Therapeutic Drug Monitoring of Cyclosporine Using Single Sampling Strategy

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Abstract

Cyclosporine is mainly used as Immunosuppressant after different kinds of transplantation including bone marrow, lungs, kidneys, liver, heart, and other types of organ transplantations. Immunosuppressants diminish organ rejection and elongate the survival of the transplanted organs. Due to the narrow therapeutic ranges and significantly high interindividual and intraindividual variability in blood levels of cyclosporine, there is essential and vital need of therapeutic drug monitoring (TDM) of this drug in order to maintain the patient within the required therapeutic concentrations, which consequently lead to optimizing the clinical outcome and decrease the hazard of toxicity or rejection following organ transplantations. The current review article was aimed to present data for using a single or possibly two blood sampling strategy to be used for TDM of cyclosporine in order to assess the optimal blood levels of cyclosporine used in organ transplant recipients. The results showed that steady state blood concentration of cyclosporine obtained after 2 hours (C2) and possibly after 3 hours (C3) of drug administration are the best sampling time points which reflect total drug exposure (area under blood concentration versus time curve=AUC) and consequently reflecting the effect and the adverse effect(s) of cyclosporine. On the other hand, blood samples obtained at other time points particularly steady state trough concentration obtained before the next dose (C0) demonstrated poor correlation with total drug exposure and consequently the clinical outcome of the drug. Moreover, this study also demonstrated that for organs transplantations TDM of cyclosporine and assessing the clinical conditions of the patients should be routinely performed in order to adjust the dose to get optimal effect and to diminish the adverse effects of the drug. This review article focused on the findings which indicated that monitoring steady-state blood levels of cyclosporine after 2 hours (C2) and likely after 3 hours (C3) of drug intake may be used as ideal surrogate index in TDM of cyclosporine and for predicting the clinical outcome of the drug in all and different types of organs transplantations.

Key words: cyclosporine, TDM, single sampling strategy.

المناطره الدوائيه لعقار السايكلوسبورين باستعمال استرتيجيه اخذ عينه دم واحده

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الخلاصة:

يستعمل السايكلوسبورين بشكل رئيسي لاحباط وتقليل المناعه في حالات زرع الاعضاء مثل الكبد والكلى والقلب والرئتين ونخاع العظم وغيرها من اعضاء الجسم وان تقليل المناعه يؤدي ال تحسين واطاله حياه المريض ويقلل رفض الجسم للعضو المزروع ونظرا لكون عقار السايكلوسبورين يعتبر دواء ضيق المجال بين التركيز العلاجي والسمي وكذلك فان هناك فوارق لتراكيز الدوا بين المرضى وحتى لنفس المريض لذلك توجد ضروره حيويه للمناطره الدوائيه للدواء لغرض حفض المريض بالتركيز الدوائي المطلوب وبهذا نزيد ونحسن من فعاله الدواء وتقليل اثاره الجانبيه والسميه بعد زرع الاعضاء ان الهدف من هذه الدراسه كان لغرض استعمال استراتيجيه سحب عينه دم واحد او اثنين لغرض المناطره الدوائيه للمريض لغرض معرفه افضل عينه تؤخذ من المريض المزوع فيه العضو ولقد تبين من الدراسات بان العينه المسحوبه بعد ساعتين او حتى ثلاثه ساعات من وصول تراكيز الدواء الى مرحله الاثبات كانت ذات علاقه جيده مع المنحني اللذي يبين التراكيزفي الدم مع الوقت بالمقارنه بالعينات الاخرى وخصوصا قبل الدواء مباشره اذ تبين بان العلاقه ضعيفه هذا يعكس ضعف العلاقه مع تاثير الدواء والتاثيرات الجانبيه للدواء ولذلك فقد تم الاستنتاج من هذه الدراسه بان قياس تراكيز الدواء والنتيجه العلاجيه له يجب ان تقاس بشكل روتيني لزياده فعاليه الدواء وتقليل اثاره الجانبيه وان المناطره الدوائيه للدواء مهمه وحيويه في حالات زرع الاعضاء وان قياس تراكيز الدواء بعد ساعتين وممكن ثلاثه ساعات بعد اخذ الدواء من قبل المريض ممكن استعماله كدليل وبديل للمناطره الدوائيه لعقار السايكلوسبورين ومن خلال هذه العينه الواحده يمكن معرفه نتائج تاثير الدوء لمختف حالات زرع الاعضاء

Introduction

Cyclosporine (known as cyclosporin A also) is a cyclic polypeptide processing potent and selective immunosuppressant activity. The FDA approved cyclo-sporine for prevention of organs transplant rejection in November 1983. Cyclosporine have molecular weight equal to 1202.63 and composed of eleven amino acids. One of the eleven amino acids is (4*R*)-4-((*E*)-2-butenyl-4, N-dimethyl-L-threonine. This amino acid allowed the synthesis of cyclosporine and specifically modified analogues. Researches on studying the structure versus activity relationships suggest that a large part of cyclosporine molecule is involved in interactions with the lymphocyte receptor including the amino acids 1, 2, 3 and 11[1].

The clinical information obtained from using cyclosporine as a calcineurin inhibitor in kidney transplantation were so encouraging and promising which prompting the usage of the drug for transplantation of other organs, in addition of using the drug for treating other and variable autoimmune disorders [2].

Adequate blood levels of immunosuppressant drugs particularly cyclosporine is required for avoiding rejection in all and different types of organs transplant patients. From clinical, pharmacodynamic and pharmacokinetics views, the rejection can be diminished first by assessing the molecular resemblance between the recipient and the donor. The second important and vital approach is by using immunosuppressant agents following organ transplantation [3, 4]. Several clinical observations demonstrated that the use of cyclosporine causes remarkable improvements in the outcomes of transplantations and reduce the occurrence of acute rejection episodes and the complications which may occur due to severe infectious [5].

In order to get prospering transplantation outcome in cyclosporine therapy, the target blood levels should be achieved in order to retain a balance between the under- and over-immunosuppression activity of the drug, since in one extreme, under-immunosuppression effect lead to rejection and failure of therapy, the other extreme situation in which there is over-immunosuppression may lead to serious adverse effects of the drug[6].

Cyclosporine has narrow therapeutic window and display great inter- and intraindividual pharmacokinetic variability that make TDM of the drug very essential. Cyclosporine blood levels below or above

the recommended therapeutic ranges, may lead to escalate the chances of rejection or appearance of many underside effects. Hence, the considerable variability in pharmacokinetics, the narrow therapeutic window, in addition to the severity of different adverse effects rationalize and advocate the application of TDM in cyclosporine therapy [7].

Cyclosporine pharmacokinetics

Cyclosporine pharmacokinetics is very complicated and influenced by several and variable factors [8] including demographic characteristics of the patients, physiological and biochemical factors, the time and sort of organ transplantation, interactions of cyclosporine with other drugs, in addition to the well documented great inter- and intra-subject variability in cyclosporine pharmacokinetics in different patient populations and even in the patient belonging to the same nations [9, 10]. Furthermore, orally given cyclosporine have more pharmacokinetic problems relative to the intravenous intake due to different, incomplete, and high within and between individual differences [8,11].

Thus, many and different clinical and pharmacokinetic factors including the dosage form used, administration route, age, the status of GIT, consumption of food and the presence of liver and kidneys malfunctions should be taken in consideration in cyclosporine therapy since these factors may cause significant alterations on the absorption rate and/or extent and consequently the extent and/or rate of bioavailability. Moreover, a clinical report demonstrated that until day 21 followed transplantation a significant decline in the in total body clearance occurred [12].

Hence, it is clinically challenging to keep a balance between the safe and effect blood levels of cyclosporine; and thus, all of the pharmacokinetic and clinical factors mentioned above should be taken in account to get optimal effect with minimal side effects(s) in cyclosporine therapy.

Cyclosporine is mostly metabolized by hepatic metabolism and its elimination following intravenous route show biexponential decline with terminal elimination half- life ranging from 5 to 18 hours and approximate mean value of 8.4 hours. The apparent volume of distribution (Vd) is about 3-5 l/kg and almost about 90% of the drug bound to plasma proteins. The elimination of cyclosporine is primarily biliary with only about 6% of the parent drug is excreted by the kidneys as unchanged drug together with its metabolites. The drug reaches its peak or maximum level in plasma within 1.5–2.0 hours post oral dosing. Administration of cyclosporine at therapeutic doses demonstrates linear pharmacokinetics with dose proportional relationship between doses given and the resulted total drug exposure (AUC) [13].

Correlation between cyclosporine pharmacokinetics and pharma-codynamics

As per international guidance particularly FDA and EMEA, from pharmacokinetic view, measurement of both the peak (Cpeak) or maximum (Cmax) drug levels in blood and the area under concentrations of drug in blood against the sampling time (AUC) representing the extent and rate of drug absorption and bioavailability, and consequently reflecting the total drug exposure. Accordingly, these pharmacokinetic parameters are regarded as the primary parameters which describe the pharmacokinetic characteristics of drugs. Besides, the time to reach the peak or maximum concentration of drug in blood (Tmax or Tpeak) can also supply useful information regarding the absorption rate of drug [14-16]. On the other hand, from pharmacodynamic view, both of these primary pharmacokinetic parameters, i.e., Cmax and AUC reflect the onset, the duration, and the intensity of drug effects

and side effects because they represent the rate and extent of drug absorption and bioavailability and in consequence the total exposure to the drug [17, 18].

The pharmacological and clinical effect of cyclosporine in both adults and paediatric organs transplant patients is related closely with its blood levels and total drug exposure represented by AUC. Concerning the relationship between blood concentrations of cyclosporine and its clinical effectiveness, it was observed that higher blood levels of the drug cause considerable diminishment in the occurrence of acute graft versus host disease (GVHD) after three weeks following transplantation of allogeneic hematopoietic stem cell [19]. Further researches emphasized that a reduction in the intensity of GVHD may be achieved by sustaining adequate blood levels of the drug by close therapeutic drug monitoring (TDM) and dose adjustments [20]. The apparent good and positive relation between the blood levels of cyclosporine and its immunosuppressant activity is rationalized by the fact that the increment in cyclosporine blood concentrations may be related to reduction in the activity of T-cells of the donor. Thus, the strong correlation found between concentrations of cyclosporine and its immunosuppressant activity (reduction of T-cells) support the recommendation for TDM of the drug since it may lead to the improvement in the clinical effect of the drug [21].

Generally, in order to characterize all the phases in the pharmacokinetic profile of drugs involving the absorption, distribution and the terminal elimination phases, the AUC of the drug should be estimated. Calculation of AUC is usually achieved by frequent blood sampling of the drug during the dosing interval after repeated oral doses. Therefore, in case of cyclosporine in particular, the most reliable blood sampling program following oral dosing twice daily is by calculating $AUC_{0–12h}$ which is usually carried out by often measuring of cyclosporine blood levels before drug administration (C0), followed by blood sampling at 1, 2, 3, 4, 6, 8 and ultimately at 12 hours (C12) after cyclosporine intake [14-18].

At steady state, the trough concentrations whether taken at C0 (pre- next dosing) or C12 (at the end of dosing interval 12 hours) is assumed and expected to be identical since both concentrations (C0 and C12) are trough concentrations obtained at the end of dosing interval (12 hours). However, determination of $AUC_{0–12h}$ in clinical practice involves many troubles and complications for organ transplant patients such as high stress on the patient, long and tedious duties and efforts for the clinical workers, high cost, and the need for obtaining large volume of blood which should be taken in consideration particularly for children since reliable calculation of $AUC_{0–12h}$ require withdrawal of at least 8 blood samples from the patient.

Relationships between cyclosporine blood levels, AUC and the response

Several distinguished investigations were conducted in solid organs transplantations to find out the relationships between cyclosporine $AUC_{0–12h}$ and its clinical activity. It was explored in these researches that prevention of acute rejection in organs transplantation is best related with obtaining the target $AUC_{0–12h}$. Similarly, in paediatric patients undergoing transplantation of hematopoietic stem cell, a good positive relationship was discovered between the prevention of acute GVHD and $AUC_{0–12h}$ [22]. Moreover, best correlation was demonstrated between cyclosporine AUC and creatinine clearance of the patients, the haematocrit and other clinical parameters [23]. It was observed that obesity and creatinine clearance displayed significant positive relationships with AUC, whereas, significant negative correlation was noticed between the haematocrit and AUC [23].

Further researches were suggested for the estimation of $AUC_{0–4h}$ as other alternative approach to $AUC_{0–12h}$. Interestingly, good positive relationships were detected

between $AUC_{0–4h}$ and the clinical results obtained from many and different kinds of organ transplantations including heart [24], lungs [25], and other organs particularly the kidneys and the liver transplantations [26]. However, measurement of $AUC_{0–4h}$ still have the above-mentioned problems, difficulties and burdens associated with the calculation of $AUC_{0–12h}$, but to less extent because fewer number of blood samples are needed to be sampled from the patients in case of measuring $AUC_{0–4h}$ in comparison to $AUC_{0–12h}$.

Thus, several ongoing, prominent and outstanding investigations were performed in many TDM centers and in many hospitals and places worldwide for different types of organs transplantation and for both adults and paediatric patients in order to establish a validated and limited blood sampling strategy for cyclosporine therapy utilizing one or possibly two blood samples obtained after one (C1), two (C2), three (C3) or four (C4) hours following cyclosporine intake which show best correlation with AUC namely, $AUC_{0–12h}$ and/or $AUC_{0–4h}$ [27].

Interestingly, many investigations conducted for variety of patient populations and for different kinds of organ transplantations revealed best relationship between cyclosporine blood concertation that obtained after two hours of drug intake (C2) and their corresponding $AUC_{0–4h}$. Among these studies were documented for transplantation of organs including lungs [25], liver [28], heart [24,29], transplantation of allogeneic stem cell [30], for children suffering from idiopathic nephrotic syndrome [31], in addition to other kinds of organs allografts [26, 32]. Other work conducted for patients with corticosteroid resistant systemic lupus erythematosus elicited best correlation between cyclosporine blood levels after two hours post-dosing (C2) and their corresponding AUC0-6h [33].

In addition, more researches exhibited highest good positive correlation between the concentrations of cyclosporine withdrawn after two (C2), three (C3) and four hours post-dosing (C4) versus their corresponding $AUC_{0–12h}$. Among these investigations were conducted for patients needed allogeneic hematopoietic stem cell transplantation [34], transplantation of allogeneic stem cell [35, 36], patients requiring kidneys allograft [37], for renal and liver transplant patients with HIV infection [38], for paediatric patients demanding hematopoietic stem cell transplantation[39], for children suffering from idiopathic nephrotic syndrome[31], and for paediatric patients demanding stem cell transplantation [40].

Interestingly, and in contrast to the general believe for relatively long time, most pharmacodynamics, pharmacokinetic and clinical studies conducted in many national and global centers, and for different types of patient populations, as well as for various kinds of organ transplantations, explored poor correlation between trough level (C0) and total drug exposure, i.e., $AUC_{0–12h}$ and $AUC_{0–4h}$ as in previous literature. On the other extreme, other pharmacodynamics, pharmacokinetics and clinical studies indicated that cyclosporine blood concentration sampled at two hours (C2) post-dosing is considered as better predictor than the trough level (C0) [24-26, 28-32].

Therefore, according to the above-mentioned interesting findings, the C2 values may be utilized as the best and proper guide to monitor the effect and the safety profiles of cyclosporine as confirmed by other clinical trials [41-43]. Accordingly, adjustment of cyclosporine dozes based on a single steady state blood concentration obtained at C2 instead of calculating the entire AUC, i.e., $AUC_{0–4h}$ and $AUC_{0–12h}$ as appeared in many investigations mentioned above [24-26, 28-32] became as one of the standard approaches in cyclosporine therapy and gained an international agreement in clinical practice [44]. Moreover, a very recent clinical trial [45] conducted for Iraqi patients underwent bone marrow transplantation in the TDM center located in Baghdad Teaching

Hospital in Medical City, Baghdad, Iraq confirmed and supported all the above stated interesting and important findings since good positive correlations were observed between cyclosporine blood concentrations obtained after 2 (C2) and possibly 3 hours (C3) post-dosing gave much better correlation with total drug exposure namely AUC_{0-4h} and AUC_{0-12h} than the trough level i.e., C0 and C12 [45].

Conclusions

Cyclosporine TDM is vital and very important for the benefits of all and different sorts of organs transplant recipients. Therefore, the drug levels and the clinical conditions of the patients should be routinely checked and examined in order to adjust the therapy with cyclosporine and reduce its adverse effects. Many clinical, pharmacodynamic and pharmacokinetic investigations demonstrated that using single steady state blood level of cyclosporine measured after 2 (C2) and possibly after 3 (C3) hours of drug intake reflect total exposure (AUC) of the patient to the drug, and in consequence the effect and the side effects of cyclosporine. Therefore, these investigations recommend the use of a single blood sampling strategy for TDM of cyclosporine as an ideal surrogate index in order to gain optimal effect and minimal adverse effects in cyclosporine therapy for different types of organs transplantations and for different patient populations.

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