Cyclooxygenase inhibition causes marked impairment of renal function in elderly subjects treated with diuretics and ACE-inhibitors

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Abstract

\textbf{Background:} Treatment with angiotensin-converting enzyme (ACE)-inhibitors is known to cause an initial reduction in glomerular filtration rate (GFR) in patients with congestive heart failure. The long-term beneficial effects of ACE-inhibitors in these patients can be counteracted by cyclooxygenase-inhibitors.

\textbf{Aims:} To quantify the negative renal effects of the cyclooxygenase-inhibitor diclofenac in elderly healthy subjects and to assess how treatment with an ACE-inhibitor, after activation of the renin–angiotensin system, influences these renal effects.

\textbf{Methods:} Fourteen elderly, healthy subjects received oral diclofenac and placebo in a double-blind cross-over fashion. The study was divided in two parts; in part one, subjects received no pre-treatment and in part two, the subjects were given pre-treatment with bendroflumethiazide and enalapril in order to activate the renin–angiotensin system.

\textbf{Results:} Diclofenac induced significant ($p < 0.05$) decreases in GFR, urine flow, excretion rates of sodium and potassium, electrolyte clearance, osmolality clearance and free water clearance both with and without renin–angiotensin system activation. Least square means (95\% CI) of all observations during the first 6 h after dosing showed that diclofenac caused a reduction in GFR from 71 (64–78) to 59 (52–66) ml/min. After pre-treatment, diclofenac further reduced GFR from 60 (52–67) to 48 (40–55) ml/min. After diclofenac administration, urine flow fell from 7.4 (6.4–8.3) to 5.1 (4.2–6.1) ml/min, after pre-treatment, diclofenac gave a further reduction from 4.1 (3.1–5.1) to 2.2 (1.3–3.2) ml/min. More than half of the reductions were caused by the pre-treatment.

\textbf{Conclusion:} Renal function in elderly, healthy subjects is impaired after acute intake of diclofenac. This impairment is observed both with and without activation of the renin–angiotensin system and ACE-inhibitor treatment but is more pronounced after pre-treatment.

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\textbf{Keywords:} ACE-inhibitors; NSAIDs; Heart failure; Renal function; Glomerular filtration rate

1. Introduction

Several clinical trials have shown beneficial effects of angiotensin-converting enzyme (ACE) inhibitors in patients with left ventricular dysfunction, with or without congestive heart failure [1–6]. The HOPE trial also showed evidence of benefit in patients who were at high risk of cardiovascular events but with normal ventricular function [7]. ACE-inhibitors act by decreasing production of angiotensin II and by potentiating the effects of bradykinin by inhibiting its breakdown. Bradykinin exerts some of its effects via vasodilating prostaglandins [8].

The fact that the cyclooxygenase-inhibitor drugs block the formation of prostaglandins [9] has led to the idea that the concomitant use of prostaglandin synthesis inhibitors, e.g. aspirin and non-steroidal antiinflammatory drugs (NSAIDs), could attenuate the beneficial effects of ACE-inhibitors. If this proves to be true, patients may not receive the full benefit of ACE-inhibition if they are treated with a combination of an ACE-inhibitor and a cyclooxygenase-inhibitor [10].
Clinical observations in the CONSENSUS II [11], SOLVD [12], and HOPE [13] trials and the randomised WASH-study [13] have shown less benefit with ACE-inhibitors for patients treated with aspirin. Furthermore, an evaluation of patients hospitalised with a diagnosis of congestive heart failure and treated with ACE-inhibitors indicated that aspirin adversely affected survival [14]. Due to these observational data, and the mechanistic evidence, the role of aspirin for patients with heart failure has been questioned [15–17].

We have previously studied patients with stable congestive heart failure treated with ACE-inhibitors. We chose to use the cyclooxygenase-inhibitor diclofenac as a model drug since it has a short half-life and in an earlier study had been shown to decrease GFR by 35% in patients with a history of ureteral colic but normal renal function at the time of the study [18]. The patients in our study received 50 mg of the cyclooxygenase-inhibitor diclofenac or placebo in a cross-over design. Diclofenac has been shown to cause a significant 40% reduction in GFR compared with placebo [19].

A study of eight patients with normal renal function [18] showed that diclofenac also has negative renal effects in patients without cardiac or renal dysfunction. The patients in this study were younger, mean age 42 years, than the average patient with congestive heart failure.

The aim of the present study was to quantify the negative renal effects of a cyclooxygenase-inhibitor, in subjects of an age more typical of the average patient with congestive heart failure, but with normal cardiac and renal function and to assess how treatment with an ACE-inhibitor after activation of the renin–angiotensin system affects these renal effects. Therefore, we performed a study in elderly, healthy subjects with normal cardiac and renal function. The primary objective was to study the influence of a single oral dose of diclofenac on GFR with and without pre-treatment to activate the renin–angiotensin system. Secondary objectives were to study the effects on urine flow, excretion rates of sodium and potassium, clearances of sodium and potassium, osmolality clearance, free water clearance and serum creatinine.

2. Methods

2.1. Study protocol

The study was divided in two parts. In part one, the subjects were given diclofenac and placebo without any pre-treatment. In part two, pre-treatment was given in order to activate the renin–angiotensin system. The subjects were pre-treated with bendroflumethiazide 5 mg daily for 6 days (i.e. days −6 to −1), this drug was not given on the morning of the study days, and enalapril, 2.5 mg daily on days −6, −5 and −4; 5 mg daily on days −3 and −2; and 10 mg daily on day −1 and the study day. The subjects were in contact with one of the investigators on days −3 and −1; if adverse events suggestive of too high dose were reported, e.g. dizziness or tiredness, the dose of enalapril was lowered.

In each part of the study, we used a double-blind, placebo-controlled cross-over design where all the subjects received 50 mg diclofenac and placebo in a random order.

The randomisation procedure was blinded to the investigators. Diclofenac was given as Voltaren® (Novartis). As placebo Polybion® (Merck) tablets were used. Each drug had similar shape, size and colour. Each dose was individually packed.

On study days, each subject had breakfast at home before arriving at the department. An intravenous indwelling catheter was inserted into both forearms, one to obtain blood and the other for administration of iohexol. Omnipaque® (Nycomed), 647 mg/ml iohexol, was diluted in saline giving a solution with a concentration of iohexol of 64.7 mg/ml. After initial measurements, the infusion of iohexol was started. Over 10 min 647 mg of iohexol was infused using an infusion pump followed by 3.45 mg/min for the rest of the examination day. The subjects were slightly over-hydrated during study days; after having emptied the bladder a loading volume of 500 ml was given. At the end of each pre-defined interval, a volume of water corresponding to the urine volume collected in that interval plus 40 ml/h to compensate for perspiration was given. Clear soup, given after 3 h, was also included. The loading volume was given 1 h prior to placebo or diclofenac. Urine was collected over 1 h prior to dose and over 6 h post-dose in the following intervals: −60–0, 0–30, 30–60, 60–90, 90–120, 120–150, 150–180, 180–240, 240–300 and 300–360 min. The volumes were noted and the urine was analysed for iohexol, sodium, potassium and osmolality.

Blood samples were obtained 30 min prior to dose, and 15, 45, 75, 105, 135, 165, 210, 270 and 330 min post-dose. The samples were analysed for iohexol, sodium, potassium, creatinine and osmolality. Blood samples for analysis of diclofenac were obtained prior to dose and 5, 10, 15, 30, 45, 55, 65, 75, 90, 105, 120, 135, 150, 165, 180, 210, 240, 270, 300 and 330 min post-dose.

2.2. Study population

The inclusion criteria were: male or female aged 65–80 years. Exclusion criteria were: any cardiac disease, severe renal insufficiency, peptic ulcer, liver cirrhosis, intolerance to NSAIDs or aspirin and intolerance to iohexol.

Each part of the study included 12 healthy elderly subjects. Of the 12 subjects from part one, 10 also participated in part two. Part one comprised 7 women and 5 men, aged 67–78 years (mean 72 ± 3.4). Part two comprised 8 women and 4 men, aged 67–78 years (mean 72 ± 3.4). Concomitant medication considered necessary during the study was allowed. Aspirin or NSAIDs were however not allowed 5 days prior to and during each study day.
On entering the study, written informed consent and the medical history were obtained, and a physical examination was made and inclusion and exclusion criteria were evaluated. The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Lund University, Lund, Sweden, and by the Swedish Medical Products Agency.

2.3. Biochemical analyses

Sodium, potassium, creatinine and osmolality in serum, and sodium, potassium and osmolality in urine, were analysed by standard methods at the Hospital Laboratory Trelleborg. Iohexol and diclofenac were analysed by high-performance liquid chromatography (HLPC) at the Hospital Pharmacy, Malmö University Hospital, as previously described [19].

2.4. Calculation of renal parameters

Urine flow was calculated from each sampling interval and expressed as ml/min. Urinary excretion rates of sodium and potassium were expressed as μmol/min. Urine and serum osmolality were given as mOsm/kg. Clearances of iohexol and electrolytes were calculated as the products of urine concentrations and flow rates divided by the serum concentrations and expressed as ml/min. GFR was determined as clearance of iohexol. Osmolality clearance was calculated as the product of urine osmolality and flow rate divided by the serum osmolality. Free water clearance was calculated as urine flow minus osmolality clearance.

2.5. Statistical analysis

The number of subjects included in each part of the study was based on the following assumptions. In an earlier study on healthy subjects [18], GFR fell by 40%, from 50.9 ml/min to 30.7, after 50 mg diclofenac [19].

As descriptive statistics, mean±S.D. are used. For statistical analysis, the MIXED procedure in SAS (version 8.2, SAS Institute, Cary, NC, USA) was used. Two sets of analyses were performed: one with a repeated measures design using all observations after dose and one using the observations obtained at the time of maximum diclofenac concentration (C_max) and the corresponding time during placebo treatment. The statistical model comprised treatments (diclofenac or placebo), pre-treatment (yes or no), interaction between treatment and pre-treatment and treatment sequences as fixed effects, and patient within sequence as random effects. As it turned out, there were no or negligible effects of sequences or interactions and the model was reduced to treatments (diclofenac or placebo), pre-treatment (yes or no) and patient within sequence. Diclofenac with pre-treatment was compared with diclofenac without pre-treatment, placebo with pre-treatment and placebo without pre-treatment. Diclofenac without pre-treatment was compared with placebo without pre-treatment. Placebo with pre-treatment was compared with placebo without pre-treatment. Arithmetic least square means and 95% confidence limits are described [19].

The treatments were generally well tolerated. However, one subject withdrew from the study since she fainted...
Fig. 1. (a–g) Elderly, healthy subjects with and without pre-treatment with a diuretic and an ACE-inhibitor. Observations in (a) GFR, (b) urine flow, (c) sodium excretion rate, (d) potassium excretion rate, (e) osmolality clearance, (f) free water clearance and (g) serum creatinine after a single dose of 50 mg diclofenac (filled circles) and placebo (empty circles) without pre-treatment, and after a single dose of 50 mg diclofenac (filled squares) and placebo with pre-treatment (empty squares).
during the second pre-treatment period. Another subject received a lower dose of enalapril, 5 mg instead of 10 mg, on the last 2 days in each pre-treatment period because of dizziness.

Least square means of the observations during the first 6 h after dose without pre-treatment showed that diclofenac caused significant reductions ($p<0.05$) in GFR, urine flow, excretion rates of and clearances of electrolytes, osmolality clearance and serum creatinine compared with placebo. Diclofenac caused a reduction of 12 (18–5) ml/min from 71 (64–78) to 59 (52–66) ml/min in GFR (Table 1). After diclofenac administration, GFR reached its lowest mean value after 75 min, 49±16 (mean±S.D.) ml/min compared with 74±28 ml/min for placebo (Fig. 1a). After diclofenac administration, urine flow fell 2.2 (2.8–1.7) ml/min from 7.4 (6.4–8.3) to 5.1 (4.2–6.1) ml/min (Table 1). The excretion rate of sodium decreased by 70 (86–54) µmol/min from 178 (151–205) to 108 (81–135) µmol/min (Table 1). The excretion rate of potassium decreased by 10 (151–205) to 108 (81–135) µmol/min (Table 1). Clearances of electrolytes, osmolality clearance and free water clearance were also significantly reduced when diclofenac was given (Table 1).

After pre-treatment with a diuretic and an ACE-inhibitor, least square means of the observations after diclofenac administration to 6 h showed significant reductions ($p<0.05$) in GFR, urine flow, excretion rates and clearances of electrolytes, osmolality clearance, free water clearance and serum creatinine compared with placebo. Diclofenac was reduced by 12 (18–5) ml/min from 60 (52–67) to 48 (40–55) ml/min after diclofenac administration (Table 1). Urine flow decreased by 1.9 (2.4–1.4) ml/min from 4.1 (3.1–5.1) to 2.2 (1.3–3.2) ml/min (Table 1). Excretion rates and clearances of sodium and potassium, osmolality clearance, free water clearance and serum creatinine were also significantly reduced ($p<0.05$) after diclofenac administration (Table 1).

The reductions between placebo without pre-treatment and diclofenac with pre-treatment were dramatic and highly significant (Fig. 1a–f). The part of the reduction derived from the effects of the pre-treatment and the part derived from diclofenac treatment were calculated. For GFR, 48.8% was caused by the pre-treatment, for the secondary variables the pre-treatment caused more than half of the reductions, 52.4–66.9% (Table 2).

Least square means of the observations at $t_{\text{max}}$ for diclofenac or corresponding time after placebo treatment showed that diclofenac without pre-treatment caused significant ($p<0.05$) reductions in GFR, urine flow, excretion rates of and clearances of electrolytes, osmolality clearance and free water clearance compared with placebo (Table 3).

### Table 2

<table>
<thead>
<tr>
<th>Total difference</th>
<th>Pre-treatment caused</th>
<th>Diclofenac caused</th>
<th>%Pre-treatment caused</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min)</td>
<td>23.1 (30.9–15.3)</td>
<td>11.3 (17.6–5.0)</td>
<td>11.8 (16.5–7.2)</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>5.2 (5.7–4.6)</td>
<td>3.1 (3.5–2.7)</td>
<td>2.1 (2.4–1.7)</td>
</tr>
<tr>
<td>Sodium excretion rate (µmol/min)</td>
<td>140 (167–112)</td>
<td>91 (116–66.0)</td>
<td>48 (60–37)</td>
</tr>
<tr>
<td>Potassium excretion rate (µmol/min)</td>
<td>36.8 (44.6–29.0)</td>
<td>24.6 (30.4–18.8)</td>
<td>12.2 (17.6–6.8)</td>
</tr>
<tr>
<td>Sodium clearance (ml/min)</td>
<td>1.02 (1.22–0.82)</td>
<td>0.66 (0.84–0.48)</td>
<td>0.36 (0.44–0.27)</td>
</tr>
<tr>
<td>Potassium clearance (ml/min)</td>
<td>8.6 (10.4–6.8)</td>
<td>5.6 (7.0–4.3)</td>
<td>3.0 (4.3–1.8)</td>
</tr>
<tr>
<td>Osmolality clearance (ml/min)</td>
<td>1.6 (1.9–1.3)</td>
<td>0.8 (1.1–0.6)</td>
<td>0.7 (0.9–0.6)</td>
</tr>
<tr>
<td>Free water clearance (ml/min)</td>
<td>3.6 (4.1–3.2)</td>
<td>2.3 (2.6–2.0)</td>
<td>1.3 (1.6–1.1)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>4.8 (1.9–7.7)</td>
<td>3.1 (0.3–6.0)</td>
<td>1.7 (0.8–2.5)</td>
</tr>
</tbody>
</table>

Calculations of the part of the reduction caused by pre-treatment and least square means and 95% confidence limits of all observations after dose.

### Table 3

<table>
<thead>
<tr>
<th>Diclofenac with pre-treatment</th>
<th>Diclofenac without pre-treatment</th>
<th>Placebo with pre-treatment</th>
<th>Placebo without pre-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR (ml/min)</td>
<td>43 (29–58)*</td>
<td>58 (44–72)*</td>
<td>57 (43–71)*</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>1.9 (0.3–3.4)*</td>
<td>5.6 (4.1–7.1)*</td>
<td>4.7 (3.1–6.2)*</td>
</tr>
<tr>
<td>Sodium excretion rate (µmol/min)</td>
<td>37 (–13–87)***</td>
<td>127 (78–176)*</td>
<td>78 (28–128)*</td>
</tr>
<tr>
<td>Potassium excretion rate (µmol/min)</td>
<td>32 (12–51)***</td>
<td>78 (59–96)</td>
<td>64 (44–83)*</td>
</tr>
<tr>
<td>Sodium clearance (ml/min)</td>
<td>0.27 (–0.10–0.63)****</td>
<td>0.93 (0.58–1.29)*</td>
<td>0.57 (0.21–0.94)*</td>
</tr>
<tr>
<td>Potassium clearance (ml/min)</td>
<td>8.1 (3.5–12.7)****</td>
<td>18.5 (14.1–22.9)*</td>
<td>16.1 (11.5–20.7)*</td>
</tr>
<tr>
<td>Osmolality clearance (ml/min)</td>
<td>1.2 (0.6–1.8)****</td>
<td>2.5 (2.0–3.1)*</td>
<td>2.3 (1.7–2.9)*</td>
</tr>
<tr>
<td>Free water clearance (ml/min)</td>
<td>0.6 (–0.6–1.8)****</td>
<td>3.1 (1.9–4.2)*</td>
<td>2.3 (1.1–3.5)*</td>
</tr>
<tr>
<td>Serum creatinine (µmol/ml)</td>
<td>80 (74–87)</td>
<td>81 (74–87)</td>
<td>82 (75–88)</td>
</tr>
</tbody>
</table>

Least square means and 95% confidence limits of observations at $t_{\text{max}}$ for diclofenac or corresponding time after placebo treatment with and without pre-treatment.

* $p<0.05$ vs. placebo without pre-treatment.
** $p<0.05$ vs. placebo with pre-treatment.
*** $p<0.05$ vs. diclofenac without pre-treatment.
After pre-treatment with a diuretic and an ACE-inhibitor, the observations after diclofenac administration showed significant reductions ($p<0.05$) in urine flow, excretion rates and clearances of electrolytes, osmolality clearance and free water clearance compared with placebo. (Table 3).

Without pre-treatment, the range of $C_{\text{max}}$ was 480–3687 ng/ml (median 1228 ng/ml) and the range of $t_{\text{max}}$ was 20–105 min (median 35 min). When pre-treatment was given, the range of $C_{\text{max}}$ was 363–1864 ng/ml (median 860 ng/ml) and the range of $t_{\text{max}}$ was 25–165 min (median 55 min).

4. Discussion

This study demonstrates that the cyclooxygenase-inhibitor diclofenac induces a decrease in GFR, urine flow, excretion rates and clearances of sodium and potassium, osmolality clearance and free water clearance in elderly healthy volunteers both with and without activated renin–angiotensin system from pre-treatment with diuretics and ACE-inhibitors. However, the effects were more pronounced after pre-treatment. We also show that more than half of these reductions were caused by pre-treatment.

In an earlier study in patients with a history of ureteral colic, but free from stone and with normal renal function at the time of the study [19], the effects of 50 mg diclofenac i.m. were studied. Urinary output fell within 10 min after the injection, and maximally by 80%, GFR fell by 35%. However, the patients in that study were younger, mean age 42 years, than the average patient with congestive heart failure. In our study, we were able to reproduce these findings in healthy subjects of an age more typical for a patient with congestive heart failure: mean age 72 years.

In conditions with activation of neurohumoral systems, e.g. congestive heart failure, the prostaglandins play an important part in maintaining renal hemodynamics, attenuating the effects of the vasoconstrictors. ACE-inhibitors act as vasodilators and impede the degradation of the strong vasodilator bradykinin which augments its vasodilating effect by releasing prostaglandins [8]. This interference suggests that the vasodilating effect of ACE-inhibitors is in part mediated by prostaglandins. Patients with an activated renin–angiotensin system therefore depend upon prostaglandins in their renal function and treatment with cyclooxygenase-inhibitors, like diclofenac, may cause serious deterioration in renal function and counteract the beneficial effects of ACE-inhibitors.

The vasodilating prostaglandins seem to contribute less to changes in vascular resistance under normal circumstances, though we have shown that they are involved. The results from the HOPE-study, where ramipril had greatest benefit in the absence of aspirin [13] among patients with high risk of cardiovascular disease but normal left ventricular function, are in line with these findings.

The proportion of elderly patients taking NSAIDs has been estimated at 25% [20] and many people buy NSAIDs over the counter. Many of these patients are likely to suffer from congestive heart failure and be receiving treatment with ACE-inhibitors. These patients therefore run the potential risk of counteracting the beneficial effects of ACE-inhibitors. NSAIDs have also been reported to be associated with an increased risk of hospitalisation with heart failure [21,22]. Indomethacin, another NSAID, has previously been shown to attenuate the peripheral hemodynamic effect of the ACE-inhibitor captopril in patients with congestive heart failure [23]. The renal effects of aspirin in patients with congestive heart failure treated with ACE-inhibitors have not been extensively investigated. Administration of high dose aspirin, 500 mg t.i.d., to patients with heart failure has been shown to reduce renal sodium excretion [24]. In a retrospective analysis, it was suggested that aspirin worsened the decrease in glomerular filtration rate (GFR) and reduced the improvement in renal plasma flow in ACE-inhibitor treated heart failure patients [25]. Our findings are in line with these observations.

The fact that at least half of the reduction in renal function was caused by pre-treatment was an unexpected finding in our study. Conditions that predict adverse renal effects from ACE-inhibitors are pre-existing hypotension and low cardiac filling pressures or when GFR is especially dependent on angiotensin II during volume depletion, or renal artery stenosis [26]. None of our healthy subjects was suffering from any of these conditions. Renal hemodynamic effects have been studied in patients with moderate or severe heart failure during treatment with trandolapril. No changes were found in GFR after 3 days, but after 8 weeks of treatment, GFR was reduced by 25% [27]. That subjects with normal renal and cardiac function respond with a fall in GFR after only 7 days of treatment with an ACE-inhibitor has, to the best of our knowledge, not been reported before. Reduced GFR is a strong independent predictor of mortality in patients with heart failure [28] and any detectable decrease in renal function is associated with increased mortality and prolonged hospital stay for patients hospitalised for congestive heart failure [29]. ACE-inhibitors may cause a decline in GFR by decreasing the efferent arteriolar resistance. The effects of cyclooxygenase-inhibitors on the afferent arteriole can further compromise GFR [30]. Thus, the combination of an ACE-inhibitor and a cyclooxygenase-inhibitor could cause very serious impairment of renal function. We also found a reduction between placebo without pre-treatment and diclofenac with pre-treatment of 33% in GFR and of 70% in urine flow. There is remarkably little work on diuretic requirements during ACE-inhibitor therapy. It has been shown that captopril does not have a diuretic sparing effect in patients with severe chronic heart failure but in some patients with moderate chronic heart failure it does have a diuretic sparing effect [31]. An increase in water excretion with ACE-inhibitors, believed to be mediated by bradykinin, has been described [32]. It
seems likely that the described impairment in GFR blunts the increase in water excretion.

Using healthy subjects at an age comparable with the average patient with congestive heart failure has many advantages. We were able to separate the effects dependent on worsening heart failure from those dependent on counteraction of the renal effects of ACE-inhibition. It was also easier to recruit healthy subjects for the study and we could avoid the potentially dangerous effects of water loading and worsened renal function like fluid congestion and pulmonary oedema. In our opinion, this model is a useful tool for studying pharmacological effects on renal function also in congestive heart failure.

A possible methodological weakness in this study was the urine collection by normal voiding. Despite emptying, urine can remain in the bladder and cause errors in volume measurements. Catheterisations are not acceptable for ethical reasons and recruitment of patients to the study probably would have been more difficult if catheterisations were to be made. The observed deterioration in renal function in our study was caused by a single dose of diclofenac and the renal effects of repeated dosing are not known. This question will be addressed in a future study. We do not know if the observations hold true for the cyclooxygenase-inhibitor aspirin and what dose is needed to cause the negative effects, though preliminary data have shown that the renal effects of aspirin are clearly dose-dependent [33]. We chose to give the results as least square means of all observations during the first 6 h after dose and as least square means of the observations at \( t_{\text{max}} \) for diclofenac or corresponding time after placebo treatment. None of them are ideal. The effect of diclofenac is short-lived (Fig. 1a–f) and the results would have been more pronounced if we had chosen a shorter observation period. The maximum effect of diclofenac does not occur at the maximum concentration and the results would probably have been more marked if had been possible to perform pharmacokinetic/pharmacodynamic modelling. The number of subjects, 12 in each part, might, intuitively, seem small but was the result of power calculations based on previous results both from our group as well as other investigators. Further, the highly significant results achieved in our study clearly show that it is sufficient.

In conclusion, our results show that diclofenac caused a deterioration in renal function in elderly healthy volunteers, with normal cardiac and renal function, with and without an activated renin–angiotensin system from pretreatment with diuretics and ACE-inhibitors. The effects were more pronounced with activated renin–angiotensin system. Half of the reductions were caused by 7-day treatment with ACE-inhibitors. Treatment with cyclooxygenase-inhibitors may potentially counteract the efficacy of ACE-inhibitors. This effect must be taken into consideration in the management of patients with congestive heart failure. Patients with heart failure treated with an ACE-inhibitor should be informed to avoid NSAIDs and only use them under strict supervision.

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References


