Gastrointestinal tolerability of meloxicam and piroxicam: a double-blind placebo-controlled study

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Aims The aim of the study was to compare the effects of meloxicam and piroxicam on the gastroduodenal mucosa in healthy adults.

Methods Forty-four healthy volunteers were given a 28 day course of either meloxicam 15 mg, piroxicam 20 mg or placebo. Damage to the oesophageal, gastric and duodenal mucosa was assessed, mucosal blood flow (MBF) measured at endoscopy and biopsies taken for prostaglandin content and microscopic assessment of damage before NSAID administration and during days 1, 7 and 28 of continued intake.

Results Maximal macroscopic gastric mucosal damage (median grade + IQR) occurred within 24 h of piroxicam administration, the damage score increasing from 0 to 2.5 (0–3) ($P=0.02$) at day 1 before falling to 2.0 (0–2) at day 7 and 0 (0–1) at day 28 with resolution of damage observed in six out of the seven subjects who sustained acute injury. No significant macroscopic gastric damage occurred in either of the two other groups although some minor damage was observed in seven subjects taking placebo and five taking meloxicam. There was a trend towards piroxicam causing more acute gastric damage than meloxicam ($P=0.06$). Baseline antral, body and duodenal MBF were similar in all three groups. No significant changes occurred in any of the groups on any of the visits. There were also no changes in gastric mucosal prostaglandin content in any group.

Conclusions These observations suggest that meloxicam causes little acute damage to the upper gastrointestinal tract and piroxicam causes some acute gastric injury but such damage resolves in most subjects by 28 days.

Keywords: non-steroidal anti-inflammatory drugs, meloxicam, piroxicam, adaptation, mucosal blood flow

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to treat rheumatological conditions and as analgesics but have a high frequency of side effects that may limit their usefulness. The most common side effects are gastrointestinal (GI) and although usually mild may include perforation and life threatening gastrointestinal bleeding [1].

The mechanism by which gastroduodenal damage occurs is still not fully understood but NSAIDs affect most mucosal defence mechanisms principally by inhibition of cyclo-oxygenase and subsequent suppression of mucosal prostaglandin synthesis [2]. One of the most important of these defence mechanisms is mucosal blood flow and initial gastric mucosal damage is associated with changes in this [3–5].

It is estimated that over 24 million prescriptions are issued for NSAIDs in the UK each year. Currently available NSAIDs are associated with an undesirably high level of side effects and therefore there is considerable interest in

developing NSAID formulations with improved side effect profiles. A number of strategies have been employed to improve the tolerability of NSAIDs including rectal administration, enteric coating, zwitterionic NSAIDs [6], nitric oxide releasing NSAIDs [7] and NSAIDs that do not suppress mucosal prostaglandin production. Since 1991 it has been known that cyclo-oxygenase (COX) exists in two isoforms, COX-1 present in the gastroduodenal mucosa and COX-2 [8] which is inducible in fibroblasts, macrophages and other cells by pro-inflammatory stimuli and cytokines. The desired anti-inflammatory actions of NSAIDs are due to the inhibition of the inducible COX-2 rather than inhibition of COX-1 which leads to suppression of prostaglandin synthesis and gastric damage. Recently NSAIDs that preferentially inhibit COX-2 have been developed. One such NSAID is meloxicam (Boehringer Ingelheim Ltd).

The purpose of this prospective double-blind, placebo controlled single centre study was to compare the effects of 4 weeks treatment with similar therapeutic doses [9, 10] of meloxicam and piroxicam on gastric, duodenal and oesophageal mucosal injury, prostaglandin production and mucosal blood flow in healthy volunteers.

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Methods

Subjects

Fifty-seven healthy subjects between 18 and 50 years of age were screened to participate in the study. They had no history or endoscopic evidence of gastrointestinal disease and were excluded from the study if they had consumed aspirin or any other NSAID within the previous 4 weeks, if they had had a previous adverse reaction or hypersensitivity to NSAIDs, or suffered from asthma. Other exclusions included pregnancy, lactating mothers, the requirement for chronic administration of any other medication other than the oral contraceptive pill, abnormal haematological or biochemical profiles at the screening visit of the study, excess alcohol consumption (male >21 units/week, female >14 units/week) or excess smoking (>20 cigarettes/day). The study was approved by the Salford Health Authority Ethics Committee.

After giving informed consent, subjects were screened for *Helicobacter pylori* using C^{13} urea breath testing and underwent baseline blood tests including full blood count, urea and electrolytes and liver function tests. All females also had a pregnancy test. Subjects returned 1 week later for baseline endoscopy. Subjects with normal endoscopic appearances, negative C^{13} urea breath test, negative pregnancy test and normal blood tests were randomised to receive a 28 day course of either meloxicam 15 mg (Mobic® Boehringer Ingelheim Ltd UK), piroxicam 20 mg (Feldene® Pfizer Ltd, UK) or placebo. The subjects returned 24 h, 7 days and 28 days later for further endoscopy. At each visit, blood was taken for haematological and biochemical profiles and measurement of plasma drug concentration. Subjects were also questioned about gastrointestinal symptoms or any other adverse reactions to the medication. Subjects returned for a final follow up visit 1 week after the last endoscopy to document any adverse events.

Endoscopy

Gastroscopy was performed after each subject had fasted a minimum of 5 h using Xylocaine throat spray as a local anaesthetic. The oesophageal, gastric and duodenal mucosa was inspected and assessed by a single endoscopist (GL), who was blinded to drug intake, using the Savary Miller and modified Lanza grading systems to grade oesophageal and stomach and duodenal damage respectively (Table 1). Biopsies were taken from macroscopically normal mucosa in the oesophagus, gastric body, antrum and duodenal bulb for histological assessment (Table 2) and prostaglandin E_2 (PGE₂) content. Mucosal blood flow was also measured in normal looking distal oesophagus, gastric antrum, gastric body and duodenal bulb using laser Doppler flowmetry as described previously [11].

Measurement of mucosal prostaglandin E_2

Immediately after biopsy, mucosal specimens were frozen in liquid nitrogen and stored at -70°C until measurement of PGE₂ content which was performed by TNO Nutrition and Food Research Institute (Holland). After thawing, the

biopsies were mixed with 0.5 ml 10 mmol l⁻¹ sodium phosphate buffer (10 mmol l⁻¹ pH 7.5), 0.5 ml ethanol (80%) and 10 µl acetic acid. The tissue was then sonicated during 30–60 s at 0°C using a frequency of 23 kHz and an amplitude of 18 µm. The homogenate was centrifuged for 5 min at 2000 g. The supernatant was then collected.

Before the first sample was homogenised, stock solutions containing 20, 80 and 300 ng l⁻¹ PGE₂ were prepared and stored at $<-18^\circ\text{C}$. In each extraction run, a sample of each concentration prepared was included as a quality control check.

Supernatant (800 µl) from the tissue homogenate, was washed on a Sep-Pak cartridge, equilibrated with 10% ethanol. The cartridge was washed with one volume of distilled water and one cartridge volume of hexane. The PGE₂ fraction was then eluted with 2.5 ml ethylacetate. The eluate was dried at approximately 40°C under nitrogen and the PGE₂ in the dried extract was converted to its methyl oximate derivative and stored at $<-18^\circ\text{C}$ until the analysis was carried out. PGE₂ was analysed as its methyl oximate derivative by radioimmunoassay (r.i.a.) using oximinated callibrators.

Patient samples with a PGE₂ concentration above the upper limit of calibration curve were reanalysed after dilution in the next assay run, using a remainder aliquot of the methyloximated derivative. No concentrations were found below the lower limit of the calibration curve. Protein was determined in the supernatant of the tissue homogenate with the Bio-Rad protein assay. Bovine serum albumin samples (25–900 mg l⁻¹, dissolved in homogenisation buffer) were used for calibration. As a quality control check, in each analysis run, two Lipocheck Quantitative urine control samples were included, normal and abnormal. Results are expressed as ng PGE₂ mg⁻¹ protein.

Statistical methods

A sample size of 12 evaluable subjects per treatment group was calculated using the total of the site specific endoscopy scores as the primary end point and basing estimates on previous studies. This calculation was based on 90% power to detect a difference of 3 units with a standard deviation of 2.2 units for the placebo group at the two-sided 5% significance level. It was estimated that 50 subjects would need to be screened in order to recruit data from 36 evaluable patients due to an estimated 30% of subjects not satisfying the inclusion/exclusion criteria.

Since this was an exploratory study looking at the effect of a defined course of treatment, it was decided that for the primary per protocol analysis no estimation of missing data would be made. The data from measurements of mucosal blood flow are expressed as means (s.e.mean) and were analysed using repeated measures of analysis of variance followed by Dunnett's post test to identify changes within groups which occurred between visits. The data from mucosal damage scores and prostaglandin concentrations are expressed as medians and inter-quartile ranges and changes between visits were analysed using Friedmans analysis of variance for repeated measures followed by Dunnett's post test. Differences between drug groups were analysed using a Kruskal Wallis test and a *P* value of 0.05 was considered

Table 1 Endoscopic scoring systems used to grade macroscopic damage.

Stomach and duodenum		Oesophagus	
0	No visible lesion	0	Normal
1	1 erosion or submucosal haemorrhages (SMH)	1	Single or isolated lesion affecting only one longitudinal fold
2	2–10 erosions or SMH	2	Multiple lesions, non-circumferential affecting more than one longitudinal fold with or without confluence
3	11–25 erosions or SMH	3	Circumferential lesions
4	>25 haemorrhages or SMH or invasive ulcer	4	Chronic lesions and/or short oesophagus. Alone or associated with lesions of grades 1–3
		5	Barrett's oesophagus

Table 2 Scoring system used by the reporting histopathologist to grade microscopic damage.

Grade 0	Normal
Grade 1	Increase in inflammatory cells—predominantly lymphoid. Intact and regular epithelium. Focal inflammation <10% of the biopsy specimen.
Grade 2	Increase in inflammatory cells—predominantly lymphoid with infiltration of glandular epithelium. Foveolar hyperplasia.
Grade 3	Increase in inflammatory—polymorphs noted with marked surface epithelial infiltration. Epithelial irregularity.
Grade 4	Ulceration with predominantly polymorph infiltration.

significant. This was undertaken using Graph Pad Prism computer software (Graph Pad Software Inc. San Diego, CA. USA).

Results

Fifty-seven subjects were screened to participate in the trial of whom thirteen subjects did not fulfil the inclusion criteria. Forty four subjects were randomised for entry into the trial, 14 to the piroxicam group and 15 to each of the meloxicam and placebo groups. The demographic characteristics of each group are listed in Table 3. Three subjects were withdrawn due to adverse events during the study, one with a maculopapular rash starting within one hour of taking the study medication (piroxicam), one with a whiplash injury due to a car accident (placebo) and one with severe

dyspepsia (meloxicam). One subject withdrew consent at visit 3 and a further subject was lost to follow up. Two subjects were withdrawn for protocol violations, one for being *Helicobacter pylori* positive (placebo) and one for taking ibuprofen during the study (piroxicam). Thirty-five subjects were therefore included in the per protocol analysis with 10 subjects in the piroxicam group, 14 subjects in the meloxicam group and 11 subjects in the placebo group. All subjects were shown to be compliant with the study medication and test drug levels corresponded to the randomisation codes.

Mucosal damage

The primary endpoint of change in total endoscopic scores between days 1 and 28 was calculated as a median of zero

Table 3 Summary of demographic characteristics of randomised subjects.

	Piroxicam	Treatment Meloxicam	Placebo	Total
Number of subjects	14	15	15	44
Age (years)	25.9 (7.0)	26.6 (6.1)	27.7 (8.6)	26.8 (7.2)
Male:Female	6:8	8:7	8:7	22:22
History of alcohol intake	14	15	15	44
Smoking history				
Never	7	8	5	20
Ex smoker	1	2	4	7
Smoker	6	5	6	17

in all three treatment groups which was confirmed by analysis of the intention to treat data set. Significant macroscopic gastric mucosal damage occurred within 24 h of piroxicam administration, the damage score increasing from 0 to 2.5 (0–3) ($P=0.02$) at day 1 before falling to 2.0 (0–2) at day 7 and 0 (0–1) at day 28 with resolution of damage observed in six out of the seven subjects who had sustained acute injury at 24 h (Figure 1). No significant macroscopic gastric damage occurred in either of the two other groups although some minor damage was observed in seven subjects taking placebo and five of those taking meloxicam (Figure 1). There was a trend towards piroxicam causing more acute gastric damage at day 1 compared with meloxicam ($P=0.06$) but otherwise no differences between groups. No changes in duodenal or oesophageal macroscopic damage were observed in any of the groups at any of the visits. The median microscopic damage scores were zero in all groups, at each site, at all visits.

Mucosal blood flow

Baseline mucosal blood flow measurements in the antrum, body, oesophagus and duodenum in each of the groups were as follows: piroxicam: 58.7 ± 3.9 arbitrary units (a.u.), 49.1 ± 6.3 a.u., 69.7 ± 4.9 a.u. and 50.6 ± 3.4 ; meloxicam: 60.5 ± 4.7 a.u.; 53.1 ± 2.8 a.u., 70.4 ± 3.4 a.u. and 56.6 ± 2.9 a.u.; placebo: 57.0 ± 4.3 a.u., 50.6 ± 3.2 a.u. 68.7 ± 4.6 a.u. and 57.3 ± 3.7 a.u. No significant changes occurred in any of the groups at any site on any of the visits. However baseline measurements of mucosal blood flow were significantly higher in the oesophagus (69.4 ± 2.3 a.u.) than in antrum (58.4 ± 2.5 a.u.), body (51.8 ± 1.7 a.u.) or duodenum (55.5 ± 1.9 a.u.) ($P=0.01$).

Mucosal prostaglandin E_2 concentrations

Mucosal biopsies were taken for assessment of prostaglandin content as described above. However very few samples from oesophagus and duodenum were available for analysis and therefore only the results from gastric body and antrum are given. Baseline body and antral mucosal prostaglandin E_2 concentration was similar in all three groups; meloxicam: 16.8 (10.1–30) ng mg^{-1} protein and 25.3 (7–65.2) ng mg^{-1}

protein; piroxicam: 35.3 (25.6–44.7) ng mg^{-1} protein and 21 (13.1–77.1) ng mg^{-1} protein; placebo: 17.2 (11.5–72.8) ng mg^{-1} protein and 34.6 (9.1–145) ng mg^{-1} protein. There were no significant differences between visits in any of the three groups.

Adverse events

No serious adverse events occurred during the study. However three subjects were withdrawn for the reasons described above. Seventy-one per cent of subjects taking piroxicam, 73% of subjects taking meloxicam and 67% of subjects on placebo experienced at least one adverse event, the most common of which were nausea and dyspepsia. Nausea was reported by 36% of the piroxicam group, 33% of those taking meloxicam and 40% on placebo. Dyspepsia was reported by 14% of the piroxicam group, 20% of those taking meloxicam and 20% on placebo.

Discussion

The results of this study suggest that there is a trend towards piroxicam causing more acute gastric damage than meloxicam but that neither drug causes much acute damage to the oesophagus and duodenum. We did not demonstrate differences between groups in any of the other parameters that were measured. A previous placebo controlled study that compared the gastrointestinal effects of piroxicam 20 mg and meloxicam 15 mg demonstrated no difference in endoscopic scores at 14 and 28 days but more subjects taking piroxicam were withdrawn due to gastrointestinal side effects [12]. However in the same study Patoia *et al.* demonstrated that piroxicam 20 mg was associated with greater faecal blood loss and more endoscopic gastroduodenal damage than a lower dose of meloxicam (7.5 mg). In our study, acute gastric damage resolved in six out of seven subjects taking piroxicam, four out of five taking meloxicam and all those on placebo, a phenomenon that has been demonstrated in a number of previous studies and is known as adaptation [4, 11, 13]. In view of this it is perhaps not surprising that there was no difference in gastroduodenal damage between groups at the end of the study. An interesting feature of this study was that some subjects taking placebo had gastric damage observed at the second endoscopy, albeit minor. This has been noted in other similar placebo controlled studies [12] and was most likely due to the prolonged gastroscopy and procedures undertaken causing damage which then resolved by the next visit one week later. There was a high rate of adverse events during the study in all three groups but no difference between groups. This was thought to be due in part to the investigators specifically asking about adverse events and in part due to reporting of minor adverse events related to endoscopy such as sore throat and abdominal discomfort.

We were surprised that the results did not demonstrate a fall in gastric mucosal prostaglandin concentration during piroxicam administration. However measurement of mucosal prostaglandins are fraught with difficulties as prostaglandin synthesis occurs in response to cell trauma. Therefore collection of biopsies, handling and homogenisation would be expected to alter mucosal prostaglandin content [14].

Figure 1 Median (IQR) gastric mucosal damage (modified Lanza grading scale) during 28 days of continuous administration of piroxicam 20 mg ($n=10$, ■), meloxicam 15 mg ($n=14$, ▨) or placebo ($n=11$, □).

*Piroxicam day 0 *vs* piroxicam day 1 $P=0.02$.

Unfortunately we can therefore not draw definite conclusions about the effect of meloxicam on gastroduodenal mucosal prostaglandin synthesis. No other human data are available but studies on rat stomach indicate that meloxicam is only a weak inhibitor of mucosal prostaglandin production compared with diclofenac, naproxen and flurbiprofen [15].

Several studies have shown that administration of NSAIDs is associated with changes in gastric mucosal blood flow [3–5] at the time of maximal damage. However this finding is not universal [11] and in this study neither piroxicam nor meloxicam was associated with such changes. The observation that oesophageal mucosal blood flow is higher than in the stomach and duodenum agree with similar findings by Allen *et al.* who also used laser doppler flowmetry [16].

Most gastric tolerability studies such as ours are performed on young and healthy subjects whereas major risk factors for serious adverse events associated with NSAIDs include age over 65 years, concomitant serious illness and the concomitant use of more than one NSAID [1, 17]. Such short term clinical studies can provide useful information but need to be combined with post marketing surveillance to further clarify the risk of individual NSAIDs. Data of this nature are emerging with regard to some NSAIDs and a recent meta-analysis of 12 studies of serious gastrointestinal side effects of individual NSAIDs suggested that piroxicam was associated with the highest risk group [18]. One factor that has been implicated in this is the long half-life of piroxicam (72 h) as it has been demonstrated in animal studies that there is less gastric mucosal adaptation with NSAIDs that have long half-lives [19]. Meloxicam has a half-life of 20 h and recent analysis of the available clinical trials in patients with osteoarthritis and rheumatoid arthritis involving over 5000 patients demonstrated that it was better tolerated than diclofenac, piroxicam and naproxen [20]. This was thought to be due to preferential inhibition of COX-2 relative to COX-1.

In conclusion this study demonstrates that meloxicam causes little acute damage to the upper gastrointestinal tract and piroxicam causes some acute gastric injury which resolves in most subjects by 28 days. This was a small study with limited power that reflects only acute toxicity and further long term clinical studies are needed to evaluate the tolerability of meloxicam.

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