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EXPERT OPINION

Letter to the editor: "Immunosuppressive drug therapy – biopharmaceutical challenges and remedies"

MA Sikma, MD[†], EM van Maarseveen, PharmD PhD, DW Donker, MD PhD & J Meulenbelt, MD PhD

[†]*Division of Anesthesiology, Intensive Care and Emergency Medicine, Department of Intensive Care and National Poisons Information Center, University Medical Center Utrecht, Utrecht, The Netherlands*

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It is with interest that we read the recent paper "Immunosuppressive drug therapy – biopharmaceutical challenges and remedies" by Kahn and co-workers.[1] We support the importance of the improvement of tacrolimus delivery and bioavailability mentioned herein by focusing on the unpredictability of its absorption through the oral route.[1] During clinical observation of four routine heart (n = 2) and lung transplants (n = 2), we perceived that gut dysmotility critically coincides with tacrolimus malabsorption early after transplantation. Given their observational nature, the ethical review board of the University Medical Center Utrecht waived the need for informed consent. Postoperatively, these patients were hemodynamically unstable, requiring high-dose catecholamines expressed as vasoactive inotrope scores of 27 up to 95 (20 has been reported as cut-off level).[2] Typically, fluid balances were highly positive and patients showed clinical signs of systemic inflammation and gut dysmotility, that is, gastroparesis and ileus, which resolved on the postoperative days 3 – 4. In these first 3 – 4 days, tacrolimus concentrations were undetectable (< 0.5 ng/ml), whereas the daily dose was increased according to the protocol. Subsequently, when gut motility restored, an abrupt concentration rise to toxic levels (> 15 ng/ml) occurred, persisting up to 4 days (range: days 4–8) even after tacrolimus withdrawal.

Delayed absorption of tacrolimus, showing early subtherapeutic and subsequently toxic concentrations, may well be mediated by gut dysmotility occurring despite adequately supported macro-circulation early after transplantation. These clinical observations are supported by the finding that high catecholamine use relates to elevated pro-inflammatory chemokines, which contribute to gut dysmotility and reduce drug absorption .[2–4] After clinical stabilization, gut motility improves and readily promotes absorption of residual tacrolimus, abruptly leading to toxic concentrations. This phenomenon is aggravated by the initial use of high doses of tacrolimus meant to counteract subtherapeutic concentrations (< 9 ng/ml).

Routes of administration surpassing oral absorption may be a valuable alternative. At present, besides oral formulations, intravenous tacrolimus (Prograft®, Astellas) is available, though limited, by inherent toxicity of the solvent polyoxyl-60-hydrogenated castor oil, which potentially causes further renal injury superimposed on tacrolimus nephrotoxicity.[5]

As present oral formulations show high interpatient bioavailability, tacrolimus dosing remains challenging especially early after transplantation.[5] Tacrolimus absorption seems to significantly interfere with gut dysmotility despite adequate circulatory support and intensive care. To prevent subtherapeutic as well as toxic concentrations, delayed tacrolimus absorption should be considered. To improve the safe and efficacious use of tacrolimus in patients with gut dysmotility, alternatives such as rectal delivery deserve further clinical exploration.

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Affiliation

MA Sikma MD[†1,2], EM van Maarseveen PharmD PhD[3], DW Donker MD PhD[4] & J Meulenbelt MD PhD[5]

[†]Author for correspondence

[1]Intensive Care Medicine, Department of Intensive Care and National Poisons Information Center, University Medical Center Utrecht, Utrecht, The Netherlands

[2]Division of Anesthesiology, Intensive Care and Emergency Medicine, Department of Intensive Care and National Poisons Information Center, University Medical Center Utrecht, B 00.118, P.O. Box 85500, 3508 GA, Utrecht, The Netherlands
Tel: +31(0)887558561;
Fax: +31(0)302541511;
E-mail: m.a.sikma@umcutrecht.nl

[3]Clinical Pharmacy, Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands

[4]Intensive Care Medicine, Department of Intensive Care, University Medical Center Utrecht, Utrecht, The Netherlands

[5]Intensive Care Medicine and Clinical Toxicology, National Poisons Information Center and Department of Intensive Care, University Medical Center Utrecht and Institute for Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands

Author's response

The authors of the manuscript "Immunosuppressive drug therapy – biopharmaceutical challenges and remedies" highly appreciate the concerns of Sikma and coworkers for the issue of tacrolimus delayed absorption and subsequent and abrupt rise to highly toxic concentration owing to gut dysmotility. As per the reports presented by Sikma et al., tacrolimus concentrations were very less and suboptimal immediately post transplantation attributable to gut dysmotility and then it increased abruptly to toxic level after a lag of few days when gut motility is restored.[1] To address this issue, Sikma et al. emphasized on exploring other routes of tacrolimus delivery rather than oral and intravenous. Nevertheless, other routes such as pulmonary and colon targeted were being investigated by various researchers worldwide. Chougule et al. studied the feasibility of pulmonary delivery of liposomaly encapsulated tacrolimus dry powder inhaler for prolonged drug retention in lungs that they anticipated would work as a rescue therapy to prevent refractory rejection of lungs after transplantation. The study findings were encouraging for enhancing direct delivery of tacrolimus encapsulated in nanoliposomes for controlled and prolonged retention in lungs.[2] This approach could play a savior role in overcoming malabsorption of tacrolimus through oral route by circumventing it and it will also minimize systemic toxicity of drug.

Another interesting approach was used by Lamprecht et al. in which they entrapped tacrolimus-loaded poly(lactic-*co*-glycolic acid) nanoparticles into pH-sensitive microspheres (NPMS) to achieve greater selectivity for treating inflammatory bowel disease.[3] They formulated a two-phase release system (NPMS) wherein drug is first loaded in biodegradable polymer poly (lactic-*co*-glycolic acid) permitting controlled and selective drug accumulation at the site of action. And then these nanoparticles are further entrapped into pH-sensitive microspheres that ensured controlled delivery of the incorporated nanoparticles to their site of action (colon) while simultaneously avoiding drug leakage during its passage through the gut. Such multiphase release delivery systems have the great potential to avoid the rise to highly toxic concentration of tacrolimus in patients post transplantation. Further exploration of design of formulation by multicoating with desirable excipients could stabilize the abrupt changes in the concentration of tacrolimus *in vivo*.

The above-mentioned approaches were the targeted approach that would be effective particularly in case of lung transplantation and inflammatory bowel disease, but as far as a common approach is considered that would be able to reduce gut dysmotility and interpatient bioavailability especially early after transplantation for all solid organ transplantation, extensive exploration of pharmaceutical delivery system is needed. Lipids that simulate the physiologically secreted ones have the potential to enhance gut motility.[4] So far, this area dealing with the effects of lipids on gut motility has remained unexplored, but it demands serious attention of researchers. As discussed in the manuscript, the principal disadvantage of cyclosporine formulation was a huge variation in drug bioavailability ranging from 10 to 60%.[5] To avoid this variation in bioavailability of cyclosporine,

microemulsion (consisting of hydrolyzed corn oil, polyglycolized glycerides, polyoxyethylene–castor oil derivative and ethanol) was formulated, which is used in the commercial product Sandimmun Neoral.[6] Cyclosporine microemulsion resulted in markedly reduced variation in C_{max} and t_{max} values and it shows a prominent initial plasma peak > 1000 ng/ml within the first 2 h. [7] Therefore, these study findings are evident of potential of lipids in decreasing drug onset of action and interpatients bioavailability. The present manuscript emphasized on lipid-based formulation approach for addressing the biopharmaceutical challenges of immunosuppressive drugs based on earlier study findings for drugs such as tacrolimus. Further, the authors anticipate that lipids-based excipients if explored for overcoming the gut dysmotility in oral delivery of tacrolimus would provide favorable results as lipids have the potential to modulate gut motility that too needs profound investigation.

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Affiliation

Saba Khan[1], Sana Khan[2], Sanjula Baboota[1] & Javed Ali[†1]

[†]Author for correspondence

[1]Department of Pharmaceutics, Jamia Hamdard, Hamdard Nagar, New Delhi, 110062, India

Tel: +91 9811312247;

Fax: +011 26059633;

E-mail: javedaali@yahoo.com

[2]Department of Pharmaceutics Faculty of Pharmacy, Jamia Hamdard, New Delhi, India