Increased systolic blood pressure with rofecoxib in congenital furosemide-like salt loss

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Abstract

Background. To analyse whether congenital furosemide- or thiazide-like renal salt loss protects against the potential prohypertensive effects of two cyclooxygenase (COX) inhibitors: rofecoxib, a COX-2 selective inhibitor, and indomethacin, an unselective COX-inhibitor.

Methods. In a retrospective analysis, the effects of rofecoxib and indomethacin on blood pressure (bp: transformed into age-independent standard deviation scores (SDS) values), creatinine clearance (CRC), fractional excretion of sodium (FeNa), and renal excretion of systemic prostaglandins were studied in 28 patients with a genetically proven congenital hypo-kalaemic salt-losing tubulopathy (SLT) (11 female and 17 male, age: 2–25 years), 19 with a furosemide-like SLT, and nine with a thiazide-like SLT.

Results. In furosemide-like SLT patients, systolic SDS bp values were significantly higher with rofecoxib (1.03±0.16 SDS, n = 107) compared with indomethacin (0.56±0.09 SDS, n = 282; P = 0.007, 95% CI: 0.12–0.8). Without the drugs, systolic SDS bp values were elevated by 0.63±0.11 SDS, n = 164. Both drugs reduced renin and aldosterone-plasma levels to a similar extent. SDS values were significantly correlated with the excretion of the vasoconstrictor thromboxane (T\(_{\text{C2}}\)) (R\(^2\): 0.038, P = 0.021, n: 159), but not with CRC or FeNa. Blood pressure was not increased in thiazide-like SLT patients treated with rofecoxib.

Conclusion. Congenital furosemide-like renal salt loss does not protect against the prohypertensive effects of rofecoxib. The positive correlation between SDS values with T \(\times\) B\(_2\) but not with FeNa or CRC point towards an altered vascular homeostasis as one mechanism increasing blood pressure.

Keywords: Bartter syndrome; coxib; hypertension; NSAID; thromboxane

Introduction

Cyclooxygenase-2 (COX-2) selective inhibitors (’coxibs’) increase the incidence of systemic hypertension [1] and thromboembolic complications, particularly in elderly adults [2]. The observation that cardiovascular side effects are increased not only with the methylsulfon-compound rofecoxib but also with arylsulfon-compound celecoxib [3] argues for a class-effect. Such an effect is not unexpected given that coxibs reduce systemic synthesis of prostacyclin (PGI\(_2\)) [4,5]. PGI\(_2\) is primarily synthesized in endothelial cells and acts as a vasodilator and anti-aggregatory prostanoid. Coxibs thus alter the balance of PGI\(_2\) and (T\(_{\text{C2}}\)), the latter agent being a vasoconstrictor and pro-aggregatory prostanoid. This shift in prostaglandin formation towards unopposed T \(\times\) B\(_2\) action may be one factor contributing to the increased incidence of cardiovascular side effects with coxibs [2]. An alteration of the T \(\times\) B\(_2\)/PGI\(_2\) ratio is not observed with classical non-steroidal anti-inflammatory drugs (NSAID) such as indomethacin, as these drugs inhibit both COX-2-dependent PGI\(_2\) and COX-1-dependent T \(\times\) B\(_2\) formation. Finally, the potential risks of unopposed T \(\times\) B\(_2\) may be deduced from the significant cardio-protective effect afforded by low-dose aspirin, which selectively inhibits T \(\times\) B\(_2\) formation in platelets, in both primary and secondary prevention [6]. Collectively, these data demonstrate a critical role of prostaglandins in vascular homeostasis.

Hypertension in patients treated with NSAID may also be caused by renal salt and fluid retention. Inhibition of renal cyclooxygenase activity reduces glomerular filtration, and increases both proximal and distal tubular reabsorption and enhances the antidiuretic effect of vasopressin [7]. The incidence of
inhibition of COX-2-dependent PGE2 formation in selective (rofecoxib) and unselective (indomethacin) for rofecoxib and indomethacin were 0.67 mg/kg/day and 1.82 mg/kg/day, respectively. Additional medications included NaCl (five points), potassium chloride (18 points), amlodipine (one point, during treatment with rofecoxib), topical budenosid (two points), and oral sulfasalazine (two points).

Protocol

Data were analysed retrospectively from both outpatient visits and from hospitalized patients. In the latter case, patients were admitted to the hospital for introduction, withdrawal or change of NSAID treatment as described earlier [14].

Blood pressure measurements

Casual blood pressure was assessed at each visit with standard oscillometric devices (Dinamap Pro 100, Florida, USA). Blood pressure recordings were transformed into SDS values using the age for height-related reference data of de Man et al. [15]. In patients with repeated elevation of the blood pressure above the 95th height adjusted percentile, systemic hypertension was confirmed by a 24 h blood pressure recording device (Spacelabs 90207, Washington, USA) using the published reference data from Soergel et al. [16].

Biochemistry

Routine haematology and clinical chemistry (blood and urine) as well as aldosterone and renin levels were analysed in the central laboratory facility. Prostaglandins were determined from cooled 24 h urine collections as published earlier [14]. Reference intervals for the excretion of prostaglandins were described previously [17]. Rofecoxib plasma levels were drawn 12 h post dosing and analysed as published recently [14].

Statistics

All statistical analyses were performed with the SPSS 11.0 statistical software package (SPSS Inc., Chicago, IL). In a first step, samples were analysed for Gaussian or non-Gaussian distribution (Kolmogorov–Smirnov-test). In case of Gaussian distribution, samples were compared with the two-sided t-test and values are given as mean ± standard error of the mean. Statistical significance is indicated by a P-value < 0.05 and 95% confidence interval (CI) < 1. Samples with a non-Gaussian distribution are given as median and first and third quartiles. Values were compared with the Mann–Whitney test. A P-value < 0.05 was considered to indicate statistical significance.

Results

In two patients with a furosemide-like SLT, arterial hypertension on rofecoxib was confirmed by a 24 h blood pressure recording device according to the reference values by Soergel et al. [16]. In one female patient treated with rofecoxib (0.2 mg/kg/day), systolic blood pressure dropped significantly within 1 week from 142 ± 9.7 mmHg at daytime to 109 ± 13 mmHg.

Subjects and methods

Between 1985–2004, 28 patients affected by congenital, hypokalaemic SLTs were followed either on an outpatient basis at the Department of Paediatrics in Marburg, Germany. Data from all patients with a congenital SLT were included in a retrospective analysis unless treated with systemic steroids because of NSAID induced colitis. In all patients, the clinical diagnosis could be confirmed by genetic testing [11]. The study included 19 patients with a furosemide-like SLT, and nine patients with a thiazide-like SLT. The age at the last visit of the patients ranged from 2 to 25 years; there were nine females and 17 male patients. Patients were treated with either indomethacin or rofecoxib to achieve a sufficient reduction of polyuria as published [14]. Median daily doses for rofecoxib and indomethacin were 0.67 mg/kg/day (0.4–0.86), and 1.82 mg/kg/day, (0.97–2.8), respectively. Unlike the cardiovascular PGE2 system however, simultaneous suppression of COX-1 and -2 does probably not prevent renal side effects [9].

To address the potential role of renal salt handling in hypertension with conventional NSAID and coxibs, children and adolescents with congenital, hypokalaemic salt-losing tubulopathies (SLTs) were analysed in this study. This heterogeneous group of disease mimicks chronic treatment with diuretics [10,11]. Patients with defects in various proteins involved in the absorption of NaCl in the thick ascending limb of Henle resemble patients on chronic treatment with furosemide (hyperprostaglandin E syndrome, antenatal Bartter syndrome). Patients with inactivating mutations in the thiazide-sensitive NaCl cotransporter or in the chloride channel (CLCkb) mimick chronic exposure to thiazide (Bartter/Gitelman-disease). Both channels are functionally important for NaCl absorption in the distal convoluted tubule. Typically, patients with furosemide-like SLT and also some with thiazide-like SLT show enhanced renal prostaglandin E2 (PGE2) formation, which is paralleled by an increased intrarenal expression of COX-2 [12] and PGE2-synthase (type 1 mPGES) [13].

Selective (rofecoxib) and unselective (indomethacin) inhibition of COX-2-dependent PGE2 formation in SLT patients reduces polyuria, salt-wasting, secondary hyperaldosteronism and hypokalaemia [14]. Although indomethacin is considered a standard therapy [11], rofecoxib has been administered to SLT-patients with gastrointestinal problems attributed to long-term indomethacin consumption [14].
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after switching to indomethacin (1.2 mg/kg/day; n: 60, P = 10–26). Blood pressure remained within the normal range 4 weeks after reintroduction of indomethacin, (Figure 1). In the other patient, arterial hypertension was not reversible after switching from rofecoxib to indomethacin.

Data from 768 blood pressure measurements were obtained from all SLT patients during this retrospective analysis, including 197 during the withdrawal period, 439 on indomethacin and 132 on rofecoxib. Patients were longer on indomethacin (median duration of treatment: 4.8 years; range: 0.01–14.4 years) than on rofecoxib (median duration of treatment: 1.79 years; range: 0.008–3.94 years). During withdrawal, systolic blood pressure was elevated by 0.54±0.09 SDS compared to reference values [15]. In patients on indomethacin, systolic blood pressure showed an insignificant trend towards lower levels (0.43±0.06 SDS), whereas in patients treated with rofecoxib, systolic blood pressure was increased by 0.86±0.14 SDS. The difference was statistically significant (P = 0.02, 95% CI: 0.15–0.7).

In a subset analysis in 19 patients with genetically proven furosemide-like SLT (NKCC2 or RomK defect), systolic blood pressure changes were even more pronounced (Table 1). Compared to washout (0.63±0.11 SDS) and indomethacin (0.56±0.09 SDS), blood pressure was increased with rofecoxib (1.03±0.16 SDS). The difference between the two NSAID was statistically significant (P = 0.007, 95% CI: 0.12–0.8). In contrast, patients with a thiazide-like SLT did not exhibit an increased systolic blood pressure when treated with rofecoxib compared with indomethacin (Table 1).

Since the hypertensive effect of rofecoxib was only observed in patients with a furosemide-like SLT, further analysis was limited to these patients. Diastolic blood pressure values were similarly increased in patients with a furosemide-like SLT during the withdrawal period (1.25±0.09 SDS) and on rofecoxib (1.0±0.13 SDS). With indomethacin, diastolic blood pressure SDS values dropped to 0.79±0.07 SDS. Differences between withdrawal and indomethacin reached statistical significance (P = 0.001, 95% CI: 0.23–0.68). In these patients, indomethacin (median dose: 1.25 mg/kg/day, 25–75%: 0.71–2.21 mg/kg/day, n = 277) and rofecoxib dosing (median dose: 0.65 mg/kg/day, 25–75%: 0.4–0.73 mg/kg/day, n = 104) was lower compared with the complete set of patients (see aforementioned). In furosemide-like SLT, median rofecoxib levels were 100 ng/ml, 25–75%: 66–144 ng/ml, n = 44.

Both NSAID suppressed systemic prostacyclin (PGI2-M) and prostaglandin E2 (PGE-M) formation compared with withdrawal, albeit statistical significance was reached only when comparing PGE-M values in patients on either NSAID compared with no NSAID (Figure 2). Indomethacin decreased systemic thromboxane (T x B2-M) excretion compared with withdrawal and rofecoxib. The difference between T x B2-M excretion in patients taking indomethacin was statistically different from patients on rofecoxib (P = 0.033, Mann–Whitney test). Systolic SDS blood pressure values were positively correlated to T x B2-M excretion in patients taking indomethacin (r = 0.038, P = 0.021. n = 159), but not to PGE-M or PGI2-M excretion (data not shown).

Compared with withdrawal (168±40 pg/ml), immunoreactive plasma renin was decreased with indomethacin (101±17 pg/ml) and rofecoxib (104±27 pg/ml) to a similar extent. Aldosterone levels were similarly

![Figure 1](https://academic.oup.com/ndt/article-abstract/21/7/1833/1821898)

**Figure 1.** Daytime systolic blood pressure in a 21-year-old female patient with a furosemide-like SLT on 12.5 mg rofecoxib (−) and subsequent change to 75 mg indomethacin (−) and 4 weeks (−) later. Individual data were averaged and shown as mean blood pressure for each hour (rofecoxib: n = 49, indomethacin: n = 63 and 20, respectively). The 95th percentile of sex and length adjusted systolic blood pressure is indicated by a straight dashed line.

<table>
<thead>
<tr>
<th>Table 1. SDS blood pressure values according to genetic defect</th>
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<td></td>
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<tr>
<td>Systolic blood pressure (SDS)</td>
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<tr>
<td>all (n: 28)</td>
</tr>
<tr>
<td>NKCC2 &amp; RomK (n: 19)</td>
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<tr>
<td>CLCkb &amp; NCCT (n: 9)</td>
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<tr>
<td>Diastolic blood pressure (SDS)</td>
</tr>
<tr>
<td>NKCC2 &amp; RomK (n: 19)</td>
</tr>
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<td>CLCkb &amp; NCCT (n: 9)</td>
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</table>

SDS values ± SEM according to genetic defect and NSAID (n: denotes multiple measurements in individual patients).

CLCkb: type B renal chloride channel; NKCC2: apical furosemide-sensitive Na–K–2Cl-cotransporter. NCCT; thiazide sensitive NaCl cotransporter; RomK: inwardly rectifying renal potassium channel; NS: non-significant.

*P < 0.05
reduced with both NSAID (Table 2). Compared with withdrawal, creatinine clearance according to Schwartz was reduced with indomethacin and rofecoxib (Table 2). Schwartz clearance was significantly higher in rofecoxib-treated patients compared with indomethacin \((P=0.02\), Mann–Whitney test). Fractional excretion of sodium did not differ significantly between withdrawal and NSAID-treated patients. Data on routine blood chemistry are given in Table 2.

Discussion

The interest in a potential effect of rofecoxib on arterial blood pressure was spurred by both occasional cases of arterial hypertension in SLT patients as well as numerous recent reports of hypertension and severe cardiovascular side effects with this class of drugs [2]. In one female with a furosemide-like SLT, rofecoxib induced arterial hypertension that was fully reversible upon switching to indomethacin. A similar trend towards increased blood pressure in response to rofecoxib was seen in patients with a furosemide-like SLT but not in those with a thiazide-like SLT. An increase of 0.48 SDS translates into 5.6 mmHg in male adults. A similar effect on systolic blood pressure was observed in patients with osteoarthritis \((n=345;\) age: >40 years) after 1 year on 25 mg rofecoxib qd compared with baseline [8]. In SLT patients however, this finding is unexpected because of chronic salt loss and also young age, which should both be protective. In contrast to normal subjects however, patients with SLT and in particular those with a furosemide SLT, showed enhanced systemic and renal PGE\(_2\) formation. Although excessive PGE\(_2\) formation is the most characteristic change in this respect, the present data also demonstrate a slightly enhanced systemic T × B\(_2\) formation during withdrawal [17]. Interestingly, T × B\(_2\) formation was significantly correlated with blood pressure, which indicates that prostaglandins may modulate blood pressure in SLT patients. No correlation was observed between PGI\(_2\)-M formation and blood pressure indicating that the reduction of PGI\(_2\)-M is less critical compared with T × B\(_2\)-M. Nevertheless, reduced PGI\(_2\)-M levels may also indirectly influence blood pressure since it has been shown that PGI\(_2\)-M can desensitize the T × B\(_2\) receptor [18].

The selective suppression of PGI\(_2\)-M formation by coxibs raised concerns about promotion of hypertension and thromboembolic events with this subgroup of NSAID. Surprisingly, despite this clear and simple mechanism originally proposed by FitzGerald [2] and its proof of concept in animal models [19], no study analysed systemic prostaglandin formation as potential biomarkers for hypertension (and thromboembolic events) in patients treated with coxibs. The present data indicate that systemic T × B\(_2\) formation might be a biomarker indicating patients at risk to develop hypertension with coxibs.

Based on the original observation in two patients with the Bartter/Gitelman syndrome, it has been assumed that patients with hypokalaemic SLT are normotensive despite high plasma renin levels [20]. In the present study, an increased blood pressure in all patients (irrespective of genotype) was observed in the withdrawal period. Most likely, enhanced renin formation contributes to this phenomenon.

Since renin secretion is primarily COX-2 (but not COX-1)-dependent in SLT patients [12,14] and in animal models of salt and/or volume depletion [7], the similar suppression of renin levels with either NSAID indicates that COX-2 inhibition was equally effective

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Table 2. Biochemical changes in patients with a furosemide-like SLT according to treatment.

<table>
<thead>
<tr>
<th></th>
<th>A No NSAID</th>
<th>B Indomethacin</th>
<th>C Rofecoxib</th>
<th>P-value (Mann–Whitney)</th>
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<tbody>
<tr>
<td>Renin (pg/ml)*</td>
<td>168 ± 40 (n=43)</td>
<td>101 ± 17 (n=17)</td>
<td>104 ± 27 (n=49)</td>
<td>NS</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>73, 34–118 (n=61)</td>
<td>48, 28–84 (n=115)</td>
<td>32, 14–95 (n=60)</td>
<td>A/C:*</td>
</tr>
<tr>
<td>Schwartz clearance (ml/min/1.73 m(^2))</td>
<td>93, 81–109 (n=164)</td>
<td>81, 63–97 (n=278)</td>
<td>89, 77–97 (n=106)</td>
<td>A:B:<em>; B:C:</em>; A:C *</td>
</tr>
<tr>
<td>FeNa (%)</td>
<td>1.06, 0.69–1.6 (n=30)</td>
<td>0.95, 0.88–1.4 (n=88)</td>
<td>1.1, 0.55–1.61 (n=42)</td>
<td>NS</td>
</tr>
<tr>
<td>Na (mmol/l)</td>
<td>144, 140–144 (n=164)</td>
<td>140, 139–143 (n=282)</td>
<td>141, 140–143 (n=107)</td>
<td>B:C:*; A:B: *</td>
</tr>
<tr>
<td>K (mmol/l)</td>
<td>3.6, 3.3–3.9 (n=164)</td>
<td>3.7, 3.3–4 (n=282)</td>
<td>3.6, 3.3–3.9 (n=107)</td>
<td>A:B:<em>; B:C:</em></td>
</tr>
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</table>

\(n\) denotes multiple measurements in individual patients. Values are shown as median values and first and third quartiles. Renin values are given as mean±SEM and were anlaysed by t-test.

NS: non-significant.

\(*P<0.05\).
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with both drugs. The selectivity of rofecoxib towards COX-2 can be concluded from T × B2 excretion, which did not differ from controls. Despite the fairly high dose of 0.6 mg/kg/day of rofecoxib used in this study (corresponding to an adult dosing of approximately 40 mg/day), steady-state blood levels were only half as high compared with a recent study in healthy adult volunteers taking 25 mg rofecoxib qd [21]. In line with these low drug levels, systemic PGI2 prostacyclin formation was found to be only moderately, and yet statistically insignificantly reduced.

Because the glomerular filtration rate (GFR) was lowest with indomethacin and not with rofecoxib, GFR changes can be disregarded as a prohypertensive mechanism of rofecoxib as well. Likewise, the data demonstrate that differences in renal salt handling (fractional excretion of sodium) did not change with either NSAID, and are thus unrelated to the prohypertensive effect of rofecoxib. However, FeNa is dependent on sodium intake, which was not assessed in this study.

This study is weakened by its retrospective nature, which does not allow exclusion of confounding effects. However, the reversible hypertension caused by rofecoxib in one furosemide-like SLT patient independently supports the main finding of this study i.e. that patients with this particular tubulopathy are susceptible to the prohypertensive effects of this drug.

In summary, this study shows an increased blood pressure in paediatric and adolescent rofecoxib-treated patients with a furosemide-like SLT. Thus, Cox-2 selective inhibitors should not be used in children with congenital SLT. The data indicate that the hypertensive effects of this drug were probably unrelated to renal side effects but were possibly brought about by vascular side effects. It remains an open question whether systemic T × B2 formation is indicative of hypertension in certain adults as well, which obviates the need for future prospective studies. Whether loop-diuretics also increase the susceptibility to the prohypertensive effects of rofecoxib remains to be analysed.

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Conflict of interest statement. None declared.

References


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