Bioavailability of Aspirin from Commercial Suppositories

MILO GIBALDI ˣ and BARBARA GRUNDHOFER

Abstract □ A comparison of the bioavailability of salicylate from five brands of commercially available aspirin rectal suppositories in an adult panel is presented. All brands show slow absorption compared to oral administration of the drug in tablet form. At best, about 40% of the dose (on the average) was absorbed when retention time in the bowel was limited to 2 hr. However, four out of the five brands gave substantially lower absorption rates so that only about 20% of the aspirin is available.

Keyphrases □ Aspirin—bioavailability from commercial suppositories, humans □ Suppositories—bioavailability of aspirin, humans □ Bioavailability—aspirin from commercially available suppositories, humans

Salicylate absorption after rectal administration of an aspirin suppository[1] to eight children and four adults was recently studied (1). The absorption of the drug from the suppository was exceedingly slow, about an order of magnitude slower than that observed after oral administration of conventional tablets. Accordingly, the amount of drug absorbed was highly dependent on the time between insertion and the first defecation (retention time). Retention times as long as 4–5 hr resulted in absorption of only about 60% of the dose.

Several other brands of aspirin suppositories were available locally in community pharmacies and still another brand was used exclusively in a local hospital. Given the relatively poor bioavailability characteristics of suppository Product L, it was of interest to study salicylate absorption from other brands of aspirin suppositories. Accordingly, five products were compared in adult subjects. The bioavailability characteristics of the four other brands of aspirin suppository were substantially poorer than that observed with Product L.

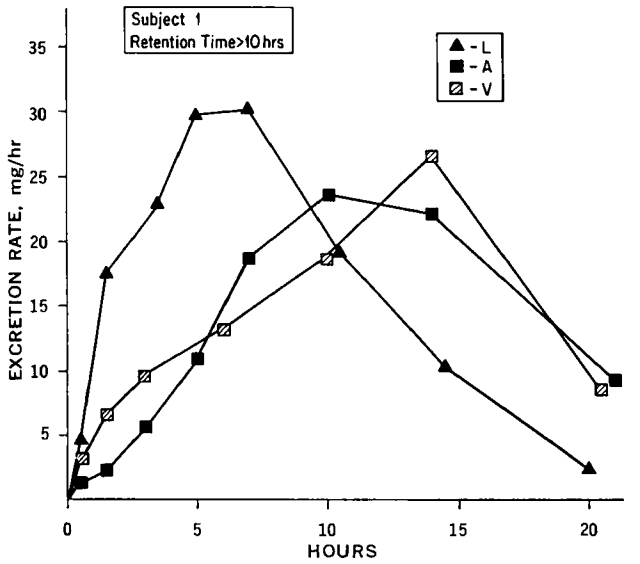

Figure 1—*Excretion rate of total salicylate* versus *time profiles after rectal administration and prolonged retention of various brands of 10-grain aspirin suppositories.*

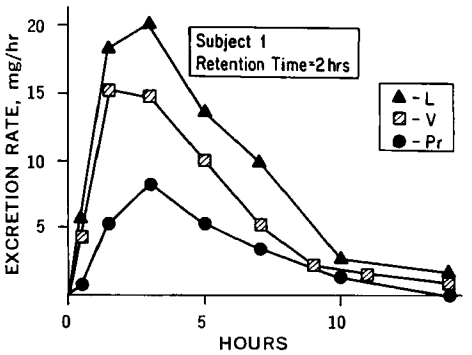

Figure 2—*Excretion rate of total salicylate* versus *time profiles after rectal administration of various brands of 10-grain aspirin suppositories.*

EXPERIMENTAL

The various aspirin suppositories were either purchased from local pharmacies or obtained from the pharmacy of a local hospital. The products were coded[2] A, L, Pp, Pr, and V. Each product claimed to contain 10 grains (600–650 mg) of aspirin. Two suppositories of each brand were assayed in duplicate for total salicylate. Expressed in terms of label claim, they were found to contain 103 and 105% (A), 108 and 105% (L), 106 and 86% (Pp), 117 and 115% (Pr), and 110 and 118% (V).

The adult panel consisted of four male volunteers, 24–35 years of age, three of whom received all five products. Each subject was instructed to insert a suppository shortly after arising in the morning and then either to evacuate his bowel as thoroughly as possible exactly 2 hr after insertion or to retain the suppository as long as possible. In the latter situation, retention times varied from 11 to >24 hr. In all cases, at least 1 week elapsed between studies.

Immediately prior to drug administration, the subjects voided their bladders and a specimen was obtained to serve as a blank. Urine was collected at appropriate intervals for 28–32 hr. The volume of each urine collection was determined and a sample was retained for drug analysis. Urine samples were hydrolyzed with an equal volume of concentrated hydrochloric acid in sealed ampuls overnight at 100°. The samples were then analyzed for total salicylate according to a modification of Brodie *et al.* (2) using carbon tetrachloride. Absorbance of the resulting ferric–salicylate complex was determined at 530 nm on a spectrophotometer[3] and corrected for blank values on an individual basis. Concentrations were determined from a previously constructed standard curve.

[1] A.S.A. suppositories, Lilly (USP) (coded L).

[2] A = APC suppositories (NDC-84-808-12, No. 808B), American Pharmaceutical Co., Bronx, N.Y.; L = Lilly A.S.A. suppositories (USP) (NDC-2-S16-16, Control 7HL14A), Lilly, Indianapolis, Ind.; Pp = Purepac aspirin suppositories (NDC-228-1028-12), Purepac Pharmaceutical Co., Elizabeth, N.J.; Pr = Premo aspirin suppositories (B11747), Premo Pharmaceutical Laboratories, Inc., South Hackensack, N.J.; V = Vitarine aspirin suppositories (127309), The Vitarine Co., Inc., New York, N.Y.

[3] Hitachi Perkin-Elmer model 139.

Table I—Initial Excretion Rates[a] (Milligrams per Hour) of Salicylate after Rectal Administration of 10-Grain Aspirin Suppositories to Adult Subjects

Hours	Product				
	L (4)[b]	A (3)	Pr (3)	Pp (3)	V (3)
0.5	6.4 ± 0.9	2.2 ± 0.4	1.4 ± 0.8	1.5 ± 1.3	3.2 ± 1.4
1.0	16.2 ± 3.7	5.6 ± 2.5	6.1 ± 2.8	5.6 ± 2.3	8.2 ± 2.9
1.5	25.6 ± 7.0	8.9 ± 4.9	10.9 ± 4.9	9.7 ± 3.9	13.2 ± 4.5

[a] Mean ± 1 *SD*. [b] Parenthetical values denote the number of subjects.

RESULTS AND DISCUSSION

Bioavailability is defined as the rate and extent of absorption of a drug from a dosage form. In the case of relatively low doses of aspirin (as used in the present study), it is well known that initial urinary excretion rates of total salicylate reflect the relative absorption rate of the drug and that the cumulative amount of total salicylate ultimately excreted in the urine serves as a quantitative index of the extent of absorption.

Table I shows the average initial excretion rates of total salicylate after rectal administration of the various products. The excretion rates at 0.5, 1.0, and 1.5 hr after insertion of Product L were at least two to three times greater than those observed with any other product. This difference is further illustrated in Fig. 1, where the urinary excretion rates of total salicylate are plotted as a function of time after administration of Products L, A, and V. The time of occurrence of maximum excretion rate was considerably less after Product L than that found after Products A and V. Moreover, the greatest peak excretion rate was observed after administration of L. Clearly, the absorption rate of aspirin must be considerably greater after rectal administration of Product L than after administration of the other suppositories studied. This finding is indeed remarkable when one considers how slowly aspirin is absorbed from Product L (1).

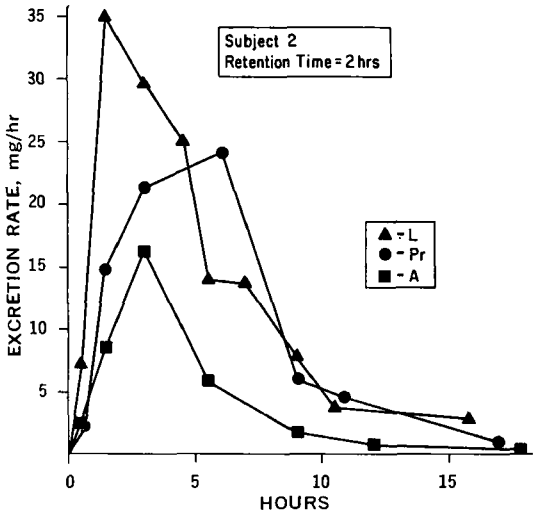

Figure 3—*Excretion rate of total salicylate* versus *time profiles after rectal administration of various brands of 10-grain aspirin suppositories.*

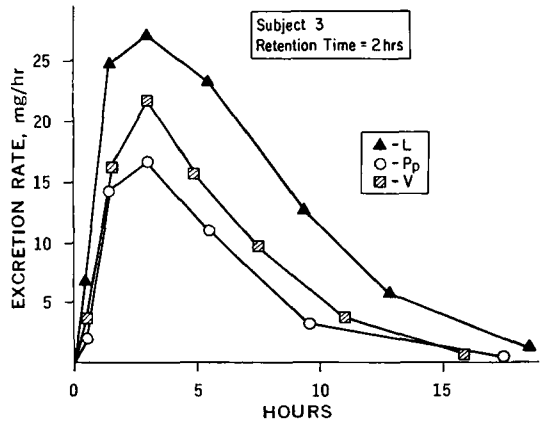

Figure 4—*Excretion rate of total salicylate* versus *time profiles after rectal administration of various brands of 10-grain aspirin suppositories.*

When drug products intended for rectal administration manifest such prolonged absorption patterns, the extent of absorption is obviously dependent on retention time. As shown in Table II, even after administration of the product from which aspirin is most rapidly absorbed (L), only about 40% of the dose was absorbed when the retention time was limited to 2 hr. During a similar 2-hr period, only about half that amount of aspirin was available, on the average, from Products A, Pp, Pr, and V, which released the drug still more slowly.

Differences between products with respect to the amount of aspirin absorbed in individual subjects are readily apparent in Figs. 2–4 when the total area under the excretion rate *versus* time plot is considered. In all three subjects, the cumulative amount of total salicylate ultimately excreted after a 2-hr retention of an aspirin suppository was consistently greater after administration of Product L. No consistent differences were obvious among the other four products.

The present results are readily extrapolated to permit one to conclude that the shorter the retention time the greater will be the difference between Product L and the other products tested with respect to the amount of drug absorbed, but in all cases the amount will be decreased. On the other hand, as shown previously (1) in studies with L, the greater the retention time the greater is the availability of aspirin. It follows that longer retention times tend to diminish differences among products with respect to the extent of drug absorption and that ultimately such differences disappear (Table II). When the aspirin suppository was retained for periods exceeding 10 hr, in most cases absorption of the drug was nearly complete and no differences among products were apparent.

Despite the substantial differences in bioavailability characteristics found to exist among various commercially available aspirin suppositories, the rate of absorption of aspirin from all products studied was sufficiently slow to raise considerable doubt as to whether efficacious body levels of aspirin or salicylate are attained after a single dose. The exceedingly slow absorption also suggests the possibility of a significantly reduced extent of absorption of the administered dose if the patient defecates even several hours after insertion of the suppository. It is anticipated that this prob-

Table II—Urinary Recovery of Salicylate after Rectal Administration of 10-Grain Aspirin Suppositories to Adult Subjects

Product	Retention Time	
	2 hr	>10 hr
L	38 ± 8[a] (4)[b]	81 ± 11 (4)
A	17 ± 6 (3)	74, 84
Pr	20 ± 10 (3)	93 ± 5 (3)
Pp	16 ± 4 (3)	88 ± 2 (3)
V	22 ± 6 (3)	80 ± 9 (3)

[a] Mean ± *SD*, expressed as percent of dose. [b] Parenthetical values denote the number of subjects.

lem would be most pronounced with Products A, Pp, Pr, and V. The slow absorption coupled with the inability to control the actual amount of drug available to a given patient raises serious questions as to the usefulness of the presently available aspirin suppository dosage forms for aspirin or salicylate therapy.

REFERENCES

(1) M. M. Nowak, B. Grundhofer, and M. Gibaldi, *Pediatrics*, 54, 23(1974).

(2) B. B. Brodie, S. Udenfriend, and A. F. Coburn, *J. Pharmacol. Exp. Ther.*, 80, 114(1944).

ACKNOWLEDGMENTS AND ADDRESSES

Received September 30, 1974, from the *Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214*

Accepted for publication November 29, 1974.

Supported in part by Grant GM20852 from the National Institute of General Medical Sciences, National Institutes of Health.

[x] To whom inquiries should be directed.

Central *versus* Peripheral Anticholinergic Activity as Assessed by Two *In Vivo* Procedures in Mice

JEFFREY B. MALICK [x] and ALLEN BARNETT

Abstract □ The activity of tertiary and quaternary anticholinergic drugs was compared in two different test procedures designed to measure cholinolytic activity in mice. The four drugs utilized were atropine sulfate, atropine methylnitrate, scopolamine hydrobromide, and scopolamine methylnitrate. The results led to the conclusion that one of these test procedures, the induction of mydriasis (increase in pupil size), primarily measures peripheral anticholinergic activity whereas the other procedure, inhibition of physostigmine lethality, primarily measures anticholinergic activity in the CNS. These two test procedures can be utilized to characterize the nature of the cholinolytic properties of prospective therapeutic drug candidates.

Keyphrases □ Anticholinergic activity—determination of central *versus* peripheral cholinolytic activity, tertiary and quaternary derivatives of atropine and scopolamine, mice □ Mydriasis induction as measure of peripheral anticholinergic activity—tertiary and quaternary derivatives of atropine and scopolamine, compared to physostigmine-induced lethality inhibition (central activity), mice □ Physostigmine-induced lethality inhibition as measure of central anticholinergic activity—tertiary and quaternary derivatives of atropine and scopolamine, compared to mydriasis induction (peripheral activity), mice □ Atropine and scopolamine, tertiary and quaternary derivatives—central *versus* peripheral cholinolytic activity, mice □ Scopolamine and atropine, tertiary and quaternary derivatives—central *versus* peripheral cholinolytic activity, mice

The measurement of anticholinergic activity is important in the evaluation of drug candidates for humans. Peripheral anticholinergic liability is considered to be an undesirable side effect of many therapeutic agents, particularly with regard to antidepressants (1) and antihistamines (2). Central [*i.e.*, within the central nervous system (CNS)] anticholinergic activity may not be as troublesome (except at toxic doses) and, in fact, may even be desirable under certain circumstances. Central anticholinergic drugs (*e.g.*, scopolamine) produce sedation in humans, and amitriptyline, a potent central anticholinergic and sedative drug, may be the antidepressant of choice in cases of agitated depression, a condition in which sedative effects have utility (3).

In the present studies, two test procedures in mice were evaluated for their ability to detect central *versus* peripheral anticholinergic activity. To evaluate these procedures, tertiary and quaternary forms of atropine and scopolamine were utilized. The tertiary forms readily cross the blood–brain barrier whereas the quaternary forms are retarded by the blood–brain barrier and, consequently, are concentrated to a much lesser extent in the CNS than they are in the periphery following parenteral administration. Thus, by comparing the relative potency of these agents in the two procedures, the induction of mydriasis and the antagonism of physostigmine-induced lethality, the extent that each can predict central or peripheral anticholinergic activity was determined.

EXPERIMENTAL

Male CF No. 1-S mice, 18–22 g, were used. All drug doses were calculated in terms of milligrams per kilogram of free base, and all drugs were dissolved in distilled water. The volume of injection was 10 ml/kg for both the intraperitoneal and subcutaneous routes of administration. The drugs used were atropine sulfate, atropine methylnitrate, scopolamine hydrobromide, and scopolamine methylnitrate.

Induction of Mydriasis (Increased Pupil Size) in Mice—Mice were administered test drugs and were tested for mydriatic activity 30 min later. These studies were performed under double-blind conditions such that the investigator did not know what drugs or doses were being tested. Normal pupil size was scored as 0 and increases in pupil size were scored as 1, 2, and 3 (slight, moderate, and maximal increases in size, respectively). A score of 2 was approximately 50% of maximal pupil size, which was a modification of the scoring system of Janssen and Niemegeers (4).

Any mouse exhibiting a pupil size of 2 or greater was considered to be significantly affected. Mean pupil sizes for each group were also calculated. The dose intervals for each test drug were kept constant (0.5 $\log_{10}$ units). The MED_{50} (minimal effective dose) for producing a significant increase in mydriasis in 50% or more of the mice tested was determined for each test drug. The ED_{50}'s could not be calculated since there were very small intervals between doses at which no animals exhibited significant effects and doses producing effects in 100% of the mice.

Inhibition of Physostigmine-Induced Lethality in Mice—