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Monitoring levels of immunosupressive medications – is it just a recommendation or a necessity?

Monitorowanie leków immunosupresyjnych u chorych po przeszczepieniu nerki – potrzeba czy konieczność?

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Słowa kluczowe
transplantacja nerek, immunosupresja, pole pod krzywą

S u m m a r y

Introduction. Enormous development of organ transplantation which took place in recent years was made possible also due to development of more diverse and targeted immunosupression. Huge progress in this area was achieved due to inroduction of calcineurin inhibitors, m-TOR inhibitors, mono- and polyclonal antibodies, and drugs containind mycophenolic acid. Nonetheless, administration of these drugs, in dfferent combinations and doses, can lead to numerous side effects. Therefore, patients after transplantation of vascular organs require regular and thorough clinical follow-up, as well as individually tailored dose of immunospuressive drugs and and monitoring its blood concentration. Currently such strategy it is commonly accepted for calcineurin inhibitors and m-TOR inhibitors, but a discusssion among transplantologists takes place about necessity of monitoring blood levels of mofetil mycophenolate or natrium mycophenolate.

Aim. The aim of this paper is to assess usefulness of monitoring blood levels of mofetil mycophenolate (MMF) in patients after kidney transplantation , based on published literature and our own clinical studies.

Material and methods. Immunoenzymatic method (EMIT) was used to calculate area under curve (AUC) for each of three consecutive blood samples in 21 patients (23 results).

Results. In several cases, achieved results were far outside the recommended limits (30-60 mg h/l), which resulted in necessity to correct drug dose. Therefore it seems that, in selected cases, monitoring MMF levels can be useful in selection of optimal drug dose and can lead to lower risk of side effects and possible rejection reactions.

Conclusions. Literature data and our own observations support the thesis that monitoring blood levels of mofetil mycofenolate (and possibly in the future also natrium mycofenolate), especially in the early post-operation period, will be the standard of care in patients after vascular organ transplantation.

S t r e s z c z e n i e

Wstęp. Burzliwy rozwój transplantacji narządów, który nastąpił zwłaszcza w ostatnich dziesięcioleciach, był między innymi możliwy dzięki coraz to bardziej urozmaiconej i celowanej immunosupresji. Ogromnym postępem w tej dziedzinie było wprowadzenie do leczenia inhibitorów kalcyneuryny, inhibitorów m-TOR, przeciwciał mono i poliklonalnych oraz leków zawierających w swojej budowie kwas mykofenolowy. Jednakże stosowanie tych leków (w różnych skojarzeniach i dawkach) nie jest pozbawione szeregu działań niepożądanych. Dlatego też chorzy po transplantacjach narządów unaczynionych podlegają systematycznej i wnikliwej kontroli klinicznej, jak również są indywidualizowane i monitorowane dawki i stężenia we krwi stosowanych leków. W chwili obecnej powszechnie przyjmuje się, że takie postępowanie jest standardem jeśli chodzi o inhibitory kalcyneuruny czy inhibitory m-TOR, natomiast trwa dyskusja wśród transplantologów co do potrzeby oceniania we krwi poziomów mykofenolatu mofetilu czy mykofenolatu sodu.

Cel pracy. Celem pracy było w oparciu o dotychczasowe doniesienia z piśmiennictwa oraz własne badania kliniczne ocena przydatności oznaczania poziomów we krwi mykofenolatu mofetilu u chorych po przeszczepieniu nerek.

Materiał i metody. Oceniano metodą immunoenzymatyczną (EMIT) pole pod krzywą (AUC) wyliczane każdorazowo z trzech kolejnych próbek krwi u 21 chorych (23 oznaczenia).

Wyniki i wnioski. Otrzymane wyniki w kilku przypadkach odbiegały dość znacznie od zalecanej normy (30-60 mg h/L), co było powodem skoregowania dawki stosowanego

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leku. Wydaje się, że zwłaszcza u wybranych chorych po przeszczepieniu nerki oznaczanie poziomów MMF powinno być pomocne w optymalizacji dawki tego leku i przez to może przyczynić się do zmniejszenia ryzyka wystąpienia objawów ubocznych, a także ewentualnych reakcji odrzuceniowych.

Podsumowanie. Coraz więcej danych z piśmiennictwa oraz nasze własne obserwacje przemawiają za tym, iż oznaczanie, zwłaszcza we wczesnym okresie pooperacyjnym, poziomów we krwi mykofenolatu mofetilu (a w przyszłości prawdopodobnie również mykofenolatu sodu) będzie stardardem naszego postępowania diagnostycznego u chorych po transplantacjach narządów unaczynionych. Stoimy na stanowisku, iż dalsze badania i obserwacje kliniczne w pełni potwierdzą powyższą tezę.

INTRODUCTION

Calcineurin inhibitors, which have been commonly used in transplantology since 1980s, have brought about considerable progress in terms of survival, both of transplants and patients. However, using these and other immunosuppressive drugs one constantly has to seek the right balance between the need to protect the patient against rejection processes and the toxic effect of such drugs. In extreme cases, administration of drugs ends up with developing the "immunosuppressive disease", which manifests itself in multisymptomatic adverse effects of the drugs, from arterial hypertension, through diabetes, the toxic effect on bone marrow, increased susceptibility to cancer and infections, to acute or chronic nephrotoxic effect. Therefore, the need for monitoring blood levels of common immunosuppressive drugs is commonly recommended and accepted in contemporary nephrology. This applies both to calcineurin inhibitors (Ciclosporin, Tacrolimus, Advagraf) and mTOR inhibitors (Sirolimus, Everolimus). The use of monoclonal (OKT_3) and polyclonal (ATG, Thymoglobulin) antibodies must be accompanied by controlling leucocytosis, and, better still, the level of CD3 lymphocytes (a decrease in these cells count should not be lower than 50-100 per 1 mm^3 of blood) (1-8).

Clinical therapists have been discussing the need for routine monitoring of the levels of mycophenolate mophetil (MMF) and even mycophenolate sodium (MPS). Therefore, we would like to present our preliminary experiments regarding the issue.

High individual diversity of calcineurin inhibitors in patients has made it necessary to monitor their blood levels following organ transplantations. Most transplantation centres determine what is referred to as C_0 level, which is the concentration of a drug 12 hours after its administration. Determination of C_2 (a drug level 2 hours after administration) is less common as its results are less reliable. Determination of the blood level profile of these drugs in order to calculate the area under the curve (AUC) has not caught on because of some practical issues and because of the cost of the procedure. The CyA level can be determined both in plasma and in whole blood. The methods employed include high performance liquid chromatography (HPLC), enzyme multiplied immunoassay technique (EMIT) and fluorescence polarization immunoassay (FPIA). Levels of tacrolimus are usually determined by MEIA (microparticle enzyme immunoassay) which involves determination of monoclonal antibodies in autoanalysers. The recommended drug levels in blood depend on the length of the post-transplant period and on the research methodology. For example, C_0 of CyA should be 250-450 ng/mL soon after the transplantation, and decrease to 150 ng/mL after several months (as determined by FPIA). Similarly, C_2 – initially, it should be 1.5-2 μg/mL, and later – 0.8-1.0 μg/mL. The recommended level of tacrolimus (C_0) with the starting dose of 0.15 mg/kg/day should range from 10 to 20 ng/mL during the initial post-transplant period, and decrease to 5-7 ng/mL several months later.

AUC is calculated by adding up the blood levels of the drug in a series of samples taken within several hours of administering the drug. However, it has been emphasised that the absolute values of the original drug levels in blood are significantly different from those of generic formulations (9-11).

The recommended blood level of mTOR inhibitors, as determined by HPLC, should lie within the range from 5 to 25 ng/dL. It has been stressed that using these drugs in combination with calcineurin inhibitors requires particular caution as the drugs of both groups are metabolised by the same enzymatic system in the liver (cytochrome P-450 IIIA) (12, 13).

Determination of blood levels of mycophenolate mophetil (especially its most common formulation – Cell-Cept) still remains controversial. Most transplantation centres routinely give the dose of 2 g/day (2 x 1.0 g) to adult recipients, as recommended by the manufacturer, with possible adjustments for the patient's body weight, or divide the daily dose into 3 or 4 portions if any adverse gastrointestinal symptoms occur. However, this regimen has been criticised increasingly in clinical and other research reports. Their authors claim that a number of adverse events following the use of the drug may result from an uncontrolled growth of its blood level despite the patient receiving the recommended dose. Moreover, increasing frequency and intensity of rejections may in some cases be attributed to too low drug level in the blood in spite of the typical dosage (14, 15). There are at least two methods of monitoring the drug level in blood. One involves the determination of the concentration of mycophenolic acid (MPA) C_0 in blood immediately before the next dose is administered. It is a simple method and it requires only single blood sampling. A recommended level is 1.3 mg/L when MPA

C_0 is combined with CyA, and 1.9 mg/L when MMF is administered in combination with tacrolimus. However, there is a low correlation of C_0 with the area under the curve (AUC), which is a disadvantage of the method. As a consequence, a three-point analysis (determination of drug concentration in blood 20 minutes, 1 hour and 3 hours following its administration) is a preferred method. It is assumed that the recommended total values of mycophenolate mophetil determined by this method (suitably adjusted when combined with CyA or tacrolimus) should range from 30 to 60 mg h/L (14).

AIM

The aim of this paper is to assess usefulness of monitoring blood levels of mofetil mycophenolate (MMF) in patients after kidney transplantation, based on published literature and our own clinical studies.

MATERIAL AND METHODS

In our Centre, we have determined the plasma level of MPA by the EMIT 2000 method, employing the homogeneous immunoassay technique. The assays were conducted on a Siemens analyser and they were based on competitive binding of anti-MPA antibodies.

MPA in the analysed sample competes with enzyme-labelled MPA (labelled with glucose-6-phosphate dehydrogenase – G6PHD). The active, unbound form of the enzyme transforms oxidised nicotinamide adenine dinucleotide (NAD) into an antibody (NADH substrate), resulting in a change of absorption, which can be measured by spectrophotometry.

Since the enzyme activity decreases following its binding to the antibody, its measurement makes it possible to determine the MPA concentration in the sample. So far we have performed 23 AUC concentration analyses (each time in three blood samples) in 21 patients. The diagram of the measurement results is attached (fig. 1).

RESULTS

The average value of AUC was found to be 46.96 ± 21.98 (the recommended value is 30-60 mg h/L, the optimum value – 40 mg h/L). The AUC deviated from the recommended values in some cases, which resulted in adjusting the drug dose. In one case, with a considerably increased AUC (75 mg h/L), symptoms of CMV infection appeared, and we believe that reducing the MMF dose considerably may have helped to control the infection within a short time.

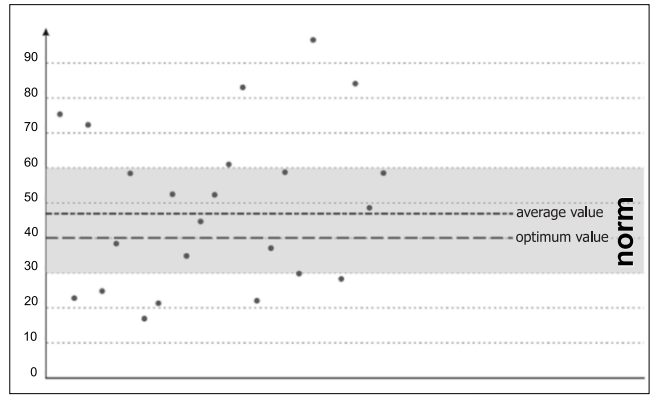

Fig. 1. Average MMF blood levels in patients (mg h/L) calculated from AUC (each time measured in three blood samples).

Currently, it is difficult to develop a practicable method of monitoring the level of mycophenolate sodium (MPS), which has been used increasingly often in transplantation centres as a result of the intolerance to mycophenolate mophetil observed in some patients, which usually manifests itself as gastrointestinal ailments. The difficulties result from the fact that the drug is released in the gastrointestinal tract soon after it is administered; the process is delayed with mycophenolate sodium, which may result partly from different stomach emptying rate in different individuals (16). The problem is made more complicated by common administration of proton pump inhibitors to such patients, which results in premature tablets dissolution and faster drug release. Attempts at solving the problem have been made by determination of blood levels of the drug 3 and 4 hours following the drug administration to the patient. Currently, clinical trials are under way which aim at planning the optimum analytical procedure (17-20).

CONCLUSIONS

The review of the literature and clinical trials, as well as our preliminary experiments have led us to the conclusion that monitoring blood levels of immunosuppressive drugs is not only a need, but it is a must. It seems that in some cases this also applies to blood levels of mycophenolate mophetil, which may be indicated by increased awareness of the fact and increasingly common conducting of assays at transplantation centres.

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