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CCC: 0377-8282/99

Dosmalfate

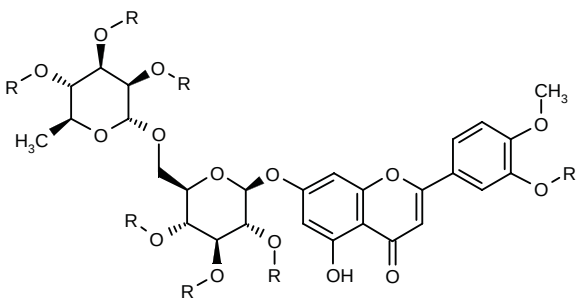
Cytoprotectant

Rec INN

F-3616

[μ_7-[7-[[6-*O*-(6-Deoxy-2,3,4-tri-*O*-sulfo-α-L-mannopyranosyl)-2,3,4-tri-*O*-sulfo-β-D-glucopyranosyl]oxy]-5-hydroxy-2-[4-methoxy-3-(sulfooxy)phenyl]-4*H*-1-benzopyran-4-onato(7–)]]tetradeca-μ-hydroxyheneicosahydroxytetradecaaluminum

Diosmin heptakis(hydrogensulfate)aluminum complex



R = $SO_3[Al_2(OH)_5]$

$C_{28}H_{60}O_{36}Al_{14}O_{71}S_7$ Mol wt: 2134.9210

CAS: 122312-55-4

EN: 162108

Synthesis

Dosmalfate is obtained in a multistep synthesis: The treatment of anhydrous 5-ethyl-2-methylpyridine (I) with chlorosulfonic acid (II) affords 5-ethyl-2-methylpyridine sulfur trioxide complex (III). Heating 1 mol of diosmin (IV) with 7 mol of (III) gives diosmin heptakis(hydrogensulfate) 5-ethyl-2-methylpyridinium salt (V), which by treatment with aqueous sodium hydroxide yields the diosmin heptakis(hydrogensulfate) sodium salt. Finally, the reaction of the sodium salt in an aqueous medium with an aqueous aluminum hydroxychloride solution yields the diosmin heptakis(hydrogensulfate) aluminum complex (1, 2). Scheme 1.

Description

Yellow amorphous solid.

Introduction

During the last years remarkable advances in the understanding of the pathophysiology of peptic ulcer disease have been achieved. The significance of nonsteroidal antiinflammatory drugs (NSAIDs) and the Gram-negative bacillus *Helicobacter pylori* in the pathogenesis of peptic ulcer disease is now well established. *H. pylori* infection is the most important cause of peptic ulcers. All patients with gastric or duodenal ulcers who are infected with *H. pylori* should be treated with antimicrobials regardless of whether they are suffering from the initial presentation of the disease or from a recurrence (3). The second most common cause of peptic ulcer disease is the ingestion of NSAIDs (4). The pathophysiology of peptic ulcer disease may be thought of as an imbalance between aggressive factors and local mucosal defenses, such as the secretion of bicarbonate, mucus and prostaglandins. Treatment is mainly aimed at reducing aggressive factors, although it can also be aimed at strengthening mucosal defenses of the stomach and the duodenum with cytoprotective agents (5).

NSAIDs are widely prescribed for inflammatory conditions, but their efficacy is offset by a significant incidence of gastrointestinal side effects, especially in elderly patients (6, 7) and those who take them chronically (8, 9). The use of selective COX-2 inhibitors would theoretically reduce inflammation without producing gastrointestinal adverse effects (10), although the long-term clinical relevance of these NSAIDs is as yet unknown. A number of studies using misoprostol in patients and volunteers administered NSAIDs have demonstrated an improvement in the gastric mucosal damage and a decrease in gastrointestinal blood loss (11, 12). In order to prevent the undesirable gastrointestinal side effects associated with NSAIDs, combination treatment with misoprostol has been successfully employed (13, 14). However, a

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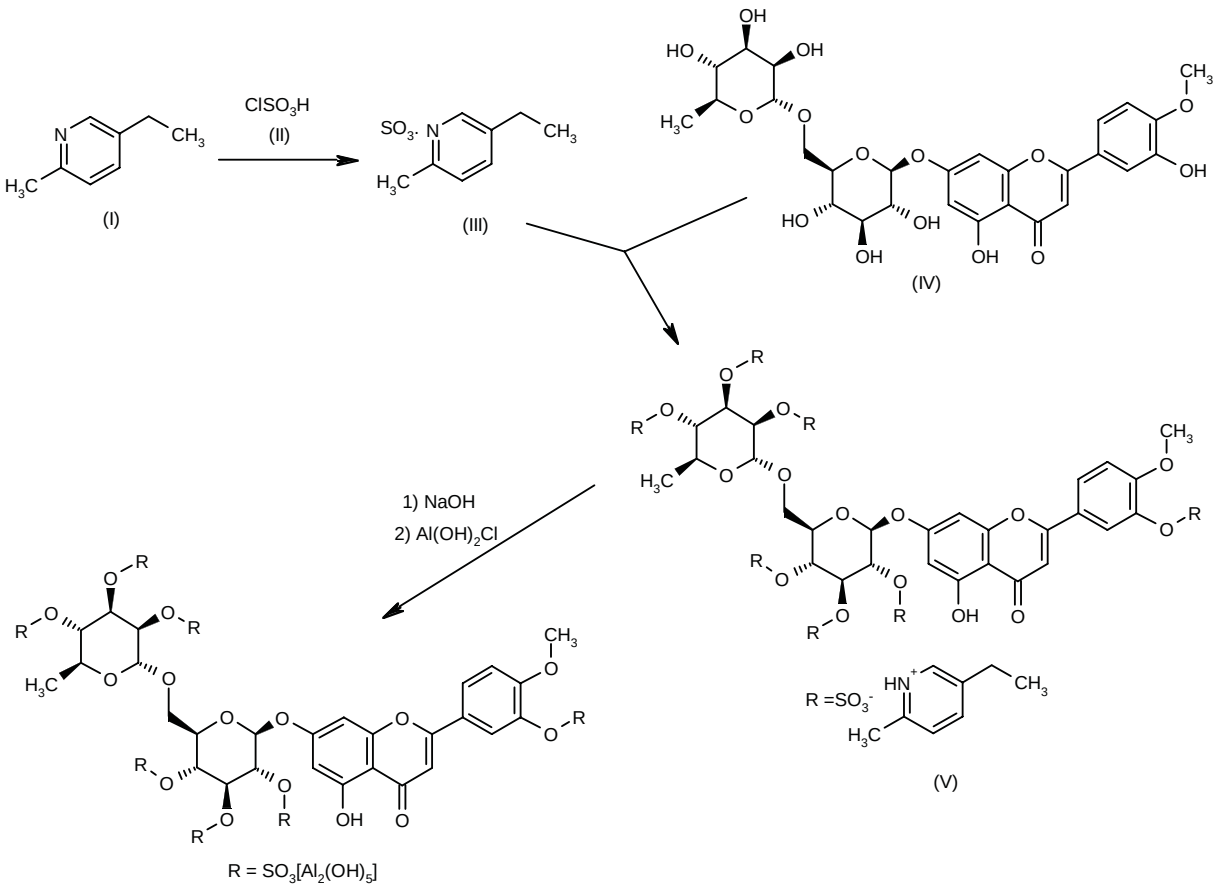
Scheme 1: Synthesis of Dosmalfate



dose-related increase in the incidence of diarrhea has been consistently reported with misoprostol, and in moderate to severe cases discontinuation of treatment is necessary (15, 16).

Investigations on the mechanism of action of the acid secretory pathway and other aspects of peptic ulcer disease have led to therapeutic advances focusing on the formation and prevention of ulcers. Dosmalfate is a new cytoprotective agent for the treatment of mucosal lesions associated with peptic ulcer disease and has a very low incidence of side effects. It is particularly effective in the prevention and treatment of NSAID-induced gastrointestinal damages.

Pharmacological Actions

Dosmalfate possesses an interesting pharmacological profile as a cytoprotective agent and has demonstrated excellent protection of the gastrointestinal mucosa in several different experimental models of acute and chronic ulcers.

The effects of dosmalfate on gastric secretion and gastric ulceration were evaluated in pylorus-ligated rats (17). Dosmalfate significantly increased the pH and slightly reduced the pepsin activity of gastric secretion accumulated 4 hours after pylorus ligation, without any change in volume and acid concentration. The effect was more pronounced when dosmalfate was administered orally immediately after pylorus ligation and was negligible when administered by intraduodenal route. Significant damage to the gastric mucosa, as well as reflux and esophagus perforation, were observed 19 hours after ligation, with more than 80% mortality in untreated animals. Dosmalfate demonstrated significant protection against these effects (2, 18).

Simultaneous ligation of the pylorus and the limiting ridge in the rat causes severe esophageal ulceration which increases with increasing duration of ligation (19). Dosmalfate at doses starting at 12.5 mg/kg significantly protected esophageal mucosa from the effects caused by gastroesophageal reflux.

Oral administration of dosmalfate dose-dependently inhibited the development of ethanol-induced gastric

mucosa lesions in rats. Under the same experimental conditions, ranitidine was devoid of any effects. Gastric protection afforded by dosmalfate seems to be mediated, at least in part, by endogenous prostaglandins, since indomethacin pretreatment partially diminishes but does not abolish its cytoprotective action (20). Moreover, the protective effect of dosmalfate on gastric mucosa when prostaglandin biosynthesis is blocked indicates the existence of an additional mechanism of action independent of prostaglandins. In another study in rats, dosmalfate reduced indomethacin-induced gastric lesions, with an ED_{50} of 145 mg/kg. The protection was greater when dosmalfate was given 30 min prior to indomethacin administration (16).

In experiments in rats, gastric ulcers were induced by submucosal injection of acetic acid at the junction of the corpus and antrum of the stomach (21). Treatment with oral dosmalfate for 20 days, beginning on the day of ulcer induction, significantly accelerated the spontaneous healing of ulcers compared with untreated animals. Size and depth of gastric ulcers of treated animals were generally smaller than those of untreated animals during the entire study, suggesting that dosmalfate has protective effects against ulcer development (22).

In stressed rats restrained for 5 h at 4 °C, oral pretreatment with high doses of dosmalfate reduced the degree of gastric lesions in a dose-dependent manner compared to animals treated with vehicle only (16). In rats restrained for 24 h, moderate to severe gastric lesions were induced (23) and the effects of dosmalfate on the rate of healing were examined. Dosmalfate caused a moderate increase in the rate of healing of gastric damage, and this effect was found to be statistically significant (24).

Pharmacokinetics and Metabolism

Studies carried out in rats with dosmalfate demonstrated a practically null absorption after oral administration. Plasma and urine concentrations of dosmalfate determined as aluminum by AA in samples after oral administration to Wistar rats were below the limits of detection. Values were not statistically different from those of the control group (25).

A study performed in humans also revealed a practically null absorption of dosmalfate after oral administration. No significant levels of the acid organic fraction of dosmalfate were detected in any of the plasma samples by HPLC. Accumulated elimination in urine 72 h after oral administration of dosmalfte 8 g was less than 0.04%, with a detection limit of 0.1 μg/ml (26).

Toxicity

Toxicity studies after acute and repeated-dose administration in mice, rats and dogs showed no evidence of significant adverse effects (27, 28).

General pharmacological studies in animals demonstrated no significant effects for dosmalfate on CNS, respiratory, cardiovascular or other systems after oral doses of 2000-5000 mg/kg (29).

Clinical Studies

A phase I clinical trial was carried out in healthy volunteers administered single oral doses of dosmalfate (1, 2, 4, 6 or 8 g) in order to establish the maximum tolerated dose. The compound was shown to be safe at all doses tested (30).

In a study in healthy volunteers, the tolerance of dosmalfate (1 or 2 g/day for 6 days) was compared with that of placebo. No changes in arterial pressure, cardiac and respiratory frequency, body temperature, biochemical parameters in blood and urine or hematological parameters were found (31).

The protective effects of oral dosmalfate on gastric mucosa were evaluated in a double-blind, crossed, randomized, placebo-controlled trial in healthy subjects. Subjects were administered dosmalfate or placebo 30 min prior to aspirin (1.5 g). Two hours later a gastroendoscopic study was performed and the results were compared with those obtained before treatment. Dosmalfate (1 and 1.5 g) significantly diminished the aspirin-induced gastric lesions as compared to placebo. Clinical and biological tolerance to dosmalfate was excellent in all subjects (32).

In a multicenter, double-blind, randomized, controlled clinical study, 90 patients with endoscopically proven duodenal ulcer received dosmalfate or placebo during 4 weeks. 79% of the patients administered dosmalfate (3 g/day) achieved complete ulcer healing as seen on the final endoscopy at the end of treatment, compared to 55% of the patients adminstered placebo (33).

The safety and efficacy of dosmalfate and misoprostol in preventing serious gastrointestinal complications were compared in patients with rheumatic disease receiving NSAID therapy. The study was a 4-week, multicenter, randomized, double-dummy, parallel trial enrolling male and female adult patients with osteoarthritis, chronic inflammatory rheumatism and abarticular rheumatism, a history of peptic ulcer disease, intolerance to NSAIDs or smoking more than 10 cigarettes a day, who were receiving NSAID therapy. Patients were excluded if gastric or duodenal ulcer was detected by gastrofibroscopy at the time of entry or if they had experienced recent active peptic ulcer disease. Patients were randomized to dosmalfate (n = 169) 1.5 g/12 h or misoprostol (n = 160) 100 μg/6 h. The efficacy of dosmalfate in preventing gastric ulcer during NSAID therapy was very high and comparable to that of misoprostol. At the end of the study no statistically significant differences between treatment groups were found (34).

A 12-week, multicenter, randomized, double-dummy, parallel study compared the efficacy and tolerability of dosmalfate and misoprostol in the prevention of gastric

and duodenal ulcers associated with long-term NSAID therapy. The study was performed in 442 adult male and female patients with a clinical diagnosis of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or osteoarthritis, presenting a history of peptic ulcer disease or intolerance to NSAIDs and receiving NSAID therapy. Elegible patients were randomly assigned to receive either dosmalfate (1.5 mg/12 h) or misoprostol (200 μg/6 h). Primary efficacy criterion was the percentage of patients who presented gastric and/or duodenal ulcers at any time of the study or upon endoscopic examination performed after 12 weeks of therapy. Secondary criteria included the evaluation of superficial lesions of the mucosa on the final endoscopic examination and complications such as bleeding and perforation. The incidence of NSAID-induced, endoscopically visualized gastroduodenal ulcers or erosions was reduced with both dosmalfate and misoprostol. Ulcers were observed in 3.8 and 4.7% of the patients on dosmalfate and misoprostol, respectively. No statistically significant differences between treatments were seen. Analysis of adverse events showed that dosmalfate was better tolerated than misoprostol. Diarrhea was the most frequently reported side effect with misoprostol (35).

Manufacturer

FAES, S.A. (ES).

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