Investigation of Pantothenyl Alcohol in Experimentally Induced Intestinal Atony

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Pantothenyl alcohol (10 mg./Kg.) given subcutaneously significantly increased gastrointestinal motility at 15 and 18 hours in mice and at 20 and 24 hours in rats following cecectomy, but exerted no effect in normal animals. Optimal conditions for evaluating pantothenyl alcohol consisted of measuring the 30- and 45-minute progression of an orally administered charcoal meal through the gastrointestinal tract, 14 to 24 hours following cecectomy.

BLY, *et al.* (1), in 1943 and Jurgens and Pfaltz (2) in 1944 were the first to report the occurrence of intestinal atony in pantothenic acid deficient animals. These observations lead to clinical investigations by Kareha, *et al.* (3), Haycock, *et al.* (4), Stone, *et al.*, (5), Frazer, *et al.* (6), and Nardi and Zuidema (7), who reported pantothenyl alcohol to be effective in preventing and treating intestinal atony and gaseous abdominal distention in postsurgical patients. In 1950 Lipmann, *et al.* (8), established pantothenic acid as an integral part of coenzyme A. The *in vivo* formation of acetyl coenzyme A and the acetate transfer to choline, elaborate the transmitter substance, acetylcholine, required for intestinal motility. Unna and Greslin (9) reported pantothenic acid to be pharmacologically inert and relatively nontoxic. Polacek, *et al.* (10), using a double blind technique, were able to significantly reduce the duration of experimental post-surgical ileus in mongrel dogs. In this study a method of evaluating pantothenyl alcohol or similarly acting agents in small laboratory animals is presented.

EXPERIMENTAL

Mice (15–36 Gm.) and rats (60–250 Gm.) were anesthetized with ether, the abdominal cavity opened, and the cecum tied off and removed. Following the closure of the abdomen by suturing, the drug was administered subcutaneously. At various intervals following cecectomy, a 12.5% powdered charcoal suspension in 1% methyl cellulose solution was given orally using a dosage equivalent to 2.5% of the body weight. At a specific time following charcoal administration, the animals were decapitated, the entire gastrointestinal tract was removed, and the distance that the charcoal meal had progressed was expressed as per cent of the total length of the gastrointestinal tract.

RESULTS AND DISCUSSION

Pantothenyl alcohol (10 mg./Kg.) given subcutaneously just after cecectomy did not alter the 12 to 18 hours passage of charcoal meal, which progressed only 60 to 100% the length of the gastrointestinal tract as determined in 106 black (C-57)[1] male mice (15–36 Gm).

Using a 30-minute charcoal passage period, pantothenyl alcohol (1000 mg./Kg.) did not affect gastrointestinal motility in normal Swiss female mice (15–30 Gm.) at 1 to 14 hours, but increased motility at 14 hours in cecectomized mice ($P < 0.10$).

Gastrointestinal charcoal passage rates at 45 minutes in mice, as shown in Table I, indicate that the optimal effect of pantothenyl alcohol occurs between 11 and 18 hours following cecectomy. Pantothenyl alcohol significantly enhanced gastrointestinal activity at 15 hours ($P < 0.05$) and at 18 hours ($P < 0.001$).

TABLE I.—EFFECT OF PANTOTHENYL ALCOHOL ON FORTY-FIVE MINUTES GASTROINTESTINAL PASSAGE OF CHARCOAL IN CECECTOMIZED MICE[a]

Time, Hr.	Total No. Mice	Control[b], % and S.E.[e]	Treated[c], % and S.E.[e]	P[d]
11	20	39.6 ± 6.0	45.5 ± 7.0	N.S.
15	16	45.1 ± 8.0	72.5 ± 5.0	<0.05
18	35	36.1 ± 2.9	58.9 ± 3.9	<0.001

[a] Black male mice (C-57) weighing 15–36 Gm. [b] Control given 8 ml./Kg. of normal saline subcutaneously immediately after cecectomy. [c] Pantothenyl alcohol 8 ml. (10 mg.)/Kg. given subcutaneously immediately after cecectomy. [d] Probability level on significance based on *t* test. [e] Mean per cent and standard error of the total distance that charcoal passed through the G. I. tract in 45 minutes.

When 45-minute charcoal passage rate was used in rats, pantothenyl alcohol enhanced gastrointestinal motility optimally at 20 hours, an increase of 72% over controls as shown in Table II. A 35% increase by pantothenyl alcohol was observed at 24 hours. No significant change was observed at 18 hours.

TABLE II.—EFFECT OF PANTOTHENYL ALCOHOL ON FORTY-FIVE MINUTES GASTROINTESTINAL PASSAGE OF CHARCOAL IN CECECTOMIZED RATS[a]

Time, Hr.	Total No. Rats	Control[b], % and S.E.[e]	P.A.,[c] % and S.E.[e]	P[d]
18	9	30.6 ± 4.3	24.4 ± 4.5	N.S.
20	10	27.2 ± 3.8	46.8 ± 1.7	<0.01
24	17	39.9 ± 3.7	53.8 ± 5.4	<0.05

[a] Male Wistar rats (75–250 Gm.). [b] Normal saline 8 ml./Kg. given subcutaneously immediately after cecectomy. [c] Pantothenyl alcohol 8 ml. (10 mg.)/Kg. given subcutaneously immediately after cecectomy. [d] Probability level of significance based on *t* test. [e] Mean per cent and standard error of the total distance that charcoal passed through the G.I. tract in 45 minutes.

Pantothenyl alcohol did not reduce the time required for a charcoal meal to pass through the entire gastrointestinal tract as determined in 27 cecectomized male Wistar rats (60–68 Gm.).

As illustrated in Figs. 1 and 2, the pattern of

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[1] Rockland Farms, New York, N. Y.

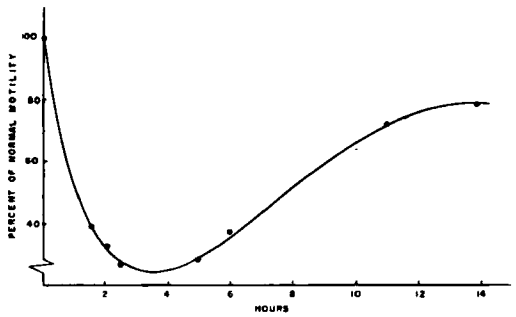

Fig. 1.—Pattern of surgically induced gastrointestinal atony and restoration in cecectomized mice as determined by the 30-minute passage of orally administered charcoal. Normal motility = 100%.

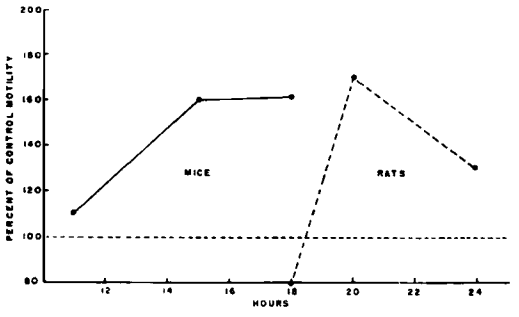

Fig. 2.—Pantothenyl alcohol (10 mg./Kg.) effect in the response phase of surgically induced atony as determined by the 45-minute passage of charcoal. Control motility in cecectomized animals = 100%.

upper gastrointestinal motility in regard to surgical cecectomy and pantothenyl alcohol effect appears to be: (*a*) an atony phase, (*b*) a restoration phase, and (*c*) a pantothenyl alcohol-effect phase.

The results suggest that upper gastrointestinal motility as measured by 30 or 45 minutes charcoal passage rates at 14 to 24 hours postoperatively in mice and rats is optimal for evaluating pantothenyl alcohol or similarly acting compounds.

The data presented tend to confirm in part the work of Unna and Greslin (9) in that pantothenic acid does not exert a direct pharmacologic effect in normal animals, and substantiates the report of Polacek, *et al.* (10), in which pantothenyl alcohol hastened the return of normal gastrointestinal motility. The difference in response of normal and post-surgical animals suggests that surgically induced atony may be related to a depression in function of the pantothenate-coenzyme A-acetylcholine biochemical pathway. Pantothenyl alcohol may act by accelerating this function in the post-surgical animal.

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Quantitative Evaluation of Surface Anesthetics in Albino Mice

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The corneal reflex of the albino mouse is satisfactory for the quantitative determination of relative potency of local anesthetics. It was found that dyclonine was more active, benzonatate equally active, and procaine less active than cocaine.

THE CORNEAL reflex of cats (1), dogs (2), rabbits, and guinea pigs (3) has been used for the detection of local anesthetic activity. Pittenger (1) suggested the use of the cornea of cats for the qualitative detection of local anesthetic action. However, Munch (2) concluded that cats are not as suitable as rabbits because of greater individual differences in activity and because of greater reluctance on the part of the test animal to permit the touching of the cornea at frequent intervals. He also concluded that qualitative tests made upon the cornea of dogs offer no particular advantage. The corneal reflex in the rabbit has not been successfully standardized and has not withstood statistical examination (3). Although Chance and Lobstein (3) report that guinea pigs show a more regular reflex response, both normally and when anesthetized, than do rabbits, Bulbring and Wajda (4) found that guinea pigs frequently fail to blink even if the cornea is not anesthetized. Regardless of the relative advantages of guinea pigs *vs.* rabbits, however, Chance and Lobstein (3) introduced a method which made possible a quantitative comparison of local anesthetics.

When preliminary tests indicated that the albino mouse might be a satisfactory animal for the bioassay of local anesthetics, an experiment was carried out to determine a dose-response curve for cocaine, procaine, dyclonine, and benzonatate. The ac-

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