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Gastrointestinal tolerability of lornoxicam compared to that of naproxen in healthy male volunteers

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SUMMARY

Background and Aim: Gastrointestinal effects are common adverse effects associated with nonsteroidal anti-inflammatory drugs (NSAIDs). Lornoxicam is a new nonsteroidal anti-inflammatory drug and its gastroduodenal tolerability was compared to that of naproxen in a randomized, double-blind, crossover study.
Methods: Eighteen healthy male volunteers received lornoxicam 8 mg b.d. or naproxen 500 mg b.d. administered orally over two 7-day dosing periods. Upper endoscopy was performed by two independent investigators at the beginning and end of each dosing regimen.
Results: Lornoxicam 8 mg b.d. caused significantly less mucosal injury than naproxen 500 mg b.d. in the stomach/duodenal bulb, as well as in the mid/distal duodenum.
Conclusion: These findings may have favourable implications for lornoxicam in the clinical setting, if this dose provides optimal control of arthritic pain.

INTRODUCTION

Of the various adverse effects associated with non-steroidal anti-inflammatory drugs (NSAIDs), gastrointestinal effects are of greatest concern in view of their frequency, potential seriousness and cost.[1] The spectrum of NSAID-induced adverse gastrointestinal effects ranges in severity from dyspepsia to acute bleeding and perforation.[2] Gastrointestinal injury resulting from NSAIDs is a function of their mechanism of action: inhibition of cyclo-oxygenase activity and prostaglandin synthesis. NSAIDs are also associated with local gastrointestinal toxicity that is independent of cyclo-oxygenase inhibition and may involve both direct and indirect effects.[3] The pathogenesis of NSAID-induced gastrointestinal injury and the role of prostaglandins in gastrointestinal mucosal defence have been reviewed in detail elsewhere.[3,4]

Lornoxicam is a new NSAID that belongs to the oxicam class. It has potent cyclo-oxygenase inhibitory activity which is consistent with the toxicity profile of this agent in animal studies.[5] Lornoxicam solution in single oral doses up to 70 mg was well tolerated in healthy adult male volunteers; dose-dependent gastric irritation similar to that caused by aspirin 500 mg was noted with lornoxicam doses between 50 and 70 mg (data on file, Hafslund Nycomed). Lornoxicam has been shown to be effective in the treatment of rheumatoid arthritis, osteoarthritis and post-operative dental pain.[6–8]

In a previous 4-week study in healthy volunteers, lornoxicam 4 mg orally twice daily and indomethacin 50 mg orally twice daily did not differ significantly as regards faecal blood loss, but greater deterioration in endoscopic scores was observed with indomethacin (data on file, Hafslund Nycomed). Clinical studies later indicated that the optimal therapeutic dosage of lornoxicam for the treatment of rheumatoid arthritis and osteoarthritis may be greater than 4 mg twice daily. Moreover, indomethacin, the drug used as the comparator agent in the study discussed above, is now prescribed less frequently than newer NSAIDs which have more favourable tolerability profiles. Against this background, the current study was conducted to assess the gastroduodenal tolerability of lornoxicam 8 mg twice daily for 7 days

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compared to that of naproxen, a standard reference NSAID for endoscopic studies.

METHODS

This phase II, randomized, double-blind, double-dummy, crossover study was conducted at Ullevål Hospital, Oslo, Norway, between February 1993 and April 1993. The study was conducted according to the updated Declaration of Helsinki and was approved by a regional Norwegian ethics committee and the Norwegian Medicines Control Authority.

Study population

Healthy male volunteers between the ages of 18 and 60 years were recruited. The participants were required to give written informed consent after receiving oral and written information about the study. Volunteers were excluded if they had recent evidence or symptoms of oesophageal varices, gastric or duodenal ulceration, enteritis or colitis; abnormal findings in the baseline health check; an endoscopic score of more than 5 cm on the 20 cm visual analogue scale (VAS: Figure 1) or more than one point for any of the variables on the fixed five-point scale (Table 1); used any drug during the 2 weeks preceding the study; ingested alcohol during the week before the study; a history of any of the following conditions; serious gastrointestinal disease, hypersensitivity to NSAIDs, haemorrhagic diathesis, asthma, alcohol or drug abuse; or if they were considered unlikely to follow the study procedures.

Study design

At a pre-study screening visit, a baseline medical history was recorded, a physical examination performed and clinical laboratory parameters were measured (blood/serum/plasma: erythrocyte sedimentation rate and count, haemoglobin, haematocrit, leucocyte count, thrombocyte count, bleeding time; urine: glucose, proteins, ketone bodies, blood). The volunteers were randomized, in blocks of six individuals, to twice daily oral dosing for a total of 6 days with either lornoxicam 8 mg film-coated tablet and placebo naproxen, or naproxen 500 mg film-coated tablet and placebo lornoxicam. After a 3-week washout period, participants crossed over to the other regimen. In each dosing period, study medication was commenced in the evening of day 1 and discontinued after the morning dose on day 7. Drug therapy with the potential to interact with the study medications or influence the results of the study was not allowed 2 weeks before or during each dosing period. Ingestion of alcohol was not permitted the week before or during each study.

Compliance was checked at the last visit in each period by asking each volunteer whether the medication regimen had been followed. In addition, the dosing container was returned at the last visit and any returned tablets were counted.

Table 1. Fixed five-point scale for endoscopic assessment (secondary variable)

Description of gastroduodenal mucosa	Grade
Normal	0
One submucosal haemorrhage or superficial ulceration	1
More than one submucosal haemorrhage or superficial ulceration, but not numerous or widespread	2
Numerous areas with submucosal haemorrhage or superficial ulceration	3
Widespread involvement of the stomach with submucosal haemorrhage or superficial ulceration; ulcer of any size	4

Assessment procedures

All volunteers fasted for at least 8 h, were given one dose of local anaesthetic in the throat and were then subjected to upper endoscopy in the afternoon of day 1 (before the first dose of study medication) and on day 7 (after the

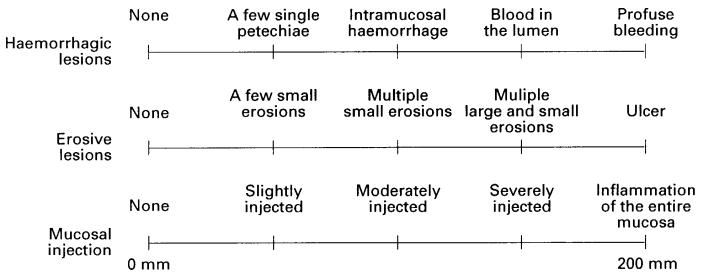

Figure 1. Visual analogue scales (VAS) used for endoscopic assessment.

Table 2. Sum of endoscopically assessed visual analogue (VAS) scores (mm) for the gastroduodenal mucosa in 18 healthy male volunteers after 6 days of oral dosing with lornoxicam 8 mg b.d. daily or naproxen 500 mg b.d. daily (mean with standard deviation)

	Lornoxicam ($n = 18$)			Naproxen ($n = 18$)			
	Day 1	Day 7	Mean change	Day 1	Day 7	Mean change	*P* value
Stomach/duodenal bulb	5 ± 9	81 ± 88	$+76 \pm 90$	6 ± 9	197 ± 99	$+192 \pm 103$	0.001
Duodenum	2 ± 3	27 ± 49	$+25 \pm 48$	3 ± 5	129 ± 115	$+126 \pm 116$	0.001

final dose of study medication) of each dosing period. All endoscopies were performed by the same investigator. Two investigators independently evaluated the gastroduodenal mucosa using two scoring methods. The second endoscopist watched the entire procedure on video, without any communication between the two investigators prior to the scoring. The primary variable was the change in the sum of VAS scores for haemorrhagic lesions, erosive lesions and mucosal injection (Figure 1).[9,10] A fixed five-point scale describing the mucosa was used as a secondary variable (Table 1).[11] For both scoring methods, an average of the scores provided by the two investigators was calculated for each volunteer. The stomach/duodenal bulb and mid/distal duodenum were evaluated separately. No participant was allowed to begin the second dosing period before the appearance of the gastroduodenal mucosa had returned to pre-study status.

At the each of each period, each volunteer was questioned as to the nature, day of onset, duration and severity (based on a 100 mm VAS) of any symptoms that had not been present prior to the start of the study. The relationship of any adverse event to the study medication was assessed by the physician and recorded as probable, possible or unclassified. At the beginning and end of each treatment period before endoscopy, laboratory investigations (haemoglobin, leucocyte count, thrombocyte count, serum creatinine, liver enzymes) were performed on blood samples.

Statistical analyses

Based on the standard deviation obtained in previous endoscopic studies using the same VAS,[12–14] it was calculated that 18 volunteers were required to detect a 35% difference (that considered to be clinically relevant) in the primary variable (change in sum of VAS scores) with 80% power at the 5% significance level.

Data were summarized by calculation of means and standard deviation values. Intergroup differences in baseline demographic and clinical laboratory variables were analysed using Student's *t*-test. Endoscopic and laboratory data were analysed by analysis of variance. Differences in the frequency and severity of adverse events were analysed using McNemar's test and Student's *t*-test, respectively. For all statistical tests, a two-sided 5% probability level was considered to be significant.

RESULTS

Volunteer characteristics

In total, 18 volunteers aged 21–30 (mean 23) years were included in this study. Nine participants were randomized to each sequence group and all completed the study. Volunteers randomized to lornoxicam/naproxen had a mean age of 23.4 (range 21–30) years and those randomized to naproxen/lornoxicam had a mean age of 22.9 (range 21–25) years. There were no statistically significant differences between the two groups in any of the demographic characteristics or baseline clinical laboratory variables.

Study drug administration

The extent of medication exposure was the same for both drugs. Eight volunteers failed to take one dose of medication: four in the lornoxicam period and four in the naproxen period. One volunteer who missed an evening dose of lornoxicam took a double dose the following morning. However, all volunteers received their last dose of medication prior to endoscopy. No instance of non-compliance was considered to have influenced the study results.

Endoscopic findings

The increase in the sum of the VAS scores for the stomach/duodenal bulb was significantly greater after dosing with naproxen compared to lornoxicam (Table 2).

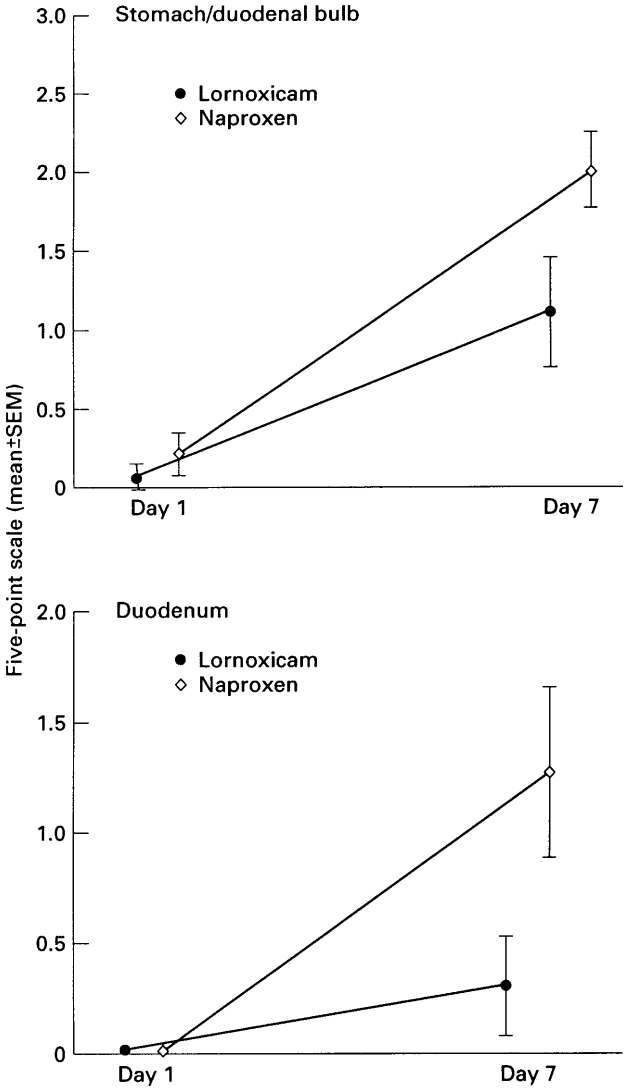

Figure 2. Mean scores (±SEM) on a fixed-point scale (Table 1) as endoscopically assessed in (a) the stomach/duodenal bulb mucosa and (b) the duodenum in 18 healthy male volunteers after 6 days of dosing with lornoxicam 8 mg b.d. or naproxen 500 mg b.d.

This was also the case for each individual VAS component (haemorrhagic lesions, erosive lesions, mucosal injection) and when the scores were examined separately. The findings for the distal duodenal mucosa mirrored those for the stomach/duodenal bulb, with the increase in the sum of VAS score significantly greater after dosing with naproxen compared to lornoxicam (Table 2). Observed changes in the mucosa were greater in the stomach/duodenal bulb than in the duodenum. No subject developed an ulcer during the study.

The increase in the fixed-point scale score was also significantly higher following dosing with naproxen compared to lornoxicam both in the stomach/duodenal bulb and in the duodenum (Figure 2; $P = 0.02$).

Additional analyses revealed a statistically significant sequence effect in the stomach/duodenal bulb. Lornoxicam caused fewer lesions, and naproxen more lesions, when administered in the second period (mean change in VAS scores 30 vs. 235 mm, respectively, $P = 0.02$). There was no indication of any sequence effect in the distal duodenum, or a period effect in the stomach/duodenal bulb or the duodenum, as assessed by the fixed-point scale.

Eleven of 18 volunteers (61%) reported a total of 23 adverse events during the study, comprising 19 gastrointestinal events, and four central nervous system events. The adverse events were generally moderate in severity, and 20 of 23 (87%) were classified as probably or possibly related to drug treatment. There was no statistically significant difference between the two drugs in terms of the frequency or severity of adverse events (Table 3). There was no correlation between endoscopic scores and subjective discomfort. No serious or unexpected adverse events were reported and no subject discontinued the medication prematurely.

There were no clinically significant differences between the trial drugs or between dosing sequences as regards clinical laboratory variables. However, there was a statistically significant decrease in the mean serum creatinine level from day 1 to day 7 within each treatment period (lornoxicam period—3.1 μmol/L, $P = 0.027$; naproxen—5.5 μmol/L, $P = 0.0001$). In

Table 3. Number of adverse events reported during a crossover study comparing 6 days of dosing with lornoxicam 8 mg b.d. and naproxen 500 mg b.d. (includes events reported during the washout period after each drug)

Adverse event	Lornoxicam ($n = 18$)	Naproxen ($n = 18$)
Abdominal discomfort	4 (22%)	3 (17%)
Stomatitis	1 (6%)	3 (17%)
Loose stool	1 (6%)	2 (11%)
Nausea	1 (6%)	1 (6%)
Abdominal pain	1 (6%)	0 (0%)
Somnolence	2 (11%)	0 (0%)
Headache	0 (0%)	1 (6%)
Insomnia	0 (0%)	1 (6%)
Oedema/easy bleeding from gingiva	0 (0%)	1 (6%)
Reduced appetite	0 (0%)	1 (6%)

addition, the mean change in serum creatinine was significantly greater in the first period compared with the second period ($P = 0.03$). In one volunteer, the aspartate aminotransferase level increased moderately during the first treatment period (naproxen) but returned to normal during washout and remained so throughout the second treatment period.

DISCUSSION

Although all NSAIDs are associated with gastrointestinal adverse events, they appear to differ in their propensity to cause such disturbances.[15,16] Piroxicam, for example, has been associated with a higher relative risk for upper gastrointestinal bleeding than other commonly used NSAIDs.[16] It has been theorized that this higher risk could be related to the longer half-life of piroxicam which precludes a 'recovery' time for the gastroduodenal mucosa with usual treatment regions. Lornoxicam, in contrast, has a relatively short half-life of approximately 4 h and this may help explain the low level of gastrointestinal toxicity associated with the drug in this study. Indeed, this investigation showed lornoxicam to cause significantly less injury to the gastroduodenal mucosa than naproxen, which has a half-life between 12 and 15 h,[17] when both drugs were administered orally at dosages in the upper range of those recommended for the treatment of rheumatoid arthritis and osteoarthritis[17] (data on file, Hafslund Nycomed). Nevertheless, the clinical significance of nonulcerative mucosal changes in healthy male volunteers treated with NSAIDs in the short term has not been established.

The model we used to study gastrointestinal tolerability is well controlled with a minimum of confounding factors.[11] In addition, it can be performed over a short period and it allows for repeated endoscopies to accurately monitor mucosal changes. We further standardized the procedure by having the same endoscopist perform all procedures and by assessing each subject at the same time of day at all visits. Two scoring systems were used in this study. Most studies of this type use a derivation of the Lanza fixed-point scale,[11] but our group has gained experience with VAS scoring and, from a statistical point of view, the continuous data provided by a VAS have advantages over a discrete scoring model.[18] The VAS has been criticized for being complicated to use but, in a previous comparison with a fixed-point scale, there was no significant difference between the two methods with respect to discrepancies between the two investigators.[19]

Although comparisons with previous studies should be viewed with caution, it is interesting to note that the mean VAS score and its standard deviation with naproxen in this study was similar to that found in earlier studies at the same centre, suggesting a certain degree of consistency in the study procedures and methods. In a series of studies, we also observed a continuum of gastrointestinal injury ranging from major erosive and petechial lesions to regular ulcers, indicating that our experimental study has some clinical relevance.[10]

Age greater than 65 years is a known risk factor for NSAID-induced gastroduodenopathic complications and female gender may possibly be a risk factor;[3,4] however, gastrointestinal tolerability studies are generally performed in young, healthy males. In addition, there have been discrepancies for some NSAIDs between the results of initial small-scale tolerability studies and post-marketing surveillance data.[15] Ongoing monitoring of adverse events in clinical trials and post-marketing surveillance of lornoxicam will help clarify the risk of gastrointestinal mucosal injury in both male and female patients.

Crossover design is often used in studies of this type because there are extensive inter-individual differences in susceptibility to adverse gastrointestinal effects. The duration of the washout phase is obviously important in this context. We previously determined that a period of 3–4 weeks was sufficient to allow endoscopy findings to return to baseline in subjects treated with naproxen.[20] The shorter half-life of lornoxicam would suggest that a washout of similar duration is suitable for studying this drug and no period effects were apparent in this study. These data do not preclude the possibility that the mucosa remains modified for a longer period of time despite normalization of visual appearance. Nevertheless, the lack of period effects in earlier studies would rule against this.[10,12–14] The sequence effect that was noted in the stomach/duodenal bulb in this study was unexpected and has not been found in previous investigations. Previous comparative studies have never reported such a phenomenon and it would not be predicted on pharmacological or clinical grounds. This finding was not reproduced in the mid and distal duodenal mucosa, which suggests that the significant sequence effect was coincidental. If the sequence effect is noted in future studies of lornoxicam, further explanation must be sought.

The type and incidence of adverse effects reported in this study were consistent with the known tolerability profiles of these drugs. The apparent lack of correlation between subjective discomfort and endoscopy findings was also in agreement with established knowledge.[3, 4]

In conclusion, the finding that oral administration of lornoxicam 8 mg b.d. caused significantly less damage to the mucosa in the stomach/duodenal bulb and duodenum than naproxen 500 mg b.d. may have favourable implications for the clinical use of this NSAID.

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