Peer reviewed article

Renal safety of combined cyclooxygenase 2 (COX-2) inhibitor and angiotensin II receptor blocker administration in mild volume depletion

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Summary

Principles: Drugs that either inhibit prostaglandin synthesis or antagonise angiotensin II effects are likely to impair renal function, especially in patients with an activated renin-angiotensin-aldosterone system. Of the former, nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used, and newer agents with cyclooxygenase 2 (COX-2) specific inhibition may have fewer renal side effects compared to non-selective NSAIDs. We therefore investigated whether combination of a COX-2 inhibitor with an angiotensin II subtype 1 (AT_1) receptor blocker is safe with regard to preservation of normal renal function in a state of slight volume contraction.

Methods: Mild volume depletion was induced by a salt-restricted diet in 5 healthy volunteers who were then given a single dose of 400 mg celecoxib, a COX-2 inhibitor, alone or in combination with 150 mg irbesartan, an AT_1 receptor blocker. Glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by measuring inulin and PAH clearance respectively, along with plasma renin activity (PRA) and urinary electrolyte excretion before and over 100 minutes after drug administration.

Results: PRA was high prior to drug administration, indicating slight salt depletion, and dropped by 65% after intake of celecoxib alone ($p = 0.008$) but only by 25% after combined intake with irbesartan (p = n.s.). GFR was not affected either by celecoxib alone or by combined administration with irbesartan. In contrast, ERPF increased by 28% 80 minutes after simultaneous drug intake ($p = 0.029$), but not after celecoxib alone. Renal sodium and potassium excretion did not significantly change under celecoxib alone or in combination with irbesartan.

Conclusion: Selective COX-2 inhibition by celecoxib in combination with an AT_1 receptor blocker (irbesartan) has no acute adverse effects on renal haemodynamics and renal salt handling in slightly volume-depleted subjects with normal renal function. Moreover, our data obtained in humans appear to confirm the co-regulatory interaction of COX-2 and angiotensin II in the control of renin release, as suggested by animal studies.

Keywords: cyclooxygenase 2 inhibitor; COX-2 inhibitor; angiotensin receptor blocker; volume depletion

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed medicines worldwide, being the drugs of first choice in the treatment of pain, rheumatic disorders and other inflammatory diseases. Unfortunately, the use of NSAIDs is associated with a wide variety of side effects, such as gastrointestinal bleeding and renal failure, which are due to the inhibition of prostaglandin synthesis via suppression of the cyclooxygenase enzymes, cyclooxygenase 1 (COX-1) and 2 (COX-2). Until recently, only non-specific non-steroidal anti-inflammatory agents were available which affected both COX-1 and COX-2 expression in a nonselective manner. COX-1 is constitutively expressed in most tissues and is thought to be involved in the basal physiological production of prostaglandins [1–5]. In contrast, COX-2 production was found to be unregulated by cytokines such as IL-1β, TNF-α and endotoxins (LPS) in a variety of cell lines and tissues, and is expressed in inflammatory cells [6–9].

This observation led to the hypothesis that selective COX-2 inhibition would provide anti-inflammatory and analgesic effects without affecting basal prostaglandin synthesis, and thus potentially avoid side effects of non-selective NSAIDs. Studies comparing NSAIDs with selective COX-2 inhibitors and in vitro data provide strong evidence that inhibition of COX-1 is indeed responsible for the serious gastrointestinal complications induced by NSAIDs in humans [10, 11]. In the kidney, among other effects, prostaglandins are involved in renal haemodynamic autoregulation and salt and water homoeostasis [12]. In a state of reduced renal blood flow they counterbalance the vasoconstrictive effect of angiotensin II in the pre- and postcapillary glomerular vasculature. Inhibition of prostaglandin synthesis may thereby result in a reduction of GFR, especially in subjects with a reduced effective arterial volume from congestive heart failure, hepatic cirrhosis with ascites, or the use of diuretics. Moreover, inadequate synthesis of prostaglandins may cause salt and water retention [13, 14]. In the adult human kidney, COX-1 expression has been demonstrated in the vasculature and the interstitium of both cortex and medulla. It is of interest that COX-1 is expressed in endothelial and smooth muscle cells of pre- and postglomerular vessels, and in increasing amounts along the collecting duct towards the medulla. In contrast, COX-2 expression in the glomeruli is prominent in the podocytes, with similar distribution to COX-1 in the medullary vasa recta [15]. With their differential expression pattern in the kidney, selective inhibition of either COX-1 or COX-2 is of potential medical importance. Accordingly, since specific COX-2 antagonists have become commercially available, thus making it possible to selectively inhibit COX-2 synthesis, interest in their renal (side) effects has been aroused. However, only a few studies have investigated their influence on renal function. Rossat et al. [16] found transient salt retention in healthy volunteers after chronic administration of celecoxib (Celebrex®), a selective COX-2 inhibitor. Also, a dose-dependent reduction in GFR was observed acutely, but not after chronic treatment for one week. As mentioned before, apart from prostaglandins Ang II is the major humoral factor regulating renal perfusion and glomerular filtration. Combined treatment with conventional NSAIDs and drugs which interfere with the production of angiotensin II or its receptor frequently induces renal insufficiency in patients with diminished effective arterial volume [17]. We therefore investigated whether acute administration of celecoxib, a new selective inhibitor of COX-2 which has been approved in the United States and most European countries for the treatment of pain and arthritis, in combination with irbesartan, a selective AT_1-receptor antagonist for the treatment of hypertension, is safe with regard to preservation of renal perfusion, glomerular filtration and normal renal salt and water handling in subjects with slight volume depletion.

Methods

Five healthy male volunteers were enrolled into this study. Prior to inclusion a medical history and informed consent were obtained from each subject. The protocol was approved by the institutional review committee.

Study design

Each subject completed two study periods, each of which was preceded by a sodium-restricted diet (2–4 g NaCl/day) for 2 days and the intake of a single dose of 40 mg furosemide on the first day of diet to achieve mild salt and volume depletion. The diet was provided, under the supervision of a dietician, by the local hospital kitchen. Except for beverages containing caffeine and/or alcohol, which were prohibited, fluid intake was not restricted. Volunteers refrained from smoking. In the morning of day 3 after an overnight fast, renal haemodynamic studies were performed and renal salt and water excretion were assessed. The volunteers were examined in the supine position, except for voiding, and they fasted throughout the study period. An intravenous catheter was inserted into an antecubital vein of each arm – one for infusion of inulin (Laevosan®, Gesellschaft, Linz, Austria) and PAH (Nephrotest®, sodium salt of para-aminohippuric acid, Pharmacy of the Inselspital, Bern, Switzerland) in a glucose-saline solution, and another for blood drawings. Between 7 and 8 a.m. the volunteers drank a water load of 4–5 ml/kg body weight. After a 45-min equilibration period, during which the volunteers drank another 800–1000 ml of water, three timed urine collections of 20 minutes each were obtained before drug intake. At the end of these baseline measurements the volunteers received orally 400 mg celecoxib (Celebrex®; Searle Research and Development), and an additional five urine collections of 20 minutes each were performed.

After a washout phase of one week another study was performed following an identical design, except for the combined intake of 400 mg celecoxib and 150 mg irbesartan (Aprovel®; Sanofi/Bristol-Myers Squibb).

Systolic blood pressure (SBP), diastolic blood pressure (DBP), urine flow, and urinary excretion of sodium, potassium, inulin, creatinine and PAH were measured in the collected urine samples. To assess GFR and ERPF, blood samples were drawn simultaneously for measurement of inulin, creatinine and PAH. Clearances for inulin and PAH were calculated according to the formula:

$$Cl_x = (U_x \times V)/P_x$$

where U and P are the urinary and plasma concentrations of x respectively and V is the urinary flow rate (ml/min). Blood pressure was measured by an upper arm cuff with an automated sphygmomanometer (Cohin Electronics Co Ltd, Japan). Blood samples for determination of plasma renin activity were obtained while subjects were in the supine position for at least 10 minutes prior to drug intake and at the end of the study period. PRA sample tubes containing EDTA were immediately put on ice and centrifuged at 4 °C, and the plasma was frozen and stored at –20 °C.

Analytical methods

Plasma and urinary inulin concentrations were measured by the Anthron method [18] and PAH concentrations were determined by spectrophotometry [19]. Urinary sodium and potassium were analysed by standard techniques. PRA was determined by RIA as described earlier [20].

Statistics

Results are expressed as mean ± SEM unless stated otherwise. Differences between groups were tested for statistical significance in a paired fashion by ANOVA for repeated measurements; SigmaStat® for Windows Version 1.0, Jandel® Corporation. P values <0.05 were considered to be significant.

Results

The mean age and body mass index of volunteers were 36.4 ± 0.8 years and 24.7 ± 0.6 respectively. Administration of celecoxib alone and in combination with irbesartan was well tolerated by all subjects, and no relevant clinical side effects were observed during or after the study.

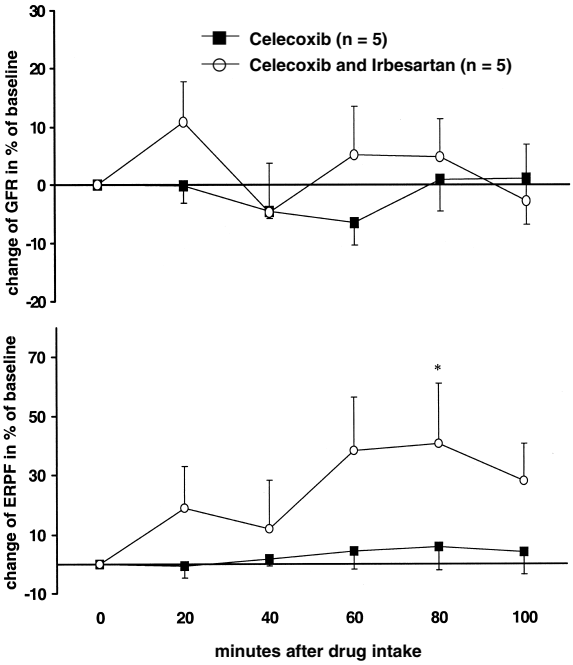

Figure 1

Relative changes in glomerular filtration rate (GFR; upper panel) and effective renal plasma flow (ERPF, lower panel) as compared to baseline resultant on administration of 400 mg celecoxib and a combination of 400 mg celecoxib and 150 mg irbesartan. Results are mean values ± SEM, *: p = 0.029 (vs. baseline).

Baseline measurements

Mean baseline values for GFR, SBP, DBP, and PRA did not differ between the two study periods (table 1). Mean baseline ERPF was lower before combined administration of celecoxib and irbesartan due to a single individual. However, results of ERPF measurements were not affected by this difference. With a daily sodium excretion ranging from 20–43 mmol/24 h among volunteers, good adherence to the prescribed low salt diet is demonstrated.

Effect of celecoxib and celecoxib/irbesartan intake

Systolic and diastolic blood pressure (SBP/DBP)

Throughout the study, neither SBP nor DBP changed significantly after administration of 400 mg celecoxib alone or in combination with 150 mg irbesartan respectively (table 1).

Renal haemodynamics

There were no significant changes in GFR or ERPF after administration of 400 mg celecoxib at each time point as compared to baseline. In contrast, combined intake of 400 mg celecoxib and 150 mg irbesartan significantly increased ERPF 80 minutes after their administration by 28% (p = 0.029). However, GFR remained unchanged

Table 1

Clinical, renal and metabolic characteristics of the subjects during the two study periods.

	baseline	minutes after drug intake				
		20′	40′	60′	80′	100′
Celecoxib						
SBP (mm Hg)	131.0 ± 1.9	136.2 ± 0.4	134.6 ± 4.0	137.0 ± 2 .7	136.6 ± 2.7	129.0 ± 3.2
DBP (mm Hg)	76.7 ± 1.5	79.4 ± 1.6	80.0 ± 2.1	76.2 ± 2.0	77.2 ± 2.0	76.0 ± 2.6
GFR (ml/min/1.72 m²)	93.9 ± 7.7	93.4 ± 6.8	90.0 ± 8.3	87.9 ± 7.9	95.3 ± 10.8	95.4 ± 11.8
ERPF (ml/min/1.72 m²)	451.7 ± 18.9	446.5 ± 10.6	459.6 ± 22.9	468.7 ± 23.0	478.1 ± 43.0	466.6 ± 27.3
PRA (ng/ml/h)	3.24 ± 0.6					1.12 ± 0.26#
Celecoxib and irbesartan						
SBP (mm Hg)	132.7 ± 3.7	133.2 ± 3.0	130.8 ± 4.1	129.0 ± 4.3	132.8 ± 4.9	126.4 ± 3.2
DBP (mm Hg)	77.7 ± 3.1	77.2 ± 2.3	76.6 ± 3.1	74.6 ± 3.4	77.6 ± 2.2	77.0 ± 3.7
GFR (ml/min/1.72 m²)	85.6 ± 7.5	95.1 ± 11.6	81.8 ± 11.6	88.2 ± 5.7	89.7 ± 10.3	81.8 ± 8.4
ERPF (ml/min/1.72 m²)	381.7 ± 67.5	421.6 ± 57.7	387.2 ± 49.6	492.9 ± 86.5	491.0 ± 65.2 *	434.8 ± 42.1
PRA (ng/ml/h)	2.36 ± 0.4					1.82 ± 0.56

SBP: systolic blood pressure, DBP: diastolic blood pressure, GFR: glomerular filtration rate, ERPF: effective renal plasma flow, PRA: plasma renin activity. Results are mean values ± SEM, *: p = 0.029 (vs. baseline), # p = 0.008 (vs. baseline)

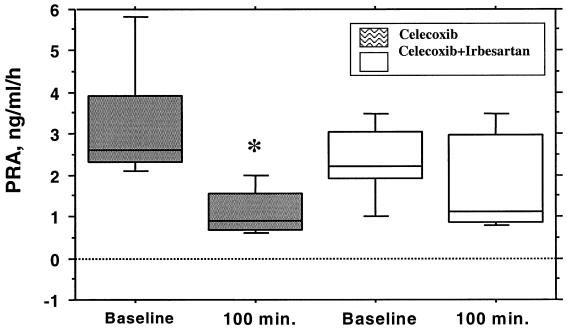

Figure 2

Box Plot graph of plasma renin activity (PRA) at baseline and after administration of either 400 mg celecoxib (n = 5; white bars) or a combination of 400 mg celecoxib and 150 mg irbesartan (n = 5; black bars); * p = 0.008 vs. baseline.

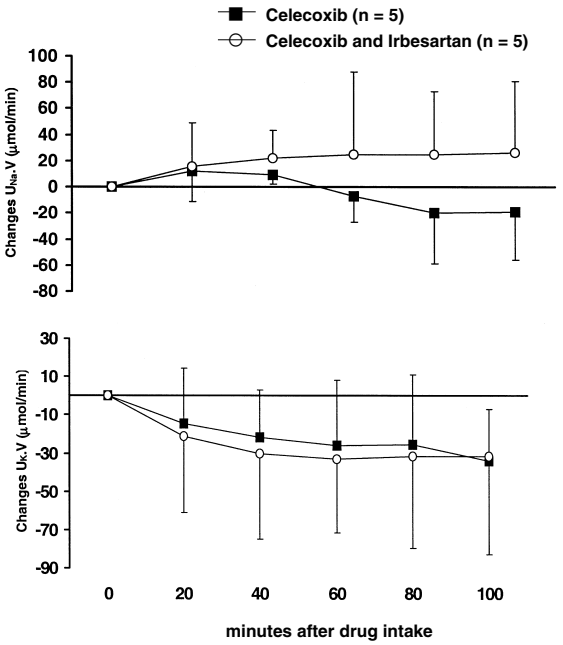

Figure 3

Changes in Na^+ excretion (upper panel) and K^+ excretion (lower panel) resultant on administration of 400 mg celecoxib, and a combination of 400 mg celecoxib and 150 mg irbesartan. Results are mean values ± SEM.

(Table 1). In Figure 1, the results of GFR and ERPF are depicted as relative changes versus baseline.

Plasma renin activity (PRA)

PRA was determined along with baseline renal function studies prior to drug intake and at the end of the study (100 minutes after drug intake). Prior to both study periods PRA levels were elevated (first period 3.24 ± 0.6 ng/ml/h, second period 2.36 ± 0.4; normal range 0.8–2.5 ng/ml/h), but were not significantly different from each other. Also, baseline PRA levels in this investigation were higher compared to those measured by the same method in male volunteers of comparable age after an overnight fast without prior salt restriction (1.9 ± 1.0 ng/ml/h) [20]. This indicates that the subjects in the current study were slightly volume-depleted. PRA dropped significantly by 65% after administration of 400 mg celecoxib (p = 0.008), but only by 25% when celecoxib was administered in combination with 150 mg irbesartan (p = n.s.; table 1 and figure 2).

Electrolyte excretion

No significant changes from baseline in sodium or potassium excretion were seen either after intake of celecoxib alone or celecoxib in combination with irbesartan (fig. 3). Like others, we observed slight potassium retention after COX-2 inhibition [16], which was also noted after combined treatment with the selective AT_1-receptor antagonist.

Discussion

The main finding of the present study is that intake of celecoxib, a drug which selectively inhibits cyclooxygenase 2 (COX-2), in combination with irbesartan, an angiotensin II subtype 1 receptor blocker, has no acute effect on GFR in healthy subjects with slight volume depletion. Moreover, renal sodium and potassium handling is not affected in a relevant manner by the interaction of these two drugs.

Selective inhibition of COX-2 by drugs which have recently become commercially available has proven to be of benefit with regard to gastrointestinal side effects such as bleeding, a major complication of non-selective NSAIDs [10]. Theoretically, based on the distribution pattern of COX-1 and COX-2 in the kidney, one would assume that selective COX-2 inhibition might reduce untoward renal effects compared to non-selective NSAIDs, such as diminished glomerular filtration and salt retention. However, only a few clinical studies have investigated this problem so far, and some of them have failed to demonstrate a beneficial effect of COX-2 inhibitors over conventional NSAIDs in preventing impairment of renal function. On the contrary, the work of Rossat et al. [16] has even demonstrated a slight decrease in GFR after acute intake of celecoxib in the same dosage as that given to volunteers in the present investigation. Unlike them, we could not detect any changes in renal haemodynamics after acute intake of celecoxib. Two possible explanations for this apparent discrepancy are: (a) differences in time of follow-up after drug intake (up to 180 minutes in the study by Rossat, vs. 100 minutes in our investigation), and (b) degree of volume depletion With regard to the latter, the substantial elevation in PRA as well as the increased ERPF after combined intake of celecoxib and irbesartan indicate a clear, though probably slight, contraction of the effective arterial volume in our study subjects. Regarding renal salt handling, our findings were comparable with those of Rossat et al. [16], showing a tendency to sodium and potassium retention under COX-2 inhibition which was not statistically significant in our experiments. We therefore conclude that in a state of slight intravascular volume depletion no relevant renal haemodynamic changes or impairment of salt excretion need be expected from acute intake of celecoxib in healthy subjects.

Combined treatment with a non-steroidal anti-inflammatory drug and an AT_1 receptor antagonist may be of potential harm to patients with heart failure, liver cirrhosis or concomitant intake of diuretics [13, 14]. These states are characterised by a reduced effective arterial volume where renal perfusion and glomerular filtration critically depend on intact autoregulation of renal haemodynamics. The latter is maintained by a balance of glomerular vasoconstriction and vasodilatation, which, on the humoral axis, are governed mainly by angiotensin II and prostaglandins respectively. Disturbance of this balance, for example through interference with drugs, may result in renal failure. We therefore investigated whether the use of a selective COX-2 inhibitor in combination with an AT_1 antagonist may adversely affect renal function in a state of slight salt and volume depletion. We found a significant increase in ERPF, of 28% compared to baseline, 80 minutes after combined intake of celecoxib and irbesartan. However, no fall in GFR occurred over the whole study period. These results correspond well with data published by others, which have demonstrated an almost identical increase in ERPF to that shown in our experiments, but no change in GFR within the same time frame after administration of 150 mg irbesartan alone to healthy volunteers with mild salt deprivation [21]. This, together with the fact that celecoxib by itself did not significantly affect renal haemodynamics, makes it highly probable that the changes in ERPF observed after combined intake of celecoxib and irbesartan are mainly the result of AT_1 receptor blockade. We therefore conclude that acute intake of COX-2 inhibitors along with AT_1 receptor antagonists does not modify the effects of the latter drug renal haemodynamics in healthy subjects with mild volume contraction. A similar conclusion can be drawn with regard to renal salt handling, which was not altered in a relevant manner by combined administration of celecoxib and irbesartan compared to baseline and versus intake of the COX-2 inhibitor alone.

How can our findings be integrated into current knowledge of the humoral balance of renal haemodynamic autoregulation? And do they add new information on the mechanisms that are operative in this process? In this regard, the changes in PRA observed in our experiments may be of particular interest. As expected, salt restriction in our volunteers resulted in high plasma renin activity. Molecular studies in rats have demonstrated that in a salt-depleted state COX-2 expression in the macula densa is enhanced [22]. It is well known that macula densa-derived prostaglandins stimulate renin synthesis and renin secretion via the prostaglandin EP4 receptor of juxtaglomerular granular (JG) cells [23–25]. Administration of celecoxib in our study subjects reduced PRA by 65%. We postulate that this decrease is due to the inhibition of COX-2 activity and the consecutive decrease in prostaglandin synthesis. Renin release triggers conversion from angiotensinogen to angiotensin I and angiotensin II. Eventually, angiotensin II has a negative feedback effect on COX-2 expression in the macula densa, mediated via AT_1 receptor [26, 27]. In addition, angiotensin II directly inhibits renin secretion from the JG cells by a negative feedback loop, mediated via their AT_1 receptor [28]. AT_1 antagonism by irbesartan in the same dose as that used in our experiments increases PRA within 90 minutes of intake in salt-restricted individuals [21]. It can be hypothesised that AT_1 receptor blockade omits the negative feedback signal on renin release from either the indirect pathway via COX-2 suppression or through direct action on JG cells, thus explaining increased PRA levels in these individuals. Again, these regulatory networks have been elaborated on the basis of molecular studies in animals, which for practical reasons are hard to validate in humans. Interestingly, the intake of celecoxib in conjunction with irbesartan in our experiments did not cause a decrease in PRA as observed with COX-2 inhibition alone. This result is compatible with the postulated regulatory pathways of renin secretion outlined above. Hence our findings strongly indicate that in humans similar regulatory and counter-regulatory pathways are operative as postulated from animal experiments.

In summary and conclusion, we have shown that celecoxib, a COX-2 inhibitor, taken in combination with an AT_1 receptor blocker, i.e. irbesartan, does not adversely affect renal haemodynamics and renal salt handling in healthy volunteers. Whether this also holds true for patients with a major reduction in effective arterial volume, for example in severe heart failure, needs to be established in clinical trials. Finally, our data from humans appear to confirm the co-regulatory interaction of COX-2 and angiotensin II in the control of renin release, as suggested by animal studies.

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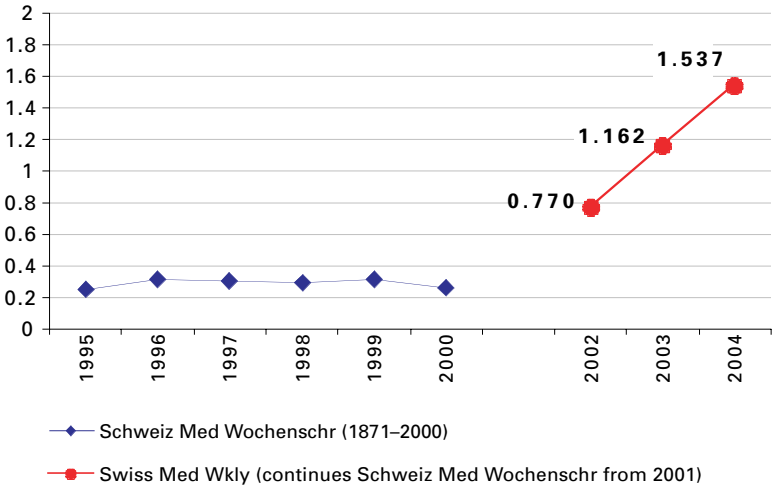

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