Evaluation of Stomach Protective Activity of Ketoprofen Floating Microparticles

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The gastric ulcerogenic effect of ketoprofen floating microparticles in comparison with the plain ketoprofen was examined. The ketoprofen loaded microparticles were found to be less ulcerogenic and they protected the stomach probably by preventing the intimate contact of ketoprofen with gastric mucosa.

Ketoprofen, chemically, (R,S)-2-(3-benzoylphenyl) propionic acid, is a well-known nonsteroidal antiinflammatory drug[1]. As with other drugs of this group it suffers gastrointestinal complications ranging from mild dyspepsia, gastric discomfort to gastric bleeding. The gastric irritation is mainly due to presence of free carboxylic acid group[1]. Entrapment of drug particles inside a polymer matrix could decrease this side effect to some extent. Several trials have been made to decrease the ulcerogenic activity of nonsteroidal antiinflammatory drugs. Sammour *et al.*[2] have reported that liposome-encapsulated piroxicam formulation exhibited improved *in vivo* performance with reference to its cytoprotective and antiinflammatory activity. Chitosan microspheres of diclofenac sodium have been reported to reduce gastric mucosal injury and enhance its antiinflammatory activity when compared to plain drug[3]. Koyama *et al.*[4] have reported that caffeine inhibited the development of gastric lesions associated with indomethacin pretreatment. It has been also reported that the chemical substitution of ibuprofen decreases its ulcerogenic activity[5]. The co-melt of indomethacin with nicotinamide in a ratio of 1:9 pharmacologically showed lesser ulcerogenicity in experimental animals compared to plain drug[6].

Floating microparticles composed of Eudragit S and Eudragit L in a ratio 1:1 and containing 1:1 ketoprofen:polymer, were prepared using solvent diffusion technique[7]. Briefly, the drug-polymers mixture was dissolved in a mixture of ethanol and dichloromethane (1:1) and dropped into 0.2% sodium lauryl sulfate solution. The solution was stirred with a propeller-type agitator at room temperature for 1 h at 150 rpm. The formed floating microparticles were filtered, washed with water and dried at room temperature in a desiccator. The percentage drug retained was about 77%. The prepared microparticles showed good floating properties, 86 and 90% microparticles still floated after 1 h in 0.1 N HCl and 0.02% Tween 80 in 0.1N HCl; respectively. In a continuing investigation, these micropatricles were tested for gastric irritancy. Ulceration index, extent of ulceration and percent protection were evaluated after oral administration of the free drug and compared with blank and drug-loaded microparticles. Female New Zealand rats (160-220 g) were taken into groups of six; they were fasted for 36 h with free access to water. Permission for the experiment was obtained from Alexandria University. Ketoprofen (75 mg/kg), blank and medicated microparticles (containing an equivalent amount of drug) were separately given orally by gastric tube as a suspension in 0.5% w/v of sodium carboxymethylcellulose. Seven hours after drug administration with no access of water, the rats were sacrificed and the stomach was excised out. The stomach was opened along the lesser curvature and mounted on a board. It was examined for the severity of ulcer and ulcer index was calculated according to the following arbitrary scale that indicates the severity of stomach lesions[8], normal stomach was given a score zero, patchily hemorrhage or hyperemia

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was scored 1, definite hemorrhagic erosion was given a score of 2, very small ulcers of less than 1mm diameter were 3, small ulcers (1 to <2 mm long) were rated 4, medium ulcers (2 to <3 mm long) were scored as 5, large ulcers (3 to <4mm long) were given a score of 6 and very large ulcers (>4mm long) were given 7.

a

b

c

Fig. 1: Photomicrographs of rats stomach.

Photomicrographs of stomach isolated from rats administered orally blank Eudragit microparticle (1a) , ketoprofen microparticles (1b) and free ketoprofen (1c). Black spots represent ulcers.

For each group the following parameters were determined, ulcer index, which is the summation of total ulcer scores, mean ulcer index, which is the total ulcer index divided by the total number of rats in that group, extent of ulceration, which is calculated using the formula, (number of animals bearing ulcer in a given group/total number of animals in that group)x100 and percent protection, which was determined by the formula, (ulcer index for ketoprofen-ulcer index for medicated microparticles/ulcer index for ketoprofen)x100.

Fig. 1 shows photomicrographs of rat stomach after oral administration of blank Eudragit microparticles, free drug (75 mg) and ketoprofen-loaded microparticles containing an equivalent amount of drug as suspension in 0.5% w/v sodium carboxymethylcellulose. The pathological evaluation of rat stomach showed that there was no degeneration when blank microparticles (fig. 1a) were given with an average ulceration index equal to zero The number of ulcerogenic lesions (black spots) was found to be less in case of administration of ketoprofen-loaded microparticles (fig. 1b) compared to that obtained after administration of free drug (fig. 1c) with average ulcerogenic index of 3.2 and 29, respectively.

The lower level of ulcerogenic index produced by the microparticles containing drug, Table 1, indicates the protective action of Eudragit, which coats the drug particles,

TABLE 1: ULCER INDEX AND EXTENT OF ULCERATION OF RATS STOMACH.

Parameter	blank microparticles (n=6)	Ketoprofen[a] (n=6)	Ketoprofen-microparticles[b] (n=6)
Total ulcer index	0	203±15	19±3
Average ulcer index	0	29±6	3.2±1.5
Extent of ulceration	0	71±9	33±7

N is the number of animals per group, a: 75 mg/kg ketoprofen suspended in carboxymethylcellulose, b: containing an equivalent amount of ketoprofen suspended in carboxymethylcellulose.

thus preventing their intimate contact with gastric mucosa for a long time. In addition, the slow release of small quantities of the drug over a long period of time, will lead to improvement of dissolution and absorption properties of ketoprofen. Consequently, the contact time of the drug with gastric mucosa decreases, so the extent of ulceration due to drug entrapped in the microparticles is reduced compared to the free drug (Table 1).

The calculated percent protection was 89% and the extent of ulceration of mucosa by free drug was 2.1 times that calculated for microparticles containing equivalent amount of drug. Analysis of variance for the calculated parameters (Table1) indicated the significant high extent of protection of mucosa ($p \leq 0.05$) after administration of ketoprofen floating microparticles.

REFERENCES

1. Dollery, C., Eds, In; Therapeutic Drugs, Churchill Livingstone, Edinburgh 1999, I1.
2. Sammour, O.A., Al-Zuhair, H.H. and El-Sayed, M.I., **Pharm. Ind.**, 1998, 60, 1084.
3. Açikgöz, M., Kas, H.S., Hasçelik, Z, Miui, Ü and Hincal, A.H., **Pharmazie**, 1995, 50, 275.
4. Koyama, R., Kataoka, H., Tanaka, Y., Nakatsugi, S. and Furukaawa, M.J., **Pharm. Pharmacol.**, 1999, 51, 817.
5. Rajasekaran, A., Sivakumar, P. and Jayakar, B., **Indian J. Pharm. Sci.**, 1999, 61, 158.
6. Hamza, Y.E., Sammour, O.A. and Abdel-Latif, A.H., **Pharm. Ind.**, 1994, 56, 286.
7. El-Kamel, A.H., Sokar, M.S., Al Gamal, S.S. and Naggar, V.F., **Int. J. Pharm.**, 2001, 220, 13.
8. Abou Zeit-Har, M.S., Verimer, T. and Long, J.P., **Pharmazie**, 1982, 37, 593.

Induction of Carbonic Anhydrase by *Cuscuta reflexa* Stem and *Corchorus olitorius* Seed in Mice

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The effects of multiple intraperitoneal doses of methanolic extract of *Cuscuta reflexa* Roxb. stem and *Corchorus olitorius* Linn. seed on the activity of carbonic anhydrase in the uterus of mice were studied. These methanolic extracts caused a significant increase in the carbonic anhydrase activity in the uterus of mice. The increased rate of enzymatic activity might be associated with elevated level of progesterone induced by these methanolic extracts. This further establishes the antifertility nature of methanol extract of *C. reflexa stem* and *C. olitorius* seed.

Cuscuta reflexa Roxb., family Convolvulaceae known as *Swarnalata* (Bengali) and *Amarvel* (Hindi) is a golden yellow dodder like parasite. The plant is common throughout India, found widely in the plains of West Bengal, growing on thorny or other shrubs as parasite annuals. Various parts of this plant were used in tribal medicine for the diseases like epilepsy, melancholy and insanity[1]. It is also useful externally against itch and internally in fevers, flatulence and induration of the liver[2-5]. The *C. reflexa* stem and its different extracts on preliminary investigation have been found to possess antifertility effect[6].

Corchorus olitorius Linn. (jute) family Tiliaceae is an annual herb with slender stems. It is cultivated in many parts of India. The seeds are used as purgative and leaves as demulcent, diuretic, febrifuge (infusion) and in chronic cystitis and dysuria[5]. *C. olitorius* seed is a traditional tribal medi-

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