Effects of Long-term Treatment with Indomethacin on Renal Function

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SUMMARY The prolonged effects (42 days) of indomethacin treatment on the renin-angiotensin-aldosterone axis, renal hemodynamics, and renal excretory function in humans were studied. Indomethacin produced a 41% sustained depression in the 24-hour excretion of prostaglandin E_2 and a mild (7%) decrease in inulin clearance but did not affect the clearance of p-aminohippurate, the 24-hour excretion of sodium and potassium, or the basal values of plasma aldosterone; however, it decreased the basal values of renin and prevented the stimulated (3 hours of walking) responses of plasma renin activity and plasma aldosterone. Indomethacin also produced a decrease in both the diuretic and saluretic response to furosemide and in the renal ability to concentrate urine. The indomethacin-induced hyporeninism and hypoaldosteronism were more pronounced when the subjects were receiving a sodium-restricted diet. This finding indicates that prolonged administration of anti-inflammatory drugs induces chronic hyporeninism and hypoaldosteronism. Prolonged treatment with indomethacin also produced some of the symptoms of a syndrome of hypoprostaglandinism, such as decreased plasma renin activity, plasma aldosterone, and urinary prostaglandin E_2 in association with increases in plasma potassium levels and diastolic pressure. (Hypertension 8: 677–684, 1986)

KEY WORDS: renin • aldosterone • prostaglandin E_2 • furosemide • degenerative joint disease • low sodium diet

RENAL prostaglandins play an important role in mediating the release of renin and in regulating renal function, as estimated through changes in renal blood flow, glomerular filtration rate, and renal handling of sodium and water. Evidence also indicates that prostaglandins have a renal protective effect, especially in situations characterized by a decrease of renal perfusion. Under normal conditions, however, blockade of prostaglandin synthesis in association with the short-term administration of nonsteroidal anti-inflammatory drugs decreases renin release without inducing a marked impairment in renal function. To our knowledge, no study has fully evaluated the effects of long-term administration of anti-inflammatory drugs on the renin-angiotensin-aldosterone axis and on renal function. For these reasons, this study was undertaken to determine the effect of a 6-week treatment with indomethacin in subjects with normal renal function who were suffering from chronic degenerative joint disease.

Subjects and Methods

The study was conducted in 10 normotensive subjects (2 men, 8 women; age range, 43–59 years). At the time of admission, renal function was determined to be normal by a complete clinical workup. These subjects were selected for treatment with nonsteroidal anti-inflammatory drugs because of chronic degenerative joint diseases. Consent forms were obtained from each subject. The subjects were hospitalized and underwent a 6-day series of tests (Figure 1).

These tests involved measurement, on Day 2, of plasma renin activity (PRA) and plasma aldosterone (PA) while the subjects were in the supine position and
after 3 hours of walking; the subjects were receiving a normal sodium diet (110–210 mEq/day). The same determinations were repeated on Day 3, except that furosemide (80 mg orally) was given immediately before subjects assumed the upright position. Furosemide was given to stimulate the release of both renin and prostaglandin and to induce sodium depletion. During the 3 hours of walking that followed the administration of furosemide, all voided urine was collected and total fluid losses were estimated by recording body weight before and after the test. Thereafter, the subjects were kept on a low sodium diet (20–30 mEq/day) for 3 days (Days 3–5). On the morning of Day 6, PRA and PA again were measured while the subjects were in the supine position and after 3 hours of walking.

Clearances of inulin (C\textsubscript{in}) and p-aminohippurate (C\textsubscript{PAH}) were measured while the subjects received a normal sodium diet (Day 2) and after 3 days of sodium restriction (Day 6). In addition, 24-hour urine collections were obtained during a normal sodium diet (Day 1) and on the third day after sodium restriction (Day 5). On Day 2, the subjects underwent 12-hour water deprivation tests to determine the ability of the kidney to increase urine osmolality.

After completion of the 6-day protocol, the subjects were dismissed for the next 42 days, during which time they were treated with indomethacin and consumed a diet containing normal amounts of sodium. Indomethacin was given orally in doses of 150 mg/day during the first week and 75 mg/day during the subsequent 5 weeks. During this time, adherence to treatment was ensured by contacting the subjects twice a week and checking for the appearance of side effects. On the fifth day of treatment with indomethacin, urine was collected for 24 hours to determine the concentration of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}). At the end of the 42-day treatment, the subjects were again hospitalized and underwent a 6-day protocol that was identical to the pretreatment protocol. During this second 6-day protocol, the early-morning doses of indomethacin were given after the completion of any functional or provocative test to ensure that the observed changes in any of the factors being measured were produced by the chronic effects of the drug rather than induced by a single dose given immediately before the test.

The C\textsubscript{in} and C\textsubscript{PAH} were measured as previously described. The PRA was estimated with the method of Haber et al. as modified by Epstein et al. The PA was measured according to the method of Sancho and Haber. Urinary PGE\textsubscript{2} was measured by a method.

Figure 1. Experimental protocol. Responses of renin-angiotensin-aldosterone system were determined after overnight rest (basal levels) and during two progressive stages of stimulation: on Day 2 after 3 hours of walking (first stage) and on Day 3 after 3 hours of walking subsequent to administration of furosemide and on Day 6 (4 days after initiation of low sodium diet) after 3 hours of walking (second stage). Clearances of inulin (C\textsubscript{in}) and p-aminohippurate (C\textsubscript{PAH}) were determined on Day 2 while subjects were receiving a normal sodium diet and on Day 6 (4 days after initiation of low sodium diet). Changes in renal excretion of electrolytes were determined from 24-hour urine collections while subjects received a normal sodium diet (Day 1) and on the third day of low sodium diet (Day 5) and from urine collection after 3 hours of walking subsequent to administration of furosemide (Day 3). Changes in concentrating ability of kidneys were partially evaluated from urine collected during 12 hours of water and fluid restriction (Day 2). All tests were repeated after 42 days of indomethacin treatment.
similar to that reported in previous studies. Statistical tests were done using the paired Student's t test or the Wilcoxon test for unpaired data.

**Results**

Changes in PRA and PA are shown in Figure 2. Before indomethacin administration, the average basal PRA while the subjects were receiving a normal sodium diet was significantly increased from 1.7 ± 0.4 to 5.0 ± 1.0 ng of angiotensin I/ml/hr after 3 hours of ambulation (p<0.01). This increase was accompanied by a similar change in the average level of PA (from 1.7 ± 0.3 to 7.7 ± 1.8 ng/dl after walking, p<0.01).

As expected, the average basal levels of both PRA (1.4 ± 0.2 ng angiotensin I/ml/hr) and PA (2.3 ± 0.4 ng/dl) recorded on the third day while the subjects were in the overnight recumbent position and had a normal intake of sodium were not statistically different from those recorded on the previous day under similar experimental conditions. However, the increases in both PRA (to 11.7 ± 2.0 ng angiotensin I/ml/hr, p<0.01) and PA (to 15.7 ± 5.4 ng/dl, p<0.01) after the administration of furosemide and 3 hours of ambulation were approximately 2.8 times greater than the increase produced by ambulation alone. The basal levels of both PRA and PA were also increased significantly (p<0.01) when measured with the subjects in the recumbent position after 3 days of dietary sodium restriction. These values were also significantly increased after 3 hours of ambulation: PRA increased from 4.9 ± 1.0 to 12.8 ± 1.7 ng angiotensin I/ml/hr, and PA increased from 5.8 ± 1.2 to 20.6 ± 3.6 ng/dl (p<0.01).

As shown in Figure 2, the effects on PRA and PA of ambulation alone or in combination with either furosemide or sodium restriction were significantly curtailed when these maneuvers were repeated under identical experimental conditions 42 days after the daily administration of indomethacin. In fact, indomethacin completely prevented the increments in PRA (from 1.0 ± 0.2 to 1.5 ± 0.3 ng angiotensin I/ml/hr, p>0.5) and PA (from 1.2 ± 0.2 to 3.4 ± 1.0 ng/dl, p>0.5) after ambulation while the intake of sodium was normal. Prolonged treatment with indomethacin failed to prevent completely the increase in PRA (from 0.9 ± 0.2 to 4.4 ± 0.8 ng angiotensin I/ml/hr, p<0.05) and PA (from 1.1 ± 0.1 to 5.7 ± 1.2 ng/dl, p<0.05) imposed by a stronger degree of stimulation (the combination of furosemide and 3 hours of ambulation). However, this level of increase was significantly lower (p<0.01) than those obtained before treatment with indomethacin.

Finally, the ability of prolonged treatment with indomethacin to blunt stimulation of the renin-angiotensin system during sodium restriction was reflected in lower basal levels of PRA and PA when compared with the pretreatment values. After 3 days of sodium deprivation, the values measured in the overnight recumbent position decreased after indomethacin therapy: PRA decreased to 2.0 ± 0.4 from 4.9 ± 1.0 ng angiotensin I/ml/hr (p<0.05) and PA to 1.8 ± 0.3 from 5.8 ± 1.2 ng/dl (p<0.05). Indomethacin also blunted these values after 3 hours of walking: PRA decreased to 5.9 ± 1.1 from 12.8 ± 1.7 ng angiotensin I/ml/hr (p<0.01) and PA to 8.4 ± 1.0 from 20.6 ± 3.6 ng/dl (p<0.01).

Changes in urinary PGE₂ are depicted in Figure 3. The average total excretion of PGE₂ determined from the 24-hour collections of urine during the first day while the subjects were receiving a normal sodium intake was 32.5 ± 6.1 ng; however, significantly higher (p < 0.01) excretions of PGE₂ were measured on the third day during the 3 hours after the administration of furosemide while the subjects walked (126.3 ± 19.7 ng) and during the 24-hour urine collections on the fifth day after 2 days of sodium restriction (78.8 ± 13.1 ng).

Prolonged administration of indomethacin produced a significant decrease (p<0.01) in the 24-hour urinary
Total excretion (ng PGE2)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total Excretion (ng PGE2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>120 ± 30</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>24 hr urine: 120, 24 hr urine after 48 hr: 20, 3 hr urine: 0</td>
</tr>
</tbody>
</table>

**Figure 3.** Changes in prostaglandin E2 (PGE2) concentration determined from 24-hour urine collections while subjects received normal or low sodium diet and from 3-hour collections after administration of furosemide before and 5 and 42 days after administration of indomethacin (indo).

Excretion of PGE2 to 8.1 ± 0.7 ng on the fifth day and 13.4 ± 1.6 ng on the 42nd day of treatment while the subjects received a normal intake of sodium. Indomethacin also blunted the increase in urinary PGE2 measured after the administration of furosemide and 3 hours of ambulation (27.4 ± 3.6 ng), and it prevented the increase of PGE2 secretion measured in 24-hour urine collections on the 45th day of treatment (after 3 days of sodium restriction; 10.1 ± 0.6 ng).

The average values of CPAH (404 ± 25 ml/min), volume of urine (1167 ± 85 ml/24 hr), and urinary excretion of sodium (159 ± 10 mEq/24 hr) and potassium (65 ± 5 mEq/24 hr) recorded while the subjects had a normal sodium intake during the second day of the control period were not significantly different from those obtained under similar experimental conditions on the 42nd day of treatment with indomethacin (CPAH, 390 ± 20 ml/min; urine volume, 1340 ± 185 ml/24 hr; urinary sodium excretion, 146 ± 17 mEq/24 hr; urinary potassium excretion, 78 ± 7 mEq/24 hr). Indomethacin, however, produced a mild but significant decrease in CPAH (from 80 ± 4 to 74 ± 3 ml/min; p < 0.02).

The average values for CPAH (363 ± 20 ml/min) and volume of urine (915 ± 135 ml/24 hr) recorded while the subjects had a low sodium intake were not significantly different from the values of CPAH (358 ± 17 ml/min) or volume of urine (1040 ± 70 ml/24 hr) recorded under similar dietary restrictions after treatment with indomethacin. However, indomethacin treatment interfered with the ability of the kidneys to maintain glomerular filtration while the subjects suggested a low sodium diet because CPAH was significantly decreased by indomethacin (from 70 ± 4 to 65 ± 3 ml/min; p < 0.02). Prolonged treatment with indomethacin also resulted in a greater urinary excretion of sodium (from 24 ± 2 to 35 ± 3 mEq/24 hr) and potassium (from 38 ± 2 to 46 ± 2 mEq/24 hr) during sodium restriction.

Prolonged treatment with indomethacin also produced a marked impairment of the diuretic response to furosemide, which was reflected in significantly decreased values for the volume of urine, urinary excretion of sodium and potassium, and weight loss compared with those recorded during the 3 hours under similar circumstances before treatment with indomethacin.

Indomethacin therapy significantly decreased the ability of the kidneys to produce concentrated urine; the total osmolality of the urine recorded during the 12 hours of water deprivation in the control phase was significantly higher than that recorded under similar conditions after treatment with indomethacin (932 ± 31.4 vs 721 ± 58.3 mosm/kg, p < 0.02).

Table 1 depicts the average changes in the plasma levels of sodium and potassium in the blood samples drawn in the recumbent position while the subjects received a normal intake of sodium (Day 2; see Figure 1) and after 3 days of sodium restriction (Day 6; see Figure 1) before and 42 days after treatment with indomethacin. The administration of indomethacin failed to induce any significant alteration in the plasma levels of sodium regardless of the nature of the diet; however, prolonged treatment with indomethacin did induce...
mild but significant ($p < 0.05$) increases in plasma potassium levels while the subjects received either a normal or a low sodium diet. Table 1 also shows that treatment with indomethacin induced a mild but significant ($p < 0.005$) increase in diastolic blood pressure.

**Discussion**

The effect of short-term treatment with indomethacin on the renin-angiotensin-aldosterone system, renal hemodynamics, and renal excretory function has been well documented. Recently, several reviews have been published on this issue. However, it is not known if these acute indomethacin-induced alterations are persistent, or if they recover totally or partially when treatment with indomethacin is maintained for longer than 1 week. This study was facilitated by the existence of a patient population with mild degrees of degenerative joint disease, which are known to have no other systemic repercussions and for which the long-term administration of indomethacin constitutes one of the elective treatments. Since the early manifestations of this disease frequently occur after the fourth decade, the ages of our population were limited (range, 43–59 years). Reports in the literature indicate the existence of a progressive derangement both in the renin-angiotensin-aldosterone system and in renal function, and with increasing age. Hence, caution should be exercised in extrapolating our findings to younger persons.

Indomethacin is capable of inhibiting various enzyme systems, of which prostaglandin synthesis is the best characterized. Because prostaglandins are known to influence renin release, renal hemodynamics, and renal excretory function, many of the observed effects could best be explained by assuming that the inhibition of prostaglandin synthesis was the initial event to influence other interdependent mechanisms. Such an assumption constitutes the major frame of reference for the following discussion.

The kidney is capable of synthesizing all primary prostaglandins, although their relative amounts vary within different subanatomical renal structures. An overall increase in the renal synthesis of prostaglandins is likely to be reflected by more of an increase in urinary PGE$_2$ than of any other prostaglandin. For these reasons, determinations of PGE$_2$ in the urine were considered the most reliable index of such a function. The results of our study were lower than those from studies in which the values of radioimmunoassay compared favorably with those of gas chromatography–mass spectrometry. These differences can be attributed to the fact that most of our subjects were women.

Convincing experimental evidence shows that the indomethacin-induced suppression of renin is mediated by prostaglandins. Thus, in our study, the observed suppressive effects of indomethacin on PRA could be regarded as reflecting a decrease of renin output from the kidney produced by a decrease in prostaglandin synthesis.

The notion of an interdependency between renin and prostaglandins is supported by the parallel directional changes observed in the level of both substances during the different experimental maneuvers. Thus, during the control period, urinary PGE$_2$ and PRA were significantly elevated after the administration of furosemide and after 48 to 72 hours of sodium restriction. Indomethacin blunted this furosemide-induced increment in both PGE$_2$ and PRA without completely preventing the increased responses of both hormones.

Our study shows that the observed changes in PRA during different stimulatory maneuvers were paralleled by similar directional changes in the levels of PA. This finding is not surprising because rapid changes in the secretion of aldosterone under most circumstances are controlled by circulating levels of angiotensin II. Indomethacin has been reported to directly inhibit the angiotensin II–induced release of aldosterone in the adrenal gland. Although such an effect cannot be ruled out on the basis of our data, it should not be an important one because a higher degree of dissociation between the levels of PRA and PA would have been observed.

The results of this study are in agreement with data showing that acute blockade of prostaglandin synthesis results in no significant renal hemodynamic alterations and in slight changes in glomerular filtration rate in normal, well-hydrated experimental animals or humans. However, our studies do not support the contention of experiments in which short-term treatment with indomethacin produced a higher significant alteration in renal hemodynamics in subjects who had previously submitted to sodium restriction. Nevertheless, the effects of long-term treatment on renal hemodynamics resemble those found in studies of short-term treatment in that anti-inflammatory drugs seem to have more effect on glomerular filtration rate than on renal blood flow.

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**Table 1. Changes in Plasma Levels of Sodium and Potassium and in Blood Pressure Before and After Treatment with Indomethacin**

<table>
<thead>
<tr>
<th>Time of measurement</th>
<th>Plasma Na (mEq/L)</th>
<th>Plasma K (mEq/L)</th>
<th>Blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal Na diet</td>
<td>Low Na diet</td>
<td>Normal Na diet</td>
</tr>
<tr>
<td>Before indomethacin</td>
<td>140 ± 1.9</td>
<td>140 ± 2.3</td>
<td>4.16 ± 0.23</td>
</tr>
<tr>
<td>After indomethacin</td>
<td>140 ± 2.9</td>
<td>140 ± 2.7</td>
<td>4.33 ± 0.21*</td>
</tr>
</tbody>
</table>

Values are means ± SE.

* $p < 0.05$, † $p < 0.005$, compared with pretreatment values.
The different effects exerted by anti-inflammatory drugs on renal hemodynamics after short-term and long-term treatment may be partly explained by the studies of Vallotton et al.,21 who reported significant qualitative differences in the effect of indomethacin on renal function, depending on whether anti-inflammatory drugs were administered simultaneously or after the production of a negative sodium balance.

In our study, prolonged administration of indomethacin did not alter the pattern of urinary volume or the excretion of sodium and potassium during a normal intake of sodium. During sodium restriction, however, prolonged treatment with indomethacin seems to have decreased the ability of the kidney to conserve sodium and potassium. The absence of balance studies does not allow for a firm conclusion regarding this issue.

Our study shows, however, that indomethacin impaired the concentrating ability of the kidney. This effect is difficult to interpret in light of the reported effects of arachidonic acid metabolites on factors that are known to participate in the regulation of water excretion. In fact, Stokes8 suggested that the net result of a decrease in renal prostaglandin synthesis is the production of concentrated urine, an effect opposite to that found in our study. Recently, evidence has been provided to suggest that PGE, mediates the release of antidiuretic hormone in the central nervous system.46 A decrease of prostaglandin synthesis at this site could have resulted in a deficient release of antidiuretic hormone and thereby a decrease in the ability of water concentration during treatment with indomethacin. Such a possibility cannot be assessed in our study.

It would be relevant to mention that one of the most prominent and constant alterations seen during analgesic-induced nephropathy is a defect in urine-concentrating ability.47-50 The dosage used in our study was much less than that of nonsteroidal anti-inflammatory drugs reported to produce nephrotoxicity.50 However, it is conceivable that at therapeutic levels indomethacin could induce renomedullary alterations similar to those seen with other nonsteroidal anti-inflammatory compounds,51 which may account for the deficit in urine-concentrating ability.

The administration of furosemide results in marked renal vasodilatation,52, 53 which is accompanied by a significant increase in the excretion of sodium and water and in urinary prostaglandins.35, 54 Also, anti-inflammatory drugs block furosemide-induced renal vasodilatation and reduce the natriuretic effect of furosemide.13, 21, 52, 53, 55-62 In our study, the inhibition of the action of furosemide induced by short-term administration of indomethacin persisted when the treatment was extended to 42 days. Furthermore, the interfering effects of indomethacin on the natriuretic responses to furosemide were reflected in a decreased weight loss during the 3 hours following administration of furosemide.

Finally, recent reports indicating that a deficient synthesis of prostaglandins could lead to the production of hypertension and type IV renal tubular acidosis have raised questions about whether the syndrome could be reproduced by prolonged treatment with anti-inflammatory drugs provided that they are capable of producing a sustained decrease in the synthesis of prostaglandins. Such an observation reinforces previous studies in which a similar syndrome was observed in patients receiving indomethacin.64-65 Prolonged treatment with indomethacin reproduced some of the characteristics of the hypoprostaglandinism syndrome, such as decreased elimination of urinary PGE, and a tendency to sodium and potassium retention associated with hyporeninism and hypoadosteronism. Furthermore, a tendency to hyperkalemia was also observed in addition to a mild but significant increase in diastolic blood pressure. No contributory comments can be made about changes in the renal handling of chloride or the existence of tubular acidosis because they were not appropriately assessed in our study. This issue has important clinical implications because the mild characteristics of the syndrome of hyporeninism and hypoadosteronism produced by indomethacin in patients with normal renal function can be greatly amplified in the presence of renal insufficiency.

In summary, to our knowledge this study is the first to establish that prolonged treatment with indomethacin does not affect basal renal hemodynamics, renal excretory function, or basal levels of PRA or PA. However, such treatment significantly impairs the adaptive responses of both renal excretory function and the renin-angiotensin-aldosterone axis to sodium restriction and the responses to furosemide and the ability to concentrate urine. In addition, a mild tendency toward hyperkalemia and hypertension was observed. However, more studies will be necessary to assess fully the significance of these changes.

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