Effects of Colestipol Hydrochloride on Drug Absorption in the Rat II

WILLIAM A. PHILLIPS ˣ, JOHN M. RATCHFORD, and JOHN R. SCHULTZ

Abstract □ The effects of colestipol hydrochloride, a hypocholesterolemic bile acid-binding anion-exchange polymer, on the GI absorption of drugs commonly used in humans were studied in the rat. Colestipol hydrochloride was given by gavage in single doses of 71.5 or 214.5 mg/kg, equivalent to 5 or 15 g, respectively, in a 70-kg human; controls received equivalent amounts of microcrystalline cellulose. Single oral doses of labeled drugs were given concurrently with colestipol hydrochloride or microcrystalline cellulose at the human therapeutic dose range on a milligrams per kilogram basis. Subsequent changes in serum drug levels were measured at several time periods, and absorption was evaluated as the total area under the time–concentration curve. Colestipol hydrochloride at either dose did not significantly alter the absorption of 6-^{14}C-nicotinic acid, 7-^{3}H-tetracycline, ^{35}S-chlorpromazine, 12α-^{3}H-digoxin, warfarin (α-^{14}C-benzyl), or clofibrate (^{14}C-carboxyl). In addition, the effects of 214.5 mg/kg of colestipol hydrochloride were compared with the same dose of cholestyramine with respect to the absorption of 3-^{14}C-hydrochlorothiazide, 2-^{14}C-phenobarbital, and ^{3}H-digitoxin. Cholestyramine reduced absorption of hydrochlorothiazide by 42%, but colestipol hydrochloride had no significant effect. Neither resin altered phenobarbital or digitoxin absorption when compared with the control, but a significant difference occurred between the two resins with digitoxin; areas under the time–concentration curve [in (dpm/0.1 ml serum) × hr] were: colestipol hydrochloride, 2001; cholestyramine, 16,300; and cellulose, 17,067. These results indicate that colestipol hydrochloride and cholestyramine can differ in their effects on the absorption of certain drugs from the GI tract of the rat.

Keyphrases □ Colestipol hydrochloride—effect on GI absorption of various drugs, rats □ Absorption, GI—various drugs, effect of colestipol hydrochloride, rats □ Anion-exchange polymers—colestipol hydrochloride, effect on GI absorption of various drugs, rats

Colestipol hydrochloride[1] is a high molecular weight anion-exchange polymer, prepared by reacting polyethylenepolyamine and 1-chloro-2,3-epoxypropane. It contains approximately one of five amine nitrogens protonated as the chloride salt. Oral administration of the bile acid-binding colestipol hydrochloride increases the fecal excretion of bile acids by reducing their intestinal reabsorption, thereby reducing cholesterol levels in experimental animals (1–3) and in humans (4–7). Since colestipol hydrochloride may bind other substances, including drugs that might be used as concurrent therapy in hypercholesterolemic subjects, studies of possible drug–polymer interactions have been continued in the rat.

Previous results with aspirin, levothyroxine, cortisone acetate, phenobarbital, and sulfadiazine indicated that both aspirin and levothyroxine absorption were inhibited by the polymer when administered concurrently to the rat (8). It was suggested that the primary interaction with aspirin and levothyroxine was electrostatic between the negatively charged carboxyl groups of the adsorbates and the positively charged groups on the adsorbent. A reinforcement by a nonelectrostatic force (9) existing between the hydrophobic portion of levothyroxine and the polymer molecules could explain the marked reduction of levothyroxine by colestipol hydrochloride in comparison to the other drugs tested.

Cholestyramine is an insoluble quaternary ammonium anion-exchange resin that binds bile acids and possesses the same potential as colestipol hydrochloride for interactions with other therapeutic agents (10). Although cholestyramine has been reported to retard absorption of radioactive drugs (*e.g.*, aspirin and phenobarbital), differences in experimental conditions made it impossible to compare the drug-binding capacities of the two polymers. To study this relationship, *in vivo* experiments were conducted on the effects of the two resins, administered under identical conditions, on the absorption of 3-^{14}C-hydrochlorothiazide, 2-^{14}C-phenobarbital, and ^{3}H-digitoxin.

EXPERIMENTAL

Ten male rats[2], with an average weight of approximately 240 g (less than 20-g range), were used in each treatment group. The rats were fasted for 18 hr prior to and during each experiment, except in the warfarin and tetracycline tests in which food was returned at 1 and 3 days, respectively; water was allowed *ad libitum*. Colestipol hydrochloride was suspended in 0.25% aqueous methylcellulose and administered by stomach tube at 71.5 and 214.5 mg/kg. Controls received equal amounts of a bulk material, microcrystalline cellulose[3], suspended and dosed similarly to colestipol hydrochloride. These levels correspond on a weight basis to 5 and 15 g of material, respectively, in a 70-kg man.

In the comparison studies, colestipol hydrochloride, cholestyramine[4], or microcrystalline cellulose was suspended in sterile water and administered at 214.5 mg/kg. Water alone served as the fourth treatment group. Within 10 sec after treatment, radioactive drug, dissolved or suspended in 0.25% methylcellulose vehicle or sterile water, was administered by stomach tube. The radioactive drugs, found by TLC on silica gel and scanning with a radiochromatogram scanner[5] to be radiochemically pure, were 6-^{14}C-nicotinic acid, warfarin (α-^{14}C-benzyl), ^{35}S-chlorpromazine[6], 7-^{3}H-tetracycline hydrochloride, 12α-^{3}H-digoxin, 2-^{14}C-phenobarbital, 7-^{3}H-digitoxin[7], clofibrate (^{14}C-carboxyl)[8], and 3-^{14}C-hydrochlorothiazide[9].

In the experiments, the microcuries given per 100 g of body weight were: nicotinic acid or warfarin, 0.45; digoxin or digitoxin, 2.0; chlorpromazine, 3.6; tetracycline, 9.5; clofibrate, 0.1; phenobarbital, 0.65; and hydrochlorothiazide, 0.91. The total doses of the drugs, as milligrams per kilogram, after addition of nonradioactive compound[10]

[1] Colestid, The Upjohn Co., Kalamazoo, Mich.

[2] Upj:TUC(SD)spf.

[3] Avicel, PH-102, FMC Corp., American Viscose Division, Marcus Hook, Pa.

[4] Cuemid, No. 3300, Merck Sharp and Dohme, Division of Merck and Co., West Point, Pa. Administered at 234.4 mg/kg to allow for 8.5% inert material.

[5] Model 885, Vanguard Instrument Corp., La Grange, Ill.

[6] Amersham/Searle, Arlington Heights, Ill.

[7] New England Nuclear, Boston, Mass.

[8] From Dr. D. M. Foulkes, Imperial Chemical Industries Limited, England.

[9] From Dr. N. Chaudhuri, Ciba-Geigy Corp., Summit, N.J.

[10] Niacin NF; tetracycline hydrochloride and phenobarbital USP; digoxin and digitoxin, Mann Research Laboratories, Division of Becton, Dickinson & Co., New York, N.Y.; and warfarin and clofibrate, synthesized at The Upjohn Co. Supplementations with chlorpromazine and hydrochlorothiazide were not necessary.

Table I—Area under Time–Serum Drug Concentration Curves for Several Drugs with Concurrent Administration of Colestipol Hydrochloride or Cellulose Control[a]

Drug[b]	Dose, 71.5 mg/kg		Dose, 214.5 mg/kg		SD, %[d]
	Control	Colestipol Hydrochloride[c]	Control	Colestipol Hydrochloride	
Nicotinic acid	1,354	1,469	1,184	1,004	30.3
Tetracycline	10,445	10,583	11,239	9,679	23.3
Chlorpromazine	14,843	14,101	15,285	14,514	17.6
Digoxin	8,410	8,256[e]	8,350	8,633[e]	15.5
Warfarin	99,879	92,118	92,045	89,821	11.7
Clofibrate	9,039[a]	10,035	—	10,567[e]	24.3

[a] Except clofibrate control group given 0.25% aqueous methylcellulose vehicle (see text). [b] Mean areas for tetracycline expressed as (dpm/0.1 ml) × day; all other values expressed as (dpm/0.1 ml) × hr. [c] Within each dosage level, none of the means between control and colestipol hydrochloride group was statistically significant. [d] Obtained from analysis of variance over all four groups. [e] Represents mean of nine animals; all other values represent mean of 10 animals.

Table II—Peak Serum Radioactivities for Several Drugs with Concurrent Administration of Colestipol Hydrochloride or Cellulose Control[a]

Drug	Dose, 71.5 mg/kg		Dose, 214.5 mg/kg		SD, %
	Control	Colestipol Hydrochloride	Control	Colestipol Hydrochloride	
Nicotinic acid	1510	1423	1389	990[b]	14.1
Tetracycline	3823	4034	3851	3751	27.1
Chlorpromazine	638	610	679	670	25.4
Digoxin	528	454[c]	568	493[c]	24.1
Warfarin	3648	3461	3271	2821	23.7
Clofibrate	653[d]	734	—	776[c]	20.6

[a] Mean values expressed as dpm/0.1 ml serum. [b] Significant difference between colestipol hydrochloride mean and mean of corresponding cellulose control: $p < 0.01$. [c] Represents mean of nine animals; all other values represent mean of 10 animals. [d] Control group given 0.25% aqueous methylcellulose vehicle (see text).

were: nicotinic acid, 14.3; tetracycline, 3.6; chlorpromazine, 0.7; digoxin, 0.065; warfarin, 0.19; clofibrate, 7.6; hydrochlorothiazide, 1.8; phenobarbital, 1.34; and digitoxin, 0.004. The doses were generally within the range given to humans on a weight basis.

The rats were then bled from the jugular vein (0.25 ml) at various time periods (11). The scintillation fluid contained 8.8% serum solubilizer[11], 0.4% 2,5-diphenyloxazole, and 0.005% 1,4-bis[2-(5-phenyloxazolyl)]benzene in toluene. Radioassay of 0.1 ml of serum was accomplished in a liquid scintillation spectrometer[12], and quenching was determined using the automatic external standard and a prepared efficiency correlation curve. Correction for sulfur-35 decay was also made in the chlorpromazine experiment.

The data for each drug were analyzed statistically for specific activity (dpm/0.1 ml) at each sampling period, peak radioactivity was obtained from the observed curve, and the area under the time–concentration curve [(dpm/0.1 ml) × hr] was calculated with the trapezoidal rule. For each parameter, a one-way analysis of variance (12) was performed on the values from the four groups of animals; comparisons were made between each colestipol hydrochloride mean and the mean of the corresponding control. In the comparison study with colestipol hydrochloride and cholestyramine, the polymers were compared with cellulose and with each other; cellulose was compared with the water treatment group.

Of the drugs tested, the one-compartment open model was appropriate only for the data obtained with phenobarbital (8). When more than two samples were lost during centrifugation or when the rat died from the bleeding procedure, the data from that animal were not included in the analyses.

RESULTS AND DISCUSSION

The results obtained with colestipol hydrochloride at 71.5 and 214.5 mg/kg and corresponding levels of cellulose on areas under the time–concentration curves and peak serum radioactivities are summarized in Tables I and II. The serum drug levels for each drug at various sampling periods are presented in the figures.

6-^{14}C-Nicotinic Acid—The results obtained with 6-^{14}C-nicotinic acid administered at 14.3 mg/kg are presented in Fig. 1. The low level of colestipol hydrochloride significantly decreased the serum drug level at 15 min and increased the radioactivity at the 4-hr period. The high level of colestipol hydrochloride significantly decreased the appearance of the ^{14}C-label in the serum at 15 and 30 min; other changes did not differ from the control. Although peak radioactivity at the high dose of the polymer was significantly reduced by 29%, total drug availability, as measured under the time–concentration curve, was reduced 15% but did not differ significantly from the control.

It was previously reported that colestipol hydrochloride can in-

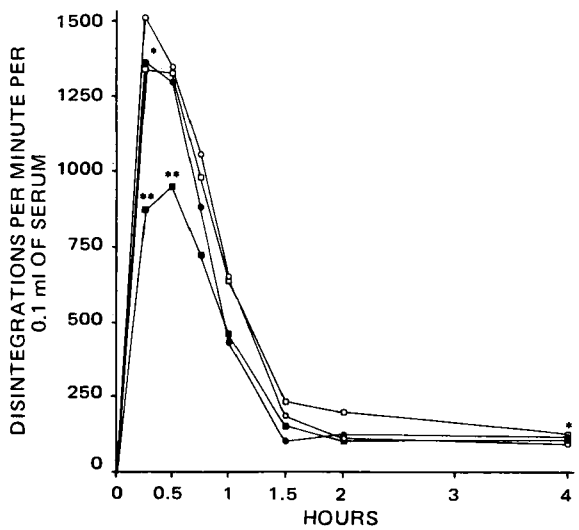

Figure 1—*Effect of colestipol hydrochloride on absorption of 6-^{14}C-nicotinic acid. Key: cellulose control at 71.5 (○) and 214.5 (●) mg/kg; colestipol hydrochloride at 71.5 (□) and 214.5 (■) mg/kg; and significant difference between colestipol hydrochloride mean and mean of corresponding control at* $p < 0.05$ (*) *and* $p < 0.01$ (**).

[11] Bio-Solv BBS-3, Beckman Instruments, Inc., Fullerton, Calif.
[12] Model 3375, Packard Instrument Co., Downers Grove, Ill.

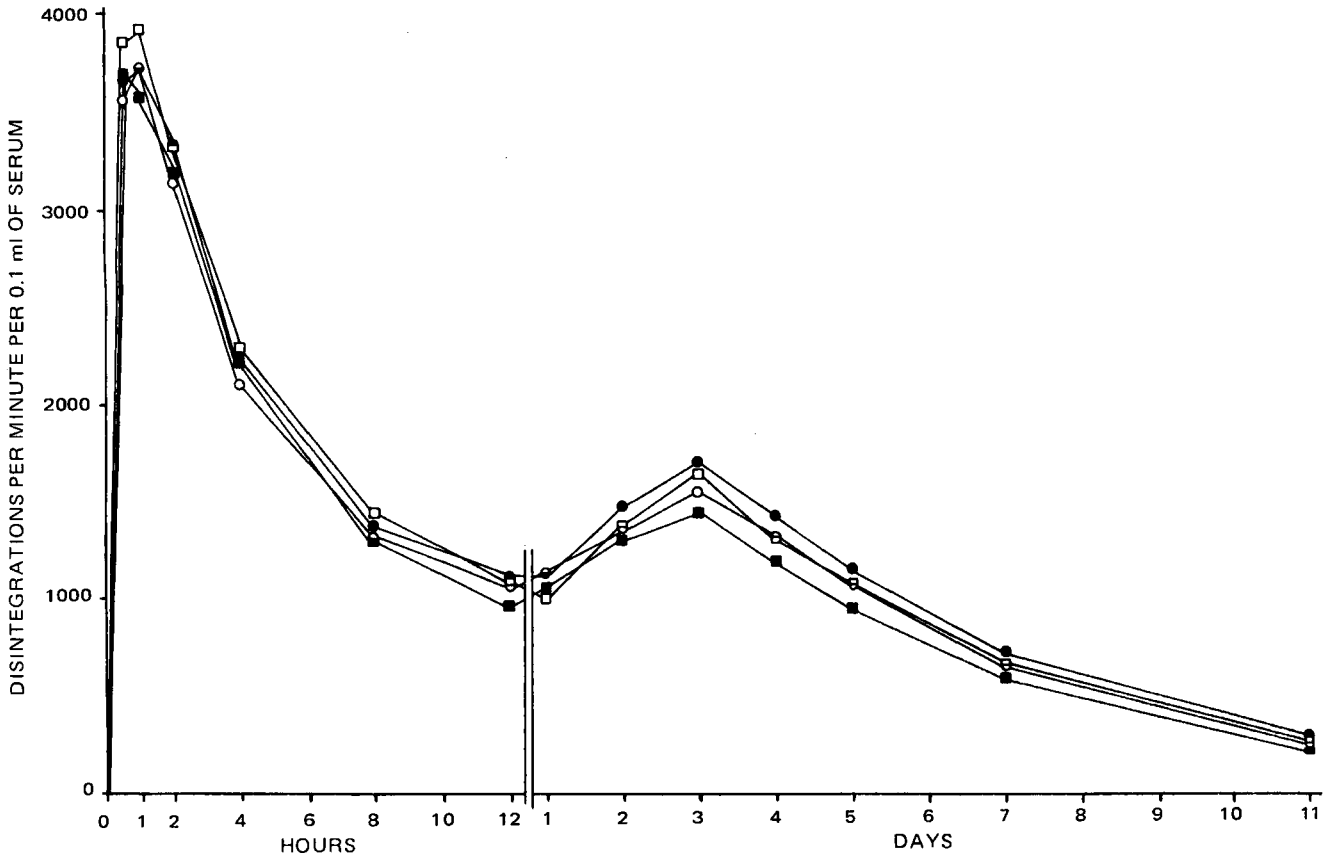

Figure 2—*Effect of colestipol hydrochloride on absorption of 7-^{3}H-tetracycline. Key: cellulose control at 71.5 (○) and 214.5 (●) mg/kg; and colestipol hydrochloride at 71.5 (□) and 214.5 (■) mg/kg.*

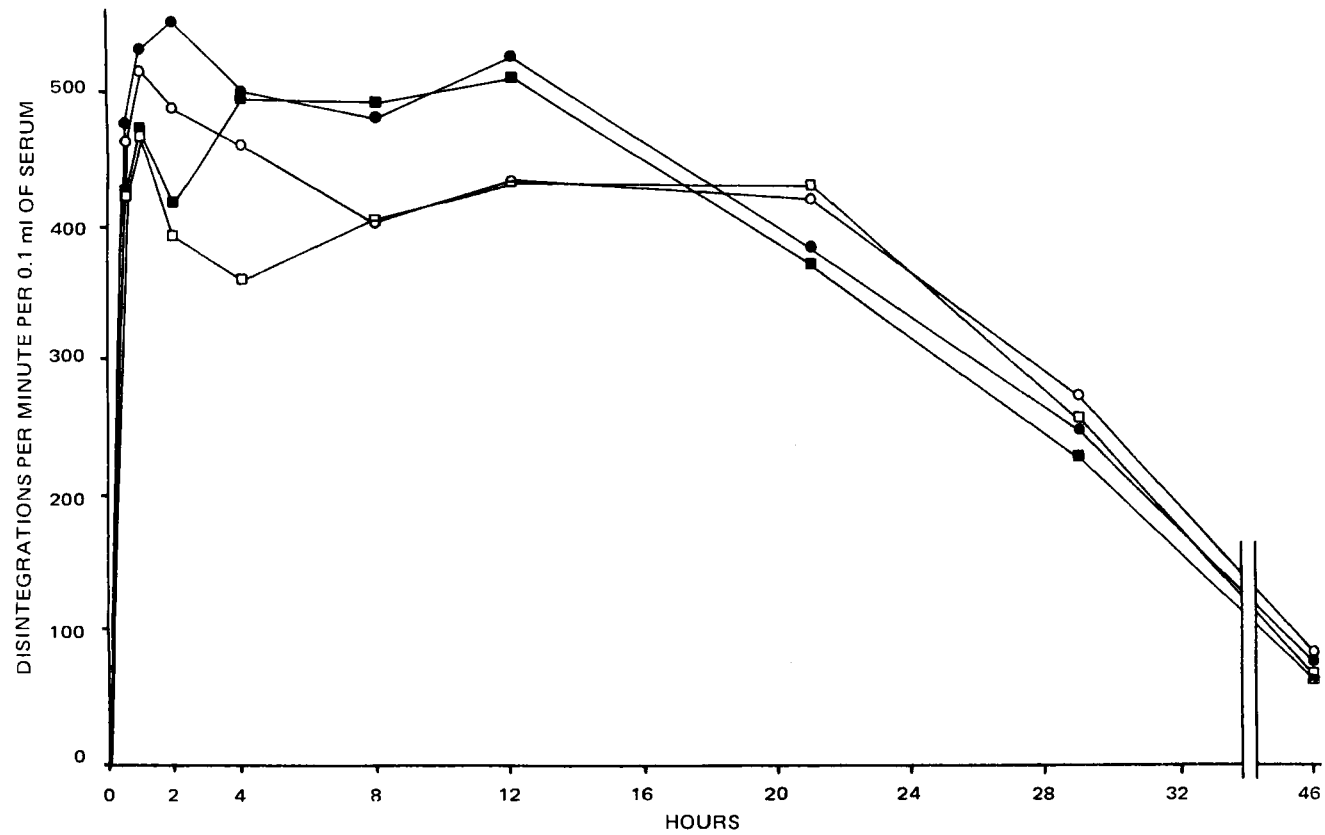

Figure 3—*Effect of colestipol hydrochloride on absorption of ^{35}S-chlorpromazine. Key: cellulose control at 71.5 (○) and 214.5 (●) mg/kg; and colestipol hydrochloride at 71.5 (□) and 214.5 (■) mg/kg.*

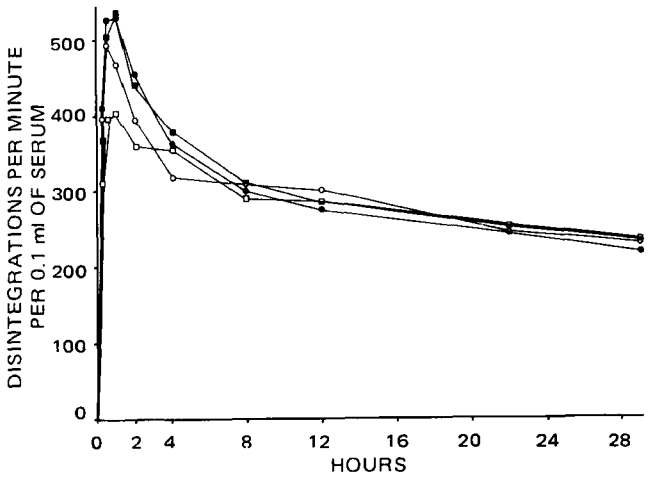

Figure 4—*Effect of colestipol hydrochloride on absorption of 12α-^{3}H-digoxin. Key: cellulose control at 71.5 (○) and 214.5 (●) mg/kg; and colestipol hydrochloride at 71.5 (□) and 214.5 (■) mg/kg.*

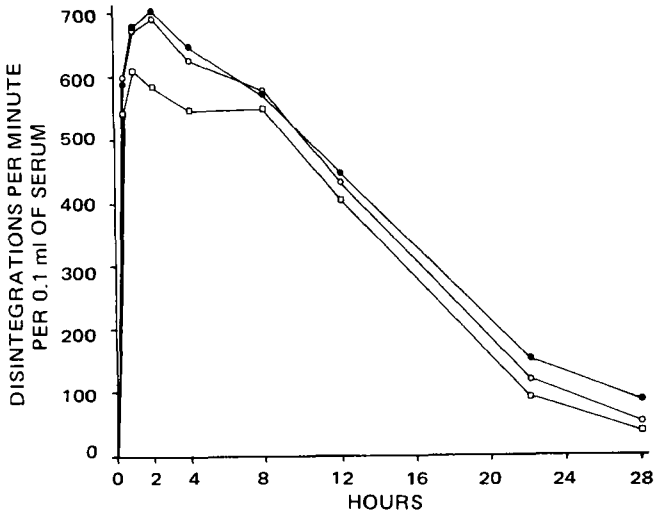

Figure 6—*Effect of colestipol hydrochloride on absorption of clofibrate (^{14}C-carboxyl). Key: methylcellulose vehicle control (□); and colestipol hydrochloride at 71.5 (○) and 214.5 (●) mg/kg.*

terfere with the absorption of aspirin (pKa 3.4) but not with phenobarbital (pKa 7.2) absorption (8). The stability of the drug–polymer interaction may be related to the pKa of these drugs. Nicotinic acid, with an intermediate pKa of 4.8, was bound less than aspirin, as evidenced by the delay of absorption or the reduction of peak radioactivity with little effect on the total amount absorbed. Electrolytes present in the GI tract could reduce the charge density on the charged adsorbate and adsorbent, thus weakening the electrostatic interaction between the polymer and nicotinic acid. Evidence for the inhibitory effect of electrolytes on the interaction of bile salt anions with cholestyramine was reported previously (13).

7-^{3}H-Tetracycline—Serum levels of 7-^{3}H-tetracycline after oral administration at 3.6 mg/kg were measured at various intervals over 11 days (Fig. 2). Serum radioactivities at various sampling periods, the amount of drug absorbed, and the peak radioactivity were not influenced at either level of colestipol hydrochloride. The unusual formation of a second peak of serum radioactivity after 24 hr may be related to the continued fasting of the animals for 3 days. The appearance of the second peak is not an artifact, since this effect was observed in all 40 animals. The explanation of this phenomenon is not clear at present, but double peaks were observed in rat blood levels with other antibiotics (14).

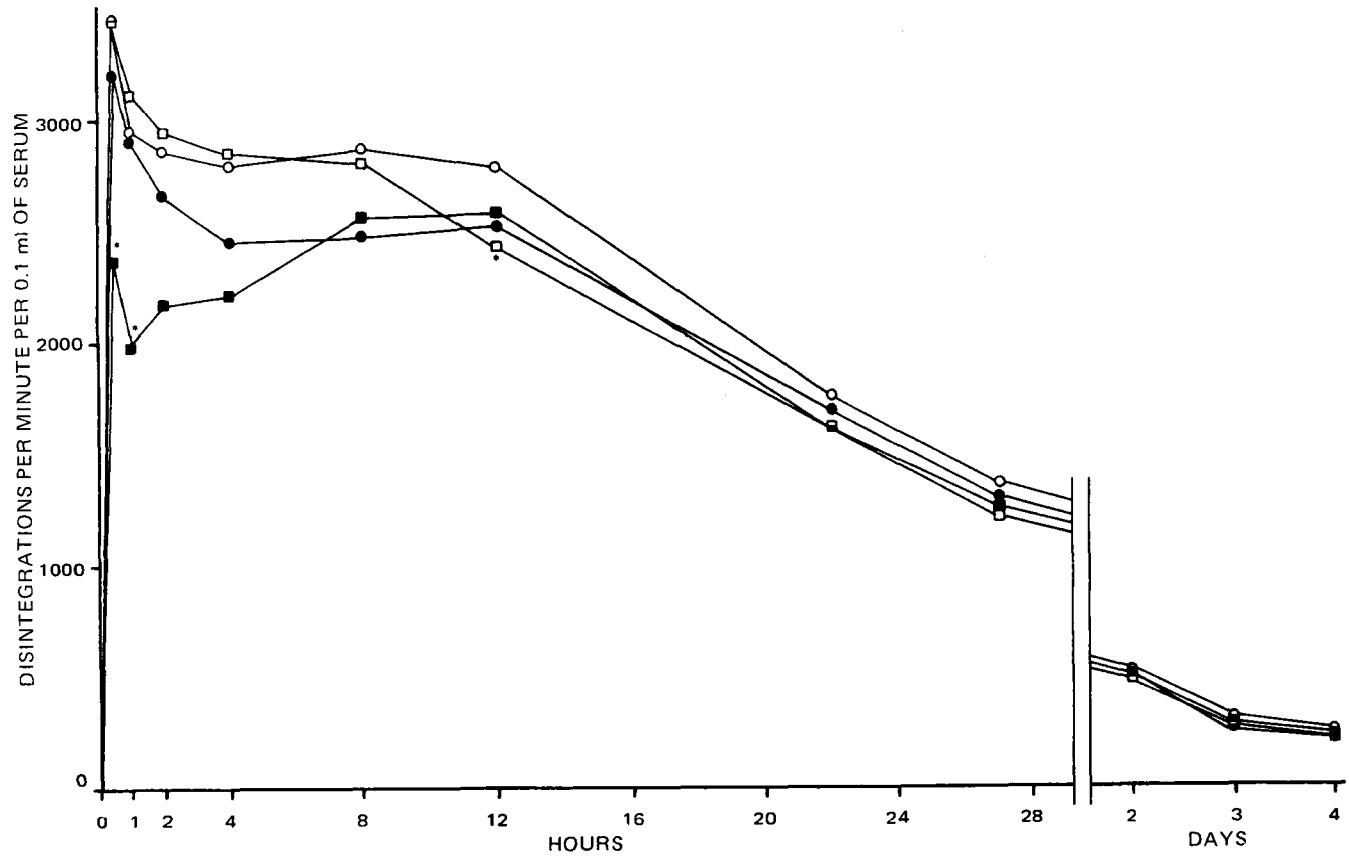

Figure 5—*Effect of colestipol hydrochloride on absorption of warfarin (α-^{14}C-benzyl). Key: cellulose control at 71.5 (○) and 214.5 (●) mg/kg; colestipol hydrochloride at 71.5 (□) and 214.5 (■) mg/kg; and significant difference between colestipol hydrochloride means and mean of corresponding control at $p < 0.05$ (*).*

Table III—Areas and Peak Radioactivities for 3-^{14}C-Hydrochlorothiazide with Concurrent Administration of Cellulose, Colestipol Hydrochloride, Cholestyramine, or Water[a]

Treatment	Area (0–11 hr)	Peak Radioactivity
Cellulose[b]	2478	486
Colestipol hydrochloride	2260	424
Cholestyramine[b]	1428	192
Water	2481	468
SD, %[c]	12.1	15.1

[a] Area under the time–concentration curve is in (dpm/0.1 ml) × hr; peak radioactivity is in dpm/0.1 ml serum. [b] Represents mean of nine animals; all other values represent mean of 10 animals. [c] Obtained from analysis of variance over all four groups.

^{35}S-Chlorpromazine and 12α-^{3}H-Digoxin—The results obtained with ^{35}S-chlorpromazine administered at 0.7 mg/kg and with 12α-^{3}H-digoxin administered at 0.065 mg/kg are shown in Figs. 3 and 4. The differences between serum radioactivity at both levels of colestipol hydrochloride and corresponding controls were not significant at any sampling period in both experiments.

Warfarin (α-^{14}C-Benzyl)—Warfarin (α-^{14}C-benzyl) was administered at 0.19 mg/kg to each rat (Fig. 5). Colestipol hydrochloride at 71.5 mg/kg reduced serum radioactivity at the 12-hr sampling period; other values did not differ significantly from the control. At 214.5 mg/kg, colestipol hydrochloride caused a significant decrease in serum drug levels at 0.5- and 1-hr sampling periods only. The early binding of warfarin may be due to the weakly acidic functional enol group of the drug. Values for drug availabilities and peak radioactivities at both levels of the polymer did not differ significantly from the corresponding controls, indicating that electrolytes present in the GI tract could weaken the electrostatic attraction of colestipol hydrochloride and warfarin.

Clofibrate (^{14}C-Carboxyl)—The results obtained with the hypocholesterolemic agent clofibrate administered at 7.6 mg/kg appear in Fig. 6. Due to the limited amount of radioactive compound, the control groups did not receive cellulose. The differences in serum radioactivities after the concurrent administration of the drug at both levels of colestipol hydrochloride and the control were not significant at any sampling period. Colestipol hydrochloride could delay or interfere with the absorption of clofibrate if the free acid was liberated in the GI tract of the animal; however, the ester after GI absorption is rapidly hydrolyzed by tissue and serum esterases to the free acid (15).

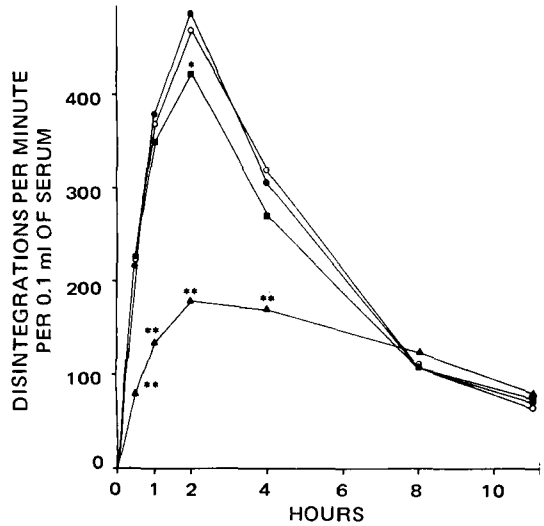

Figure 7—*Effect of colestipol hydrochloride or cholestyramine on absorption of 3-^{14}C-hydrochlorothiazide. Key: cellulose control at 214.5 (●) mg/kg; colestipol hydrochloride at 214.5 (■) mg/kg; cholestyramine at 214.5 (▲) mg/kg; water (○); and significant difference between colestipol hydrochloride or cholestyramine means and mean of corresponding cellulose control at p < 0.05 (*) or p < 0.01 (**).*

Table IV—Statistical Comparisons for Data Shown in Table III[a]

Comparison	Area (0–11 hr)	Peak Radioactivity
Cellulose *versus* colestipol hydrochloride	N.S.	$p < 0.05$
Cellulose *versus* cholestyramine	$p < 0.01$	$p < 0.01$
Colestipol hydrochloride *versus* cholestyramine	$p < 0.01$	$p < 0.01$
Cellulose *versus* water	N.S.	N.S.

[a] *The p values indicate level of significance; N.S. indicates not significant.*

The following results were obtained in comparison studies with colestipol hydrochloride and cholestyramine at 214.5 mg/kg.

3-^{14}C-Hydrochlorothiazide—The results obtained with 3-^{14}C-hydrochlorothiazide administered at 1.8 mg/kg are presented in Table III and Fig. 7. Colestipol hydrochloride significantly reduced the serum drug level at 2 hr by 13%; other values did not vary significantly from the cellulose control. Cholestyramine significantly reduced drug levels at 0.5, 1, 2, and 4 hr by 47–65%; values were significantly less than those obtained with colestipol hydrochloride. Colestipol hydrochloride and cholestyramine reduced peak radioactivity by 13 and 60%, respectively; cholestyramine reduced absorption by 42%, whereas drug availability with colestipol hydrochloride did not significantly vary from the control. There were no significant differences between cellulose and water treatments in this test (Table IV).

Cholestyramine is a relatively nonpolar resin, with the basic quaternary ammonium exchange groups attached to a styrene–divinylbenzene copolymer skeleton. Colestipol hydrochloride is a relatively polar hydroxyl aliphatic amino resin. Since both are anion-exchange resins, they would be expected to bind the acidic drug hydrochlorothiazide by electrostatic attraction. The increased binding efficiency of cholestyramine for the drug may be due to the greater lipophilic character of the phenyl rings of the resin. No information is available

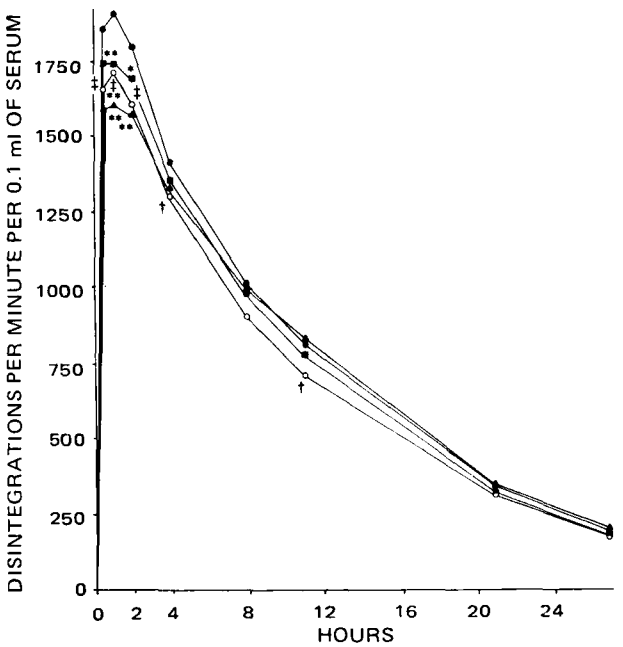

Figure 8—*Effect of colestipol hydrochloride or cholestyramine on absorption of 2-^{14}C-phenobarbital. Key: cellulose control at 214.5 (●) mg/kg; colestipol hydrochloride at 214.5 (■) mg/kg; cholestyramine at 214.5 (▲) mg/kg; water (○); significant difference between colestipol hydrochloride or cholestyramine and corresponding cellulose control at p < 0.05 (*) and p < 0.01 (**); and significant difference between water and cellulose means at p < 0.05 (†) and p < 0.01 (††).*

Table V—Kinetic Parameters for Phenobarbital with Concurrent Administration of Colestipol Hydrochloride, Cholestyramine, Cellulose, or Water

Model Parameters[a]	Dose, 214.5 mg/kg				
	Cellulose	Colestipol Hydrochloride[b]	Cholestyramine[b,c]	Water[c]	*SD*, %
K_A	5.88	5.82	5.64	4.84	37.7
$A^{1/2}$	0.130	0.124	0.136	0.145	28.1
K_E	0.091	0.087	0.076*	0.090	16.2
$E^{1/2}$	7.82	8.11	9.31*	7.87	15.4
Area	23,300	22,470	23,750	20,910	14.5
Observed area	20,932	19,853	20,139	18,729*	10.8
Peak radioactivity	1,925	1,780*	1,619**	1,705**	7.0

[a] K_A (hours^{-1}) = rate of absorption, $A^{1/2}$ (hours) = absorption half-life, K_E (hours^{-1}) = rate of elimination, $E^{1/2}$ (hours) = elimination half-life, area under the time–concentration curve is in (dpm/0.1 ml) × hr, and peak radioactivity is in dpm/0.1 ml serum (8). [b] Significant difference between colestipol hydrochloride, cholestyramine, or water means and cellulose control at (*) $p < 0.05$ and (**) $p < 0.01$. [c] Represents mean of eight animals; all other values represent mean of 10 animals.

comparing the influence of cholestyramine and colestipol hydrochloride on the absorption of this drug. However, differences between the polymers with the coumarin anticoagulant phenprocoumon in humans were reported (16, 17). Absorption of the phenprocoumon given concurrently with cholestyramine was significantly reduced; colestipol hydrochloride did not influence GI absorption of the coumarin anticoagulant.

2-^{14}C-Phenobarbital—The results obtained with 1.34 mg of 2-^{14}C-phenobarbital/kg appear in Table V and Fig. 8. Estimations of model parameters were made with phenobarbital, since the values were applicable to first-order kinetics (8). Colestipol hydrochloride significantly delayed the absorption of drug at 1 and 2 hr and cholestyramine at 0.5, 1, and 2 hr; the other values did not differ significantly from the cellulose control. Colestipol hydrochloride and cholestyramine significantly reduced peak radioactivity by 8 and 16%, respectively; drug availability with both polymers did not differ from the control. Therefore, neither polymer interfered with total absorption of the drug in the rat. Cholestyramine was reported to interfere with GI absorption of phenobarbital during a 2-hr test (10); evaluation of drug availability was not made due to insufficient data.

Estimated model parameters for absorption and elimination of phenobarbital with colestipol hydrochloride did not vary significantly from the cellulose control. Cholestyramine significantly reduced the rate of elimination (from 0.091 to 0.076 hr^{-1}) and increased the elimination half-life (from 7.82 to 9.31 hr) of the drug. The apparent reduction in the rate of elimination may reflect the latent absorption of loosely bound drug which dissociated from the drug–polymer molecule.

In this experiment, cellulose increased phenobarbital availability and serum drug levels at most time periods when compared to the water-treated group. These results may reflect the bulk effect of cellulose, which would increase stomach emptying time and delay entrance of drug into the intestine. Phenobarbital exists in the stomach almost totally in the absorbable nonionized form, becoming more ionized in the intestinal tract. Water alone has no influence on stomach emptying time (18) and permits more rapid entry of drug into a less favorable medium for absorption.

G-^{3}H-Digitoxin—The results obtained with ^{3}H-digitoxin administered at 0.004 mg/kg are presented in Table VI and Fig. 9. Colestipol hydrochloride caused significant increases in serum radioactivity at 21 and 27 hr; none of the other values varied significantly from the cellulose control. Values for observed peak radioactivity and the area under the curve were not altered significantly. Cholestyramine reduced significantly the serum radioactivity at 0.5, 1, and 2 hr and increased the serum radioactivity at 27 hr; observed peak radioactivity was reduced significantly (from 1489 to 1150 dpm), but the area under the curve did not differ significantly from the cellulose control (Table VII). Drug availability with cholestyramine was significantly less than with colestipol hydrochloride [16,300 *versus* 20,001 (dpm/0.1 ml) × hr], as was peak radioactivity (1150 *versus* 1524 dpm).

Studies in animals demonstrated that digitoxin participates in enterohepatic circulation (19). The reason for the significant elevation of serum drug levels with both polymers at the end of the test is not known, but it is reasonable to speculate that it is due to the appearance of newly synthesized bile acids, stimulated by administration of the polymers, which may aid in the reabsorption of digitoxin and its metabolites (20). When compared to the water-treated group, drug availability [17,067 *versus* 20,668 (dpm/0.1 ml) × hr], peak radioac-

Table VI—Areas and Peak Radioactivities for G-^{3}H-Digitoxin with Concurrent Administration of Cellulose, Colestipol Hydrochloride, Cholestyramine, or Water[a]

Treatment	Area (0–27 hr)	Peak Radioactivity
Cellulose	17,067	1,489
Colestipol hydrochloride[b]	20,001	1,524
Cholestyramine	16,300	1,150
Water	20,668	1,877
SD, %	20.2	21.2

[a] Area under the time–concentration curve is in (dpm/0.1 ml) × hr; peak radioactivity is in dpm/0.1 ml serum. [b] Represents mean of nine animals; all other values represent mean of 10 animals.

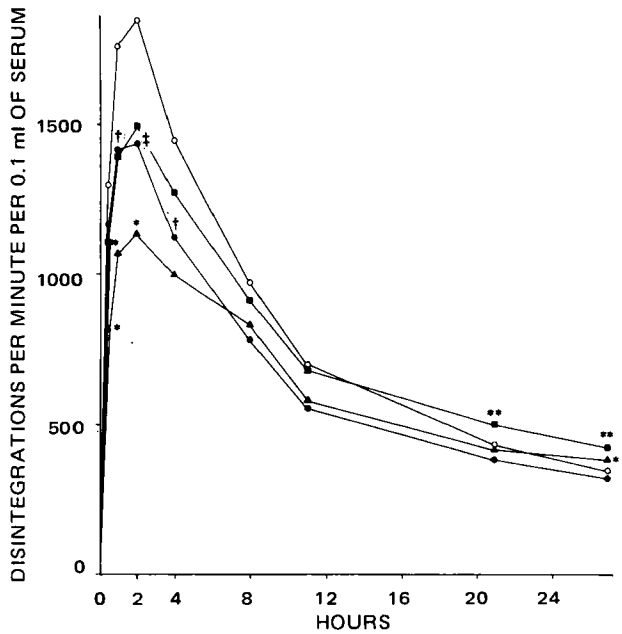

Figure 9—*Effect of colestipol hydrochloride or cholestyramine on absorption of ^{3}H-digitoxin. Key: cellulose control at 214.5 (●) mg/kg; colestipol hydrochloride at 214.5 (■) mg/kg; cholestyramine at 214.5 (▲) mg/kg; water (○); significant difference between colestipol hydrochloride or cholestyramine means and mean of corresponding cellulose control at* $p < 0.05$ *(*) and* $p < 0.01$ *(**); and significant difference between water and cellulose control at* $p < 0.05$ *(†) and* $p < 0.01$ *(††).*

Table VII—Statistical Comparison for Data Shown in Table VI[a]

Comparison	Area (0–27 hr)	Peak Radioactivity
Cellulose *versus* colestipol hydrochloride	N.S.	N.S.
Cellulose *versus* cholestyramine	N.S.	$p < 0.05$
Colestipol hydrochloride *versus* cholestyramine	$p < 0.05$	$p < 0.05$
Water *versus* cellulose	$p < 0.05$	$p < 0.05$

[a] The p values indicate level of significance; N.S. indicates not significant.

tivity (1489 *versus* 1877 dpm), and serum radioactivity at 1, 2, and 4 hr were significantly reduced by cellulose treatment. These results may reflect the bulk effect of cellulose, which would increase stomach emptying time and delay entrance of the drug into the intestine, where presumably the major portion of digitoxin is absorbed.

Colestipol hydrochloride is an anion-exchange polymer that would be expected to bind with ionized drugs by electrostatic forces, although other forces such as hydrogen bonding, dipole–dipole interactions, van der Waals forces, nonelectrostatic interactions, and intermolecular attractions of like molecules may be important factors in the binding process. The concurrent administration of nicotinic acid and colestipol hydrochloride reduced peak radioactivity at the high dose of the polymer; total drug availability, as measured under the time–concentration curve, was reduced but did not vary significantly from the control. Competition for binding sites on the polymer with bile acid anions and inorganic physiological anions (*e.g.*, phosphate, chloride, and bicarbonate) present in the GI tract could possibly explain these results.

The early binding of warfarin and the subsequent release from the drug–polymer interaction by these competing forces could weaken the electrostatic attraction of colestipol hydrochloride and the drug. Similarly, cholestyramine (357.5 mg/kg) in rats significantly depressed the plasma warfarin levels at all time intervals during a 4-hr test (10). Further tests on plasma prothrombin times used to calculate the relative clot index, at time intervals for 4 days, indicated that, although cholestyramine may delay early absorption of warfarin, the pharmacological effect was not significantly altered by a single dose of the drug and the polymer.

However, significant differences were noted between cholestyramine and colestipol hydrochloride in interfering with hydrochlorothiazide or digitoxin absorption from the GI tract of the rat. Whether results in rats are predictive of results in humans remains to be determined.

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[x] To whom inquiries should be directed.

Effects of Film Coatings on Tablet Hardness

PHILIP W. STERN

Abstract □ The effects of five conventional film-coating materials on tablet hardness were studied. Placebos showed apparently linear increases in hardness as coatings were applied. Completely coated samples exhibited hardness increases from 50 to 140%, with a corresponding 3% increase in tablet weight. Equations were derived relating hardness changes to the "breaking strength" of the film on the tablet. Findings indicate that the coatings exert their influence primarily along the diameter of the tablet in a direction perpendicular to an applied compressional force. Furthermore, the coating process itself did not alter core hardness since tablets from which the film could be stripped showed original values.

Keyphrases □ Film coatings—five different, effects on tablet hardness □ Hardness, tablet—effects of five different film coatings □ Tablet hardness—effects of five different film coatings □ Dosage forms—tablets, effects of five different film coatings on tablet hardness

The term "tablet hardness" is widely used today in a nonspecific or generic manner as an all-inclusive description of several important tablet parameters. Included among these parameters are bending or attrition resistance and impact or crushing strength (1–4). Of the four, measurement of crushing strength is probably the