

Effects of Selective vs. Nonselective Cyclooxygenase Inhibition on Dynamic Renal Potassium Excretion: A Randomized Trial

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Both selective and nonselective cyclooxygenase (COX) inhibitors can reduce potassium excretion and can produce or exacerbate hyperkalemia.^{1–12} We investigated whether there is a difference between the effects of nonselective COX-1/COX-2 inhibitors and selective COX-2 inhibitors on provoked dynamic renal potassium excretion. We apply a mixed-effects model statistical approach that allows investigation of drug-induced delays in reaching maximal potassium excretion, blunting/flattening of potassium handling curves, and shift/separation in potassium handling at peak potassium excretion.

BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Forty-three of fifty-nine potential subjects met eligibility criteria and were enrolled into the study. Two participants were withdrawn due to gastrointestinal symptoms. The celecoxib and ibuprofen randomization groups were similar in age, proportion of females, body mass index, blood pressure, heart rate, and estimated creatinine clearance at baseline.

DYNAMIC RENAL POTASSIUM EXCRETION

Both celecoxib and ibuprofen produced statistically significant reductions compared to placebo in urinary potassium excretion (UkV) at hour 3 (Figure 1a and b). For celecoxib, mean UkV was reduced from 275 $\mu\text{mol}/\text{min}$ on placebo to 160 $\mu\text{mol}/\text{min}$ on active treatment (40% reduction in UkV; $P = 0.04$). For ibuprofen, mean UkV was reduced from 186.6 $\mu\text{mol}/\text{min}$ on placebo to 124.9 $\mu\text{mol}/\text{min}$ on active treatment (33% reduction in UkV; $P = 0.038$). A nonparametric bootstrap t -test verified the results ($P = 0.016$ and 0.013 for celecoxib and ibuprofen, respectively). The changes in UkV at hour 3 did not differ between celecoxib and ibuprofen ($P = 0.46$). There was a reduction in UkV for both drugs compared to placebo at hour 2, but this did not reach statistical significance ($P = 0.1$ and 0.0725 for celecoxib and ibuprofen, respectively).

FRACTIONAL EXCRETION OF POTASSIUM

Both celecoxib and ibuprofen produced statistically significant reductions in fractional excretion of potassium (FEK) at hour 2 (Figure 1c and d). For celecoxib, mean FEK was reduced from 0.41 on placebo to 0.32 on active treatment (22% reduction; $P = 0.00859$). For ibuprofen, mean FEK was reduced from 0.22 on placebo to 0.16 on active treatment (27% reduction; $P = 0.0012$). Both these results were confirmed via a nonparametric bootstrap t -test (celecoxib $P = 0.007$ and ibuprofen $P = 0.005$). There was no statistically significant difference between celecoxib and ibuprofen in FEK at hour 3 ($P = 0.30$). There was a reduction in FEK for both drugs compared to placebo at hour 3, but this was only significant for ibuprofen ($P = 0.015$ for ibuprofen (bootstrap $P = 0.037$) and $P = 0.26$ for celecoxib).

SERUM POTASSIUM

Neither celecoxib nor ibuprofen produced statistically significant increases in potassium at hour 2 or 3 compared to placebo (Figure 1e and f).

MIXED-EFFECTS MODELS RESULTS

The final mixed model was a full interaction model with quadratic time trend, random intercepts, and fixed effects for drug ($i = \text{patient index}, j = \text{time index}, k = \text{drug index}$):

$$Y_{ijk} = (\gamma_{10} + \gamma_{11} \text{Drug}_k + u_{1ik}) + (\gamma_{20} + \gamma_{21} \text{Drug}_k)t_{ij} + (\gamma_{30} + \gamma_{31} \text{Drug}_k)t_{ij}^2 + \varepsilon_{ij}$$

where γ_{10} signifies the predicted baseline UkV with placebo treatment, γ_{11} signifies the predicted shift from this predicted baseline UkV under active treatment and similarly for the corresponding linear and quadratic coefficients. The random variable u_{1ik} represents the residual difference between the mean population curve and patient i 's individual curve.¹³

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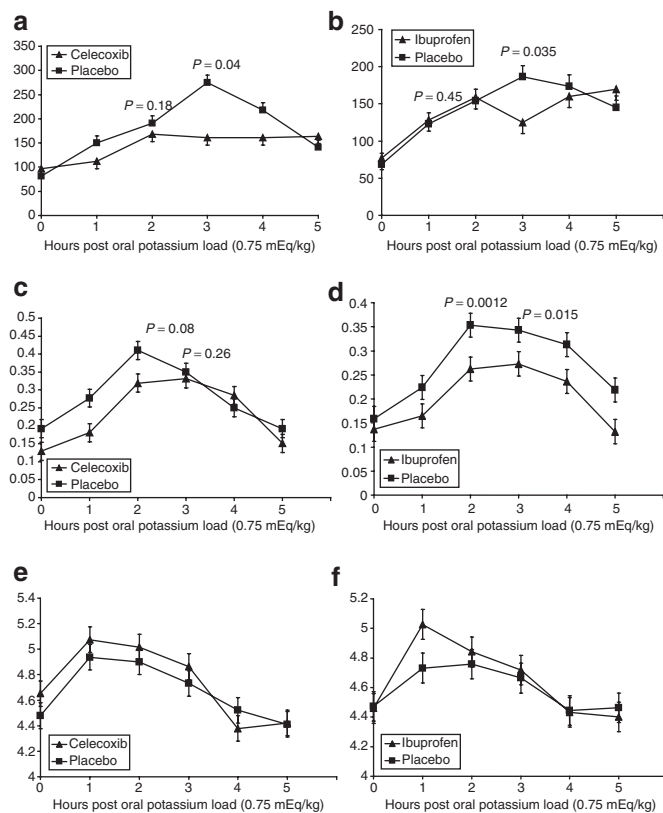


Figure 1 Effects of celecoxib and ibuprofen on dynamic renal potassium handling. **(a)** Mean (s.e.m.) urinary potassium excretion UkV ($\mu\text{mol}/\text{min}$) vs. time. Celecoxib vs. placebo ($n = 19$). **(b)** Urinary potassium excretion UkV ($\mu\text{mol}/\text{min}$) vs. time. Ibuprofen vs. placebo ($n = 22$). **(c)** Fractional excretion of potassium vs. time. Celecoxib vs. placebo ($n = 19$). **(d)** Fractional excretion of potassium vs. time. Ibuprofen vs. placebo ($n = 22$). **(e)** Serum potassium concentration (mEq/l) vs. time. Celecoxib vs. placebo ($n = 19$). **(f)** Serum potassium concentration (mEq/l) vs. time. Ibuprofen vs. placebo ($n = 22$).

Table 1 Fixed-effects estimates for celecoxib and ibuprofen

Fixed parameters	Estimate	s.e.	t	P value
Celecoxib				
γ_{10} : Intercept	67.374	26.611	2.532	0.012
γ_{11} : Drug	25.605	36.470	0.702	0.477
γ_{20} : Time	117.043	22.874	5.117	0.000
γ_{21} : Time: Drug	-78.176	32.349	-2.417	0.016
γ_{30} : Time ²	-20.052	4.391	-4.566	0.000
γ_{31} : Time ² : Drug	14.998	6.210	2.415	0.016
Ibuprofen				
γ_{10} : Intercept	66.189	22.143	2.989	0.0031
γ_{11} : Drug	21.329	28.875	0.738	0.460
γ_{20} : Time	68.984	18.187	3.792	0.0002
γ_{21} : Time: Drug	-37.012	25.720	-1.439	0.151
γ_{30} : Time ²	-10.546	3.491	-3.020	0.0028
γ_{31} : Time ² : Drug	7.153	4.937	1.448	0.148

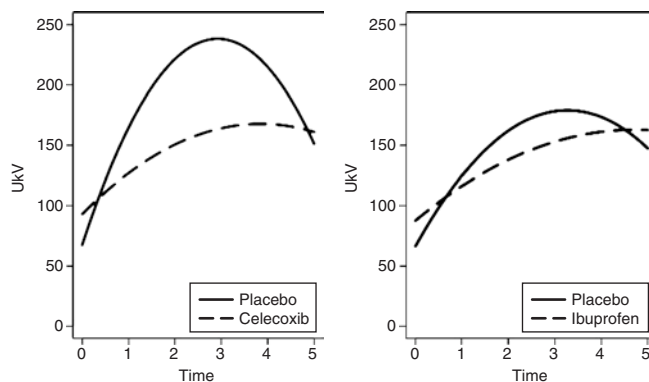


Figure 2 Estimated growth curves for celecoxib vs. ibuprofen.

Table 1 contains the results for the celecoxib and ibuprofen groups, respectively. For both celecoxib and ibuprofen, the γ_{11} coefficient indicates that the predicted UkV at baseline does not statistically differ between placebo and active treatment. In addition, the coefficients of the model may be used to assess the following three dimensions of potassium handling.

DELAY IN REACHING MAXIMAL POTASSIUM EXCRETION

Using the model, we could estimate the delay in reaching maximal potassium excretion while on active treatment compared to placebo. For the celecoxib group, the model predicts that maximal excretion is reached at hour 2.9 on placebo and hour 3.9 on active treatment. For the ibuprofen group, the corresponding results are hour 3.3 and hour 4.7. Thus, the mixed model indicates that the average time to reach maximal potassium excretion was delayed by COX inhibition ($P = 0.0003$ celecoxib, $P = 0.0004$ ibuprofen, and $P = 0.21$ celecoxib vs. ibuprofen).

BLUNTING/FLATTENING OF POTASSIUM-HANDLING CURVE

The linear and quadratic parameters of the model indicate whether the potassium-handling curve is blunted/flattened while on active treatment. For the celecoxib group, the linear time trend on drug ($38.867 = \gamma_{20} + \gamma_{21}$) is significantly lower than the linear time trend on placebo ($117.043 = \gamma_{20}$), while the quadratic term on drug ($-5.054 = \gamma_{30} + \gamma_{31}$) is significantly higher than the quadratic term on placebo ($-20.052 = \gamma_{30}$). These results provide evidence for a flattened/blunted dynamic potassium handling while on drug; see **Figure 2**. The results are similar for the ibuprofen group, although lower in magnitude and not quite statistically significant.

SHIFT OF POTASSIUM-HANDLING CURVES AT HOUR 3

In addition to blunting/flattening of the potassium-handling curve and delay in reaching maximal excretion, we investigated the separation or distance between the placebo and drug curves at hour 3. For the celecoxib group, the difference is significant ($P < 0.01$), while for the ibuprofen group the difference does not reach statistical significance ($P = 0.22$). However, when the treatment groups are combined, the difference at hour 3 remains statistically significant ($P < 0.01$).

The primary objective of the current investigation was to compare the quantitative effects of the selective COX-2 inhibitor

celecoxib vs. the nonselective COX-1/COX-2 inhibitor ibuprofen on dynamic renal potassium handling. Both celecoxib and ibuprofen produced large and statistically significant reductions in mean UkV at hour 3 compared to placebo—40% with celecoxib and 33% with ibuprofen. FEK was reduced at hour 2—22% with celecoxib and 27% with ibuprofen. The reductions in UkV and FEK did not differ statistically between the two drugs. This significant blunting of UkV and FEK may correspond to a clinically reduced capacity to clear a potassium load.

Other investigators have carefully examined the effects of COX inhibition on basal, nonprovoked levels of potassium excretion.^{9–11} Swan *et al.*⁹ found an 11.28% reduction with rofecoxib (95% confidence interval 4.27–18.30) but not indomethacin following a single dose of study drug and no difference in potassium excretion in a corresponding multiple dose study. Rossat *et al.*¹⁰ compared 200 mg celecoxib twice a day, 400 mg celecoxib twice a day, 500 mg naproxen twice a day, or placebo for 7 days and found a decrease in nonprovoked basal urinary excretion rates celecoxib and naproxen, but only the 400 mg dose of celecoxib induced a sustained (hours) significant reduction in potassium excretion. Stichtenoth *et al.*¹¹ found small but statistically significant reductions in potassium excretion rates with both celecoxib and indomethacin compared to placebo following 20 mg furosemide i.v.

In contrast, utilizing our method of acute potassium challenge, we detected large reductions in provoked potassium excretion rates compared to placebo for both celecoxib and ibuprofen. Quantitative testing of the effects of drugs on dynamic changes in potassium excretion following an oral potassium challenge provides a simple, noninvasive, and rigorous method to amplify and detect quantitative effects of drugs on renal potassium handling that may not be detected as easily by studying changes in basal potassium excretion or changes in serum potassium.

Limitations of our study include a small sample size, although we achieved adequate power for the primary end-point. Furthermore, a more highly selective COX-2 comparator could possibly make a stronger statement that COX-2 inhibition primarily reduces renal K⁺ excretion.

In addition to standard statistical methods, we applied a mixed-effects model approach that provides a more integrated and complete description of the UkV vs. time curve. The results of the mixed-effects model quantify several additional dimensions of impaired potassium excretion induced by COX inhibition that could not be evaluated by evaluating a single time point. Specifically, we identified and quantified a delay in reaching maximal excretion, blunting of the maximal UkV, and separation of the entire potassium excretion vs. time curves. Although mixed-effects models have wide applicability in a broad range of applications such as population pharmacokinetics and nonlinear pharmacokinetics,^{14,15} they have not been applied to serial measurements of electrolyte excretion such as undertaken in this study. Given the richness and flexibility of mixed-effects models, they could be useful and informative in future studies in which serial electrolyte measurements are performed.

METHODS

The specific aim of this single-center, randomized, two parallel-group study was to determine the comparative effects of celecoxib vs. ibuprofen on dynamic renal potassium handling in normal volunteers. Recruitment and written informed consent of study participants was performed in accordance with the guidelines of the University of Miami Human Subjects Research Office.

Subjects were randomized to one of two treatments: celecoxib 200 mg q.d. and ibuprofen 800 mg t.i.d. Endpoints were 2- and 3-hour UkV (mmol/min), FEK, and serum potassium (mEq/l) following a standard oral potassium load of 0.75 mEq/kg body weight. The trial consisted of five phases: screening visit and eligibility, 2-week placebo run-in phase, confinement inpatient phase for baseline renal potassium handling study, 4-week treatment phase with either celecoxib or ibuprofen, and confinement inpatient phase for renal potassium handling study on active study medication.

Study participants. Potential participants were eligible, if they were aged 18–75 years and in good health, had no significant history of medical illness including diabetes mellitus were taking no medications, and had a normal clinical and laboratory assessment.

Study procedures. At the end of the 2-week placebo run-in, and following the 4-week active treatment period, study participants were confined in the inpatient research unit of the Division of Clinical Pharmacology for the potassium-handling study.^{16–20} One hour after study medication was administered, a 1-oral water load was given, followed by a 2-hour baseline urine collection. A potassium load of 0.75 mEq/kg of body weight (as 20% potassium chloride) was administered over a 5–10-min period in 240 ml of ginger ale. Urine was collected hourly for five additional periods by spontaneous voiding. Blood was drawn at the midpoint of the 2-hour baseline control period and at the midpoint of the second, fourth, and fifth 1-hour experimental periods. A 12-lead electrocardiogram was performed at baseline and at hour 3 and reviewed immediately for changes suggestive of hyperkalemia.

Study subjects were then randomly assigned to receive either celecoxib 200 mg once daily or ibuprofen 800 mg t.i.d. At the end of week 6, following the 4-week active treatment period, study participants were again confined and underwent the potassium-handling study as detailed above on active study medication.

Statistical methods

Standard methods. Differences in UkV and FEK at hours 2 and 3 of the potassium handling study between the two treatments were detected via unpaired *t*-tests, while paired *t*-tests were employed to assess corresponding reductions compared to placebo. In addition, nonparametric bootstrap *t*-tests were implemented to avoid overly relying on the assumptions of the standard *t*-test for small sample sizes.²¹ Results involving multiple comparisons for the primary end point (UkV) were assessed via stepwise multiple comparison procedures to control a familywise error rate of $\alpha = 0.05$ (refs. 22,23).

Mixed-effects models. The mixed-effects model approach utilizes all the available potassium excretion data and represents a more rigorous examination of the UkV vs. time curves.^{24–27} We used the R-open source code nlme package^{28,29} to estimate and diagnose a series of nested models via maximum likelihood methods. We examined the final model with respect to three dimensions:

1. We investigated whether COX inhibition induced a delay in reaching maximal potassium excretion by estimating the time at which the rate of change in potassium excretion equaled zero. Because this time delay is a derived quantity from the estimated model curves, we employed the time delays from the estimated individual curves to assess significance of the respective groups.
2. Approximate *t*-tests were employed to test hypotheses regarding the fixed effects in the model (intercept, linear, and quadratic terms),

which determine the extent to which the potassium-handling curve is blunted/flattened while on active treatment.

- We assessed the shift between the curves by determining whether the separation of the curves is statistically significant at hour 3. To accomplish this, we reparameterized the model such that hour 3 corresponds to $t = 0$ (hence the intercept now corresponds to hour 3).

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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