Effect of misoprostol on concentrations of prostaglandins in synovial fluid

A Doube, J Davies, L Notarianni, K Holgate, G C Fenn

Abstract
The effect of misoprostol, a synthetic analogue of prostaglandin E, on prostaglandin concentrations in synovial fluids was investigated in a randomised placebo controlled, double blind study. The synovial fluid concentrations of prostaglandin E₁, 6-keto-prostaglandin F₁₅, and thromboxane B₂ were measured at the beginning and end of a 24 hour period in 25 patients with effusions of the knee joint. During this period the patients were treated with diclofenac (50 mg every eight hours) and either misoprostol (400 μg) or placebo every 12 hours. The concentrations of prostaglandin E and 6-keto-prostaglandin F₁₅ were not significantly altered during treatment. There was an unexpected significant reduction in thromboxane B₂ concentrations in the group treated with misoprostol (within group analysis). Although the mean concentration with misoprostol was about half the mean concentration with placebo, this difference was not statistically significant in the between group analysis. These results indicate that misoprostol is unlikely to exert a proinflammatory effect or to interfere with the prostaglandin mediated effects of non-steroidal anti-inflammatory drugs. The significant decrease in thromboxane B₂ concentrations in the misoprostol treated group suggests that misoprostol may exert an anti-inflammatory effect.

The management of upper gastrointestinal lesions induced by non-steroidal anti-inflammatory drugs (NSAIDs) is difficult in patients with a clinical need for continued anti-inflammatory treatment. Non-steroidal anti-inflammatory drugs interfere with a number of important cytoprotective mechanisms by inhibiting the synthesis of prostaglandin in the gastric mucosa. Misoprostol, a synthetic analogue of prostaglandin E₁, prevents gastric mucosal damage by enhancing prostaglandin dependent cytoprotective mechanisms, resulting in increased blood flow in gastric mucosa, the production of mucus,¹ and also the secretion of duodenal bicarbonate.² It also reduces the secretion of gastric acid.¹ Misoprostol has been shown to be significantly more effective than a placebo in preventing gastric ulcers² and in healing gastric and duodenal damage,⁴ even when NSAID treatment is continued.

In theory, an exogenous source of prostaglandin might increase the endogenous prostaglandin concentrations in joint tissues, resulting in a proinflammatory effect and clinical deterioration in patients with inflammatory joint disease. Although earlier studies have not indicated any deleterious clinical effect,⁴ we examined the possible biochemical effect of misoprostol on the synovial fluid concentrations of the prostaglandin E series, 6-keto-prostaglandin F₁₅, and thromboxane B₂ in patients with effusions of the knee joint.

Patients and methods
Patients with rheumatoid arthritis, seronegative polyarthritis or osteoarthritis and with clinical evidence of a knee effusion were eligible for inclusion in the study. Patients were excluded if they had taken salicylates or a slow release preparation of an NSAID within the previous two weeks.

After an initial drug washout period of at least three days, during which paracetamol was provided for the relief of pain, the patients were randomly allocated to treatment with either misoprostol or a placebo. The two groups received diclofenac (50 mg) at time 0, 8 and 16 hours, with either misoprostol (400 μg) at time 0 and 12 hours, or matching placebo. The study was double blind in design with all preparations given by mouth.

The presence or absence of clinical signs of inflammation (warmth, tenderness, synovial thickening) was recorded for both knees at the beginning and end of the study period.

At time 0 and 24 hours synovial fluid was aspirated from the same knee without the use of local anaesthesia. Between two and four millilitres, of the synovial fluid was immediately mixed with 0-05 ml of 0-2% indomethacin in a glass tube, then frozen and stored at −20°C until required. The prostaglandin E series was measured by assaying the stable metabolite 11-deoxy-13,14-dihydro-15-keto-11,16-cycloprostaglandin E₂ and the analogous E₁ metabolite, prostacyclin was assayed as 6-keto-prostaglandin F₁₅, and thromboxane as thromboxane B₂ using radioimmunoassay kits supplied by Amersham (TRK 800, RPA 515 and RPA 516, respectively) with the methods described in the accompanying data sheets. All the assay procedures were validated before this study. Synovial fluid samples were assayed in five batches, the two samples from a given patient being assayed in the same batch.

STATISTICAL METHODS
Owing to the distributional form of the results of the prostaglandin assay, analyses were performed on the logarithms of the data. The treatments were compared by the analysis of
Comparison of pretreatment and post-treatment prostaglandin concentrations, expressed as the geometric mean, in the misoprostol and placebo groups. The only comparison to reach statistical significance is the reduction in thromboxane B<sub>2</sub> in the misoprostol group (p=0.009)

<table>
<thead>
<tr>
<th>Prostaglandin</th>
<th>Time (hours)</th>
<th>Concentration of prostaglandin (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Misoprostol group</td>
</tr>
<tr>
<td>Prostaglandin E</td>
<td>0</td>
<td>7.6</td>
</tr>
<tr>
<td>6-Keto-prostaglandin F&lt;sub&gt;1α&lt;/sub&gt;</td>
<td>24</td>
<td>8.6</td>
</tr>
<tr>
<td>Thromboxane B&lt;sub&gt;2&lt;/sub&gt;</td>
<td>0</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>81</td>
</tr>
</tbody>
</table>

covariance on the post-treatment results with the pretreatment results as covariate. The significance tests for the treatment comparison were two sided with a 5% level of statistical significance.

Results
Twenty eight patients were enrolled into the study, with three patients subsequently being excluded. In two patients synovial fluid was not obtained at the initial knee aspiration and one patient was unable to tolerate the initial washout period. The results from 25 patients were eligible for analysis. The placebo (n=12) and misoprostol (n=13) groups were well matched with five women in the placebo group compared with eight women in the misoprostol group. The mean age in the placebo group was 64 years (range 32–87) compared with 65 years (range 52–75) in the misoprostol group. In the placebo group five patients had rheumatoid arthritis, four had osteoarthritis, and three had seronegative polyarthritis; the respective numbers in the misoprostol group were six, six, and one. The signs of inflammation—that is, warmth, tenderness, and synovial thickening, were similar in both groups.

The concentrations of the three prostaglandins measured, expressed as the geometric means, were not statistically different in the misoprostol and placebo groups. Concentrations of prostaglandin E<sub>2</sub> and 6-keto-prostaglandin F<sub>1α</sub> did not alter significantly with treatment. The table shows that only the reduction of thromboxane B<sub>2</sub> concentrations in the misoprostol group (256 pg/ml reducing to 81 pg/ml) reached significance (p=0.009) in the within group analysis.

Discussion
The use of non-steroidal anti-inflammatory drugs is associated with a high occurrence of upper gastrointestinal lesions. Peptic ulceration has been demonstrated by endoscopy in 80 of 230 unselected patients receiving regular NSAID treatment.\(^7\) In one prospective endoscopic study NSAID treatment resulted in a 50% incidence of ulceration and mucosal inflammation.\(^6\) Non-steroidal anti-inflammatory drug induced gut lesions lead to significant morbidity through dyspepsia, bleeding and perforation, and can lead to an appreciable rate of death.\(^7\) Such lesions may often be asymptomatic.\(^9\) If the withdrawal of the NSAID is impractical for a particular patient, the prevention of NSAID induced gut lesions assumes additional importance. Misoprostol, a methyl ester analogue of prostaglandin E<sub>1</sub> has been shown to ameliorate NSAID induced mucosal damage,\(^10\) but because it is structurally similar to naturally occurring prostaglandin it might theoretically enter the prostaglandin cascade, resulting in a proinflammatory effect.
Misoprostol is usually co-prescribed with an NSAID in patients with arthritis, and the study design reflected this clinical practice. A single NSAID was used to achieve more consistent results and diclofenac was chosen because it is commonly prescribed in the United Kingdom. This study was based on a previously validated design in which diclofenac reduced the concentrations of prostaglandin E<sub>2</sub> and thromboxane B<sub>2</sub> in synovial fluid after 24 hours of treatment.\(^11\) The inhibition of prostaglandin synthesis in synovial fluid is maintained for at least 12 hours after a single 75 mg oral dose of diclofenac.\(^12\)

The effect of misoprostol on synovial fluid has not previously been examined. Misoprostol has an elimination half life of less than 30 minutes so it is technically difficult to measure its concentration in synovial fluid. However, in the gastrointestinal tract the biological effects of misoprostol are persistent and do not appear to be directly related to its short half life. It was expected that if misoprostol was exerting a significant effect on prostaglandin concentrations then this would persist until the second sample of synovial fluid was taken.

No significant change was detected in the clinical variables over the 24 hour period in either treatment group. This suggests that misoprostol does not interfere with the clinically beneficial effect of diclofenac, confirming data from other longer term studies that misoprostol does not interfere with the clinical control of arthritis by NSAIDs.\(^4\)\(^13\)\(^14\)

This study also showed that misoprostol has no appreciable effect on the synovial fluid concentrations of prostaglandin E<sub>2</sub> and 6-keto-prostaglandin F<sub>1α</sub>. The lack of effect of diclofenac on prostaglandin concentrations in this study could be a result of the wide interindividual variability in the measured baseline levels, or because the study duration was too short for a significant effect to have occurred.

An unexpected finding was the significant decrease in thromboxane B<sub>2</sub> concentrations in the group treated with misoprostol. Data reported previously have raised the possibility that misoprostol may have immunomodulatory properties.\(^15\) In addition, prostaglandin E<sub>2</sub> can act as an in vivo modulator of inflammation.\(^16\) Prostaglandin E<sub>2</sub> has been shown to inhibit the induction of interleukin 1 secretion by T cell hybridomas.\(^17\)

This study shows that misoprostol does not increase the concentrations of prostaglandins in synovial fluid and a proinflammatory effect is unlikely. However, it is possible that misoprostol is capable of exerting an anti-inflammatory effect by reducing thromboxane B<sub>2</sub> concentrations. If this result is confirmed it is possible...
that the coprescription of an NSAID and misoprostol may be beneficial for both the gut and the joint.

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