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Alterations in Absorption of Dicumarol by Various Excipient Materials

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Abstract □ A plasma level study was conducted in dogs to determine the effects of various excipient materials on the absorption of dicumarol. The drug was combined with the excipients by an equilibration process and administered orally. Plasma concentrations of dicumarol after administration with excipients were compared to control levels produced by the drug given alone. Significant differences in the plasma levels of dicumarol were observed with six of the 10 excipients used in the study. Significantly higher plasma levels (up to 180% of control values) were observed when dicumarol was administered with magnesium oxide or hydroxide. This effect may be due to chelate formation because the magnesium chelate of dicumarol produced higher plasma levels of dicumarol than the drug administered alone. Dicumarol administration with talc, colloidal magnesium aluminum silicate, aluminum hydroxide, or starch resulted in significantly lower plasma levels of the drug. It is suggested that these types of interactions may be an explanation for differences in the bioavailability of dicumarol from different dosage formulations.

Keyphrases □ Dicumarol absorption—effect of various excipients on plasma levels, dogs □ Absorption, dicumarol—effect of various excipients on plasma levels, dogs □ Plasma levels, dicumarol—effect of various excipients, dogs □ Excipient effect—dicumarol absorption, plasma levels, dogs □ Bioavailability, dicumarol—effect of various excipients on plasma levels, dogs □ Magnesium oxide, hydroxide excipients—effect on dicumarol absorption, dogs

Substantial evidence is available to show that the absorption characteristics and, ultimately, the therapeutic performance of a drug can be significantly altered by changes in the materials and methods used in its formulation. Wagner (1) recently provided a review of studies involving the determination of generic equivalency or inequivalency of different commercial brands of a single drug. Ten of the 12 drugs studied showed significant differences in the bioavailability of drug when two or more commercial brands of the same drug were compared.

Lach and his coworkers (2–4), through diffuse reflectance spectroscopic studies, demonstrated that some adjuvants used in product formulation interact with certain drugs to form complexes. These combinations exhibited markedly different diffuse reflectance spectroscopic characteristics compared to those of the drug alone. The oral anticoagulant dicumarol was shown to interact with various organic and inorganic formulation materials, and it was suggested that these types of interactions may alter the bioavailability of the drug (3). Dicumarol has been shown to be poorly absorbed (5), and its bioavailability may be particularly susceptible to formulation changes. Losinski (6) reported that formulation changes involving the addition or reduction of inert fillers in tablets of dicumarol resulted in significant therapeutic variations.

The purpose of this study was to investigate whether the absorption of dicumarol could be altered by administration of the drug in combination with various formulation materials. The characteristics of its absorption and elimination, coupled with a pharmacological response dependent on plasma concentration, permitted the use of dicumarol to show that drug–excipient interactions may be an explanation for differences in therapeutic efficacy among different dosage formulations.

EXPERIMENTAL

Materials—Dicumarol[1] was recrystallized from dioxane (m.p. 288–289°). Other materials used were: magnesium oxide, heavy[2]; magnesium hydroxide, reagent grade[2]; magnesium stearate USP; dibasic calcium phosphate NF, hydrous[2]; aluminum hydroxide powder[2]; colloidal magnesium aluminum silicate[4]; silicic acid[5]; starch USP; talc USP; polyvinylpyrrolidone[6]; and polysorbate 80[7].

Elemental analysis of the magnesium chelate of sodium dicumarol[8] showed it to have the form $(dicumarol\text{-}Na)_2Mg$. A method for the preparation of the chelate was reported previously (4).

Animals—Eight healthy mongrel dogs of either sex, weighing 10–21 kg., were utilized in the study. The animals were housed in stainless steel cages and fed dog chow[9] between 8 a.m. and noon daily, unless specified otherwise.

Dicumarol–Excipient Mixtures—Dicumarol was mixed with an excipient in two different weight to weight ratios—6 dicumarol:94 excipient and 1 dicumarol:1 excipient. Dicumarol was dissolved in chloroform to make a solution containing 0.3 g. in 50 ml. An appro-

[1] K and K Laboratories.
[2] Mallinckrodt.
[3] Matheson, Coleman and Bell.
[4] Veegum, regular, Vanderbilt.
[5] Fisher.
[6] Antara Chemicals.
[7] Tween 80, Atlas.
[8] A gift from Dr. L. Bighley, College of Pharmacy, University of Iowa.
[9] Purina.

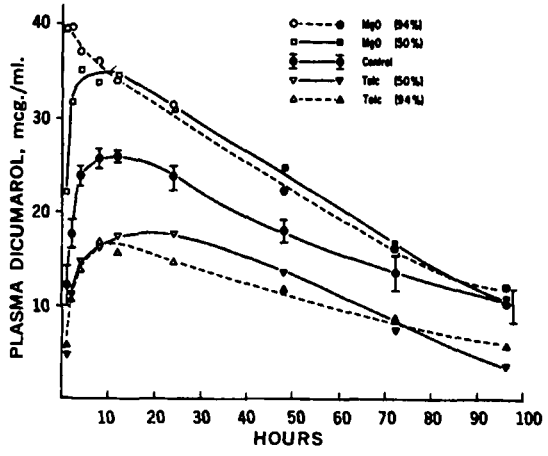

Figure 1—*Plasma concentrations of dicumarol after single oral doses of the drug given alone (control) or with various excipient materials. The values shown are the mean of four animals. Open data points indicate significant differences from control. Variation about the mean values was not statistically different from that of the control values which are shown with* SEM.

priate amount of excipient was added to the solution, and the mixture was stirred briefly by hand and allowed to stand in a glass-stoppered flask for 16 hr. The solvent was removed on a rotary evaporator, and the dry powder was collected after passing through a U. S. Standard No. 100 sieve.

Drug Administration—The dogs were fasted approximately 8 hr. before and 24 hr. after drug administration. Water was allowed at all times during the experiments. Dicumarol alone or the dicumarol–excipient mixtures were administered as aqueous suspensions by gastric intubation using a soft rubber catheter. The suspension was prepared by stirring the required amount of drug with 1–2 ml. of distilled water containing 0.05% polysorbate 80. Additional distilled water was added to bring the volume to 25 ml. and the suspension was immediately administered to the animal. A wash of 50 ml. of distilled water followed the dose to ensure quantitative administration.

The dose of the magnesium chelate of dicumarol was prepared in an identical fashion. In one dog, an intravenous dose of 5 mg./kg. of dicumarol was given after the animal had repeatedly received the same dose of drug orally. The vehicle used was 5 ml. of a dilute sodium hydroxide solution.

Blood Samples—Blood samples (7 ml.) were withdrawn by venipuncture and collected in heparinized Vacutainers[10]. A sample was obtained just prior to dosage administration, and subsequent samples were obtained 1, 2, 4, 8, 12, 24, 48, 72, and 96 hr. after the dose. Starting at 12 hr. after the dose, an additional blood sample (2.7 ml.) was withdrawn at each sampling time in Vacutainers containing sodium citrate for prothrombin time measurements. Heparinized plasma was stored at −20° prior to dicumarol analysis.

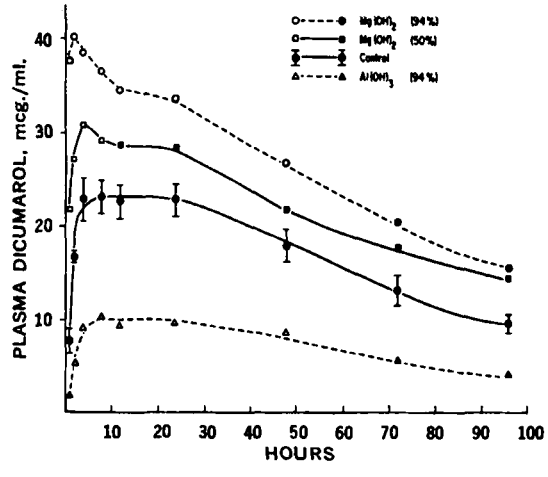

Figure 2—*Same as Fig. 1.*

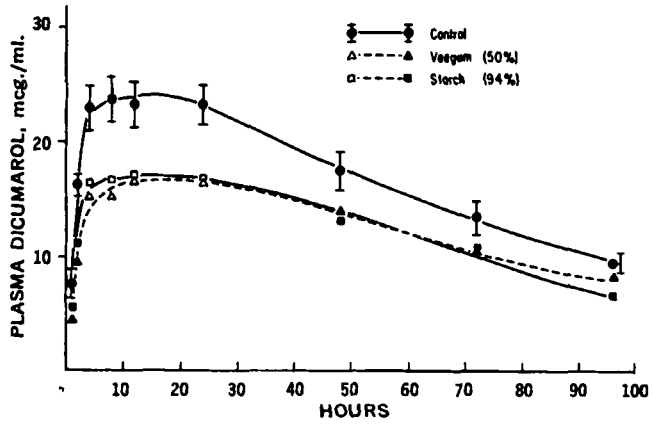

Figure 3—*Same as Fig. 1.*

Analysis of Plasma—Plasma samples were analyzed for dicumarol following the spectrophotometric procedure of Axelrod *et al.* as revised by Nagashima *et al.* (7). Plasma samples were analyzed by the same method after oral administration of the magnesium chelate of dicumarol. The UV absorbance maximum and molar absorptivity of the chelate in 2.5 *N* NaOH were the same as those for dicumarol. Analysis of dog plasma containing known amounts of the magnesium chelate of dicumarol produced an identical standard curve when compared to dicumarol.

Prothrombin Time Measurements—The one-stage method of Quick (8) was used on fresh plasma. Measurements were made on a BBL Fibrometer[11] using rabbit brain thromboplastin[11].

Pharmacokinetic Analysis—Absorption and elimination rate constants were obtained by submitting plasma level data to a nonlinear regression analysis[12]. Areas under the individual animal plasma level curves (0–96 hr.) were calculated using the trapezoidal technique. Areas from 96 hr. to infinity were calculated by the usual method (9), using the elimination rate constant determined by linear regression analysis of the logarithms of the 48-, 72-, and 96-hr. plasma dicumarol concentrations.

Experimental Design—Plasma levels of dicumarol after an oral dose of the drug in a mixture with excipient were compared to those resulting from oral administration of dicumarol powder. To reduce interanimal variation in plasma levels, a recognized characteristic of dicumarol administration (5), the dose of the drug used in each dog was that which produced a peak plasma level of 20–25 mcg./ml. after an oral dose of dicumarol powder. On the basis of the results of a preliminary test dose of dicumarol, the animals received 4, 5, or 7 mg./kg. of the drug. Each of the animals received three control doses (pure dicumarol powder) and from seven to 10 different dicumarol–excipient mixtures. A control dose was given first to each animal, and the subsequent control and dicumarol–excipient doses were given in a completely randomized manner. Blood samples were taken at selected intervals after each dose for plasma dicumarol and prothrombin time analyses. There was at least a 2-week interval between doses of the drug, during which time the drug plasma levels fell to undetectable levels and the prothrombin times returned to normal.

Statistical Analysis—The following parameters were analyzed statistically: plasma concentrations, areas under the plasma level curves, and peak prothrombin responses. The control values for each animal were the averages obtained from three doses of pure dicumarol given at different times. Mean parameters were computed from the data obtained from four dogs. Each dog in a group of four dogs received the same complement of dicumarol–excipient mixtures and three control doses. The means were compared by a one-way analysis of variance randomized complete block design, and statistical

[10] Becton-Dickinson.

[11] Bioquest Laboratories.

[12] Using the IBM-360 computer and the NONLIN program of Dr. Carl Metzler, The Upjohn Co.

Table I—Control Dicumarol Plasma Levels for Each Dog Used in the Study

	Dog 1	Dog 2	Dog 3	Dog 4	Dog 6	Dog 7	Dog 8	Dog 9
Sex	M	M	M	M	M	M	M	F
Weight, kg.	10	11	18	20	17	22	21	20
Dose, mg./kg.	4	7	7	4	5	5	5	5

Hours	Mean (*SE*) Concentration of Plasma Dicumarol, mcg./ml. Dog 1	Dog 2	Dog 3	Dog 4	Dog 6	Dog 7	Dog 8	Dog 9
1	14.5[a]	16.5[a]	10.1 (2.4)	9.8 (0.6)	5.6 —	6.1 (1.5)	5.2 (1.3)	11.3 (4.0)
2	20.2 (1.0)	19.4 (1.5)	17.7 (0.6)	15.2 (0.3)	16.8 (1.8)	13.3 (1.8)	17.2 (4.5)	17.8 (4.0)
4	21.9[a]	23.1[a]	25.8 (1.3)	16.5 (0.8)	26.0 (1.2)	25.4 (1.2)	23.5 (1.0)	24.9 (3.0)
8	24.6 (0.4)	24.2 (1.7)	25.9 (1.8)	17.8 (1.0)	25.2 (0.9)	26.3 (1.1)	23.8 (0.4)	27.4 (4.9)
12	24.9 (0.5)	25.5 (0.8)	25.7 (1.6)	17.1 (0.7)	24.6 (1.5)	27.9 (1.8)	23.2 (0.4)	25.2 (4.6)
24	20.4 (1.0)	22.4 (0.5)	27.3 (1.5)	18.2 (2.7)	18.2 (2.7)	24.4 (1.7)	26.9 (3.0)	24.8 (3.8)
48	17.8 (0.7)	14.6 (0.6)	21.6 (1.2)	12.6 (1.3)	17.7 (0.6)	20.6 (2.3)	19.4 (0.4)	18.8 (1.8)
72	13.4 (0.5)	8.1 (1.5)	16.6 (1.0)	9.4 (1.0)	12.5 (0.4)	17.7 (2.1)	14.5 (0.3)	14.6 (1.4)
96	12.4 (0.4)	4.6 (1.0)	11.6 (1.5)	7.0 (1.7)	8.9 (0.8)	13.4 (1.4)	10.6 (0.0)	10.5 (1.4)

[a] Only one value at this time. The rest of the values are the mean of three experiments.

differences from control values were determined by the least significant difference method (10).

RESULTS

Reproducibility of Dicumarol Plasma Levels—Considerable interanimal variation was observed in dicumarol plasma levels after identical oral doses to dogs. Because of this, the oral dose of dicumarol necessary to produce a standard (control) level from which alterations in drug absorption could be evaluated was determined in preliminary experiments on each dog. Adequate plasma levels and prothrombin time responses were produced with oral doses ranging from 4 to 7 mg./kg. Each dog was given the same dose of dicumarol throughout the experiments. Plasma levels of dicumarol after an oral dose were found to be reproducible in each animal. The mean plasma levels resulting from control doses of dicumarol powder administered to each dog at three different times throughout the study are shown in Table I. Analysis of the control plasma levels in each dog showed that time- or drug-dependent changes in dicumarol absorption and elimination did not occur in these experiments. The reproducibility of the control plasma levels of dicumarol is indicated by the low standard errors of the mean values. These mean values were used for comparison to plasma levels resulting when the drug was administered in combination with various excipient materials.

Dicumarol Plasma Levels after Oral Administration with Various Excipients—The mean plasma levels of dicumarol administered alone or in combination with various excipient materials are shown in Figs. 1–3. Significant increases in dicumarol plasma levels over control resulted when the drug was administered with magnesium oxide (Fig. 1). Slightly higher levels were observed with the mixture containing 94% magnesium oxide compared to the mixture containing equal weights of the drug and magnesium oxide. Significant decreases in dicumarol plasma levels were observed when the drug was administered with talc. Decreasing the proportion of talc in the mixture had little effect on the ability of this material to lower drug plasma levels (Fig. 1).

The results in Fig. 2 show that significant increases in dicumarol plasma levels resulted when the drug was given in a mixture containing either 94 or 50% magnesium hydroxide. In contrast, significant decreases in drug plasma levels were observed after administration of dicumarol in a mixture containing 94% aluminum hydroxide. No

Table II—Plasma Level Parameters and Prothrombin Time Responses following Oral Doses of Dicumarol in Combination with Various Excipient Materials[a]

Excipient	Percent of Excipient in Dose Mixture, % w/w	Peak Plasma Level Time, hr.	Dicumarol Concentration at Peak Level, mcg./ml.	Area under Plasma Level Curve, % Change from Control 0–96 hr.	0–∞ hr.	Maximum Prothrombin Time Response[b], sec.
Group I (Dogs 1, 2, 7, and 9)						
Control	0	8–12	25.8 (0.6)	—	—	16.3 (1.1)
Magnesium oxide	94	1–2	*39.6 (5.0)	*+31.4 (11.9)	+22.8 (17.5)	*23.3 (4.0)
Magnesium oxide	50	4	*35.1 (3.6)	*+30.0 (11.2)	+11.6 (20.4)	18.1 (2.1)
Talc	94	8	*16.9 (1.4)	*−37.0 (5.1)	*−45.7 (6.0)	14.1 (1.6)
Talc	50	12–24	*17.5 (1.0)	*−34.2 (4.7)	*−56.5 (3.0)	18.0 (2.3)
Silicic acid	94	8	26.4 (1.5)	−10.0 (12.2)	−1.3 (22.1)	15.0 (1.9)
Group II (Dogs 3, 4, 6, and 8)						
Control	0	8–12	23.1 (1.8)	—	—	14.7 (1.0)
Magnesium hydroxide	94	2	*40.1 (5.2)	*+56.6 (22.3)	*+71.0 (40.0)	*20.2 (1.8)
Magnesium hydroxide	50	4	*30.8 (3.6)	*+27.7 (18.6)	*+63.6 (33.1)	15.0 (1.3)
Aluminum hydroxide	94	8	*10.1 (1.7)	*−56.6 (5.2)	*−60.0 (5.6)	11.3 (1.1)
Aluminum hydroxide	50	8	25.1 (1.2)	+5.4 (12.5)	+12.2 (23.4)	14.4 (1.6)
Magnesium stearate	94	4	30.1 (5.1)	+10.4 (20.0)	+11.9 (21.3)	15.7 (1.6)
Colloidal magnesium aluminum silicate	50	12–24	*16.7 (3.3)	*−23.7 (13.2)	+1.1 (31.5)	11.7 (0.5)
Calcium phosphate	94	8	22.1 (2.1)	*−26.2 (5.0)	−28.5 (8.3)	14.7 (1.7)
Group III (Dogs 4, 6, 7, and 9)						
Control	0	8–12	24.1 (2.3)	—	—	15.8 (2.9)
Starch	94	4–24	*16.8 (2.5)	*−25.0 (8.2)	−30.9 (4.3)	15.7 (3.3)
Group IV (Dogs 3, 4, 6, and 7)						
Control	0	8–12	24.2 (2.0)	—	—	15.1 (2.4)
Polyvinylpyrrolidone	50	12–24	27.2 (2.5)	−19.0 (4.0)	+12.3 (17.2)	17.3 (2.6)

[a] Values are mean (*SE*) for four dogs; asterisks (*) indicate a significant difference from control, $p < 0.05$. [b] Normal prothrombin times were not subtracted. Range of normal values was 7.3–8.5 sec.

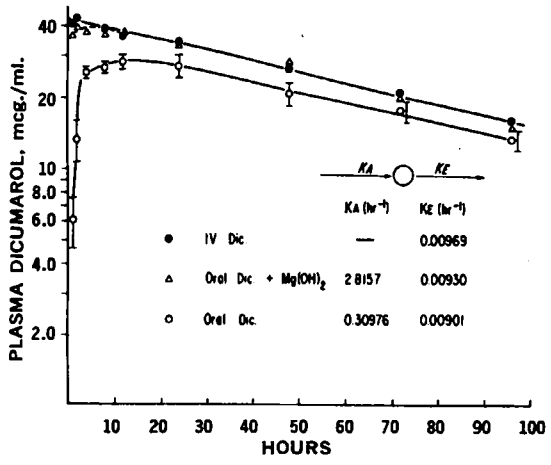

Figure 4—*Semilogarithmic plots of plasma dicumarol concentrations after identical doses of the drug were given intravenously* (●), *orally alone* (○), *or orally with 94% magnesium hydroxide* (△) *to Dog 7. First-order rate constants for absorption and elimination were determined from a nonlinear regression analysis as described in* Methods.

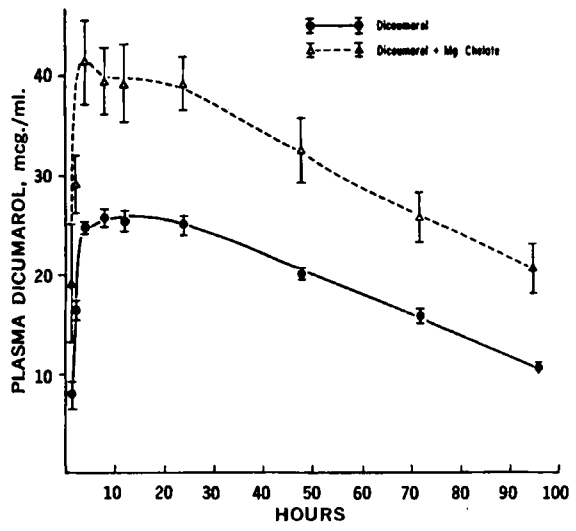

Figure 5—*Mean plasma concentrations of dicumarol after oral administration of the drug or its magnesium chelate to Dogs 3, 4, 8, and 9. Open data points are statistically different from the corresponding values at the same time.*

difference in the dicumarol plasma levels was observed when the drug was administered as a 50% mixture with aluminum hydroxide (Table II). It is evident from the results presented in Fig. 3 that the combination of dicumarol with starch or colloidal magnesium aluminum silicate resulted in lower plasma levels of the drug compared to those resulting from administration of the drug alone.

It can be observed in Figs. 1–3 that the postabsorptive decline in dicumarol plasma levels was similar whether the drug was given alone or with excipients. This suggests that the differences in plasma levels observed were due to absorption of the drug and not to its elimination from the plasma.

Dicumarol administered in combination with several other excipients did not alter the dicumarol plasma levels compared to those produced by the drug given alone. These results are not given in the figures, but the pertinent parameters measured are presented in Table II. The excipients that did not alter dicumarol absorption were silicic acid, magnesium stearate, dibasic calcium phosphate, and polyvinylpyrrolidone.

Comparison of Bioavailability Parameters—Table II presents data commonly used to evaluate bioavailability. Both magnesium oxide and magnesium hydroxide increased the peak plasma concentration of dicumarol in addition to shortening the time necessary to reach the peak levels. The time for peak plasma concentrations to be reached was reduced from 8–12 hr. after administration of the control doses to 1–4 hr. when the magnesium oxide or magnesium hydroxide combinations were administered. Peak plasma levels of dicumarol were increased by as much as 80% compared to controls when the drug was combined with these agents. If it is assumed that these agents do not alter the elimination of the drug from the plasma, these parameters suggest that magnesium oxide or hydroxide increased the absorption rate of dicumarol.

Table II presents the effects of the excipient materials on the areas under the dicumarol plasma level curves. Magnesium oxide and hydroxide, which were observed to increase the peak plasma concentrations of dicumarol compared to control, also increased the area under the 0–96-hr. plasma level curve. A significant increase was observed for magnesium hydroxide but not for magnesium oxide when the 0–∞ areas were compared to control. This indicates that magnesium hydroxide may increase the total amount of drug absorbed.

The rapidity of the absorption of dicumarol when given in a mixture with magnesium oxide was evaluated in one dog by comparing the plasma levels after an oral dose of the mixture to that produced by an identical intravenous dose of the drug. The results (Fig. 4) show that shortly after an oral dose of dicumarol as a mixture containing 94% magnesium oxide, the plasma levels of the drug were nearly identical to those resulting from an intravenous dose. A pharmacokinetic analysis shows that the absorption rate constant (K_a) of dicumarol given with magnesium oxide was 2.8157 hr.$^{-1}$, which is nine times larger than the K_a value of 0.3098 hr.$^{-1}$ obtained when the drug was administered alone. The elimination rate constants (K_e) calculated from oral and intravenous doses to the dog were similar: 0.00901 and 0.00969 hr.$^{-1}$, respectively. Comparison of areas under the plasma level curves indicated that only 70% of a control dose of dicumarol was absorbed and that magnesium oxide increased bioavailability to near 100%.

Prothrombin times were measured after the administration of the anticoagulant either alone or combined with excipient materials. The maximal prothrombin time responses, which usually occurred at 48 hr. after the dose, are also listed in Table II. These values were increased by 50% over the control when dogs were given the drug–excipient combinations containing 94% magnesium oxide or hydroxide, indicating that these agents increased the pharmacological response.

Those excipients, which when combined with dicumarol significantly reduced drug plasma levels, generally delayed the time at which the peak plasma levels were attained. The time for the peak plasma level to be reached was extended from 8–12 hr. after administration of dicumarol alone to 12–24 hr. after a dose of the drug combined with talc (50%) or colloidal magnesium aluminum silicate and to 4–24 hr. after dicumarol was administered with starch. Although aluminum hydroxide did not delay the peak plasma level time, the mixture containing 94% aluminum hydroxide produced the greatest reduction in the concentration of dicumarol at the peak plasma level. This mixture reduced the peak plasma concentration to 44% of that produced by the drug given alone. Both talc and aluminum hydroxide (94%) significantly reduced the areas under the plasma level curves; it is suggested that these materials reduced the total amount of drug absorbed compared to control. Colloidal magnesium aluminum silicate and calcium phosphate showed a small reduction in the area under the 0–96-hr. blood level curve. This reduction was not apparent in the 0–∞ area value.

None of the dicumarol–excipient combinations that exhibited decreased absorption of the drug produced a statistically significant different prothrombin response. A trend existed, however, toward lower prothrombin times when the dicumarol was administered with aluminum hydroxide, talc, or colloidal magnesium aluminum silicate.

Absorption of Magnesium Chelate of Dicumarol—Since dicumarol has been shown to form chelates with metals, including magnesium, the role of chelation in the production of increased dicumarol plasma levels by magnesium oxide and hydroxide was investigated. The magnesium chelate of sodium dicumarol was administered to four dogs. Plasma concentrations of dicumarol resulting from dicumarol–magnesium chelate administration were compared to those produced by oral administration of sodium dicumarol to the same animals. The results (Fig. 5) indicate that the magnesium chelate produced significantly higher plasma levels of dicumarol. The plasma level curve of dicumarol after administration of the chelate was almost identical to that produced by administration of the drug

as a mixture with 94% magnesium hydroxide (Fig. 2). The mean $\pm SE$ peak prothrombin time after administration of the dicumarol–magnesium chelate was 21.7 ± 4.0 sec. This value is statistically larger than that observed after administration of dicumarol alone (15.1 ± 1.0 sec.), showing that the higher plasma levels of the drug resulting from the chelate also increased the biological effect of the drug.

DISCUSSION

The results presented indicate that certain excipient materials can dramatically alter the absorption of dicumarol. Both increases and decreases in the absorption of dicumarol were observed as a result of administering the drug with these materials. The well-recognized adsorbent properties of aluminum hydroxide (11) probably account for the reduced bioavailability of dicumarol when it was administered with this agent. Decreasing the proportion of aluminum hydroxide in the dose mixture to 50% eliminated its inhibiting effects on the absorption of dicumarol. This concentration effect was not seen with talc, which decreased dicumarol absorption at both drug concentrations tested. Thus, it may not be possible to assume in every case that an excipient effect on drug absorption can be reduced by lowering the amount of excipient given with the drug. Colloidal magnesium aluminum silicate and starch were only tested at one concentration, and no assessment of a concentration dependence on their inhibitory effects can be made. It is assumed that the adsorptive properties of these excipients coupled with their water insolubility are the chief characteristics that serve to decrease dicumarol absorption. The lack of effect of polyvinylpyrrolidone on dicumarol absorption was somewhat surprising in view of its recognized ability to complex drugs (12) including dicumarol (13).

Magnesium oxide and hydroxide enhance the absorption rate of dicumarol and also potentiate its anticoagulant action when combined with dicumarol in a mixture containing 94% excipient and 6% drug. Dicumarol is a weak organic acid; as such, it is considerably more soluble in alkaline solutions and is less readily absorbed from the acidic stomach contents (14). When the drug is administered with a basic substance such as magnesium oxide or hydroxide, it is possible that these excipients increase the rate of dissolution and allow a more rapid rate of absorption of the drug from the GI tract.

The administration of the magnesium chelate of dicumarol significantly increased the bioavailability of the drug. Comparison of dicumarol plasma levels produced by the chelate and those produced by the mixture with magnesium oxide or hydroxide show that they are similar except at the earliest sampling time. The mixture produced significantly higher dicumarol levels than the chelate 1 hr. after an oral dose. It is possible that magnesium oxide or hydroxide increases the absorption of dicumarol by a combination of factors: (*a*) increasing the pH of the microenvironment of the drug in the GI tract, thereby increasing the solubility and perhaps the dissolution rate; and (*b*) causing the formation of a dicumarol–magnesium chelate which is more readily absorbed. Administration of magnesium hydroxide 30 min. after a dose of dicumarol significantly increased plasma levels of the drug in dogs (unpublished observations). These results suggest that chelate formation may take place in the GI tract.

It is not known whether the chelate is absorbed as such or whether it releases dicumarol for absorption. The physical characteristics of the magnesium chelate that may explain how it increases plasma levels of dicumarol will be reported separately. Magnesium stearate did not increase the absorption of dicumarol. This material may be so insoluble in the GI fluids that magnesium was not available for chelate formation.

It can be speculated that the interactions between drug and excipient, which were observed in this study to alter the absorption of the therapeutic agent, could account for differences in drug bioavailability from various commercial formulations. The processes involved in tableting may even increase these interactions. Further experimentation is necessary, however, to determine whether the actual physical interactions involved are between drug and excipient or between the excipient and the biological system involved in the absorption of drugs.

Several reviews of drug interactions state that the concurrent administration of antacids reduces the absorption of weakly acidic coumarin anticoagulants (15, 16). The results reported here show that the antacid magnesium hydroxide can increase the absorption of dicumarol. Concurrent administration of milk of magnesia with dicumarol increased plasma levels of the anticoagulant in two dogs (unpublished observations). As a result of this study in dogs, the effects of concurrent administration with antacids on the absorption of dicumarol in man are being investigated.

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