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ORIGINAL ARTICLE

Impact of thrice-weekly cotrimoxazole prophylaxis on creatinine and potassium plasma levels in kidney transplant recipients

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Abstract

Introduction Cotrimoxazole (CTX) 800/160 mg daily or thrice-weekly is recommended as prophylaxis of *Pneumocystis jirovecii* pneumonia in kidney transplant recipients. Cotrimoxazole 800/160 daily elevates plasma creatinine and potassium levels but whether the thrice-weekly regimen does so is unknown.

Methods Medical records of 225 kidney transplant recipients at Cliniques Universitaires Saint-Luc were analyzed retrospectively. All received thrice-weekly CTX 800/160 for 6 months after transplantation. Monthly laboratory results, co-medications, and tacrolimus trough levels were compared. Standard statistical tests were used.

Results One month after CTX stop, creatinine level decreased by 0.11 mg/dl (8%, $p = 0.029$). This contrasts with its stability in previous and subsequent months. No co-medication change accounted for this decrease. The decrease averaged 0.17 mg/dl ($p < 0.01$) in the highest initial creatinine tertile. The higher the initial creatinine level, the greater the decrease after CTX stop ($p < 0.001$), and urea levels remained stable after CTX stop. Potassium levels decreased by 0.09 mmol/L ($p = 0.021$) one month after CTX stop, and decreased by 0.23 mmol/L ($p < 0.01$) in the highest initial potassium level tertile.

Conclusions Our study pinpoints the impact of CTX 800/160 thrice-weekly on creatinine and potassium levels in kidney transplant recipients. This should be considered when interpreting the evolution of plasma creatinine over time, especially in patients with graft dysfunction. Thus, creatinine levels of cohorts with 6 months versus lifelong CTX require different interpretations.

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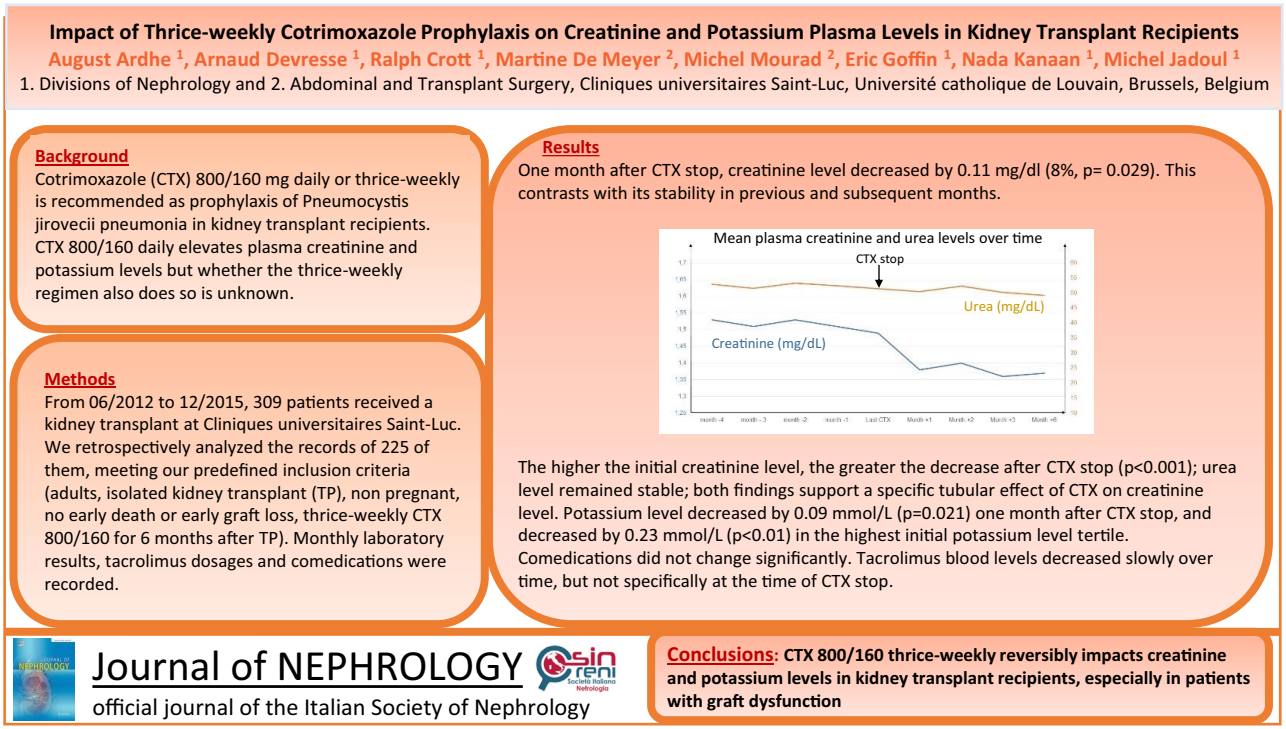
Graphical abstract



Keywords Cotrimoxazole · Creatinine · Potassium · Transplantation

Introduction

Cotrimoxazole (CTX) either daily or thrice-weekly is recommended in kidney transplant recipients (KTRs) as prophylaxis for *Pneumocystis jirovecii* pneumonia, a serious opportunistic infection [1–3]. Patients at Cliniques Universitaires Saint-Luc (CUSL), Brussels, Belgium receive CTX 800/160 mg thrice-weekly for 6 months following kidney transplantation, the period during which immunosuppression is highest [4–6].

The elimination of creatinine by the kidney is reduced by CTX [7]. In 1975, Berglund et al. reported a reversible, glomerular filtration rate (GFR)-independent, creatinine increase of 0.22 mg/dl (or 20%) in subjects given CTX 800/160 daily [8]. The higher the baseline creatinine, the greater the creatinine increase under CTX. This was interpreted as a competitive inhibition of the tubular secretion of creatinine, which in healthy subjects accounts for 13–23% of total renal creatinine elimination, but is increased in chronic kidney disease (CKD) patients, in whom plasma creatinine levels may increase by over 35% under CTX [7]. Berglund et al. were further able to demonstrate that trimethoprim, rather than sulfamethoxazole, is the causal agent of this reversible creatinine increase [8].

The impact of trimethoprim on creatinine plasma level has not been studied for dosages lower than 160 mg daily [7]. Trimethoprim is also a reversible inhibitor of sodium channels in the amiloride-sensitive collecting duct of the nephron, but whether a thrice-weekly dose-regimen of CTX prophylaxis impacts potassium levels is also unknown [9–11]. We thus decided to study the effect of CTX on creatinine and potassium plasma levels at the prophylactic dose of 800/160 mg 3-times-a-week.

Methods

Patients

In this retrospective study, we included all consecutive adult patients who received an isolated kidney transplant at CUSL from June 25th, 2012 to December 31st, 2015. Kidney transplant recipients were followed-up (including routine laboratory tests) at the outpatient Nephrology clinic of CUSL bi-weekly for 2 to 3 months, then at least monthly during the rest of the first post-kidney transplantation year. When not contra-indicated and not stopped early for medical reasons, they received 6-month post-transplant thrice-weekly

CTX-prophylaxis as recommended [1–3]. Follow-up for this study was restricted to the first 12 months after kidney transplantation (thus 6 months after CTX stop).

The study protocol was approved by the biomedical Ethics Committee of CUSL/UCLouvain (reference: 2019/15JAN/013). As this was a retrospective observational study using anonymized data, informed consent was not required by the ethics committee.

Study population

Out of 309 patients who received a kidney transplantation at CUSL during the study period, 225 met the inclusion criteria. Eighty-four KTRs were excluded for one of the following reasons: non-adult, pregnant, combined organ transplant, therapeutic doses of CTX, CTX discontinuation before 3 months of prophylaxis, restart of dialysis or death before one month of post-CTX-discontinuation period (Fig. 1).

Data were collected from the patients' electronic medical records at CUSL. Laboratory results, outpatient nephrology clinic and hospitalization reports were reviewed. The following KTR characteristics were recorded: age at transplantation, gender, number of kidney transplantations, cause of kidney failure, preoperative dialysis status. As donor characteristics, we recorded: living or deceased donors.

The following biological data were collected monthly: plasma creatinine, urea, potassium. We also recorded all comedications and tacrolimus trough levels one month before, at the time of CTX discontinuation and one month later. Laboratory tests were performed on a Beckman Coulter Olympus 5400 until June 2014 and a Roche Cobas 8000 module c702 thereafter.

Statistical methods

Continuous variables were compared using a t-test with unequal variances or paired t-test as appropriate. In order to test the impact of CTX stop on creatinine level, a mixed linear model was used. This model was used with a binary dummy variable (cotrimoxazole or not). The same type of model was also used with the period as an indicator variable (10 periods in total). p values < 0.05 were considered statistically significant.

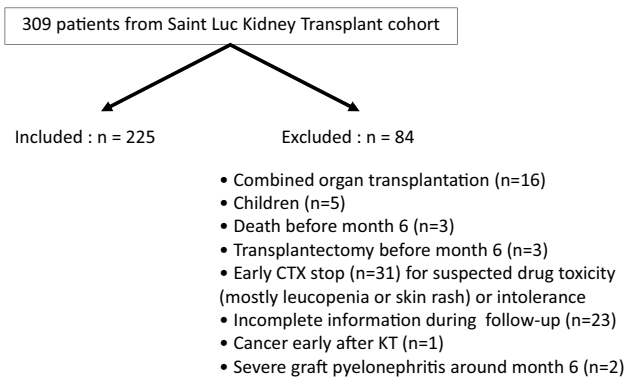


Fig. 1 Flowchart of study population

Results

Patients

Table 1 summarizes the baseline characteristics of the patient population.

The standard immunosuppressive regimen at the time of the study period included tacrolimus, mycophenolate mofetil (500 mg bid) and steroids. Tacrolimus target trough levels were 10–13, 7–10, and 5–7 ng/mL at month 1, months 2–3 and after month 3, respectively.

With the exception of subjects seronegative for cytomegalovirus who received a kidney from a seronegative donor, all KTRs received a daily dose of 900 mg (adapted for kidney function) valganciclovir prophylaxis during the 6 first months post-kidney transplantation [12].

Table 1 Patients' characteristics

Variable	Value
Number of patients	225
Gender, Male	149 (66.2%)
Mean age at transplantation (years)	51 (range 18–82)
Cause of kidney failure	
Polycystic kidney disease	36 (15.9%)
Alport syndrome	10 (4.4%)
Other congenital	8 (3.5%)
Auto-immune/vasculitis	12 (5.2%)
Nephrosclerosis	9 (4%)
Diabetic kidney disease	18 (7.9%)
Glomerulonephritis	50 (22%)
Chronic interstitial nephritis	17 (7.5%)
Drug toxicity	6 (2.6%)
Other	22 (9.7%)
Unknown	37 (16.3%)
Pre-transplant status	
Hemodialysis	166 (73.7%)
Peritoneal dialysis	21 (9.3%)
No dialysis	38 (16.9%)
Number of current kidney transplantations (number)	
1	197 (87.6%)
2	27 (12%)
3 or more	1 (0.4%)

Evolution of plasma creatinine and potassium levels before versus after CTX stop

Plasma creatinine levels decreased by 8% or 0.11 mg/dl ($p = 0.029$) between the day of CTX stop and 1 month later (Fig. 2 and supplementary table 1). The higher the plasma creatinine at the time of CTX stop, the greater the decrease of creatinine after CTX withdrawal (p value < 0.001). The decrease reached 0.17 mg/dl in the highest tertile of initial creatinine level. Unlike creatinine levels, urea levels were unchanged between the time of CTX stop and 1 month later.

Plasma potassium levels decreased by − 0.09 mmol/L ($p = 0.021$) between last administration of CTX and one month later (Fig. 3 and supplementary table 1). Here again, the higher the plasma potassium at the time of CTX stop, the greater the decrease of potassium after CTX withdrawal (p value < 0.001). In the highest tertile of potassium level, the decrease after CTX stop reached 0.24 mmol/L ($p < 0.01$) (Table 2).

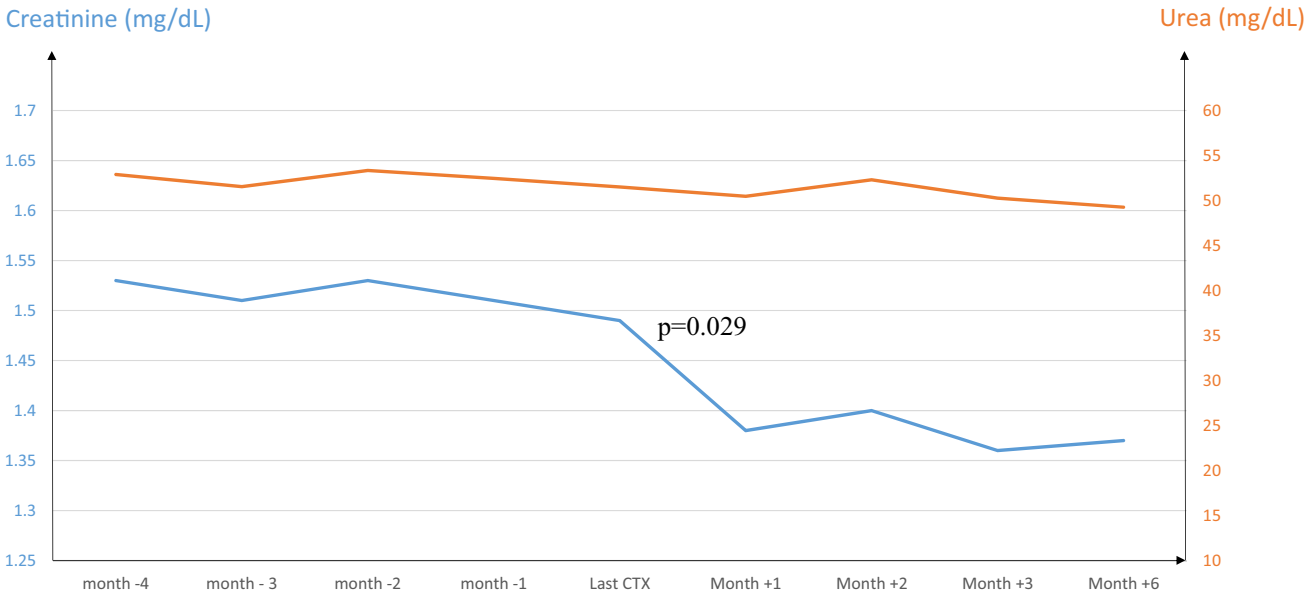


Fig. 2 Mean plasma creatinine and urea levels over time (months). The SD of creatinine and urea over time is available in supplementary table 1 but omitted from this figure for the sake of readability

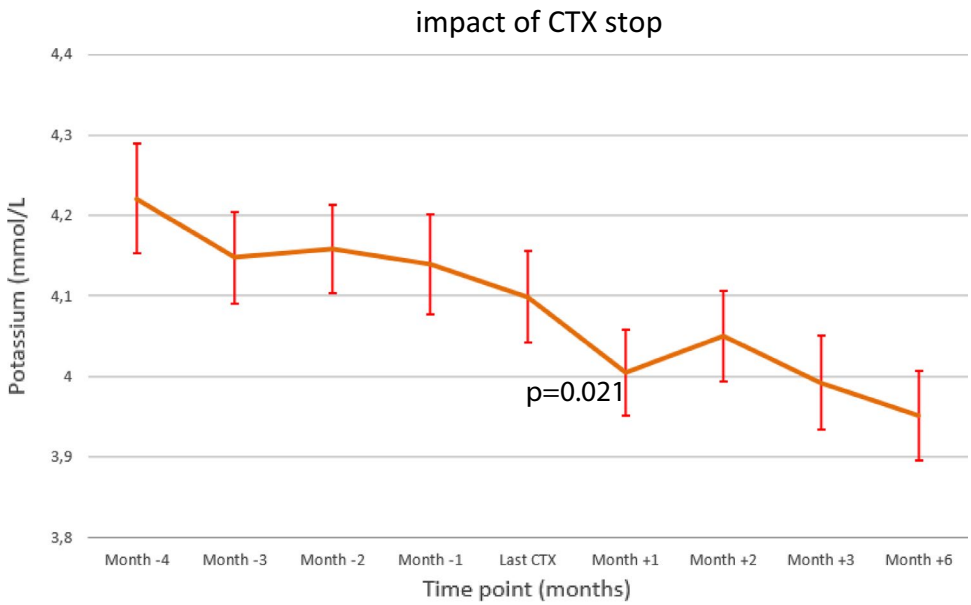


Fig. 3 Potassium plasma level after kidney TP: impact of CTX stop

Table 2 Evolution of potassium plasma levels by tertile at the time of CTX stop versus one month after CTX stop

At CTX stop	one month after stop	*p* value
Tertile 1		
3.67 ± 0.17	3.71 ± 0.28	NS
Tertile 2		
4.06 ± 0.98	4.00 ± 0.27	NS
Tertile 3		
4.57 ± 0.32	4.33 ± 0.35	< 0.01

Finally, we assessed whether changes in co-medications, especially those with an impact on creatinine or potassium levels, occurred around the time of CTX discontinuation. As shown in Table 3, the number of patients under various drug classes remained virtually unchanged around that time, and tacrolimus trough levels decreased slowly per protocol around the time of CTX stop (Table 4).

Discussion

We here demonstrate that withdrawal of CTX 800/160 thrice-weekly significantly decreases plasma creatinine levels, by 8%, or 0.11 mg/dl in KTR. To the best of our knowledge, this is the first study pinpointing that thrice-weekly CTX prophylaxis impacts plasma creatinine in KTRs. The impact of CTX withdrawal on plasma creatinine is greater if initial plasma creatinine is higher. This is consistent with the evidence that trimethoprim is a reversible inhibitor of tubular creatinine secretion [7]. This creatinine-specific and non-nephrotoxic tubular mechanism is further supported by stable urea plasma levels at the time of CTX discontinuation (Fig. 2 and supplementary table 1). Similarly, we demonstrate a reversible impact of prophylactic doses of CTX on potassium levels. We again found that the plasma potassium elevating effect of CTX was dependent on initial potassium level.

Overall, the implications of our results are both for clinicians and registries. For clinicians, the significant impact of low dose CTX prophylaxis on plasma creatinine should be considered when interpreting the evolution of plasma creatinine over time. The absence of such a drop or a mild increase (otherwise not a source of concern) at the time of CTX discontinuation should trigger suspicion of a problem, such as rejection. For registries and large databases, the main implication is that comparisons of creatinine-based eGFR between studies or registries are not completely reliable if some units continue low dose CTX prophylaxis indefinitely whereas others stop CTX after 3 or 6 months (like at CUSL).

Admittedly, the results of this study strongly suggest but do not demonstrate, because of the observational design, that the withdrawal of thrice-weekly CTX improves both creatinine and potassium plasma levels. Another limitation is that the medical record information was not completely standardized. Thus, patients with unclear timing of CTX withdrawal were excluded from the study. Also, our analysis was based on prescribed medications but patient compliance was certainly not perfect in this real-world study. However, this inaccuracy would have blurred our results towards the null hypothesis. Finally, GFR should ideally have been measured (e.g. by iohexol clearance) or estimated from creatinine-independent markers, such as cystatin, but such data were not available. Yet, for the

Table 3 Number of patients prescribed relevant drug classes one month before, at the time of CTX stop, and one month after CTX stop

	Number of patients being prescribed each drug											
	A	B	C	D	E	F	G	H	I	J	K	L
1 month before	219	220	40	25	31	3	86	37	48	18	4	2
Stop CTX	222	221	39	24	33	3	84	37	48	19	4	2
1 month after	220	219	42	23	34	3	87	37	41	22	6	1

A. Tacrolimus; B. Methylprednisolone; C. ACEI; D. ARB; E. Loop Diuretic; F. Thiazide; G. Beta-blocker; H. NaHCO3; I. Drinking water rich in sodium bicarbonate (Vichy Celestins); J. Insulin; K. Polystyrene sulfonate; L. Everolimus

Table 4 Tacrolimus blood levels (mean ± 95%CI) one month before CTX stop, at the time of stop, and one month after stop

Tacrolimus blood levels (ng/dL)		
1 month before CTX stop	At the time of CTX stop	1 month after CTX stop
7.55 ± 0.23	7.29 ± 0.24	7.06 ± 0.28
Change between 1 month prior to and at the time of CTX stop	Change between time of CTX stop and 1 month later	
0.26 (0.03–0.54), *p* value 0.077	0.23 (− 0.05 to 0.50), *p* value 0.106	

reasons detailed above, we are confident that the tubular interpretation is the correct one.

In conclusion, our study pinpoints the impact of prophylaxis with CTX 800/160 thrice-weekly on creatinine and potassium plasma levels in KTRs. This impact should be considered when interpreting the evolution of plasma creatinine over time and managing hyperkalemia in kidney transplant recipients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40620-023-01773-y.

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Data availability The data used in this study are available from the senior author upon any reasonable request.

Declarations

Conflict of interest The authors have no relevant conflicts of interest to declare.

Ethical approval This study was approved by the Comité d'Ethique Hospitalo-facultaire of UCLouvain (2019/15JAN/013).

Informed consent Informed consent was not required because of the retrospective observational design and the analysis of anonymized data.

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