A six week double blind, placebo controlled, crossover study of the effect of misoprostol in the treatment of aspirin sensitive asthma

Wojciech Wasiak, Miroslaw Szmidt

Abstract
Background—Prostaglandins of the E series and misoprostol (a stable analogue of prostaglandin E₁) prevent bronchoconstriction following aspirin ingestion or inhalation in subjects with aspirin sensitive asthma. A study was undertaken to investigate the influence of misoprostol on the course of aspirin induced asthma.

Methods—A double blind, crossover, randomised, placebo controlled study was performed in 17 patients with aspirin sensitive asthma (13 women) aged 26–68 years. All subjects had aspirin sensitivity confirmed by means of oral aspirin or inhaled lysine aspirin challenge. Misoprostol (Cytotec, Searle, 800 or 1600 µg daily according to individual tolerance) or placebo were administered over a period of six weeks. Morning and evening peak expiratory flow rate (PEFR), β₂ agonist use, asthma and rhinitis severity scores, and defaecation score were measured daily. At the beginning and end of each treatment period spirometric tests were performed and blood was taken for eosinophil count. Eight subjects took misoprostol at a dose of 800 µg and nine subjects at a dose of 1600 µg daily.

Results—No differences were seen in asthma control between misoprostol and placebo except for the rhinorrhoea score which was lower on misoprostol during the period of the study.

Conclusion—Misoprostol in a daily dose of 800 or 1600 µg does not significantly improve asthma control in subjects with aspirin sensitive asthma.

Keywords: aspirin sensitive asthma; prostaglandin E₁; misoprostol

Prostaglandins, leukotrienes, and other arachidonic acid (AA) metabolites form a group of substances essential for the pathogenesis of inflammation. Prostaglandins of the E series (PGE), products of AA derived from the cyclo-oxygenase (COX) pathway, exert many anti-inflammatory effects. They inhibit activation of neutrophils, basophils, monocytes, and mast cells and production of interleukin (IL)–1, IL–2, tumour necrosis factor (TNF)–α, and interferon (IFN)–γ. The synthesis and release of leukotrienes is also likely to be downregulated by PGE. Misoprostol, a stable analogue of PGE₁, inhibits PGE₂, which is normally present in the bronchial mucosa at concentrations some 10–50 times higher than that of other AA metabolites, might be a powerful local protective factor, preventing bronchoconstriction in response to numerous stimuli and helping to maintain homeostasis. We hypothesised that altered PGE, production might be involved in the pathogenesis of aspirin induced asthma. Inhaled PGE₂, although a weak bronchodilator, prevents bronchoconstriction following inhalation of allergen, nebulised distilled water, and sodium metabisulphite, and after physical exertion. Oral misoprostol, intravenous PGE₁, and inhaled PGE, have inhibited or completely abolished aspirin induced bronchocnstriction in aspirin sensitive asthmatic subjects in several studies.

Misoprostol can prevent and heal gastrointestinal ulcerations induced by non-steroidal anti-inflammatory drugs. It has been reported to have a similar effect to natural PGE on immunological processes. The purpose of the present study was to investigate the effect of regular administration of misoprostol on the course of aspirin sensitive asthma.

Methods
Seventeen patients (13 women) were included in the study and in all cases asthma was diagnosed according to the criteria used in the Global Initiative for Asthma Management and Prevention. Aspirin intolerance, suggested by a history of bronchospasm after aspirin ingestion, was confirmed by means of inhaled lysine aspirin or oral aspirin challenge as described below. Patients who suffered from any clinically significant pulmonary, heart, renal or liver disorder and women of childbearing potential not using adequate contraception were excluded. The baseline forced expiratory volume in one second (FEV₁) was 83 (15)% predicted and patients responded with more than a 15% increase following inhalation of 1 mg terbutaline (Bricanyl Turbuhaler, Astra, Sweden) on at least one occasion during the six months after.
The study was a double blind, placebo controlled, randomised, crossover trial. Patients were supplied with peak flow meters (Clement Clarke, UK) for the purpose of measuring peak expiratory flow (PEF) at home during the study. After a two week run-in period subjects were randomised to receive misoprostol (Cyto tec, Searle) 400 µg four times daily or matching placebo for a period of six weeks. This relatively high dose was reached by a gradual increase in the number of 200 µg tablets, from four to eight, over the first five days of each treatment period (first day: 1 + 1 + 1 + 1 tablets; second day: 2 + 1 + 1 + 1 tablets; third day: 2 + 2 + 1 + 1 tablets; fourth day: 2 + 2 + 2 + 1 tablets; fifth day and thereafter: 2 tablets q.i.d.). The dose of placebo was increased in the same manner. Patients who did not tolerate a dose of 400 µg four times daily due to gastrointestinal symptoms (increased number of daily defaecations, diarrhoea, abdominal pain producing remarkable discomfort and interfering with their normal activities) were allowed to receive the lower dose of 200 µg four times daily, which was generally well tolerated. After six weeks the subjects stopped taking the trial drug for a three week washout period. They then crossed over to the other limb of the study for another six weeks.

Each treatment period was started and finished with a clinic visit when physical examination, spirometric tests, ECG recording, and peripheral blood collection for eosinophil count were performed and blood pressure measured. During each period of the study subject data were collected on diary cards, including morning and evening PEF, consumption of rescue medication (short acting β2 agonist), and asthma severity score (dyspnoea, 0–3 points), both separately for daytime and night time, cough, expectoration, nasal congestion, rhinorrhoea (0–2 points), and defaecation scores. The clinical symptoms were scored as follows:

Night time asthma score: 0 = slept all night, no symptoms; 1 = one awakening due to...

### Table 1 Characteristics of patients in the study

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<th>Aspirin intolerance duration (years)</th>
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Mean (SD) 90.5 (11.5) 11.7 (8.4) 9.1 (7.6) 2.82 (0.73)

**Notes:**
- **ICS** = inhaled corticosteroids; **OCS** = oral corticosteroids; **NCS** = nasal corticosteroids; **STP** = sustained release theophylline preparations; **DCSG** = disodium cromoglycate; **NS** = nedocromil sodium; **KET** = ketotifen fumarate; **AST** = astemizol; **LAB** = long acting β2, mimetic.
- **Table 1** shows the characteristics of patients in the study.
- **Patient no.**
- **Sex:** male (M) or female (F)
- **Age (years):** age in years
- **Atopy:** yes or no
- **Nasal polyps:** yes or no
- **Asthma duration (years):** duration of asthma in years
- **Aspirin intolerance duration (years):** duration of aspirin intolerance in years
- **Oral aspirin threshold dose (mg):** dose of oral aspirin at which a 20% decrease in FEV1 from the post-saline placebo test was considered to be aspirin sensitive
- **Inhaled lysine aspirin threshold concentration (mg/ml):** concentration at which a 20% decrease in FEV1 from the post-saline placebo test was considered to be aspirin sensitive
- **Treatment:** combination of treatments used
- **Asthma severity grade (GINA):** severity grade based on GINA standards

### STUDY DESIGN

The study was a double blind, placebo controlled, randomised, crossover trial. Patients were supplied with peak flow meters (Clement Clarke, UK) for the purpose of measuring peak expiratory flow (PEF) at home during the study. After a two week run-in period subjects were randomised to receive misoprostol (Cyotec, Searle) 400 µg four times daily or matching placebo for a period of six weeks. This relatively high dose was reached by a gradual increase in the number of 200 µg tablets, from four to eight, over the first five days of each treatment period (first day: 1 + 1 + 1 + 1 tablets; second day: 2 + 1 + 1 + 1 tablets; third day: 2 + 2 + 1 + 1 tablets; fourth day: 2 + 2 + 1 + 1 tablets; fifth day and thereafter: 2 tablets q.i.d.). The dose of placebo was increased in the same manner. Patients who did not tolerate a dose of 400 µg four times daily due to gastrointestinal symptoms (increased number of daily defaecations, diarrhoea, abdominal pain producing remarkable discomfort and interfering with their normal activities) were allowed to receive the lower dose of 200 µg four times daily, which was generally well tolerated. After six weeks the subjects stopped taking the trial drug for a three week washout period. They then crossed over to the other limb of the study for another six weeks.

Each treatment period was started and finished with a clinic visit when physical examination, spirometric tests, ECG recording, and peripheral blood collection for eosinophil count were performed and blood pressure measured. During each period of the study subject data were collected on diary cards, including morning and evening PEF, consumption of rescue medication (short acting β2 agonist), and asthma severity score (dyspnoea, 0–3 points), both separately for daytime and night time, cough, expectoration, nasal congestion, rhinorrhoea (0–2 points), and defaecation scores. The clinical symptoms were scored as follows:

Night time asthma score: 0 = slept all night, no symptoms; 1 = one awakening due to...
dyspnoea, dyspnoea not too severe; 2 = several awakenings, didn’t sleep for more than half of the night; 3 = didn’t sleep all night, severe dyspnoea.

Daytime asthma score: 0 = no symptoms at all; 1 = mild and short lasting dyspnoea, well tolerated; 2 = moderate dyspnoea, interfering with normal activity; 3 = severe incapacitating dyspnoea.

Nasal congestion: 0 = no nasal obstruction; 1 = difficulties with breathing through nose; 2 = can’t breathe through nose at all.

Rhinorrhoea: 0 = no running nose; 1 = moderately running nose, well tolerated; 2 = severe rhinorrhoea, often needs handkerchief.

Cough: 0 = no cough; 1 = moderate well tolerated cough; 2 = severe fatiguing cough.

Expectoration: 0 = no expectoration; 1 = small amount of sputum, especially after bronchodilator usage; 2 = large amounts of sputum, expectorated all day long.

Patients also recorded the amounts of other asthma drugs they were taking, although they were asked not to change concomitant treatment without advising the investigator. At each visit subjects were specially asked for any adverse events and health problems that may have occurred. All unusual signs and symptoms were recorded for further consideration. The safety of the treatment was evaluated by monitoring ECG and blood pressure at clinic visits.

ANALYSIS OF DATA

The primary outcome variables were morning PEFR for asthma and both rhinorrhoea and nasal congestion scores for rhinitis. For analysis of the results, data from patients’ diary cards were averaged over consecutive seven day periods. The highest value of every three morning and evening PEFR measurements was used in the analysis. In addition, for each patient diurnal variability of PEFR was calculated according to the following formula:

\[ \text{PEFR variability} = \frac{2|\text{PEF}_{\text{evening}} - \text{PEF}_{\text{morning}}|}{(\text{PEF}_{\text{evening}} + \text{PEF}_{\text{morning}})} \times 100\% \]

Data from the weeks of misoprostol and placebo treatments and averaged data from the whole six weeks of the study were independently compared using the Student’s paired t test (PEFR) and Wilcoxon matched pairs test (spirometric data, eosinophil counts, PEFR variability, all symptom scores, \( \beta_2 \) agonist usage, and defaecation scores).

Results

Mean (SD) morning PEFR during the run in period (333 (129) l/min at week 1 and 336 (130) l/min at week 2) and symptom scores changed significantly.

The rhinorrhoea score was significantly lower on misoprostol (median 0.36 points/day, range 0.00–2.00) than on placebo (median 1.04 points/day, range 0.00–2.00) over the whole treatment period (mean difference 0.30 points/day, 95% CI 0.01 to 0.59; \( p = 0.031 \)). The defaecation score was higher on misoprostol (median 1.39/day, range 0.93–3.79) than on placebo (median 1.10/day, range 0.55–2.02) during the whole treatment period (mean difference 0.55/day, 95% CI 0.22 to 1.07; \( p = 0.004 \)) and in each separate week. None of the remaining parameters (cough, expectoration, and nasal congestion scores) changed significantly.

Discussion

Prostaglandins of the E series inhibit synthesis and release of many inflammatory mediators and cytokines and activation of some inflammatory cells.\(^{14} \) Increased leukotriene synthesis and release has been clearly demonstrated in aspirin sensitive asthmatic patients.\(^{28, 29} \) It is likely that leukotriene production is controlled by PGE\(_2\).\(^{11} \)

It has been postulated that inadequate PGE\(_2\) production may be a factor or cofactor in
enhancing the acute aspirin intolerance reaction or being responsible for the permanent symptoms in subjects with aspirin sensitive asthma. Several studies have recently been undertaken to examine the effect of PGE on aspirin induced bronchoconstriction. Szczeklik et al.10 and Sestini et al.20 found that inhaled PGE, diminished the bronchoconstrictor response to aspirin in aspirin sensitive asthmatic subjects. In our previous study18 and the study by Szczeklik et al.20 misoprostol, a PGE, stable analogue, caused the same effect, although its inhibitory potency was weaker than that of inhaled PGE, and inhibition did not occur in every subject.

As PGE2 inhibits bronchoconstriction following exercise21 and allergen inhalation,1 it is not known whether the mechanism of PGE protection against aspirin is specific for this reaction. Direct proof of interference with the basal phenomenon of aspirin intolerance was provided by Sestini et al20 who reported an inhibition of the rise in the urine concentration of LTE4 by PGE. Taniguchi et al showed that intravenous PGE caused no protection against allergen under the same conditions as it did against aspirin. Nevertheless, the most convincing explanation for its protective effect was inhibition of mast cell and/or eosinophil activation. It is unlikely that the protective effect of misoprostol against aspirin induced bronchoconstriction is due to a direct action on smooth muscle cells as natural PGE, and misoprostol are relatively weak and short acting bronchodilators.14 16

Considering the anti-inflammatory properties of PGE and its anti-eosinophilic effect in particular, some beneficial effects of prolonged treatment with a stable oral PGE, analogue in aspirin induced asthma might be anticipated. The overall effect of misoprostol in humans is harder to predict and interpret than that of natural PGE, or PGE2. Misoprostol is an agonist of two of the four known PGE receptors (EP2 and EP3 receptors), the former causing an increase and the latter causing a decrease in intracellular CAMP. Nevertheless, in studies on some immunological activities misoprostol resembled natural PGE, and PGE2, in their effects, with differences being small and only in potency.7 8 10 15 24 It’s pharmacokinetics and stability make misoprostol an adequate candidate for the study.

In our placebo controlled trial misoprostol given to aspirin sensitive asthmatic subjects in a dose of 800 µg or 1600 µg daily showed no significant effect on the course of the disease.

One of the possible explanations for the poor clinical effect of misoprostol in this study is that it did not reach a sufficiently high concentration in the bronchial mucosa. Misoprostol has an especially high affinity for the liver, kidney and gut compared with the bronchi. Nevertheless, its protective effect against oral aspirin over a similar dose range10 seems to exclude this hypothesis. Increased numbers of defeacations per day suggest that patients’ compliance and drug intake were satisfactory. However, oral misoprostol at a single dose of 400 µg showed somewhat poorer protection than inhaled PGE2, against aspirin provocation.11

Misoprostol given regularly to aspirin sensitive asthmatics appears to have no beneficial effect on asthma control in this study. This does not exclude a role for PGE in diminishing the acute reaction to aspirin ingestion. The question of the potential use of any PGE analogue in the treatment of aspirin induced asthma remains unanswered. Studies with inhaled PGE2 or its analogue are now needed.

Misoprostol (Cytotec) was obtained from Searle. Placebo tablets were prepared by Biocom (Racowice, Poland).

23. Smallwood JI, Malavita SE. Misoprostol stimulates leukocyte cyclic adenosine 5’-monophosphate production and


