EFFECTS OF SELECTIVE AND NON-SELECTIVE CYCLOOXYGENASE-2 INHIBITORS ON THE INTEGRITY OF GASTRIC MUCOSA

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Introduction. The use of non steroidal anti-inflammatory drugs (NSAIDs) is associated with gastric mucosal ulceration.[1] This adverse effect is currently ascribed to the reduction of prostaglandin production through the inhibition of cyclooxygenase (COX).[2] Two isoforms of COX have been identified: COX-1, that is constitutively expressed in many tissues, including the gastrointestinal tract, and COX-2, that is rapidly induced during inflammation.[3] Accordingly, it has been proposed that the selective blockade of inducible COX-2 at inflammatory sites would spare the synthesis of prostaglandins mediated by constitutive COX-1, thus reducing the risk of digestive adverse events.[4] The present study investigates the gastric effects of different NSAIDs acting as a non selective COX-1/COX-2 inhibitor (indomethacin, IND), preferential COX-2 inhibitor (meloxicam, MEL), or selective COX-2 inhibitor (L-745,337).
Methods. Male albino Wistar rats (200-220 g; n=6-8 per group) were subjected to single or repeated (15 days) intragastric administrations of test drugs at equivalent anti-inflammatory doses. Control animals received an equal volume of vehicle (1% carboxymethylcellulose). Four hours after the end of treatments, the stomachs were removed and processed for the following assays: histomorphometric evaluation of mucosal damage (percent length of lesions versus total length of mucosa); quantitative estimation of adherent mucus layer (Alcian blue binding); assay of PGE_2 in the gastric juice after pylorus ligation for 4 hours (immunoenzymatic method); quantitative evaluation of oxidative damage through the assay of malondialdehyde (MDA) in the gastric mucosa (colorimetric assay).
Results. In single-dose experiments, MEL and L-745,337 (3 and 6 mg/kg, respectively) caused significant lower degrees of gastric injury than that observed for IND (6 mg/kg) (Fig. 1A). Treatments with IND, MEL or L-745,337 (0.5, 1 and 1 mg/kg, respectively) for 15 days were also associated with a different severity of mucosal damage (Fig. 1B). Alcian blue recovery from pre-epithelial mucus layer accounted for 168.7±11.3 µg/g in control rats. Gastric mucus secretion was significantly inhibited by IND, whereas it was moderately decreased by MEL or L-745,337 (Table 1). Analogously, PGE_2 release into the gastric juice was significantly reduced by IND, but not MEL or L-745,337 (Table 1). By contrast, MDA levels in gastric mucosa increased after treatment with IND, whereas MEL and L-745,337 were without effect (Table 1).

Table 1. Effects of single-dose treatments with indomethacin, meloxicam or L-745,337 on gastric mucus secretion (Alcian blue recovery), intraluminal prostaglandin release (PGE_2), and mucosal oxidative damage (MDA). ** $p<0.01$, *$p<0.05$ (ANOVA followed by Dunnett test)

Treatment	Alcian blue recovery (%)	PGE_2 (ng/ml)	MDA (ng/mg)
Control	**100**	**32.8±2.7**	**1.70±0.23**
IND 6 mg/kg	**38.5±7.6****	**17.4±4.6***	**2.55±0.35***
MEL 3 mg/kg	**72.0±10.5***	**26.2±4.2**	**1.77±0.30**
L-745,337 6 mg/kg	**73.0±9.0***	**33.6±1.6**	**1.96±0.30**

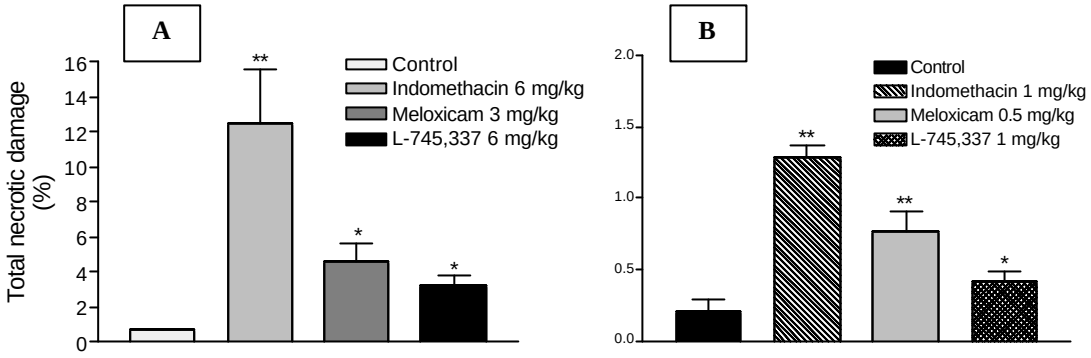

Figure 1. Effects of indomethacin, meloxicam and L-745,337 on gastric mucosal integrity following single (A) or repeated intragastric administrations (B) of test drugs. ** p<0.01, *p<0.05 (ANOVA followed by Dunnett test)

Conclusions. The present results indicate that MEL and L-745,337 affect the integrity of gastric mucosa to a lesser extent than IND, after either single dose or repeated treatments. The weak influence on mucus secretion and the absence of inhibitory effects on prostaglandin synthesis by MEL and L-745,337 are consistent with the affinity profiles of these NSAIDs for COX-2. However, since both MEL and L-745,337 do not seem to elicit an oxidative damage of gastric mucosa, it is also suggested that, at variance with conventional NSAIDs, preferential or selective COX-2 blockers are not able to promote the activation of COX-independent mechanisms of mucosal injury.

References

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