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Controlled-release dosage forms and gastrointestinal blood loss: four clinical studies

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Summary

Four clinical studies were conducted to assess gastrointestinal (GI) blood loss during use of the OROS® dosage form. These were open-label, randomized, parallel studies of 176 healthy volunteers 18–78 years of age. Blood loss was measured using the ^{51}Cr red blood cell tagging method and stool guaiac tests. GI blood loss from a drug associated with GI irritation, indomethacin [as OROS (sodium indomethacin) or as immediate-release indomethacin], was greater than that from lactose placebo but less than that from aspirin. GI blood loss following ingestion of the OROS dosage forms containing cold/allergy drugs – a combination of pseudoephedrine hydrochloride and brompheniramine maleate, chlorpheniramine maleate, or pseudoephedrine hydrochloride – was statistically indistinguishable from that of marketed reference slow-release cold/allergy products or placebos. Blood loss in volunteers 50 years of age or older was similar during use of OROS (mannitol) placebo or oral lactose placebo tablets. Baseline GI blood loss in all four studies was age-invariant. In these studies, GI blood loss, when present, was associated with specific drugs, aspirin and indomethacin, and not with a particular OROS dosage form.

Introduction

OROS® technology was developed to provide controlled constant or patterned delivery of a particular drug or combination of drugs for 3–24 h. The OROS system is ALZA Corporation's dosage form for human therapy that, after ingestion, delivers drugs to the gastrointestinal (GI) tract at a rate controlled by osmosis. An OROS system has a solid core that is usually shaped like a standard tablet and contains the therapeutic agent or agents, standard tablet excipients, and often osmotic agents. This core is coated with a semipermeable, rate-controlling polymer membrane containing one or more minute laser-drilled orifices. In an aqueous environment, the osmotic activity of the core components establishes an osmotic pressure gradient across the membrane, drawing water into the OROS system at a rate controlled by the composition and thickness of

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the membrane. Drug delivery begins when the water enters the system to dissolve or suspend the drug in the core; the resulting drug solution or suspension flows out of the orifice(s) at a rate equal to the rate of water inflow through the membrane. One type of OROS system, the Elementary Osmotic Pump, combines drug and sometimes an osmotic agent in a monolithic core and delivers drug in solution (Theeuwes, 1975).

OSMOSIN®, an elementary osmotic pump system delivering sodium indomethacin, was introduced in 1983 in England and in Germany but was withdrawn from the market shortly thereafter because of a perception of a higher-than-expected incidence of gastrointestinal bleeding and perforation. Subsequently, numerous investigations have focused on mechanisms by which an oral dosage form could irritate mucous membranes of animals and man (Committee on Safety of Medicines, 1983; John et al., 1986; Kircher et al., 1987; Place et al., 1988; Fara and Myrback, 1990). These studies have documented that local irritation is a function of the chemical delivered, its rate of administration (and therefore the local concentration), and its duration of contact with the tissue. In general, lower or controlled-delivery rates and shorter durations of exposure to an irritating drug created less irritation. Leese and colleagues (1990) reported that aspirin caused significant fecal blood loss compared to lactose placebo, but that OROS (albuterol) (Volmax®), OROS placebo, and immediate-release (IR) albuterol tablets (Ventolin®) were not associated with increased fecal blood loss. The studies reported here were designed to assess gastrointestinal blood loss in humans using OROS controlled-drug-delivery systems containing various drugs or a mannitol placebo.

We report results of four GI blood loss studies in healthy volunteers with OROS Elementary Osmotic Pump formulations designed to provide relatively constant drug plasma levels throughout the day. Individual studies to determine GI blood loss were randomized, open-label, and parallel. GI blood loss was measured by labeling subjects' red blood cells with ^{51}Cr and then measuring ^{51}Cr in the stool; in some studies occult blood was also measured by the less sensitive guaiac method (Physicians' Desk Reference [PDR], 1988; Stelling et al., 1990). The first study, conducted on indomethacin products known to be moderate gastrointestinal irritants, served as background for subsequent GI blood loss studies to assess safety of the OROS dosage form in the GI tract with three OROS cold/allergy products: OROS (pseudoephedrine hydrochloride with brompheniramine maleate), OROS (chlorpheniramine maleate), and OROS (pseudoephedrine hydrochloride). None of the drugs contained in these three dosage forms is known to be associated with GI irritation or bleeding. Studies also included determination of GI blood loss after plain aspirin administration. In addition, to determine the safety of the dosage form without drug, GI blood loss after administration of an OROS placebo delivering mannitol was evaluated in one study.

The effect of age on blood loss was also examined. Baseline and aspirin-induced GI blood loss was evaluated in younger (18–50 years of age), older ($\geq$ 50 years of age), and elderly ($\geq$ 64 years of age) volunteers. Older and elderly volunteers participated in two of the OROS cold/allergy product studies.

Materials and Methods

We evaluated four OROS formulations and an OROS placebo delivering mannitol in four GI blood loss studies with populations of different ages at two study sites. All studies were open-label, randomized, parallel group comparisons of GI blood loss during a placebo week (week 1) and a treatment week (week 2, which began on day 8). Protocols for each study were approved by a duly constituted ethical review board.

Patient exclusion criteria for all studies

Subjects were excluded from the study if they had a history of intolerance to aspirin, salicylate, or other drugs – including lactose – used in the study; excessive alcohol consumption; peptic ulcer or gastrointestinal disease; ulcerative colitis or regional enteritis; hematologic, renal, hepatic,

cardiac, or malignant disease; diabetes with renal or cardiac disease; or tuberculosis. Subjects with clinically significant diseases, hemorrhoids, tooth or gum pathology, or positive stool guaiac (Hemoccult®) tests were also excluded (subjects were not given Hemoccult tests in study I).

In order to enter the treatment week (week 2), subjects had to have negative stool guaiac tests during the placebo week (week 1). In studies II–IV, average ^{51}Cr blood loss during week 1 placebo treatment had to be less than 0.75 ml/day with no single value greater than 1.5 ml/day (Arnold et al., 1985).

Overall study design

After giving written informed consent, subjects were sequestered at the study site for 15 days. Standardized meals provided at the study center excluded red meats and horseradish because these foods can cause false positive results in the Hemoccult test (PDR, 1988). To avoid confounding GI blood loss from sources other than the treatments, the studies required subjects to brush their teeth with soft toothbrushes and limit their caffeine intake to one cup of coffee or tea per day and their smoking to 10 or fewer cigarettes per day.

During week 1, all subjects took eight oral lactose placebo tablets per day for 7 days to establish baseline blood loss values and accustom them to the study procedures (confinement at the study center and stool collection). On the first day of week 1, a 20 ml aliquot of red blood cells was removed from each subject; red blood cells were labeled with ^{51}Cr (250–300 μCi) and reinjected intravenously (Mollison, 1955; Leonards and Levy, 1967; Fussell, 1969). Baseline gastrointestinal blood loss was measured by determining the amount of ^{51}Cr in the stool on days 4–7.

During week 2, subjects took either the OROS drug(s), reference product, aspirin, OROS placebo, or oral lactose placebo tablets (except in study I) with 240 ml of water for 7 days. In studies II–IV, OROS drug(s) or OROS placebo were taken once a day 30 min before breakfast. The reference slow-release cold/allergy products were taken twice a day: 30 min before breakfast and 30 min before the evening meal. Lactose placebo tablets and aspirin tablets were taken 30 min before each of three meals and at bedtime.

GI blood loss was measured by the ^{51}Cr method on days 4–7 and 11–14; ^{51}Cr decay was determined by measuring the ^{51}Cr content of blood samples taken on days 3–6 and 10–13 in studies I–III, and on days 2, 4, 6, 8, 10 in study IV. Blood sample ^{51}Cr was used as a control to account for ^{51}Cr decay in red blood cell half-life. In studies II–IV, blood loss was also monitored by the guaiac method (Hemoccult test) on all stools produced during days 1–14 of the study. The guaiac method was used to detect any blood loss in the lower GI tract.

Study I: OROS (sodium indomethacin)

Subjects

64 healthy men (18–50 years of age) were enrolled, and 56 subjects completed the study.

Study design and medications

During week 1, all subjects took lactose placebo tablets for 7 days. Qualifying subjects were randomly allocated to one of three treatment groups for week 2. During week 2, subjects took one of the following oral medications for 7 days:

OROS (sodium indomethacin 75 mg) 2 × /day (17 subjects)

Indocin® (immediate-release indomethacin 50 mg) 3 × /day (19 subjects)

Plain aspirin (975 mg) 4 × /day (20 subjects)

Study II: OROS (pseudoephedrine hydrochloride with brompheniramine maleate)

Subjects

31 healthy men and 18 healthy women 64 years of age or older were enrolled; 25 men and 15 women completed the study. Women taking hormone replacement therapy – including progestins – were excluded.

Study design and medications

During week 1, all subjects took lactose placebo tablets for 7 days. During week 2, subjects took

one of the following oral medications for 7 days:

OROS (pseudoephedrine hydrochloride 240 mg with brompheniramine maleate 16 mg) 1 × /day (10 subjects)

A combination of Afrinol® Repetabs® (Schering) (pseudoephedrine sulfate 120 mg) and Dimetane® Extentabs® (Robins) (brompheniramine maleate 8 mg) 2 × /day (10 subjects)

Lactose placebo tablets (568 mg) 4 × /day (10 subjects)

Plain aspirin (Lilly) (650 mg) 4 × /day (10 subjects)

Study III: OROS (chlorpheniramine maleate) and OROS (pseudoephedrine hydrochloride)

Subjects

58 healthy men 18–50 years of age were enrolled; 50 subjects completed the study.

Study design and medications

During week 1, all subjects took lactose placebo tablets for 7 days. During week 2, subjects took one of the following oral medications for 7 days:

OROS (chlorpheniramine maleate 16 mg) 1 × /day (10 subjects)

OROS (pseudoephedrine hydrochloride 240 mg) 1 × /day (10 subjects)

Chlor-Trimeton® Decongestant Repetabs® (pseudoephedrine hydrochloride 120 mg/chlorpheniramine maleate 8 mg) 2 × /day (10 subjects)

TABLE 1

Comparison of gastrointestinal blood loss during placebo and active therapy in four clinical studies

Treatment	Number of subjects	Blood loss with placebo (ml/day) (week 1)		Blood loss with treatment (ml/day) (week 2)	
		Mean	SD	Mean	SD
Study I (subject age 18–50 years)					
Plain aspirin [a]	20	0.24	(0.15)	3.62	(2.06)
OROS® (sodium indomethacin) (Osmosin®)	17	0.28	(0.19)	1.17	(0.76)
Immediate-release indomethacin (Indocin®)	19	0.31	(0.16)	0.92	(0.56)
Study II (subject age ≧ 64 years)					
Plain aspirin	10	0.21	(0.13)	3.03	(1.88)
Afrinol® Repetabs®/Dimetane® Extentabs®	10	0.43	(0.16)	0.58	(0.48)
Placebo (lactose) tablets	10	0.33	(0.20)	0.51	(0.28)
OROS (pseudoephedrine HCl/ brompheniramine maleate)	10	0.32	(0.19)	0.42	(0.26)
Study III (subject age 18–50 years)					
Plain aspirin	10	0.30	(0.15)	3.75	(2.48)
Placebo (lactose) tablets	10	0.33	(0.13)	0.37	(0.15)
OROS (chlorpheniramine maleate)	10	0.25	(0.13)	0.35	(0.19)
OROS (pseudoephedrine HCl) (Efidac/24®)	10	0.28	(0.17)	0.31	(0.17)
Chlor-Trimeton® Decongestant Repetabs®	10	0.23	(0.11)	0.29	(0.18)
Study IV (subject age ≧ 50 years)					
Plain aspirin	10	0.30	(0.11)	3.90	(2.98)
Placebo (lactose tablets)	10	0.37	(0.11)	0.46	(0.15)
OROS (mannitol) placebo	10	0.30	(0.15)	0.38	(0.18)

[a] The aspirin dose was 3.9 g/day in study I and 2.6 g/day in studies II–IV.

Lactose placebo tablets (568 mg) 4 × /day (10 subjects)

Plain aspirin (Lilly) (650 mg) 4 × /day (10 subjects)

Study IV: OROS placebo

Subjects

35 healthy men 50 years of age and older were enrolled; 31 completed the study, but one completed subject was excluded from the analysis because of protocol violation.

Study design and medications

During week 1, all subjects took lactose placebo tablets for 7 days. During week 2, subjects took one of the following oral medications for 7 days:

OROS placebo (mannitol 291 mg) 1 × /day (10 subjects)

Lactose placebo tablets (568 mg) 4 × /day (10 subjects)

Plain aspirin (Lilly) (650 mg) 4 × /day (10 subjects)

Statistical analysis

Analysis of variance (ANOVA) was calculated on the logarithms of the week 1 blood loss values. To equalize the variability in blood loss among the five treatment groups, logarithms of the week 2 blood loss values were used for the statistical analysis. This was necessary because the variability of the week 2 blood loss in the aspirin treatment group was substantially greater than that in the other groups. The significance of differences in mean GI blood loss by treatment groups was calculated by ANOVA and the Student-Newman-Keuls multiple comparisons test. In the ANOVA model, the main effect was for the treatment group, and the logarithm of week 1 blood loss was included as a covariant (p values less than 0.05 were considered statistically significant).

Results

Younger men (18–50 years of age) participated in studies I and III, older men ($\geq$ 50 years of age) in study IV, and elderly men and women ($\geq$ 64 years of age) in study II (Table 1). Despite the differences in subject age in these studies, mean daily blood loss during the week 1 lactose placebo tablet treatment did not differ statistically among studies (the p value from the F test for the study effect was 0.20) (Fig. 1).

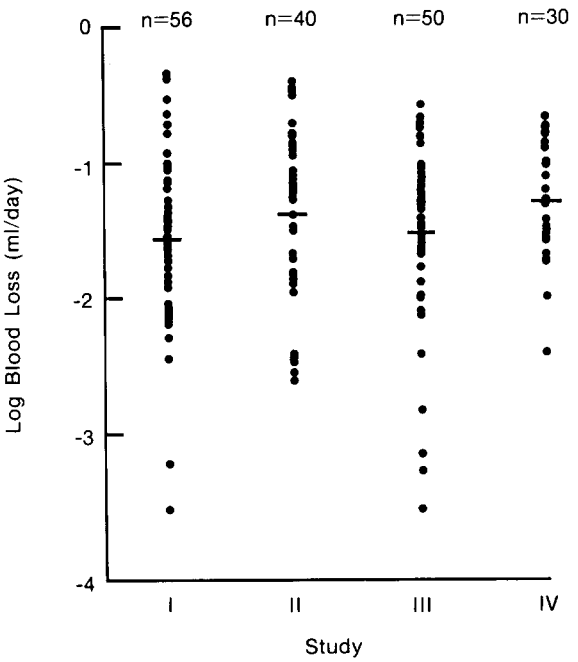

Fig. 1. Week 1 mean daily gastrointestinal blood loss in normal volunteers while taking lactose placebo tablets (logarithmic scale). Subjects in studies I and III were 18–50 year old men, those in study II were $\geq$ 64 year old men and women, and subjects in study IV were $\geq$ 50 year old men. Mean daily blood loss (measured over days 4–7 of week 1) is indicated by a horizontal line.

Analysis of GI blood loss was also performed on treatment groups. The treatment groups were plain aspirin, indomethacin (OROS or immediate-release form), marketed reference slow-release cold/allergy products, OROS cold/allergy products, and placebo [OROS (mannitol) and lactose tablets]. The five treatment groups had comparable blood loss for week 1 ($p = 0.13$). The lack of statistical differences among studies justified grouping mean blood loss during the treatment week (week 2) by treatment type (Fig. 2). There were no significant differences in blood loss values among the four placebo groups for either week 1 ($p = 0.80$) or week 2 ($p = 0.14$).

Mean blood loss was not statistically different among groups in all four studies for subjects taking either 2.6 or 3.9 g of plain aspirin. Subjects who took aspirin, a known gastrointestinal irritant (Graham and Lacey Smith, 1986; Ivey, 1986; Lewis, 1986), had significantly more blood loss than subjects who took OROS or IR indomethacin, marketed reference cold/allergy products, OROS cold/allergy products, or either placebo. For subjects taking OROS or IR in-

TABLE 2

Adverse experiences in four clinical studies (n = 176) [a]

Symptom (no. of subjects exposed)	No. of subjects	Therapy				
		Aspirin (50)	Indomethacin (OROS or IR) (36)	Reference cold/allergy (20)	OROS cold/allergy (30)	Placebo [OROS (mannitol) and lactose] (40)
Total no. of subjects reporting symptoms		8	22	10	7	5
No. of adverse experiences by body system						
Body as a whole						
Asthenia	1	0	0	0	0	1
Back pain	1	1	0	0	0	0
Headache	25	1	18	2	2	2
Upper respiratory tract infection	1	0	0	0	0	1
Total	28	2	18	2	2	4
Digestive system						
Abdominal pain	13	3	9	1	0	0
Anorexia	1	0	0	0	0	1
Constipation	1	0	0	1	0	0
Diarrhea	2	0	2	0	0	0
Dry mouth	2	0	0	1	1	0
Dyspepsia	10	1	10	0	0	0
Gingivitis	2	1	0	1	0	0
Nausea	4	0	3	0	1	0
Vomiting	1	0	1	0	0	0
Total	37	5	25	4	2	1
Nervous system						
Dizziness	2	0	2	0	0	0
Nervousness	1	0	0	0	1	0
Somnolence	1	0	0	0	1	0
Total	4	0	2	0	2	0
Skin and appendages						
Perspiring hands	2	0	2	0	0	0
Rash	1	1	0	0	0	0
Total	3	1	2	0	0	0
Special senses						
Ear pain	1	0	0	0	1	0
Urogenital system						
Scrotal pain	2	0	0	2	0	0

[a] All adverse experiences judged by investigators to be probably, probably not, possibly, and definitely related to therapy are included. Experiences judged to be definitely not related are not included.

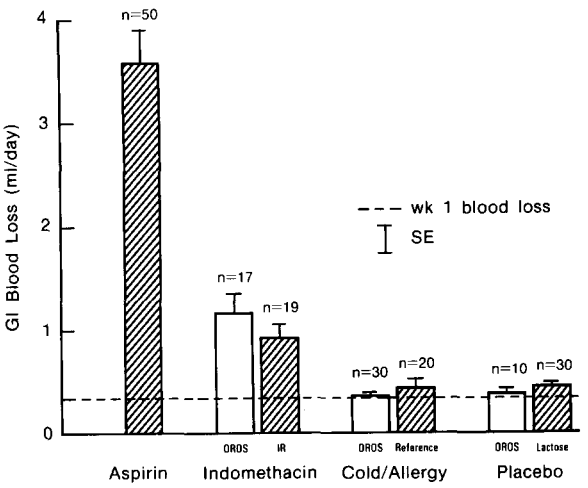

Fig. 2. Week 2 mean daily GI blood loss in normal volunteers taking various drugs or placebos in four clinical studies (I–IV) grouped by treatment type. Error bars indicate ±S.E. IR (indomethacin) indicates immediate-release. Reference slow-release cold/allergy medications included a combination of Afrinol® Repetabs® and Dimetane® Extentabs®, and Chlor-Trimeton® Decongestant Repetabs®. OROS cold/allergy medications included a combination of pseudoephedrine hydrochloride and brompheniramine maleate, chlorpheniramine maleate, and pseudoephedrine hydrochloride. OROS placebo delivered mannitol, and placebo tablets delivered lactose.

domethacin, mean blood loss was not statistically different between groups ($p = 0.37$). The GI blood loss of subjects who took indomethacin in either formulation was significantly less than that of the subjects who took aspirin but greater than that of subjects who took reference cold/allergy products (Afrinol Repetabs with Dimetane Extentabs, Chlor-Trimeton Decongestant Repetabs), OROS cold/allergy products (a combination of pseudoephedrine hydrochloride and brompheniramine maleate, chlorpheniramine maleate, pseudoephedrine hydrochloride), or placebo (OROS [mannitol] and lactose tablets) (nominal $p = 0.05$). There was no significant difference in week 2 blood loss between the reference cold/allergy or OROS cold/allergy groups and the placebo groups.

In studies II–IV (2067 stools collected), guaiac-positive stools were infrequent. Subjects taking OROS placebo, OROS (pseudoephedrine hydrochloride with brompheniramine maleate) OROS (chlorpheniramine maleate), and OROS (pseudoephedrine hydrochloride) had no guaiac-positive stools. Of subjects taking the reference cold/allergy products, only one taking Chlor-Trimeton had one guaiac-positive stool. Three subjects taking lactose placebo tablets had a total of five guaiac-positive stools, and three subjects taking aspirin had a total of four guaiac-positive stools.

Adverse experiences

The symptoms that physicians reported to be probably not, possibly, probably, or definitely related to treatment are shown in Table 2. COSTART (Coding Symbols for a Thesaurus of Adverse Reaction Terms) was used to classify symptoms. All subjects enrolled in the clinical studies were included in the analysis. The majority of complaints reported by subjects taking OROS or IR indomethacin were headaches and digestive system complaints (Table 2). The minor complaints reported for both the reference and OROS cold/allergy products were representative of symptoms known to be associated with these drugs.

Premature terminations during placebo week

The two premature terminations in study I included one subject who failed to meet the baseline blood loss criteria and one subject with a sore throat and otitis media necessitating antibiotic and analgesic treatment. The seven subjects who withdrew from study II included four subjects who failed to meet the baseline blood loss criteria and three subjects who withdrew because of personal reasons. In study III, the eight premature terminations included four subjects who failed to meet the baseline blood loss criteria, one who withdrew because of personal reasons, and one who did not comply with the protocol. In study IV, four subjects failed to meet baseline blood loss criteria.

Premature terminations during treatment week

The six premature terminations in study I included three subjects taking IR indomethacin and three taking OROS (sodium indomethacin). Reasons for subject withdrawal from IR in-

domethacin treatment were family illness, intolerance to indomethacin indicated by headache, and periodontal abscess requiring antibiotic therapy. Three subjects taking OROS (sodium indomethacin) were withdrawn from the study at the time the product was withdrawn from the market.

There were only two premature terminations during the treatment week of studies II–IV. In study II, one subject taking aspirin was withdrawn because of rectal bleeding associated with previously undiagnosed hemorrhoids, and one subject taking a combination of Afrinol Repetabs and Dimetane Extentabs became psychotic and was subsequently hospitalized and treated.

Discussion

The ^{51}Cr-labeled red blood cell tagging method has been used extensively in clinical research to assess GI blood loss during use of many drugs, including aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) (Frenkel et al., 1968; Schmid and Culic, 1976; Loebl et al., 1977; Arnold et al., 1985; Aabakken et al., 1989). This method is not specific for a particular region and will identify blood loss anywhere in the GI tract. Unlike endoscopy or proctoscopy, it is indirect and non-invasive; yet it is far more sensitive than the stool guaiac test. Although the stool guaiac test favors detection of blood loss in the lower GI tract and shows a high rate of false positives (PDR, 1988; Sampliner, 1990), it was also used in this study.

A 1-week study of GI blood loss, as reported in this study, is considered sufficient to predict blood loss over a longer period. In a ^{51}Cr-labeling study to detect blood loss after ibuprofen and aspirin, most patients showed no appreciable change in blood loss value between the initial 2-week study and after a year of treatment (Schmid and Culic, 1976).

Clinically significant blood loss has been defined as either greater than 3.0 ml/day (Tauxe and Orvis, 1974) or greater than 1.5 ml/day when this value exceeds baseline loss by 0.7 ml/day (Arnold et al., 1985). In all four studies discussed in this paper, only plain aspirin, the positive control, caused blood loss that was clinically significant by this criterion. It is well known that aspirin often damages gastric mucosa (Graham and Lacey Smith, 1986). This safety consideration dictated the lower aspirin dose for studies with older subjects; it suffices to provide a positive control for GI blood loss studies but is safer than the maximum over-the-counter daily dose of 3.9 g. It was not surprising that both indomethacin formulations caused significantly more blood loss than the non-aspirin treatments; numerous case-control and cohort studies of clinically apparent GI bleeding and peptic ulcer disease have demonstrated that NSAID users incur increased risk of upper GI bleeding compared to non-users (Strom et al., 1990). There is a 1% risk of symptomatic upper-GI ulcers, gross bleeding, or perforation for these highly effective and widely used drugs (PDR, 1990). Aspirin- or NSAID-induced blood loss may also be clinically significant because it can contribute to anemia, common in arthritis patients (Bjarnason et al., 1987; Butt et al., 1988).

In contrast to indomethacin, there was no statistically or clinically significant GI blood loss with the OROS cold/allergy products, reference cold/allergy products, OROS (mannitol) placebo, or lactose placebo tablets. In these clinical studies, the safety profile of these drugs in OROS once-a-day dosage forms was the same as that reported for these drugs in other dosage forms.

In addition, GI blood loss detected with the ^{51}Cr method was age-invariant in these clinical studies. Neither baseline nor aspirin-induced blood loss was higher in older and elderly subjects than in younger subjects. Other studies in which ^{51}Cr-labeled blood loss due to aspirin was measured in older (mean age near 50 years) arthritis patients (Frenkel et al., 1968; Lussier et al., 1978; Arnold et al., 1985) confirmed that blood loss in this older population is similar to aspirin-associated blood loss in healthy, younger subjects (Arnold et al., 1986). In a recent endoscopy study, aspirin-induced GI damage was shown not to be age-dependent (Moore et al., 1991). The observation that healthy older and elderly subjects have no higher baseline blood

loss than younger subjects is important for the design of future GI blood loss studies.

In conclusion, GI blood loss appears to be associated with the drug administered and not the OROS dosage form. OROS (mannitol) placebo and lactose placebo tablets were similar in having no effect on GI blood loss when tested in male volunteers 50 years of age and older. Blood loss from the cold/allergy drugs in OROS systems (a combination of pseudoephedrine hydrochloride and brompheniramine maleate, chlorpheniramine maleate, or pseudoephedrine hydrochloride) or in reference slow-release cold/allergy products was indistinguishable from placebo blood loss. GI blood loss from a relatively irritating drug, indomethacin [either as OROS (sodium indomethacin) or IR indomethacin], was greater than that from placebo but less than GI blood loss from plain aspirin.

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