pulsion between the resin and the ion as the net charge difference increased. The resin introduced an additional driving force, which reduced the activation energy required for each ion to permeate the membrane.

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Antipyretic Effect of Acetaminophen Suppositories in Rats

ALBERT LOCK, BRENDA McALLISTER ECKMAN, and JAMES AYRES ˣ

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Abstract □ An animal model used yeast-fevered rats to measure the relative antipyretic effects of different commercially available acetaminophen-containing suppositories. A laboratory-prepared acetaminophen-containing suppository and placebo suppositories also were investigated. Release from the suppositories was measured *in vitro*. All acetaminophen products containing 600 mg of drug elicited significant decreases in the rectal temperature of fever-induced rats.

Keyphrases □ Antipyretic agents—acetaminophen, suppositories, rats □ Acetaminophen—antipyretic effects, suppositories, rats □ Dosage forms, solid—suppositories, acetaminophen, antipyretic effects, rats

The antipyretic effect of acetaminophen is well known. However, formulation factors can influence the rate and extent of acetaminophen bioavailability from rectal dosage forms (1–5). Drug release from suppository vehicles is necessary before absorption can occur. Acetaminophen release from various polyethylene glycol vehicles appears to be related to its solubility in the vehicle, which, in turn, is related to vehicle dielectric properties (1, 2). Different formulations of polyethylene glycol suppositories show fairly wide variation in total urinary acetaminophen excretion due to differences in absorption patterns of the rectally administered acetaminophen (1).

The use of rectal suppositories for systemic acetaminophen administration has been the subject of recent studies in humans. The results from a well-controlled, double-blind study in humans indicated no significant differences in antipyretic effect between acetaminophen administration of a hospital pharmacy-prepared suppository and a commercially available tablet dosage form (4). However, large differences in acetaminophen bioavailability from suppositories prepared in two different hospitals were found when they were compared to a commercial rectal product in a urinary excretion study using human subjects (5). The large differences found in the relative bioavailability, peak excretion rates, and times of peak action between the hospital-manufactured acetaminophen suppositories themselves and the commercially obtained product prompted the investigator to suggest the need for *in vivo* testing of hospital-prepared suppositories (5).

The purpose of this study was to compare *in vivo* the antipyretic effects of five different generic acetaminophen suppository products purchased from different commercial sources with acetaminophen-containing and placebo suppositories prepared in this laboratory. The animal model used was a modified version of a previously reported *in vivo* method for measuring the antipyretic effect of aspirin in rats (6).

EXPERIMENTAL

Reagents and Equipment—Petrolatum[1], polyethylene glycol 1540[2], polyethylene glycol 6000[2], polyethylene glycol 400[2], acetaminophen[3], brewer's yeast[4], and ether[5] were used as supplied.

Acetaminophen suppositories, A–E[6], were obtained from commercial sources.

The equipment used included a rectal thermometer[7], thermistor probe[8], wound clip applier[9], and 9-mm wound clips[10].

[1] Matheson, Coleman and Bell, Norwood, OH 45212.
[2] J. T. Baker Chemical Co., Phillipsburg, NJ 08865.
[3] Lot 7032-LSR-43, S. B. Penick, Lyndhurst, NJ 07071.
[4] E. R. Squibb & Sons, Princeton, NJ 08540.
[5] Mallinckrodt, St. Louis, MO 63147.
[6] Product A, Westward, Inc., Eatontown, NJ 07724; Product B, American Quinine, Hospital Division of Natcon Chemicals, Plainview, NJ 11803; Product C, Consolidated Midland Corp., Brewster, NY 10509; Product D, Reiss Williams Co., Division of G & W Laboratories, Port Reading, NJ 07064; and Product E, Upsher-Smith Laboratories, Minneapolis, MN 55415.
[7] Model 47TD, Yellow Springs Instrument Co., Yellow Springs, Ohio.
[8] Series T2 605, Yellow Springs Instrument Co., Yellow Springs, Ohio.
[9] Model 7630, Clay Adams, Division of Becton, Parsippany, NJ 07054.
[10] Clay Adams, Parsippany, NJ 07054.

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Table I—Antipyretic Effect [a] of Various Acetaminophen Suppository Products Administered Rectally in Yeast-Fevered Rats

Product	$\bar{X}$ Predrug Temperature	Time Postdrug 0.5 hr	1.0 hr	2.0 hr	3.0 hr	4.0 hr	5.0 hr	6.0 hr
A	39.38°	1.62 ± 0.259°	2.25* [b] ± 0.217°	1.95* ± 0.242°	1.37 ± 0.436°	0.983 ± 0.489°	0.695 ± 0.500°	0.261 ± 0.411°
B	39.49°	1.43* ± 0.076°	2.00* ± 0.166°	2.14* ± 0.109°	2.26* [b] ± 0.146°	1.64* ± 0.229°	1.13 ± 0.321°	1.05 ± 0.310°
C	39.33°	1.88* ± 0.109°	2.11* [b] ± 0.142°	2.01* ± 0.173°	1.35* ± 0.226°	1.15 ± 0.337°	0.943 ± 0.427°	0.990 ± 0.400°
D	39.49°	2.01* ± 0.264°	2.26* [b] ± 0.227°	2.10* ± 0.134°	1.66* ± 0.159°	1.26* ± 0.235°	0.880 ± 0.280°	0.992 ± 0.388°
E	39.34°	2.00* ± 0.368°	2.40* [b] ± 0.565°	2.28* ± 0.191°	1.87* ± 0.221°	1.56* ± 0.195°	1.13 ± 0.297°	0.998 ± 0.382°
F	39.38°	1.40 ± 0.228°	1.90* ± 0.226°	1.94* [b] ± 0.244°	1.63* ± 0.332°	1.19 ± 0.400°	0.934 ± 0.368°	0.590 ± 0.256°
Prestudy control	39.61°	0.946 ± 0.384°	0.710 ± 0.123°	0.710 ± 0.181°	0.500 ± 0.292°	0.378 ± 0.331°	0.368 ± 0.326°	0.448 ± 0.161°
Poststudy control	39.30°	0.563 ± 0.100°	0.526 ± 0.102°	0.155* ± 0.048°	0.036* ± 0.061°	0.008 ± 0.032°	0.071 ± 0.039°	0.081 ± 0.066°
Combined control	39.41°	0.737 ± 0.108°	0.610 ± 0.065°	0.407 ± 0.097°	0.247 ± 0.097°	0.167 ± 0.089°	0.206 ± 0.080°	0.248 ± 0.096°

[a] Values are mean decreases in temperature ± *SE*. The asterisk (*) indicates significant difference ($p = 0.05$) from prestudy control. [b] Maximum temperature decrease.

Pharmacology and Methodology—Male Sprague-Dawley rats, 300–400 g, in groups of six were used for each of the five commercially obtained acetaminophen suppositories as well as for the laboratory-manufactured acetaminophen and control suppositories. To examine the variations due to tests run on different days, the control suppositories were tested twice. The first group of control suppositories was tested prior to the main study; and the second control group was tested afterward. A rectal thermometer[7] was used to obtain rat rectal temperatures.

The ambient temperature of each rat was obtained before inducing fever by inserting a prewarmed (38°), lubricated thermistor rectal probe exactly 4 cm into the rectum for 45 sec. Accurate probe insertion to the exact distance was critical to obtain reproducible results. The animal was lightly anesthetized with ether[5]. Fever was induced by 20 ml/kg of a 20% aqueous suspension of brewer's yeast[4], which was injected subcutaneously into the back below the nape of the neck (6).

Food was then withheld from the animals, but water was available *ad libitum* for the rest of the experiment. Room temperature was maintained at 23°. Room lighting was maintained from 7:00 am to 7:00 pm and turned off from 7:00 pm to 7:00 am. Rectal temperatures were obtained at about the same time each day throughout this study. Twenty-four hours after the yeast injections, the rectal temperature was recorded for each rat. The rat was then anesthetized with ether, and the appropriate modified suppository was inserted rectally. A wound clip was applied to the rectal opening to prevent its expulsion.

The animal was returned to its cage between temperature recordings. Rectal temperature readings were obtained at 0.5 and 1 hr and hourly thereafter for 6 hr after administration of the modified suppository. Rectal temperatures were obtained as described previously, except that the thermistor probe was inserted from above or below the wound clip depending on which direction facilitated a more direct probe insertion. For each animal, the probe was inserted from the same direction for every temperature reading.

All commercially obtained suppositories (A–E) and those manufactured in the laboratory (F) were adult size; each contained 600 mg of acetaminophen. To test for antipyretic activity in rats, each suppository was reduced to one-fourth of its original size. It was quartered with a scalpel longitudinally and weighed. All quartered suppositories were within 25–27% of their original weight. The control placebo suppositories (G) contained no drug and were quartered in the same manner.

The laboratory-manufactured suppositories (F) were prepared by incorporating sufficient analytical grade acetaminophen into the vehicle so that each suppository contained 600 mg of drug. They were made by the fusion process using the double pour technique (7). The control suppositories (G) were prepared by the fusion process and contained no drug. The control suppository and the laboratory-manufactured suppository vehicle contained polyethylene glycol 1540 (34%), polyethylene glycol 6000 (46%), and polyethylene glycol 400 (20%).

RESULTS AND DISCUSSION

Subcutaneous injections of aqueous brewer's yeast suspensions induced fever in 60 rats, from a preinjection mean rectal temperature of 37.8° (*SE* = 0.049) to a 24-hr postinjection rectal temperature of 39.4° (*SE* = 0.034). The temperature elevations induced by the brewer's yeast injection agree with those reported previously (6).

The results (Table I and Fig. 1) on rat rectal temperatures were obtained when the five commercially obtained products (A–E) and the laboratory-manufactured acetaminophen suppositories (F) were compared to control placebo suppositories (G). Since each product was tested on a different day, the controls were tested both on a prestudy day and on a poststudy day to examine the influence of day-to-day variability (Table I).

There were no significant differences between the prestudy and poststudy controls at 0.5, 1, 4, 5, or 6 hr. At 2 or 3 hr, the poststudy controls exhibited smaller temperature decreases in the yeast-fevered rats than the prestudy controls. Use of the poststudy controls would have given a larger difference in temperature between the controls and the products tested. For this reason, the prestudy controls were used for statistical comparison to the products as a conservative estimate of significant antipyretic effect.

The Student *t* test was used to determine significant differences ($p < 0.05$) for the control *versus* the products. At 0.5 hr after drug administration, Products B–E elicited significant decreases in rat rectal temperatures but Products A and F did not. This finding indicates a slower onset of action for Products A and F since both differed significantly from controls at 1 hr after drug administration. At 1 and 2 hr, all products elicited significant decreases in rectal temperatures. At 3 hr, all products except A continued to maintain lowered rectal temperatures. At 4 hr, only B, D, and E still elicited significant lowering of rat rectal temperatures.

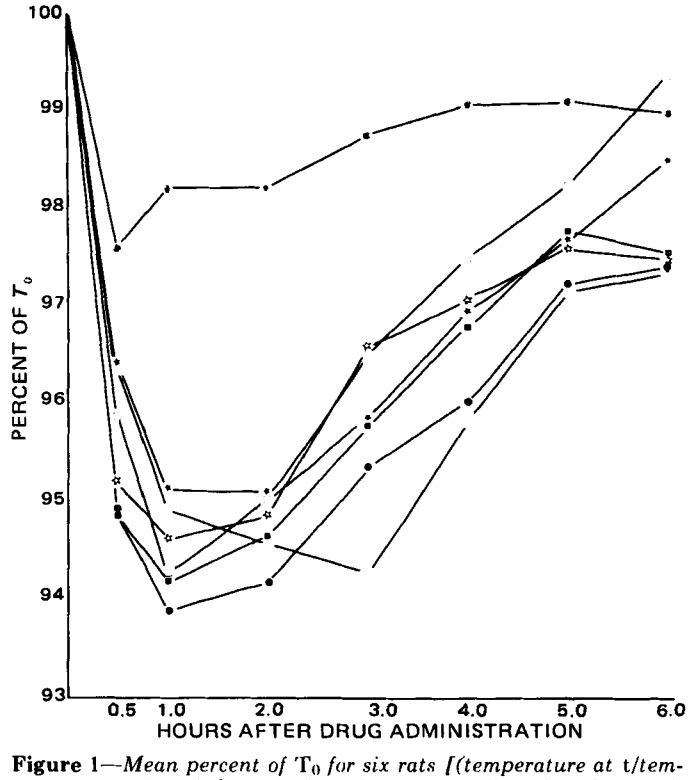

Figure 1—*Mean percent of* T_0 *for six rats [(temperature at t/temperature at* t_0*) × 100] versus time t in hours postinsertion of suppository. Key:* □, *Product A;* ○, *Product B;* ☆, *Product C;* ■, *Product D;* ●, *Product E;* ★, *Laboratory Product F; and* ⊙, *placebo control, G.*

By 5 and 6 hr, none of the products elicited any significant antipyretic effect.

When the various commercial acetaminophen suppositories (A–E) were compared to each other and to the laboratory-prepared product (F), no significant differences in antipyretic response were found at 0.5, 1, 2, 4, 5, and 6 hr. At 3 hr, there were no significant differences among Products C–F; however, Products A and B showed some differences. Product B showed its maximum effect at 3 hr (Table I) and exhibited the slowest onset of action; Product A was indistinguishable from the controls at 3 hr and thereafter, thus providing the shortest duration of action.

The magnitude of the variability, as indicated by the standard error (*SE*) (Table I), differed among products, with some showing more intraproduct variability than others. Because of the large variability when compared with other products, Product A was retested; the results were not significantly different from the original results. Product A showed a marked variability *via* visual examination in consistency and coloration when quartered longitudinally. Uniform drug distribution is essential for consistent absorption; and since only one-fourth of the suppository was inserted rectally into the animal, the lack of homogeneity and uniformity among Product A suppositories may account for the large variability in effect.

All five commercial products were stated to contain polyethylene glycol vehicles, but none listed the types or percentages of polyethylene glycol. Thus, a comparison of the differences in effect among formulations was not possible. The differences in the polyethylene glycol vehicle formulations, as well as other formulation factors, could account for the slight differences in the onset of action, duration of action, and time to reach peak antipyretic effect among the products tested.

All products were obtained from commercial sources and were tested within their expiration dates, but their shelftime prior to purchase was not known. The laboratory-manufactured acetaminophen and control suppositories were prepared and used within 1 month of manufacture. Stability of the vehicles is an important consideration in efficacy. Aging can influence the physical–chemical properties of the vehicle (3, 8) and may have contributed to the slight differences in effect among the products tested.

Correlation between *in vivo* and *in vitro* results was previously reported for benzocaine suppositories (9). Similar *in vitro* testing of acetaminophen suppositories A–F did not show any significant differences in drug release. The effects of aging, the polyethylene glycol composition, and other manufacturing and formulation factors all could account for the slight differences among products in this study. Nevertheless, all products tested, including the laboratory-manufactured product, did decrease the rectal temperatures of the yeast-fevered animals significantly. This animal model was a viable method for studying the efficacy of rectally administered antipyretic agents.

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Species Difference in GI Motor Response to Somatostatin

MARTIN F. TANSY ˣ, JOHN S. MARTIN, WENDELL E. LANDIN, and FRANK M. KENDALL

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Abstract □ Acute experiments were performed on overnight fasted chloralose–urethan anesthetized dogs, cats, rabbits, and rats. Under these conditions, somatostatin practically abolished gastric contractions and decreased GI tonus in all species examined. The canine duodenum, jejunum, and ileum exhibited only a contractile response to somatostatin, whereas motor activities of the small intestines of the cat, rabbit, and rat were inhibited. In all instances and at all dosages, both the inhibitory and excitatory effects showed suggestions of tachyphylaxis. The data also indicate that excitatory or inhibitory effects were not dependent on the presence of long arc pathways. It is concluded that somatostatin exerts a direct stimulatory effect on the canine small intestine that is mediated by the muscularis mucosa.

Keyphrases □ Somatostatin—effect on GI motor activities, species specificity, dogs, cats, rabbits, rats □ GI motility—somatostatin effect, species specificity, dogs, cats, rabbits, rats □ Growth hormone inhibitors—somatostatin, effect on GI motor activities, species specificity, dogs, cats, rabbits, rats

Intravenous somatostatin administration to the anesthetized dog is associated with anatomically defined GI motor effects: gastric antrum relaxation and a generalized augmentation of the small intestine segmenting activities (1). Similar observations have been made in conscious dogs.

Because more recent abstracts (2, 3) documented similar observations for the canine small intestine, a series of experiments in four mammalian species was designed to determine the mechanism of the excitatory effect on the small bowel as well as its species specificity.

EXPERIMENTAL

Animals and General Procedure—Acute experiments were performed on 15 mongrel dogs, four cats, four rabbits, and four adult male Sprague–Dawley rats. Following an overnight fast with tap water *ad libitum*, all animals were anesthetized by the intravenous administration of a mixture of α-chloralose (5%, dissolved in polyethylene glycol 200) and urethan (50% in 0.9% saline). Each animal was individually titrated to a surgical plane of anesthesia using this mixture. Anesthesia was maintained by individual administration of the chloralose–urethan mixture.

Surgical and Recording Procedures—In all species, a tracheal cannula was inserted to ensure airway patency or, when necessary, to maintain artificial ventilation with a positive pressure pump. The femoral artery was cannulated to record blood pressure. The ipsilateral vein was cannulated to permit either bolus or infusion administration of drugs and fluids. A midline laparotomy was performed.

Recording balloons were inserted *via* the oral route for gastric recording and retrograde *via* a stab wound in the ileum for small intestinal recording. Motor activities of the large intestine were monitored by surgi-

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