mild inhibitory effect on the direct vasoconstrictor activity of angiotensin II on vascular smooth muscle.

SUMMARY

No centrally induced hypotensive effect could be demonstrated with JB 5058 in the dog cross-circulation preparation.

Alpha adrenergic blocking activity in the absence of ganglionic blockage was demonstrated with JB 5058 in the cat superior cervical ganglion nictitating membrane preparation.

Cardiac output, except for a brief (1–2 minutes) reduction, was not altered by the administration of JB 5058.

Following the administration of JB 5058, femoral blood flow was increased, coronary vascular resistance was transiently decreased, and renal blood flow was unchanged.

A modest antagonism of angiotensin II was observed with JB 5058 both *in vivo* and *in vitro*.

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Effect of the Site of Release on the Absorption of Trimeprazine-S^{35} and Penicillin G in Dogs

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A radiofrequency generator described in a previous paper was applied to release trimeprazine-S^{35} and potassium penicillin G at selected sites in the gastrointestinal tract of dogs. Plasma and urinary excretion data indicate that trimeprazine-S^{35} is readily and efficiently absorbed when released in the stomach and the upper and middle small intestine. Potassium penicillin G in its biologically active form is more available for absorption when released just beyond the pylorus than when released in either the stomach or more than 3 ft. beyond the pylorus.

THE EFFECT of drug release site on the rates and efficiency of drug absorption has been a subject of great interest to pharmaceutical investigators. A technique developed in our laboratories using a radiofrequency generator for opening specially designed capsules at selected sites in the gastrointestinal tract offers a useful tool for studying the effect in intact animals under normal physiologic conditions. Useful information thus can be gathered for the design and evaluation of oral dosage forms. This report describes the application of this technique to a study of the effect of release site on the absorption of a phenothiazine antipruritic, trimeprazine, and an antibiotic, potassium penicillin G.

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EXPERIMENTAL

The design and the filling of the capsule and the release of drugs from the capsule by induction heating from a radiofrequency generator have been described in detail in a previous report (1).

Adult mongrel dogs were fasted (18–20 hours) prior to the oral administration of a capsule. Induction heating (approximately 5 minutes) was applied either 15–30 minutes after capsule administration to release the drug in the stomach or after sufficient time had been allowed for the capsule to reach certain sites in the intestine, determined by a marked thread attached to the capsule or by fluoroscopy (1). Usually the dog had been fasted for 21–25 hours prior to drug release. Urine was collected up to 24 hours following drug release by catheterizing the dogs and for longer periods by housing the animals in a metabolic cage. Blood samples were drawn from the jugular vein.

Absorption of Trimeprazine-S^{35}.—Each capsule was filled with 0.3–0.4 ml. of an aqueous solution of the drug to provide the dose of 2.5 mg. of trimeprazine-S^{35} tartrate/Kg. body weight. To help provide adequate urine collection, each dog was given 20 ml./Kg. of water 1 hour before drug release. Blood was drawn prior to induction heating and at 0.5, 1, 2, 3, 6, 9, 12, and 24 hours thereafter. Urine was collected for the periods: 0–0.5, 0.5–1,

1–3, 3–6, 6–9, 9–24, 24–48, 48–72, and 72–96 hours. Fecal samples were collected every 24 hours for 4 days. The animals were fed following the ninth hour sampling and allowed drinking water at all times.

Assay of S^{35} Activity.—The specific activity of the trimeprazine-S^{35} tartrate was 0.15–0.25 mcg./mg. Sulfur-35 activity in samples was determined by liquid scintillation counting with a Tricarb liquid scintillation spectrometer. Four-tenths of a milliliter of urine was counted in 20 ml. of a POPOP[1] solvent system and 0.2–0.5 ml. of plasma in 20 ml. of the solvent containing 5% w/v of Cab-O-Sil. Fecal samples were dissolved in concentrated nitric acid. A 10-ml. aliquot was oxidized with a HNO_3-$HClO_4$ mixture (v/v, 1 part of concentrated HNO_3, 1 part of water, and 2 parts of 60% $HClO_4$). The clear colorless digest was adjusted to 10.0 ml., and a 0.2-ml. aliquot was counted in 20 ml. of POPOP solvent system.

Absorption of Penicillin G.—The potassium salt of penicillin G (about 1600 units/mg.) was formulated into a tablet which disintegrated readily in an aqueous medium. This tablet was placed in a capsule. Each dog received approximately 20,000 units (12.5 mg.) of the antibiotic per kilogram body weight. To help maintain adequate urine flow rate, each dog received water *via* stomach tube: 20 ml./Kg. 1 hour before drug release and 10 ml./Kg., 1, 3, and 5 hours after drug release. Blood samples were drawn at 0 time and 0.5, 1, 2, 4, 6, 8, and 24 hours after drug release. Urine was collected at 0, 0.5, 1, 2, 4, 6, 8, and 24 hours. An aliquot of each collection was diluted with an equal volume of a pH 6.0 buffer. The animals were fed after the eighth hour collections. The penicillin activity in the plasma and urine was determined by a standard *B. subtilis* agar-diffusion plate assay.

RESULTS AND DISCUSSION

Trimeprazine-S^{35} Absorption.—Figures 1 and 2 show that trimeprazine-S^{35} was absorbed rapidly and attained a peak level in plasma usually within 1 hour following its release. As shown in Fig. 2, the plasma S^{35} patterns were quite similar, whether the drug was released in the stomach, in the proximal portion (1.5 ft. past the pylorus sphincter), or in the distal portion (5 ft. past the pylorus) of the small intestine,[2] except that drug release in the small intestine appeared to give rise to slightly higher peak levels and faster absorption than did drug release in the stomach.

The bulk of S^{35} excretion occurred within 24 hours. As shown in Table I, 4-day urinary excretion of S^{35} activity appeared similar for each of several experiments (Dogs 250 and 300) and irrespective of the site of drug release (Dog 300). The total urinary and fecal excretion also appeared similar in these experiments. Although fecal excretion of the drug varied between 20 and 36% of the dose administered, this variation is not unusual. Previous studies with dogs in our laboratories have shown that phenothiazine tranquilizers are actively metabolized in the biliary system. A considerable portion of the fecal S^{35} activity appears to be derived from trimeprazine which was absorbed and metabolized and returned to the intestinal tract *via* the biliary route.

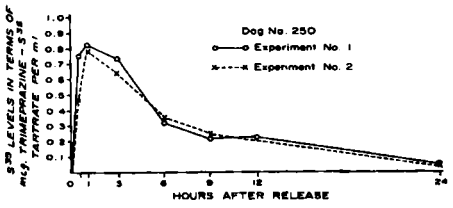

Fig. 1.—Plasma S^{35} levels after the release of 2.5 mg./Kg. trimeprazine-S^{35} tartrate in the stomach of a dog.

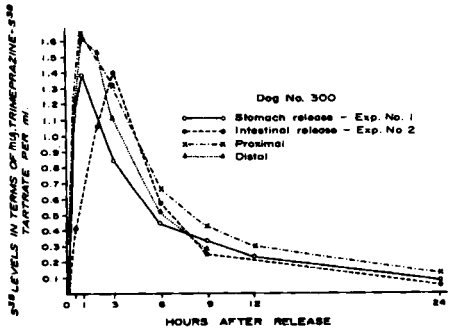

Fig. 2.—Plasma S^{35} levels following the release of 2.5 mg./Kg. trimeprazine-S^{35} tartrate at different sites in the dog gastrointestinal tract.

TABLE I.—TOTAL 4-DAY URINARY AND FECAL EXCRETION OF S^{35} ACTIVITY FOLLOWING ORAL ADMINISTRATION AND RELEASE OF TRIMEPRAZINE-S^{35} AT VARIOUS SITES IN THE GASTROINTESTINAL TRACT[a]

	Dog 250		Dog 300			
Site of Release	Stomach Exp. 1	Stomach Exp. 2	Stomach Exp. 1	Stomach Exp. 2	Intestine Proximal	Intestine Distal
Urinary	42.06	37.56	43.99	52.70	54.59	50.04
Fecal	36.34	34.15	36.08	29.63	20.90	24.06

[a] Expressed as % of total administered.

Inspection of the plasma and excretion data tends to show that trimeprazine was absorbed rapidly and to the same order when it was released at different sites in the gastrointestinal tract, even though the apparent increase in pH from the stomach to the distal portion of the small intestine might have been expected to affect the ionization of trimeprazine, which decreases as pH increases.

Studies in humans (2–4) corroborate the view that trimeprazine is absorbed well through a reasonable length of the gastrointestinal tract, evidenced by good plasma levels and urinary recovery of the drug that result when it is given in a sustained-release dosage form.

A valuable technique for measuring absorption efficiency as a function of drug release site is illustrated in this study. Whether a drug is absorbed efficiently from different regions of the small intestine is important because it is a criterion which determines whether the drug may be used successfully in a sustained-release dosage form.

Penicillin G Absorption.—The antibiotic activity in the plasma and urine indicated an absorption

[1] POPOP liquid scintillation solvent system for aqueous samples: 1,4-dioxane, 400 ml.; toluene, 400 ml.; absolute alcohol, 240 ml.; *p*-bis [2-(5-phenyl-oxazolyl)] benzene, 5 Gm.; and 2,5-diphenyloxazole, 5 Gm.

[2] Length of small intestine of these dogs is approximately 10 ft.

capability for penicillin G when it was released in the stomach or as far as 3 or 4 ft. beyond the pylorus. Considerable variability in results was encountered when the drug was released in the stomach. This may be explained as follows. When potassium penicillin G was released in the stomach, it might have been wholly absorbed at this site or only partly absorbed there and partly absorbed in the intestine, following its passage through the pylorus. Plasma levels could have been influenced by gastric acidity and by the time required for the penicillin to pass through the stomach. Wide fluctuations in these levels could have occurred because the penicillin was inactivated to a different degree, depending on the pH of the stomach and the rate of stomach emptying.

A comparison of the plasma and urinary data obtained after penicillin release at different sites in the gastrointestinal tract (Table II and Fig. 3) shows that absorption was most efficient in the small intestine, approximately 1 to 2 ft. beyond the pylorus. These data also show that while penicillin appeared rapidly in the plasma, it was reduced to trace amounts by the end of 5 hours in all instances.

Penicillin, when released 3 or 4 ft. beyond the pylorus, might be expected to remain stable because of the high pH in this area. But since penicillin has a pKa near 2.8, its high degree of dissociation may impede its absorption. In addition, its inactivation by penicillinase probably becomes greater in the lower intestinal tract. Thus, urinary recoveries of penicillin released 3 to 4 ft. beyond the pylorus were consistently much lower than the recoveries when penicillin was released immediately beyond the pylorus. A comparison of the urinary recoveries resulting from the release of penicillin at three distinct sites is shown in Table II.

The capacity of the various sections of the human gastrointestinal tract to absorb penicillin has been studied by introducing penicillin into these sections using capsules with enteric coatings of different thicknesses (5), laparotomy (6), a probe (7), and sustained-release coated pellets (8). The observations made in dogs in the present study generally agree with those made in humans by several investigators—namely, penicillin is available for absorption most readily in the upper small intestine and is considerably less available in the stomach and lower intestine. The lesser availability may be due not to the poor absorption of the drug, but rather to its rapid destruction at around pH 2, where its chemical half-life is in the order of only a few minutes (9).

TABLE II.—PENICILLIN RECOVERY IN DOG URINE FOLLOWING RELEASE OF POTASSIUM PENICILLIN G (20,000 u./Kg.) AT VARIOUS SITES IN THE GASTROINTESTINAL TRACT

	% Total Penicillin Recovered in Urine in 6 Hr.		
Dog	Release in Stomach	Released in Small Intestine Distance Past Pylorus, <2 Ft.	Distance Past Pylorus, 3–4 Ft.
201	6%	13% (20)[a]	
215	8	24 (18)[a]	16% (36)[a]
265	22	26 (10)[a]	10 (36)[a] (run 1)
			14 (40)[a] (run 2)
			9 (>36)[a] (run 3)

[a] Number in parentheses is the distance (in inches) past the pylorus where the drug was released.

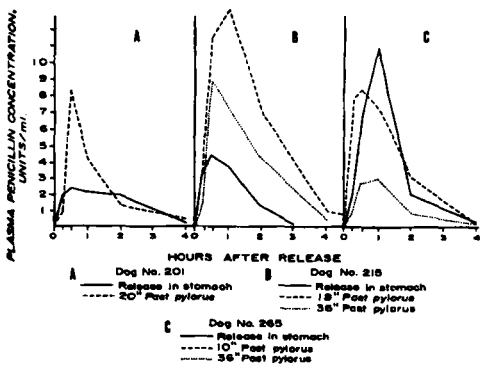

Fig. 3.—Plasma penicillin concentrations following the release of 20,000 U.S.P. units potassium penicillin G per Kg. at different sites in the gastrointestinal tract.

Penicillin G's short biologic half-life (about 0.5 hour), coupled with its reduced absorption efficiency as it is released further and further beyond the pylorus, makes it a poor candidate for a sustained-release product that would give uniformly high plasma blood levels for 10 to 12 hours. Furthermore, our data suggest that the drug's availability for absorption would be decreased. Studies in our laboratories (but not reported here) indicate poor availability to humans of penicillin G from lipid-coated pellets.

This part of the present study again illustrates the applicability of the radiofrequency method for the study of absorption as a function of release sites under near physiologic conditions in intact experimental subjects.

SUMMARY

The study describes how the site of drug release in the gastrointestinal tract affects the absorption of trimeprazine-S^{35} and penicillin G in dogs, and how the drug release at selected sites is accomplished with a radiofrequency generator. Using data on drug blood levels and urine recoveries, we show how the technique employed can be applied to study, under near physiologic condition, absorption efficiency in relation to drug release site. These data are useful in considering the design of oral dosage forms. The data obtained on trimeprazine are consistent with the view that this drug is available for efficient absorption, whether released in the stomach, in the intestine near the pylorus, or midway in the small intestine. The data obtained on penicillin G show it to be readily available when released in the intestine just beyond the pylorus, and not so available when released in the stomach or deeper in the small intestine.

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