Influence of indomethacin on extracellular calcium homeostasis

J W J Bijlsma, A J Rabelink

Abstract
Rheumatoid arthritis is associated with a generalised loss of bone mass. One of the factors that have been implicated in the pathogenesis of this bone loss is the chronic use of non-steroidal anti-inflammatory drugs (NSAIDs). These drugs are known to increase gastrointestinal permeability and may thus influence the absorption of calcium; they may also influence glomerular filtration rate and the renal excretion of calcium; in addition, NSAIDs may inhibit osteoblast function as well as osteoclastic bone resorption.

Calcium homeostasis was studied in eight healthy volunteers during eight days' treatment with 150 mg indomethacin daily. No changes in serum concentration of calcium, phosphorus, parathyroid hormone, 25-hydroxyvitamin D₃, and 1,25-dihydroxyvitamin D₃ were found. The creatinine clearance and the urinary excretion of phosphorus and sodium did not change, but a decrease in calcium excretion was noted (mean (SEM) calcium/creatinine excretion 0.52 (0.05) v 0.28 (0.06)). This decrease is probably due to renal retention of calcium. Whether this decrease of urinary calcium excretion has a positive or a negative effect on bone is presently unknown.

In patients with rheumatoid arthritis (RA) a generalised disturbance of bone metabolism has been described, leading ultimately to a loss of bone mass. Bone tissue has both a mechanical and a metabolic role, but, when necessary, bone may be depleted of mineral in order to maintain calcium homeostasis. Extracellular calcium homeostasis is regulated by the absorption of calcium from the gut, the excretion of calcium by the kidneys, and the transport of calcium from bone into plasma.

In identifying risk factors for bone loss in patients with RA reduced mobility was found to be a potent factor that diminished bone mass. Other factors have been implicated as well, such as the use of glucocorticosteroids and of non-steroidal anti-inflammatory drugs (NSAIDs). We investigated whether indomethacin had any influence on extracellular calcium homeostasis in healthy volunteers, and we found a decrease in renal excretion of calcium during indomethacin treatment.

Patients and methods
After extensive explanation and with approval of the ethical committee of our hospital eight male medical students agreed to take part in the study. All were healthy, none had evidence of kidney dysfunction, hypertension, or gastrointestinal problems, none was taking any drugs. Mean age was 23 years (range 22–25). They were supplied with a diet with a fixed amount of calcium (30 mmol/day) and sodium (200 mmol/day), which remained unchanged during the whole study period.

On days 3 and 4 they were asked to pass ‘fasting urine’—that is, they passed urine at 8.30 am, while in a fasting state, then drank 500 ml water, and their urine was collected during the following two hours. Blood samples were taken at 9.30 am. On day 5 the subjects started to take indomethacin 50 mg three times a day for eight days. On the last two days of this period sampling of blood and urine was repeated as in the control period. The following determinations were performed: (a) calcium in blood and urine by atomic absorption; the serum calcium concentration was corrected for the serum protein concentration (calcium corrected = calcium measured – (0.025 × serum albumin g/l) + 1 mmol/l); (b) creatinine, inorganic phosphorus, and sodium in blood and urine by Technicon's AutoAnalyzer; (c) parathyroid hormone in serum by a two step radioimmunoassay that recognises the intact 1–84 parathyroid hormone molecule; (d) 25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ by competitive protein binding assays.

The excretion of calcium, phosphorus, and sodium in the urine was corrected for the creatinine excretion.

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Influence of indomethacin on indices of calcium homeostasis and kidney function. Values are given as means (SEM)

<table>
<thead>
<tr>
<th>Index</th>
<th>Before*</th>
<th>During*</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.40 (0.02)</td>
<td>2.40 (0.03)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum phosphorus (mmol/l)</td>
<td>1.08 (0.05)</td>
<td>1.25 (0.06)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum parathyroid hormone (pmol/l)</td>
<td>4.58 (0.85)</td>
<td>5.58 (1.28)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D₃ (ng/l)</td>
<td>43.5 (11.8)</td>
<td>41.9 (14.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum 1,25-dihydroxyvitamin D₃ (ng/l)</td>
<td>40.0 (6.1)</td>
<td>34.6 (13.4)</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (m/dl)</td>
<td>119.8 (4.7)</td>
<td>111.6 (6.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary calcium excretion</td>
<td>0.52 (0.05)</td>
<td>0.28 (0.06)</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary phosphorus/creatinine excretion</td>
<td>0.92 (0.28)</td>
<td>1.00 (0.18)</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium/creatinine excretion</td>
<td>13.2 (1.6)</td>
<td>14.7 (1.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Before the use of indomethacin and during the use of 150 mg indomethacin daily.
The mean values for the two prestudy days were compared with the mean values for the two days during indomethacin use. The results were analysed with a two tailed t test for paired observations.

Results
All subjects completed the study uneventfully. The table shows the results of the different variables. No changes were found in the mean serum concentration of calcium, inorganic phosphorus, parathyroid hormone, 25-hydroxyvitamin D₃, and 1,25-dihydroxyvitamin D₃. After eight days' use of indomethacin creatinine clearance was unchanged, as were the sodium and phosphorus excretion in the urine. Excretion of calcium by the kidneys, however, decreased significantly, from 0·52 (90% confidence interval 0·42 to 0·61) to 0·28 (90% confidence interval 0·13 to 0·42). The figure shows individual data.

Discussion
Generalised loss of bone in patients with RA has been associated with the long term use of NSAIDs; the following observations may be relevant.

NSAIDs and the Gut
The pharmacological effects of NSAIDs depend on the inhibition of cyclooxygenase, and thus on the formation of prostaglandins, of which prostaglandin E₂ is a major factor in the gastrointestinal mucosal defence. During the use of NSAIDs intestinal permeability, as measured by urinary excretion of polyethylene glycols or radiolabelled chrome given orally, increases.6 7 Oral supplementation with small doses of prostaglandin E₂ restores this increased permeability.

It is presently not known whether this change in gastrointestinal permeability facilitates calcium absorption or actually hinders it. Hindrance has been shown to occur during the use of glucocorticosteroids, which also inhibit prostaglandin E₂ production.8 One study in patients with RA of recent onset, all using NSAIDs and none using corticosteroids, suggested a primary reduction of gastrointestinal calcium absorption.9

NSAIDs and the Kidneys
Renal prostaglandin suppression results in maximal urinary concentration and consequent reduction of free water excretion and glomerular filtration rate. Indomethacin enhances sodium reabsorption by a direct tubular effect in the distal nephron, presumably located in the thick ascending limb of Henle's loop.10 This may stimulate voltage dependent renal calcium reabsorption.11

Previously we noted that indomethacin caused initially a marked sodium as well as calcium retention, but that at the sixth day, when renin and aldosterone were suppressed, sodium escaped completely but calcium did not.12 13 Thus the generally observed close relation between renal handling of sodium and calcium may be dissociated in the distal tubule.

NSAIDs and the Bone
Indomethacin, aspirin, and possibly other NSAIDs may have an inhibitory effect on osteoblast function. These drugs inhibit the secretory activity of human osteoblasts in culture and decrease the uptake of radiolabelled thymidine by osteoblasts in a dose dependent fashion, even at therapeutic concentrations.14 Prostaglandins and especially prostaglandin E₂ may stimulate osteoblasts; it was recently shown that indomethacin and other NSAIDs inhibit the osteoclastic mediated bone resorption.15 Thus indomethacin suppresses bone cell activity.

Interpretation of Results
We have to consider these possible influences of NSAIDs on calcium and bone metabolism in interpreting the results of our study. The serum concentration of calcium, and to a lesser extent of phosphorus, are tightly regulated by calcitropic hormones. No changes in serum concentrations of calcium, phosphorus, nor of the calcium regulating hormones, parathyroid hormone and 1,25-dihydroxyvitamin D₃, are noted, indicating that a new balance of calcium regulation is already set after one week of treatment with indomethacin. As has been reported previously no decrease in creatinine clearance or urinary sodium excretion was found after one week's treatment with indomethacin. The urinary calcium excretion was significantly decreased, however. This decrease in calcium excretion may theoretically be due to: (a) a decrease in calcium absorption by the gut; (b) a decrease in renal calcium excretion; (c) an increase of calcium uptake by bone.

Decreased Calcium Absorption
A decreased calcium absorption from the gut is quite possible, as explained above. In this study we measured calcium excretion in the fasting
Influence of indomethacin on extracellular gastrointestinal calcium absorption

by this method is not dependent on gastrointestinal calcium absorption as the patients are fasting overnight. If this holds true in this particular condition the decrease in urinary calcium excretion cannot reflect a decrease in gastrointestinal calcium absorption.

Decreased renal excretion of calcium

The effects of indomethacin on renal tubular electrolyte transport are probably located in the distal nephron. It has been shown that after treatment for one week with indomethacin sodium escapes from indomethacin induced retention to the distal nephron. We suggest that this bypassing mechanism is not effective for calcium, and that in this situation the handling of calcium in the distal tubule is dissociated from the handling of sodium.

Increase of calcium uptake by bone

All the present evidence about the effect of indomethacin on bone cells points to a suppression of bone cell activity. This suppression would probably lead to less instead of more calcium uptake by bone cells. It is unlikely that the decreased calcium excretion in the urine reflects an increased uptake of calcium by the bone.

In conclusion, the most likely explanation for the decreased urinary excretion of calcium during the use of indomethacin is a renal retention of calcium. Whether this retention of calcium has a positive or a negative influence on bone homeostasis is presently unclear. It has been noted that in patients with non-steroid treated RA bone mineral mass is decreased. The role of NSAIDs in the pathogenesis of this osteopenia is not well reported. Attention should be given to the influence of NSAIDs on calcium homeostasis via the gut and the kidneys and to the effect of NSAIDs on bone cells. This study suggests that indomethacin, a potent NSAID, may have a profound influence on the renal handling of calcium.

It should be stressed, however, that our study relates to normal young volunteers during a relatively short period. It is possible that in older subjects or in patients with multisystem rheumatoid disease, who are using NSAIDs for a prolonged period, different results may be found.

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