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Effect of Curcumin at Various Doses on the Pharmacokinetic Profile of Tacrolimus in Healthy Rabbits

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Abstract

The purpose of present study was to evaluate the effect of co-administration of curcumin (CUR) at various doses on the pharmacokinetic (PK) profile of tacrolimus (TAC), a CYP 3A4 substrate in healthy male rabbits. Healthy male rabbits (n=18) were employed in an in vivo, parallel-randomized study. Three groups of rabbits were selected and separated: The rabbits in the first group (control group) received 1 mg/kg TAC orally. Blood samples (1.5-2 mL) were drawn from rabbits' ear marginal veins at the following time frames: 15.0, 30.0, 45.0, 60.0, 90.0, 120.0, 150.0, 180.0 and 300 minutes after TAC administration and analyzed by using a TAC Chemiluminescent Enzyme Immunoassay (CLIA) detection kit. In the second and third groups (test groups), rabbits received TAC (1mg/kg) at identical conditions as in the control group with volumes equivalent to (30 and 90 mg/kg/day) of prepared CUR suspension in normal saline for seven continuous days. Blood samples from the control group were obtained on the eighth day. Non-compartmental analysis was used to derive different PK parameters of TAC for the three groups. When CUR was co-administered at both concentrations, statistically insignificant small changes between the control and testing groups were found. The current results revealed that the differences for the three groups in PK parameters as C_{max}, T_{max}, ke, AUC_{0-6} and $AUC_{0-\infty}$ were statistically insignificant (*P>0.05*). In conclusion, it has been found that CUR at the experimented doses does not affect the PK of TAC. Further confirmation of our findings is required before these results can be applied in patient care.

Keywords: Tacrolimus, Curcumin, Pharmacokinetics

تأثير الكركمين بجرعات مختلفة على ملف الحرائك الدوائية للتاكروليموس في الأرانب السليمة

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الخلاصة

الغرض من هذه الدراسة هو تقييم تأثير أضافة مادة الكركمين (CUR) بجرعات مختلفة على الخواص الحركية الدوائية (PK) لعقار التاكروليموس (TAC) والذي يستقلب بواسطة الانزيم CYP3A4 في ذكور الأرانب السليمة صحيا. في هذه الدراسة تم توظيف أرانب ذكور صحية (ن = ١٨) في دراسة عشوائية متوازية. تم اختيار وفصل ثلاث مجموعات من الأرانب: تلقت الأرانب في المجموعة الأولى (المجموعة الضابطة) ١ مجم / كجم من TAC عن طريق الفم ومن ثم تم سحب عينات الدم (١,٥-٢ مل) من الأوردة الهامشية لأذن الأرانب في الأطر الزمنية المحددة بعد إعطاء دواء التاكروليموس و تحليلها باستخدام مجموعة أدوات الكشف عن المقايسة المناعية الإنزيمية المضيئة (CLIA) الخاصة بدواء التاكروليموس. اما فيما يتعلق بمجموعتي الاختبار الثانية والثالثة (مجموعتي الاختبار) ، أعطيت الأرانب نفس الجرعة الخاصة بدواء التاكروليموس فى نفس الظروف كما في المجموعة الضابطة بتراكيز تعادل (٣٠ و ٩٠ مجم / كجم / يوم) من معلق CUR المحضر في محلول ملحي عادي لسبعة أيام متواصلة. في اليوم الثامن ، تم جمع عينات الدم كالمجموعة الضابطة وتم تحديد معلمات الحركية الدوائية المختلفة لـ TAC للمجموعات الثلاث باستخدام التحليل غير الجزئي. لوحظ أنه ، كانت هناك اختلافات غير ذات دلالة إحصائية بين المجموعة الضابطة والمجموعات المختبرة عند الاضافة مع CUR في كلا التركيزين. كشفت نتائجنا أن الفروق بين المجموعات الثلاث في معاملات الحرائك الدوائية مثل C_{max}, T_{max}, , ke, AUC_{0-6} and $AUC_{0-\infty}$ كانت غير ذات دلالة إحصائية (*p>0.05*). فى الختام ، لقد وجد ان الكوركمين عند الجرعات المجربة لا يؤثر على معاملات الحركية لدواء التاكروليمس ولكن هناك حاجة إلى مزيد من التأكيد على هذه النتائج التي تم التوصل إليها قبل تطبيقها في رعاية المرضى.

الكلمات المفتاحية: تاكروليموس ، الكركمين ، حركية الدواء.

Introduction

Tacrolimus (TAC), a calcineurin inhibitor, is an important component of the traditional immunosuppressive regimen after renal transplantation. Due to its narrow therapeutic index and the fact that various factors intervene with its metabolism [(1)]. TAC's PK pathways involve cytochrome P450 (CYP) 3A4 and P-glycoprotein (P-gp), and drugs that interact with these enzyme systems will influence TAC blood concentrations [(2)]. Because TAC covers a restricted therapeutic window and lacks a strong correlation between dosage and serum concentration, it may cause toxicity, subtherapeutic failure, and organ rejection [(3)]. TAC interacts with several other treatments used in transplantation therapy that are known CYP3A and/or P-gp inhibitors and/or inducers as a substrate of CYP3A enzymes and P-gp [(4)].

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The CYP450 enzymes are membrane-bound hemoproteins that play a pivotal role in the detoxification of xenobiotics, cellular metabolism and homeostasis. Induction or inhibition of CYP450 enzymes is a major mechanism that underlies drug-drug interactions [5].

Natural products have shown a promising source of components for the development of new drugs [6,7]. One of the most common example is turmeric (Curcuma longa Linn.), which is a member of the Zingiberaceae family [8]. The rising importance of natural remedies around the world has sparked concerns concerning herb-drug interactions. These interactions are especially important for drugs with narrow therapeutic indices and may either be pharmacodynamic or PK in nature when used with P-gp and CYP3A4 substrates [9,10]. Herb-drug interactions are one of the most serious clinical concerns while using herbal remedies and prescribed drugs simultaneously [11].

The likelihood of PK medication interactions involves two key challenges: pharmacotoxicity and treatment failure. The earlier can be produced by inhibiting drug metabolism and clearance enzymes, whereas the latter can be triggered by enzymatic stimulation resulting in increased drug metabolism [12]. Numerous in vitro studies have reported that curcumin inhibited not only P-gp, but also CYP3A4. Based on these in vitro results, coadministration of curcumin should increase the oral bioavailability of substrates of P-gp or CYP 3A4 [13]. The effect of co-administration of CUR at various doses on the PK profile of TAC, a CYP 3A4 substrate, was investigated in the present study.

Materials and Methods

Animals

In this study, eighteen New Zealand strains of adult male rabbits weighing (3.1-3.4 kg) and aged (8-10) months were used. The Research and Ethics Committee granted permission to the Experimental Animal Care Facility, College of Pharmacy, Al-Azhar University of Gaza (AUG), Palestine. The rabbits were randomly split into three groups (six for each group). All rabbits were housed in controlled conditions with a 12-hour light/dark cycle at (25°C ± 2°C), pellet feeding, and free access to water (*ad libitum*). Prior to the trial, they also fasted over the night.

Study design and blood sampling

Eighteen healthy male rabbits were used in an *in vivo*, parallel-randomized controlled study. Three groups of rabbits were selected and separated: The rabbits in the first group (control group) received 1 mg/kg TAC orally from a hard capsule (5 mg, prograf®, *astellas*) kindly provided by the Palestinian Ministry of Health's medication stores. Blood samples (1.5-2 mL) were drawn from rabbits' ear marginal veins at the following time frames: 15.0, 30.0, 45.0, 60.0, 90.0, 120.0, 150.0, 180.0 and 300 minutes following TAC administration [14]. In the second and third groups (test groups), rabbits were given TAC (1mg/kg) at the same conditions as in the control group with volumes equivalent to (30 and 90 mg/kg/day) from prepared CUR suspension in normal saline (Turmeric® Curcumin 550 mg, *Jamieson*) hard gelatin capsules purchased from a local pharmacy in Gaza, Palestine) for seven continuous days. On the 8th day, TAC was given one hour after the last dosage of CUR suspension, and blood was collected from the second and third test groups at the same time as the control group. Whole blood samples were stored in EDTA tubes at 2-8°C until they were tested (Whole blood sample is stable for up to 3 days).

Blood samples analysis

At the Medical Relief Society-Gaza laboratory, whole blood samples were tested to detect TAC concentrations using the Maglumi 800 System and TAC detection kit. The TAC detection Kit is based on a chemiluminescent enzyme immunoassay (CLIA). It's utilized in hospitals to check TAC doses by doing fast TAC assays on whole blood.

PK of TAC and statistical analysis

The PK parameters, C_{max}, T_{max}, K_e, AUC_{0-6}, and $AUC_{0-\infty}$ were determined for the control and CUR-treated test groups. The C_{max} and T_{max} were accurately observed through plasma concentration versus time curves. The AUC_{0-6} was determined using the linear trapezoidal method. The $AUC_{0-\infty}$value was calculated using the formula: $AUC_{0-\infty} = AUC_{0-6} + Ct / K_e$, where Ct is the final measured blood concentration at time t and K_e is the elimination rate constant. The K_e was calculated using semilogarithmic dependency, which corresponds to first-order kinetics, by least-squares regression of blood concentration-time data points in the terminal region. The PK analysis was determined using a model-independent method (Non-Compartmental Approach), WinNonlin Professional Software (Version 6.3, Pharsight Corporation, Cary, NC), and (GraphPad Prism version 4.00; San Diego, CA, USA). The PK parameters of TAC alone (control group) and TAC co-administered with CUR in the first and second test groups were compared using statistical methods such as descriptive analysis and the Mann-Whitney test.

The data was analyzed by using the SPSS program (version 22.0). A statistically significant difference was considered when $P \leq 0.05$.

Results

CUR's effect at various dosages on the PK parameters of TAC was explored *in vivo*. The PK parameters of TAC in the control group (first group) were compared to those of the test groups treated with CUR 30 and 90 mg/kg/day (second and third groups respectively) and the blood concentration-time profiles of TAC in the first group and in the co-administered with CUR (test groups) are shown in Figure 1 and Table 1.

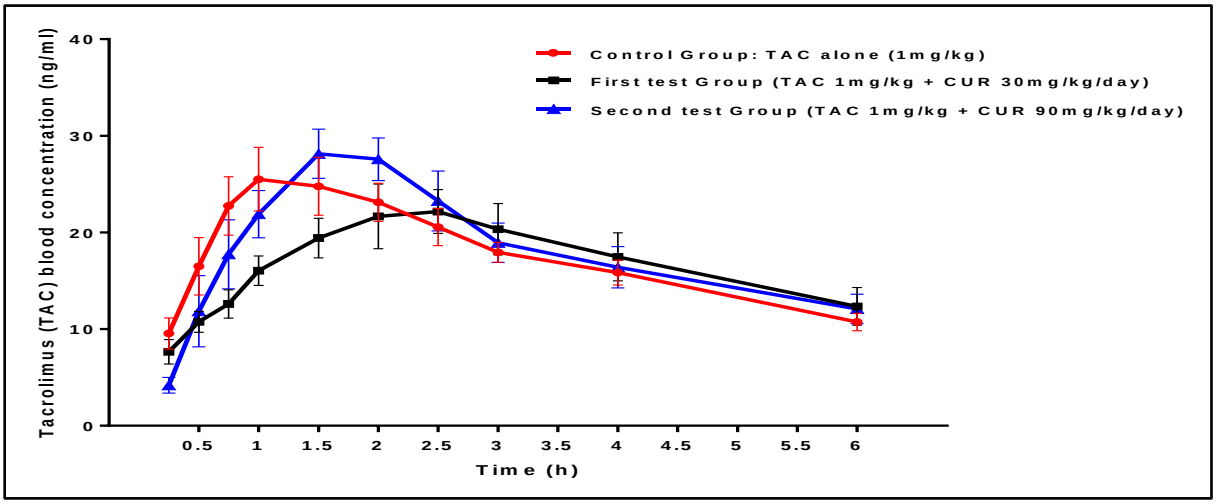

Figure 1. Plot of TAC concentration-time profile with and without CUR for the control, first and second test groups.

Table 1. Calculated PK parameters of the control, the first and second test groups (6 for each).

PK Parameters	Groups	Mean ± SD	P-values
[a]C_{max} (ng/mL)	Control group	27.44 ± 5.83	0.668¥
	First test group	25.78 ± 7.60	0.338§
	Second test group	31.20 ± 4.33	
[b]T_{max} (hr^{-1})	Control group	1.50 ± 0.50	0.405¥
	First test group	1.90 ± 0.54	0.690§
	Second test group	1.65 ± 0.65	
[c]k_e (hr^{-1})	Control group	0.102 ± 0.04	0.736¥
	First test group	0.124 ± 0.10	0.570§
	Second test group	0.091 ± 0.03	
[d]AUC_{0-6} (ng*hr/mL)	Control group	97.37 ± 18.06	0.524¥
	First test group	112.42 ± 49.14	0.052§
	Second test group	130.02 ± 20.54	
[e]$AUC_{0-\infty}$ (ng*hr/mL)	Control group	204.49 ± 75.82	0.564¥
	First test group	167.05 ± 71.42	0.679§
	Second test group	189.60 ± 25.80	

(¥): *P-value* of the differences between the control and first test group; (§): *P-value* of the differences between the control and the second test group. *:$P \leq 0.05$ Statistical significance, SD: Standard deviation, [a]maximum blood concentration, [b]time to peak concentration, [c]elimination rate constant, [d]area under the concentration-time profile curve from 0 to 6 hours and [d]area under the concentration-time profile curve from 0 to infinity.

Discussion

TAC is an immunosuppressive agent that has emerged as a valuable therapeutic alternative to cyclosporine following solid organ transplantation [(15)]. The most important human CYP isozyme is CYP3A4, which is involved in the metabolism of the majority of therapeutically prescribed drugs [(16)]. TAC is a lipophilic compound that is metabolized by the CYP450 3A subfamily and is eliminated after extensive metabolism. Because of its low

therapeutic index, TAC requires blood level monitoring. Therefore, metabolic studies, such as drug-drug interaction and metabolite identification studies, are vital and urgent for the development of clinically optimal medication use [(17)].

Herb-drug interactions are among the most frequent medical concerns when taking herbs and pharmaceutical prescriptions concurrently [(11)]. In addition, TAC bioavailability decreased when concurrently administered with St John's wort (SJW), cranberry, rooibos tea, and boldo in human models by induction of CYP450 system isoenzyme and/or P-gp efflux pump [(18-21)]. Meanwhile, TAC bioavailability was enhanced in human and/or animal models when grapefruit juice, schisandra, pomelo, and ginger were given concurrently, presumably due to an inhibitory effect on the CYP450 system or the P-gp efflux pump [(22-24)].

The PK investigations evaluating the interaction between herbal supplements and the bioavailability of various therapeutically monitored drugs, such as digoxin, cyclosporine and carbamazepine revealed that herbal supplements have a clinically insignificant effect on the PK profiles of digoxin and cyclosporine [(25-27)].

Our findings, statistical examination of TAC PK parameters revealed statistically insignificant differences between the three groups (Table 1). The control group's mean C_{max} decreased slightly from 27.44±5.83 ng/mL to 25.78±7.60 ng/mL in the first test group and a slight increase to 31.20±4.33 ng/mL in the second test group were observed. Similarly, Liu and his colleagues found comparable results when they investigated the effect of various CUR administrations (25 and 50 mg/kg) on the PK parameters of warfarin alone (control group). In this investigation, the increasing in C_{max} in the herbal treated groups from 1.14±0.33 to 1.49±0.38 and 1.15±0.29 µg/mL was insignificant when compared to the control group ($P>0.05$). However, in the large dose CUR groups (100 mg/kg) were statistically significant [(28)].

Also, the current results revealed that the decrease in $AUC_{0-\infty}$ from 204.49±75.82 to 167.05±7.10 in the first test group and 189.60±25.80 ng*hr/mL in the second test group respectively, was also similar and statistically insignificant ($P>0.05$). Furthermore, the remaining PK parameters showed insignificant variations, including AUC_{0-6}, T_{max} and K_e between the control and tested groups.

Additional investigations need to be conducted with higher doses of curcumin and over longer periods of time, or recruit a larger number of animals, to support the interpretation of previous research findings.

Conclusion

Drug interactions with herbs are critically important for patient safety, especially as herbal remedies become more popular and are used more frequently. The CUR had systemically insignificant effect on the PK profile of TAC in this investigation at the dosages examined.

Ethical Statement

The study was approved and performed under ethical principles laid down by the Faculty of Pharmacy, Al-Azhar University-Gaza, Palestine.

Conflict of Interest

No conflicts of interest relevant to this article.

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