Pharmaceutical Research, Vol. 7, No. 6, 1990

Report

Formulation and Dosage Form Design in Drug-Induced Topical Irritation of the Gastrointestinal Tract

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Received February 8, 1989; accepted January 5, 1990

To test drugs for topical effects on gastrointestinal mucosa, a new *in situ* rabbit colon model was used that permits direct application of drugs in suspensions from gel cups, solutions, or commercially available tablets and capsules onto rabbit colonic mucosa for up to 8 hr. For each agent tested an irritation index was calculated—the product of the area of the mucosa affected by drug exposure and a numerical score for observed effect. Irritation indices ranged from 0 (no effect) to 25.6 (maximal irritation measurable). In general, the immediate release of drug onto tissue elicited the greatest effect, whereas slow or controlled release of drug produced the least response. Topical irritation was found to be a function of (1) the drug, (2) the formulation, (3) the delivery rate, and (4) the concentration. The gastrointestional therapeutic system (GITS) of potassium chloride and of brompheniramine/pseudoephedrine produced far less irritation than current commercial formulations of these drugs. The rabbit colon model is proposed as a useful screening tool during drug development to aid in selecting the formulation of an oral dosage form that will minimize topical irritation.

KEY WORDS: drug-induced irritation; rabbit colon model; animal model; gastrointestinal therapeutic system (GITS).

INTRODUCTION

Many compounds commonly used in medical therapy today irritate the gastrointestinal mucosa, but this adverse effect is often unknown to the physician and has seldom been studied. Gastrointestinal irritation can occur by a local topical action, as when rapid dissolution of a tablet releases large quantities of drug onto the mucosa, or secondarily by a systemic action. For example, among nonsteroidal antiinflammatory drugs (NSAIDs), conventional doses of aspirin irritate the mucosa topically (1–3), whereas indomethacin adversely effects the gastrointestinal tract through both enterohepatic recirculation and systemic effects (1,2,4,5).

While drug development and formulation have little effect on inherent adverse systemic drug actions, topical irritation can be decreased or eliminated by appropriate formulations and dosage forms, such as a controlled-release dosage form which presents less drug to the gastrointestinal mucosa per unit time than an immediate-release form. This study was designed to explore and to illustrate these means of reducing topical effects.

MATERIALS AND METHODS

Agents and Animals Tested

Compounds tested as commercially formulated tablets or capsules are listed in Table I; those tested as various formulations in the gel cup in the acid or salt form are given in Table II. Male and female New Zealand white rabbits (2–4 kg) were acclimated to laboratory conditions for a minimum of 2 weeks and fed Purina certified rabbit chow. Food was removed but water was available ad libitum 18–24 hr before studies began.

Anesthesia

Rabbits were anesthetized with an induction dose of xylazine HCl (14–18 mg/kg im) and ketamine HCl (80–90 mg/kg im) supplemented with intermittent doses of pentobarbital sodium (13 mg/ml iv) as needed.

Test procedure (Described in Ref. 6)

The rabbit colon was exposed through a 10-cm midline abdominal incision, and a segment immediately distal to the cecum was isolated by placing two ligatures around the colon 15–20 cm apart. The isolated segment of colon was separated from the remaining intestine by cutting between the ligatures, taking care to leave the nerves and blood vessels supplying the isolated segment intact. A longitudinal incision along the antimesenteric border of the entire length of the segment preserved the blood supply directly beneath the mucosa. The isolated segment was clamped into a three-chambered test cell to form the floor of each chamber.

After completion of the surgical preparation, the test cell was placed in a level position on top of the abdomen. During a 1-hr control period, a Harvard infusion pump continually circulated Ringer's solution or artificial intestinal

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Table I. Dosages Tested for Irritation on Rabbit Colonic Mucosa

Brand name	Generic name	Dose/dose form	Manufacturer
Vitamin C	Ascorbic acid	1000-mg tablet	Schiff
Vitamin C (timed release)	Ascorbic acid	500-mg tablet	Nutrition Square
AcuSystem C (GITS)[a]	Calcium ascorbate	500-mg tablet	ALZA
Inderal	Propranolol HCl	60-mg & 80-mg tablet	Ayerst
Inderal LA	Propranolol	80-mg capsule	Ayerst
GITS propranolol HCl[b] (prototype)	Propranolol HCl	160-mg tablet	ALZA
Slow-K	Potassium chloride	8 mEq/600-mg tablet	Ciba
GITS KCl[b]	Potassium chloride	750-mg tablet	ALZA
Bromfed	Brompheniramine maleate/ pseudoephedrine HCl	6 mg/60-mg tablets	Muro Pharmaceuticals
Dimetane Extentab	Brompheniramine maleate	8-mg tablets	A. H. Robins
Sudafed Plus	Pseudoephedrine HCl/ chlorpheniramine maleate	60 mg/4-mg tablet	Burroughs Wellcome
Drixoral	Pseudoephedrine sulfate dexbrompheniramine maleate	120 mg/6-mg tablet	Schering
GITS[b]	Pseudoephedrine HCl/ brompheniramine maleate	60 mg/6-mg tablet	ALZA
Vibra-Tabs	Doxycycline hyclate	100-mg tablet	Pfizer
Acutrim	Phenylpropanolamine	75-mg tablet	Ciba

[a] Gastrointestinal therapeutic system.
[b] Not commercially available.

Table II. Drug/Gel Formulations Delivered from Gel Cups on Rabbit Colonic Mucosa Ranked by Irritation Index: Because the Area of Exposure Was Relatively Constant with the Gel Cup, Only Mean Score and Index Are Presented

Formulation/Compound	mg	n[a]	Irritation Score	Irritation Index
Placebo (3)[b]		8	0	0
Hydrochlorothiazide, USP (3)	25	4	0	0
Diclofenac acid (3)	25	4	0	0
Naproxen acid (3)	100	4	0	0
Indomethacin acid (3)	25	4	0	0
Indomethacin acid, N.T. (8)	25	2	0	0
Acetaminophen (3)	150	4	0	0
Albuterol (3)	2	4	0	0
Albuterol (8)	2	4	0	0
Methyldopa, USP (3)	125	4	0	0
Methyldopa, USP (8)	125	4	0	0
Furosemide, USP (3)	20	4	0	0
Furosemide, USP (8)	20	6	0	0
Brompheniramine maleate (8)	4	2	0	0
Pseudoephedrine HCl (8)	30	6	0	0
Ibuprofen base (3)	175	4	0.3 (0.5)[c]	0.1 (0.2)
Brompheniramine maleate (3)	4	4	0.6 (0.8)	0.1 (0.1)
Salicylate, sodium, USP (3)	40	4	2.3 (0.3)	0.7 (1.0)
Pseudoephedrine HCl/ brompheniramine maleate (3)	60 4	8	1.2 (1.2)	1.2 (1.8)
Diclofenac, sodium (3)	25	4	1.5 (0.7)	1.2 (1.3)
Pseudoephedrine (3)	60	4	2.4 (0.8)	1.7 (1.9)
Naproxen, sodium (3)	100	4	3.3 (0.3)	2.4 (0.5)
Salicylate, sodium, USP (3)	150	4	3.1 (0.3)	3.7 (0.9)
Indomethacin trihydrate, sodium (3)	30	4	3.3 (0.3)	4.4 (0.8)
Acetylsalicyclic acid, USP (3)	150	4	3.6 (0.5)	5.1 (3.6)
Potassium chloride (3)	155	4	3.9 (0.3)	14.5 (8.9)

[a] Number of exposures per drug formulation.
[b] Number of hours of exposure.
[c] Standard deviation.

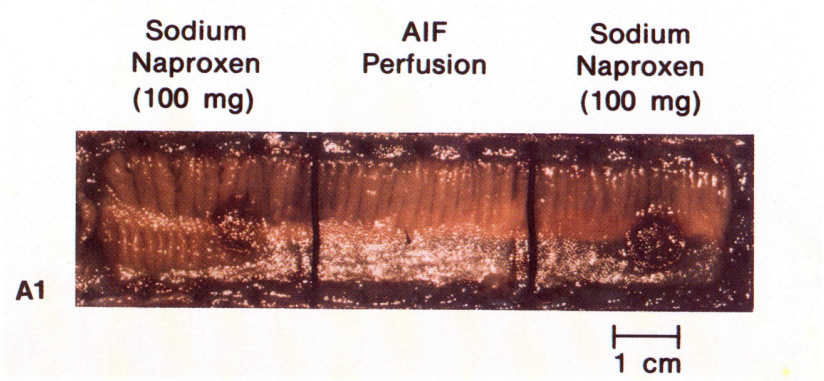
fluid, USP (AIF) over the mucosa in each chamber at approximately 2.0 ml/min; a water bath maintained the temperature at 37°C. Test agents were placed directly on the mucosa in each chamber for 3 to 8 hr while Ringer's or AIF circulated through the chambers.

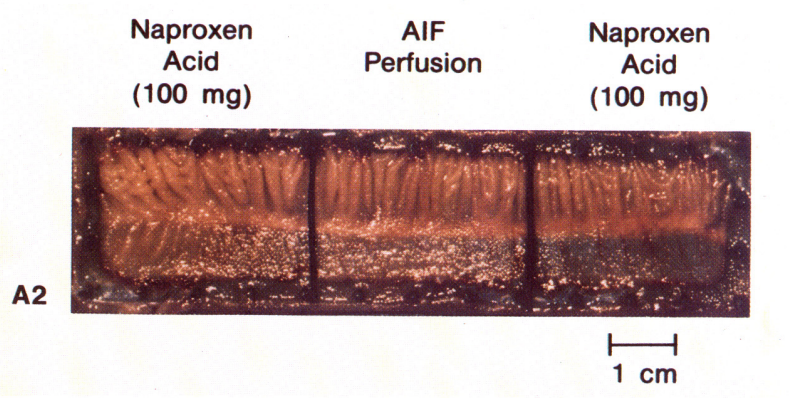
Commercial tablets and capsules were placed directly on the rabbit colonic mucosa. ALZA gastrointestinal therapeutic systems (GITS) were placed directly onto the mucosa with the delivery orifice in direct contact with the mucosa. Other drugs were formulated in a suspension with Klucel HF hydroxypropylcellulose (nonionic water soluble cellulose ether manufactured by Hercules Inc.) and then placed in a 250-μl polycarbonate cup. The open end of the cup was placed on the tissue, bringing the drug formulation into contact with the mucosa. Drug solutions were perfused onto the tissue at constant rate by a Harvard infusion pump through a polyethylene catheter (PE 60) positioned with the tip resting gently on the mucosal surface.

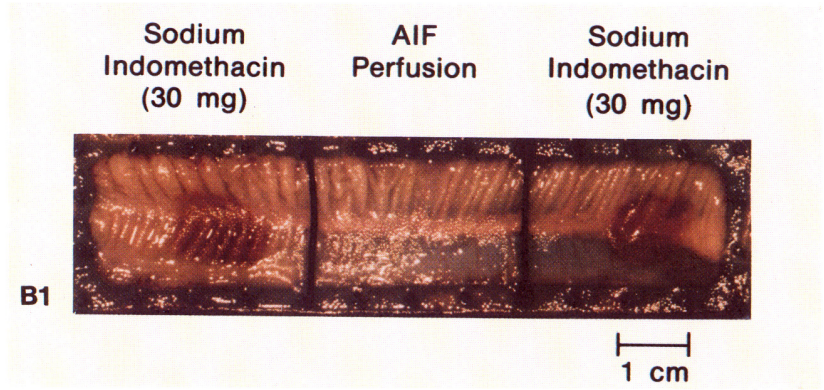
Mucosal tissue was exposed to test agents for 3 hr; if no effect was noted the exposure was continued for up to 8 hr. After drug exposure, the colon was removed from the animal, photographed, and evaluated macroscopically for degree (0–4, as defined in Table III) and area (0–6.4 cm^2) of visible mucosal irritation. These two values were then multiplied to calculate an irritation index of 0 (no topical irritation) to 25.6 (the maximum achievable response—very severe irritation). This index thus reflected both severity and extent of response within the test chamber.

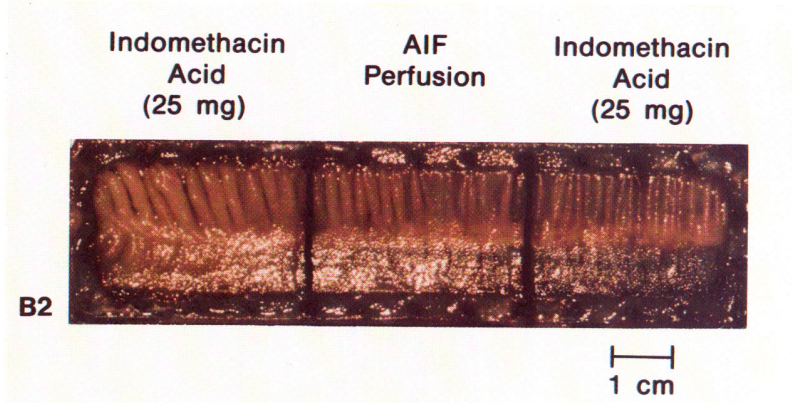
Table III. Scale for Visible Macroscopic Mucosal Irritation

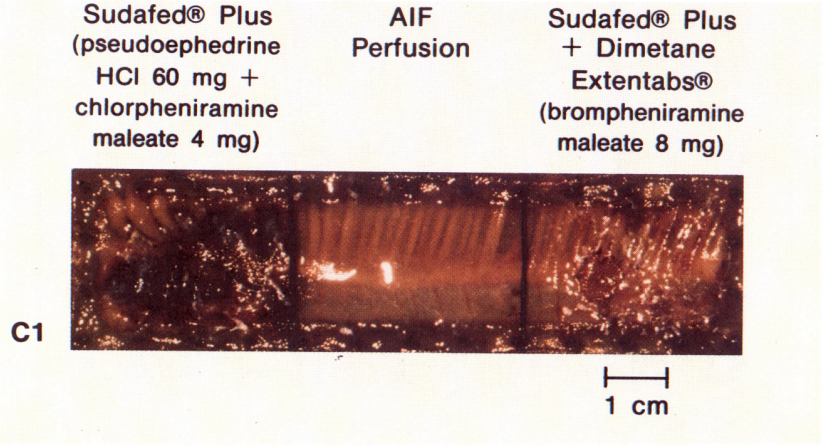
0	= Normal mucosa
1	= Barely perceptible color change
2	= Mucosa slightly red/pale to white; area definable
3	= Mucosa red/purple or white; possible surface erosion
4	= Mucosa very red/dark purple or white/gray; necrotic in appearance/frank ulceration

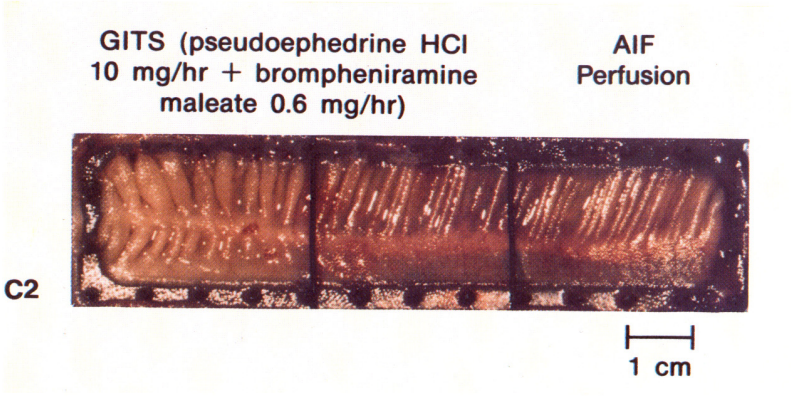

Sodium Naproxen (100 mg)
AIF Perfusion
Sodium Naproxen (100 mg)
A1
1 cm


Naproxen Acid (100 mg)
AIF Perfusion
Naproxen Acid (100 mg)
A2
1 cm


Sodium Indomethacin (30 mg)
AIF Perfusion
Sodium Indomethacin (30 mg)
B1
1 cm


Indomethacin Acid (25 mg)
AIF Perfusion
Indomethacin Acid (25 mg)
B2
1 cm


Sudafed® Plus (pseudoephedrine HCl 60 mg + chlorpheniramine maleate 4 mg)
AIF Perfusion
Sudafed® Plus + Dimetane Extentabs® (brompheniramine maleate 8 mg)
C1
1 cm


GITS (pseudoephedrine HCl 10 mg/hr + brompheniramine maleate 0.6 mg/hr)
AIF Perfusion
C2
1 cm

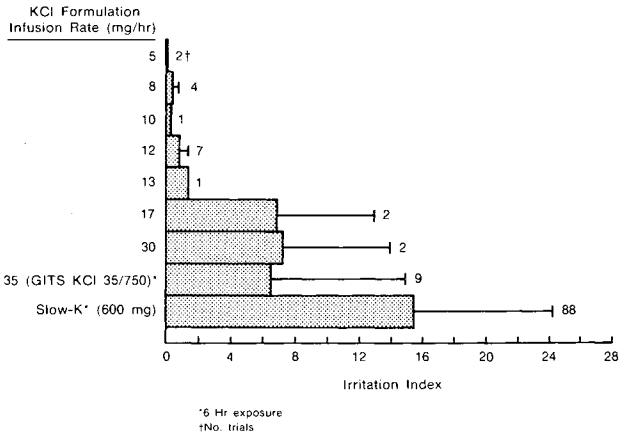


Fig. 2. Dose–response relationship of potassium chloride delivered onto rabbit colonic mucosa (3-hr exposure). Results are mean ± SD.

A detailed description of the rabbit colon model and the test methodology used in this study may be found in a publication by Fara and colleagues (6). Because of the excellent correlation of macroscopic and histological results previously reported (6), we report only the macroscopic irritation in this paper.

RESULTS

Mucosal tissue responses ranged from an irritation index of 0 to 25.6 (Figs. 2–4, Table II). Responses depended not only on the drug tested but also its form (e.g., acid or base), concentration, and delivery rate. The acid forms of certain drugs were substantially less irritating than the salt forms (Fig. 1, Table II). This was particularly true for NSAIDs tested: the sodium salts of naproxen, diclofenac, and indomethacin caused topical irritation while the acid forms did not. Furthermore, acid forms that elicited no irritation after 3 hr did not elicit irritation after 8 hr.

Figure 2 illustrates the dose–response relationship for KCl delivered onto the mucosa as a solution at 5–30 mg/hr or as a tablet (Slow-K, GITS KCl). A marketed product, Slow-K, released 80–100 mg/hr in the first 4 to 6 hr (ALZA data) and had the highest irritation index.

Various dosage forms of propranolol behaved similarly to KCl dosage forms. The irritation index for the immediate-release propranolol tablet (Inderal, 60 and 80 mg) was 25.6,

Fig. 1. Comparison of the effect of various drugs and drug forms on rabbit colonic mucosa after a 3-hr exposure unless otherwise noted. (A) Sodium naproxen (A1) and naproxen acid (A2). Macroscopic irritation scores from left to right were 3.0, 0, and 3.5 for sodium naproxen and 0, 0, and 0 for naproxen acid, respectively. (B) Sodium indomethacin (B1) and indomethacin acid (B2). Macroscopic irritation scores from left to right were 3.0, 0, and 3.0 for sodium indomethacin and 0, 0, and 0 for indomethacin acid, respectively. (C) Sudafed Plus (C1) and GITS (pseudoephedrine/brompheniramine) (C2). Macroscopic irritation scores from left to right for Sudafed Plus and Dimetane Extentabs were 4, 0, and 4 (3-hr exposure) and 3, 3, and 0 for GITS pseudoephedrine/brompheniramine (ALZA) (6-hr exposure), respectively.

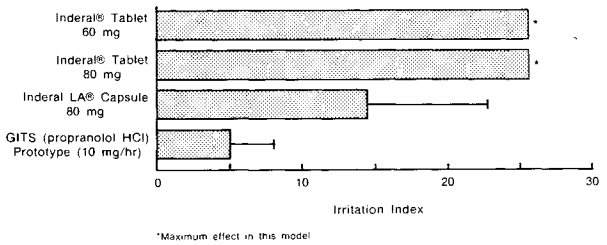


Fig. 3. Effect of propranolol dosage form on irritation index measured on rabbit colonic mucosa (3-hr exposure). Results are mean ± SD.

the highest achievable with this model. Long-acting, slow-release propranolol (LA) had an index of 15. A prototype of GITS propranolol (release rate of 10 mg/hr) had an index of 4.9—the lowest irritation index of propranolol products tested (Fig. 3).

Other controlled-release dosage forms caused less irritation than immediate-release forms (Fig. 4). For example, calcium ascorbate in a dosage form designed to control rate and duration of ascorbic acid release (AcuSystem C) had very little effect compared to an immediate-release formulation of ascorbic acid (Schiff and Nutrition Square). A controlled-release form (GITS) of pseudoephedrine/brompheniramine caused less irritation than immediate-release forms (Drixoral and Sudafed Plus), although differences in the quantities present in each formulation prevent exact comparison.

DISCUSSION

This study shows that many products prescribed and used routinely can elicit profound topical mucosal irritation on gastrointestinal tissue. In the rabbit colon model used here, commercial tablets of doxycycline, propranolol, and potassium chloride were particularly irritating and confirm clinical reports of gastrointestinal irritation with these compounds (7–9). Topical irritation is greatly reduced, however, when an irritating compound was presented to the mucosa in a controlled manner by precisely metering measured quantities per unit time.

Furthermore, these findings indicate that topical irritation may be reduced or eliminated by optimal selection of the drug form. Salt and acid forms of drugs elicited differing degrees of irritation in the rabbit colon model. For example, the salt forms of many NSAIDs elicited minor irritation, whereas the acid forms of these compounds did not. Kircher and colleagues (10) reported similar findings with NSAIDs. Similarly, vitamin C sold as ascorbic acid (Schiff) was irritating, whereas the calcium salt was not. In general, low-solubility drug forms caused less irritation than the more soluble forms of the same drug.

Irritation caused by salt and acid forms of three drugs was compared in the rabbit colon model and a human buccal model (11). Acetylsalicylic acid, indomethacin acid, and naproxen acid were less irritating in both models than were salt forms of the drugs. Because both models represent only one section of the alimentary canal, neither will always predict clinical consequences of drug administration.

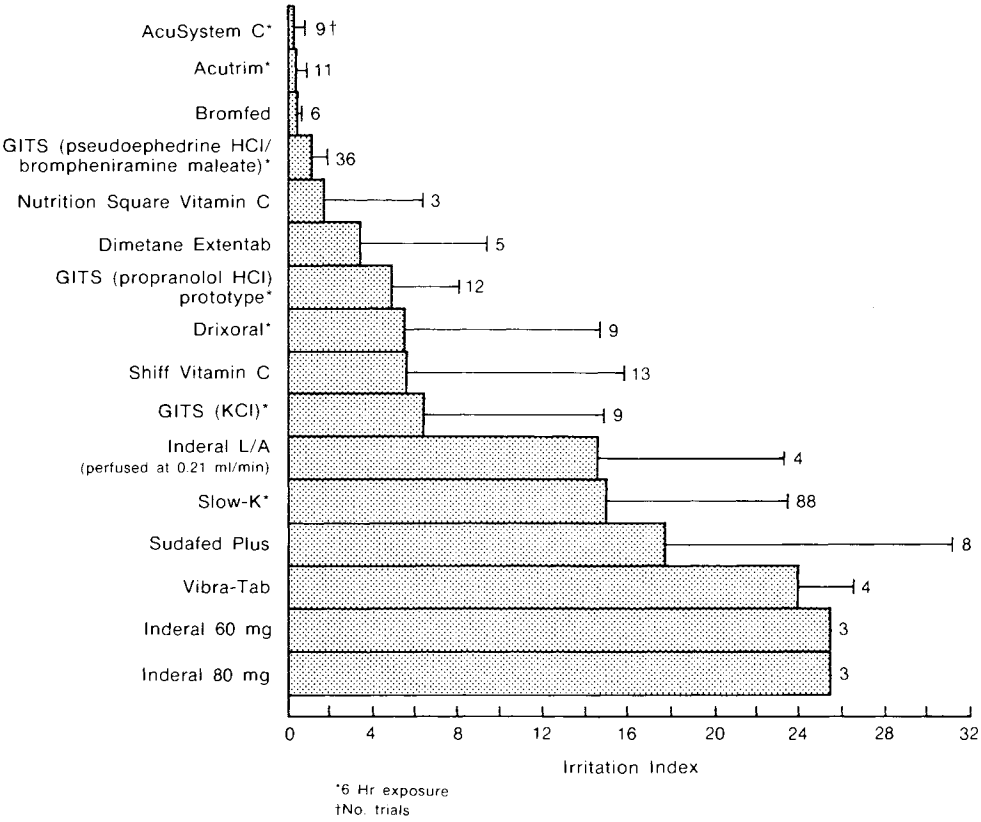


Fig. 4. Effect of drugs (formulated as either rapid or controlled-release tablets or capsules) on rabbit colonic mucosa (3-hr exposure unless noted). Results are mean ± SD.

Previous animals models to investigate topical effects of drugs on gastrointestinal mucosa included oral administration (12), cat stomach preparations (13), and a 24-hr *in vivo* pig model (14). The rabbit colon model utilizes a thin, sensitive mucosal layer allowing simultaneous visual comparison on adjacent tissue samples of the effects of up to three different agents. The use of the gel cup for suspensions allows investigators to easily formulate a large number of substances to test for topical mucosal effects, and it offers a simple and reproducible method of presenting compounds to the tissue for qualitative evaluation for preliminary screening. Furthermore, because drugs in solution can be delivered easily by catheter, this model allows comparison of the effects of various delivery rates.

The rabbit colon model is a rapid, reproducible, and highly sensitive method of comparing local effects of different agents on the gastrointestinal mucosa in a worst-case situation of prolonged drug delivery to one site in the rabbit gastrointestinal tract. Although the correlation between the rabbit model and the human gastrointestinal mucosa needs to be studied further, this rabbit colon model can identify topical irritation potential of a drug early in its development and can aid in appropriate formulation and dosage form design.

ACKNOWLEDGMENTS

The authors wish to acknowledge Kirstin Nichols and Dan Liberthson for editorial assistance.

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