 2008 / Accepted: 21 August 2008 / Published online: 16 September 2008
© The Author(s) 2008. This article is published with open access at Springerlink.com

Ciclosporin is an essential drug in preventing graft rejection after solid organ and hematopoietic stem-cell transplantation. However, it interacts in multiple ways with other drugs and its therapeutic window is narrow. Major and frequent side effects are hypertension and renal failure [1–3].

We report on a 61-year-old woman 5 years after renal transplantation who experienced a nephrotoxic increase in ciclosporin concentrations during antibiotic therapy with tigecycline. The patient was admitted with urinary tract infection caused by *E. coli* carrying ESBL (extended spectrum β -lactamases) susceptible only to meropenem, gentamicin, and tobramycin. Despite initial improvement under treatment with meropenem, dysuria returned after 5 days, C-reactive protein (CRP) rose and urine culture again yielded *E. coli* (ESBL) and *Staphylococcus epidermidis*. To avoid nephrotoxicity of drugs such as gentamicin, antimicrobial therapy was switched to tigecycline.

During intravenous therapy with tigecycline, serum concentrations of ciclosporin rose, closely followed by creatinine levels (max. 167.9 $\mu\text{mol/l}$) (Fig. 1). The daily dosage of 120 mg ciclosporin had to be reduced by 50% and omitted for 1 day. When tigecycline was discontinued after successful anti-infectious treatment, ciclosporin dosages had to be increased again to the initial dosage of 120 mg daily to maintain therapeutic concentrations. The patient was at no time point septic and despite dysuria in a good condition. During the entire period no other potentially interacting drugs were administered or tapered; in particular no other antibiotics were given. This suggests an interaction between tigecycline and ciclosporin, resulting in increased serum concentrations of ciclosporin.

Ciclosporin displays an oral bioavailability of 20–50%, has a high plasma binding of up to 90%, is mainly metabolised in the liver, and excreted via bile [4]. It is a substrate of the 3A4 and 3A5 members of cytochrome P₄₅₀ (CYP₄₅₀) and of the drug efflux pump p-glycoprotein [5]. Concentrations were measured in whole blood prior to the next dose as trough level.

Tigecycline is a new antimicrobial agent of the glycycline group with structural similarities to tetracyclines. It inhibits bacterial protein synthesis by binding to the 30S subunit of ribosomes and acts bacteriostatically. One of its major advantages is its ability to overcome the two most important tetracycline resistance mechanisms: ribosomal protection and efflux [6]. In vitro plasma protein binding is approximately 71–89%. It is primarily eliminated via bile (59%); renal excretion (33%) and glucuronidation are secondary ways of elimination. Its elimination half-life is approximately 40 h (37–67 h) [7, 8].

As a relatively new agent, little is known about interactions with other drugs. Potential mechanisms which may explain the pharmacological interaction in our case

A. N. Stumpf (✉)
Department of Experimental Hematology,
LUMC, Leiden University Medical Center,
Albinusdreef 2,
2333 ZA Leiden, The Netherlands
e-mail: a.n.stumpf@lumc.nl

C. Schmidt · W. Hiddemann
Department of Internal Medicine III, University of Munich, LMU,
Marchioninstr. 15,
81377 Munich, Germany

A. Gerbitz
Department of Hematology/Oncology, Charité Berlin,
Campus Benjamin Franklin,
Hindenburgdamm 30,
12200 Berlin, Germany

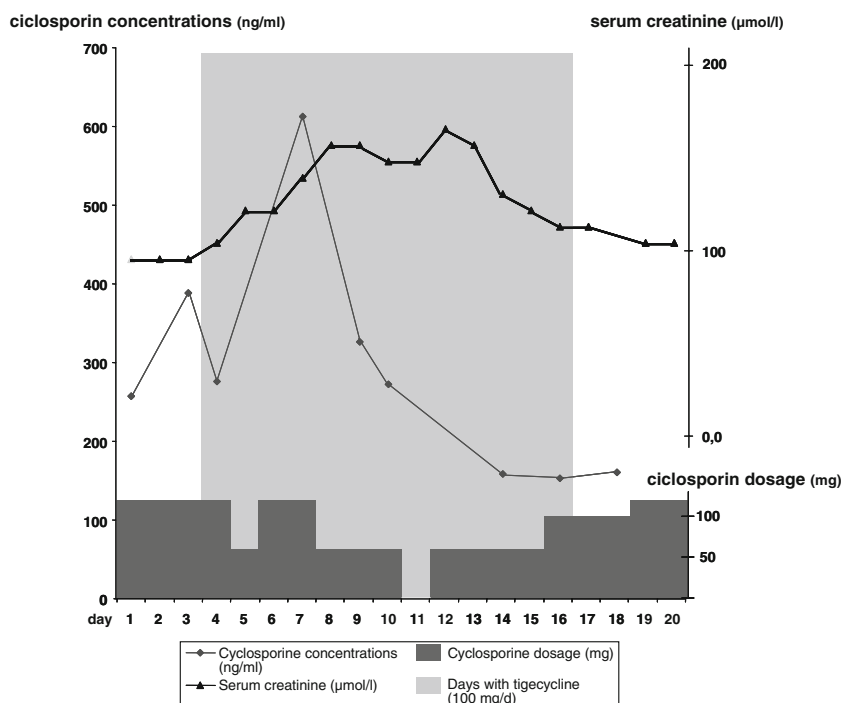


Fig. 1 Concentrations of cyclosporin and serum creatinine are shown in relation to cyclosporin dosage during administration of tigecycline. After start of tigecycline, concentrations of cyclosporin and subsequently of creatinine required a reduction and short interruption of

cyclosporin medication. After discontinuation of tigecycline, cyclosporin dosage could be increased up to the initial amount to maintain therapeutic concentrations

include the following: (1) In vitro studies showed that tigecycline does not inhibit CYP₄₅₀, but its influence on CYP₄₅₀ in vivo cannot be excluded. For instance it has been shown that tigecycline decreases clearance of warfarin, which is also metabolised by CYP₄₅₀ [9]. (2) Cyclosporin is also a substrate of the multidrug efflux pump p-glycoprotein (p-gp). To our knowledge, possible interactions between tigecycline and p-glycoprotein have not been refuted. Inhibition of p-gp by tigecycline as described for other antibiotics [10] could lead to increased concentrations of cyclosporin. Cyclosporin is measured in terms of whole blood concentrations. Thus, competition of the two drugs for protein-binding sites is not a tenable explanation for the increased levels of cyclosporin.

In our case, 3 days after discontinuing tigecycline, cyclosporin could be given at prior dosage again. The onset of increased cyclosporin concentrations and retention parameters after administrating tigecycline and their normalization after its discontinuation suggest a probable drug-drug interaction [11, 12].

Although tigecycline seemed to be securely administered in combination with cyclosporin, our observations suggest the urgent need for close monitoring of cyclosporin

concentrations and retention parameters during treatment with tigecycline.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

References

1. Canafax DM, Ascher NL (1983) Cyclosporine immunosuppression. *Clin Pharm* 6:515–524
2. Vine W, Bowers LD (1987) Cyclosporine - structure, pharmacokinetics, and therapeutic drug-monitoring. *CRC Crit Rev Clin Lab Sci* 4:275–311
3. Vathsala A, Goto S, Yoshimura N et al (1991) The immunosuppressive antagonism of low doses of FK506 and cyclosporine. *Transplantation* 1:121–128
4. Akhlaghi F, Trull AK (2002) Distribution of cyclosporin in organ transplant recipients. *Clin Pharmacokinet* 9:615–637
5. Mourad M, Wallemacq P, De Meyer M et al (2008) Biotransformation enzymes and drug transporters pharmacogenetics in relation to immunosuppressive drugs: impact on

- pharmacokinetics and clinical outcome. *Transplantation* 7 (Suppl):S19–S24
6. Projan SJ (2000) Preclinical pharmacology of GAR-936, a novel glycylycylcline antibacterial agent. *Pharmacotherapy* 9:219S–223S
 7. Hoffmann M, DeMaio W, Jordan RA et al (2007) Metabolism, excretion, and pharmacokinetics of [¹⁴C]tigecycline, a first-in-class glycylycylcline antibiotic, after intravenous infusion to healthy male subjects. *Drug Metab Dispos* 9:1543–1553
 8. Meagher AK, Ambrose PG, Grasele TH et al (2005) The pharmacokinetic and pharmacodynamic profile of tigecycline. *Clin Infect Dis* 41:S333–S340
 9. Stein GE, Craig WA (2006) Tigecycline: a critical analysis. *Clin Infect Dis* 4:518–524
 10. Capone D, Palmiero G, Gentile A et al (2007) A pharmacokinetic interaction between clarithromycin and sirolimus in kidney transplant recipient. *Curr Drug Metab* 4:379–381
 11. Naranjo CA, Busto U, Sellers EM et al (1981) A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 2:239–245
 12. Nebeker JR, Barach P, Samore MH (2004) Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med* 10:795–801