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Significance of Kinetic Aspects in the Simultaneous Administration of Drugs

By MILDRED J. TARASZKA and ARLINGTON A. FORIST

Kinetic aspects, such as half-lives for absorption and elimination, as well as limiting solubilities, which should be considered in the simultaneous administration of drugs are discussed. Two simple hypothetical cases are presented: the selection of the ratio of two drugs with different rate constants for absorption and elimination to obtain similar average asymptotic serum levels of each drug on multiple-dose administration, and the selection of the ratio of two drugs with different rate constants for absorption and elimination and different solubilities to minimize the risk of crystalluria. Extension of the latter to the triple sulfas, on the basis of solubility and human blood level data in the literature, has given a "best" ratio of 1:3:4 for sulfadiazine:sulfamerazine:sulfamethazine, respectively, rather than the 1:1:1 now used.

WHEN TWO or more drugs are combined in a single formulation or are given in separate dosage forms at the same time, several factors should be considered in choosing the individual drugs and the amounts of each drug to be used: (*a*) biological spectra, (*b*) minimum effective circulating concentrations for biological activity, (*c*) possibilities of reactions between the combined drugs, (*d*) possibility of one drug affecting the biological response to the other drug(s), (*e*) rate constants for absorption or absorption half-lives, (*f*) rate constants for elimination or biological half-lives, (*g*) rates of production and elimination of metabolites (especially if the metabolites may be active or toxic), (*h*) intrinsic solubilities of the individual drugs and/or metabolites if crystalluria is a potential side reaction.

It is the authors' opinion that drug combinations could be more beneficial if all of the above factors are considered. However, only kinetic aspects that affect drug combinations are con-

sidered in this paper; that is, all the calculations are based on the assumption that the individual drugs have the correct spectra of biological activity, similar minimum effective circulating concentrations, and that they are compatible in the *in vitro* and *in vivo* systems. The importance of the kinetic aspects can be seen if the selection of the optimum dosage schedule is considered for multiple-dose therapy with a combination of two drugs which have biological half-lives of largely different magnitudes.

DISCUSSION

Example 1—When two or more drugs are combined in a single formulation, or the drugs are given in separate dosage forms at the same time, the multiple-dose serum levels attained with each drug will depend on each biological half-life plus *other* factors. The ratio of two drugs given in combination, which should be used to attain similar serum levels on multiple dosing, can be estimated in the following manner, assuming that the intrinsic drug solubilities, biological activities, and production of metabolites do not have to be considered. Furthermore, it is assumed that the single-dose serum level and urinary data for each drug fit the following model:
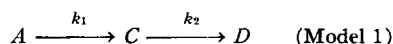
$$A \xrightarrow{\ k_1\ } C \xrightarrow{\ k_2\ } D \qquad \text{(Model 1)}$$

where k_1 is the first-order rate constant for absorption, k_2 is the first-order rate constant for excretion and/or metabolite production, C is the serum compartment for the drug, and D is the excretion and/or metabolite compartment for the drug. Since more than one drug is involved, the rate constants and serum concentrations are labeled k_{1i}, k_{2i}, and C_i where $i = 1$ or 2 and denotes which drug is being considered.

According to Wagner *et al.* (1), the average asymptotic serum level of a drug on a multiple dose schedule is given by

$$\bar{C} = \frac{FD}{V_d k_2 \tau} \qquad \text{(Eq. 1)}$$

where F = fraction of dose absorbed, D = dose, V_d = volume of distribution, τ = dosage interval, and k_2 = first-order rate constant characterizing the biological half-life. This equation holds for any model as long as a series of simultaneous linear differential equations can be written describing the model; transfer from the serum is first order; and F, D, V_d, k_2, and τ are constants for each dose of the multiple-dose regimen in a given subject (1). Since two drugs are being considered, the following equations can be written corresponding to Eq. 1.

$$\bar{C}_1 = \frac{F_1 D_1}{V_{d1} k_{21} \tau_1} \qquad \text{(Eq. 2)}$$

$$\bar{C}_2 = \frac{F_2 D_2}{V_{d2} k_{22} \tau_2} \qquad \text{(Eq. 3)}$$

The same average asymptotic serum levels for the two drugs means $\bar{C}_1 = \bar{C}_2$. The ratio of the two drugs in the fomulation is found by rearranging and setting $\tau_1 = \tau_2$ since both drugs are given together.

$$\frac{D_1}{D_2} = \frac{F_2 V_{d1} k_{21}}{F_1 V_{d2} k_{22}} \qquad \text{(Eq. 4)}$$

The parameters on the right-hand side of Eq. 4, or the ratio D_1/D_2, can be calculated from single-dose data if it is assumed each drug reacts independently and will be unaffected by the presence of the other. The dosing interval τ is adjusted according to the smaller biological half-life.

Figures 1a and 1b show the effect on multiple-dose-serum levels of adjusting the ratio of two hypothetical drugs with differing absorption and biological half-lives, which are given in combination. Serum levels in Fig. 1 are computer calculated. Both drugs, 1 and 2, obey Model 1 with the listed assumptions and have the following values for their kinetic parameters: $k_{11} = 0.693$ hr.$^{-1}$, $k_{21} = 0.174$ hr.$^{-1}$, $F_1/V_{d1} = 0.025$ l.$^{-1}$, $\tau_1 = \tau_2 = 6$ hr., $k_{12} = 1.39$ hr.$^{-1}$, $k_{22} = 0.087$ hr.$^{-1}$, and $F_2/V_{d2} = 0.0350$ l.$^{-1}$. In Fig. 1a, drugs 1 and 2 are combined in the ratio of 1:1, respectively. In Fig. 1b, drugs 1 and 2 are combined in the ratio of 1:0.36, as predicted by Eq. 4. Identical serum-level curves of the two drugs cannot be obtained by altering the combination ratio of the two drugs; only the average asymptotic serum levels can be adjusted to be the same as seen in Fig. 1. The amount of variation about this average asymptotic serum level depends on the model, the dosing interval, and the magnitude of the absorption rate constant (1).

Example 2—The best ratio of two drugs which are given in combination to assure a minimum probability of crystallization of drug in the kidneys can

be calculated, assuming the six following conditions: (a) each drug has an intrinsic solubility, S_1 and S_2, unaffected by the presence of the other drug; (b) the serum level data and urinary excretion data for each individual drug follow Model 1; when given as a single dose (the rate constants k_1 and k_2 are first order); (c) the absorption and elimination of each drug is unaffected by the presence of the other; (d) metabolites do not have to be considered; (e) the appearance of drug crystals in the urine is dependent on the concentration of the drug in the urine; (f) the urine flow is independent of the drug given.

According to Model 1, the rate of appearance of the drug in the urine is $d[D]/dt = k_2[C]$. The kinetic equations for Model 1 can be easily derived (2), and it is found that

$$[C] = \frac{[A_0] k_1}{k_2 - k_1} (e^{-k_1 t} - e^{-k_2 t}) \text{ when } k_1 \neq k_2$$

$$\text{(Eq. 5)}$$

where $[A_0]$ is the initial concentration in compartment A and equals FD/V_d.

The concentration of the drug in the urine at the time of saturation will equal the solubility of the drug. This time of saturation can be found from

$$[D]\Big]_0^S = \int_0^{t_s} \frac{d[D]}{dt} dt \qquad \text{(Eq. 6)}$$

where $[D]$ = concentration of drug in the urine, t_s = time of saturation, and S = saturation concentration (solubility at a given pH).

Substituting for $d[D]/dt$ and integrating Eq. 6 gives

$$S = \frac{[A_0] k_1 k_2}{k_2 - k_1} \left(\frac{-e^{-k_1 t_s}}{k_1} + \frac{e^{-k_2 t_s}}{k_2} \right) \quad \text{(Eq. 7)}$$

The two equations corresponding to Eq. 7 can be written by using the second numerical subscript to indicate which drug is being considered and substituting FD/V_d for $[A_0]$.

$$S_1 = \frac{F_1 D_1 k_{11} k_{21}}{V_{d1}(k_{21} - k_{11})} \left(-\frac{e^{-k_{11} t_{s1}}}{k_{11}} + \frac{e^{-k_{21} t_{s1}}}{k_{21}} \right)$$

$$\text{(Eq. 8)}$$

$$S_2 = \frac{F_2 D_2 k_{12} k_{22}}{V_{d2}(k_{22} - k_{12})} \left(-\frac{e^{-k_{12} t_{s2}}}{k_{12}} + \frac{e^{-k_{22} t_{s2}}}{k_{22}} \right)$$

$$\text{(Eq. 9)}$$

Also,

$$D_1 + D_2 = D_T \qquad \text{(Eq. 10)}$$

where D_1 = dose of drug 1, D_2 = dose of drug 2, and D_T = total dose given.

To have the least chance for crystalluria, D_1 and D_2 have to be adjusted so the time of saturation for each drug is the same, $t_{s1} = t_{s2}$. Equations 8 and 9 are too complex to solve for t_{s1} and t_{s2} explicitly. However, they can be solved for D_1 and D_2 and substituted into Eq. 10 with $t_{s1} = t_{s2} = X$ to give:

$$\frac{S_1 (k_{21} - k_{11}) V_{d1}}{(k_{11} e^{-k_{21} X} - k_{21} e^{-k_{11} X}) F_1} +$$

$$\frac{S_2 (k_{22} - k_{12}) V_{d2}}{(k_{12} e^{-k_{22} X} - k_{22} e^{-k_{12} X}) F_2} = D_T \quad \text{(Eq. 11)}$$

or

$$\sum_{i=1}^{2} \frac{S_i (k_{2i} - k_{1i}) V_{di}}{(k_{1i} e^{-k_{2i}X} - k_{2i} e^{-k_{1i}X}) F_i} = D_T \quad \text{(Eq. 12)}$$

In Eq. 11 everything is known from individual single-dose experiments except X and D_T. For a given value of D_T the value of X, which satisfies the equation, is determined by trial and error with a computer. Once X is determined the values of D_1 and D_2 are just equal to the individual terms in the summation.

When $X = \infty$ the terms on the left-hand side of Eq. 12 will become infinite. Therefore, for any value of D_T, a finite value of X exists and a given ratio of drug 1:drug 2 can be obtained to assure a minimum probability of crystalluria.

If the rate constants of absorption and elimination, the fraction absorbed, and the volume of distribution were the same for both drugs, then the best ratio of drug 1:drug 2 would be the ratio of their solubilities at the "mean" pH of human urine, $S_1 : S_2$.

Application of Example 2—Example 2 has been extended to determine what ratio of sulfadiazine, sulfamerazine, and sulfamethazine gives the least chance of crystalluria in man.

According to the literature, the serum level and urinary excretion data indicated Model 2 for the absorption and elimination of sulfonamides.[1]

Both the excreted sulfonamide and the excreted acetylsulfonamide may precipitate in the urine and have to be considered. The times of saturation of the acetylsulfonamides, t_{sai}, can be found from

$$[D_i]_0^{sai} = \int_0^{t_{sat}} \frac{d[D_i]}{dt} dt \quad \text{(Eq. 13)}$$

where i denotes which acetylsulfonamide and S_{ai} their solubilities. Similarly, the times of saturation of the sulfonamides, t_{si}, can be found from

$$[E_i]_0^{si} = \int_0^{t_{si}} \frac{d[E_i]}{dt} dt \quad \text{(Eq. 14)}$$

According to Model 2, $d[D_i]/dt = k_3 C_i$ and $d[E_i]/dt = k_4 B_i$ and the corresponding integrated Eqs. for 13 and 14 become, respectively,

$$S_{ai} = k_{1i}k_{2i}k_{3i}A_{oi}\left[\frac{-e^{-k_{1i}t_{sai}}}{k_{1i}(k_{3i} - k_{1i})(k_{2i} + k_{4i} + k_{5i} - k_{1i})} \right.$$
$$+ \frac{e^{-(k_{2i} + k_{4i} + k_{5i})t_{sa_i}}}{(k_{2i} + k_{4i} + k_{5i})(k_{3i} - k_{2i} - k_{4i} - k_{5i})(k_{2i} + k_{4i} + k_{5i} - k_{1i})}$$
$$\left. + \frac{e^{-k_{3i}t_{sat}}}{k_{3i}(k_{3i} - k_{1i})(k_{2i} + k_{4i} + k_{5i} - k_{3i})} \right] + \frac{k_{2i}A_{oi}}{k_{2i} + k_{4i} + k_{5i}} \quad \text{(Eq. 15)}$$

Fig. 1—Computer-calculated, multiple-dose serum levels of a combination of two hypothetical drugs with different kinetic constants. Key: ---, drug I with k_1 = 0.693 hr.$^{-1}$, k_2 = 0.174 hr.$^{-1}$, F/V_d = 0.025 l.$^{-1}$ *and* τ = 6 hr.; ———, *drug 2 with* k_1 = 1.39 hr.$^{-1}$; k_2 = 0.087 hr.$^{-1}$, F/V_d = 0.035 l.$^{-1}$ *and* τ = 6 hr.; *curves 1a represent 100 units each of drug 1 and drug 2 administered simultaneously; curves 1b represent 100 units of drug 1 and 35.7 units of drug 2 administered simultaneously.* A, C_2 = 6.7 *units l.*$^{-1}$; B, C_1 = 2.4 *units l.*$^{-1}$; C, $\bar{C}_1$ = $\bar{C}_2$ = 2.4 *units l.*$^{-1}$.

$$S_i = \frac{k_{1i}k_{4i}A_{oi}}{k_{2i} + k_{4i} + k_{5i} - k_{1i}}\left[\frac{e^{-(k_{2i} + k_{4i} + k_{5i})t_{si}}}{k_{2i} + k_{4i} + k_{5i}} - \right.$$
$$\left. \frac{e^{-k_{1i}t_{si}}}{k_{1i}} \right] + \frac{k_{4i}A_{oi}}{k_{2i} + k_{4i} + k_{5i}} \quad \text{(Eq. 16)}$$

For ease of manipulation, Eq. 15 may be written as

$$S_{ai} = A_{oi} f_i (t_{sai}) \quad \text{(Eq. 17)}$$

where $f_i (t_{sai})$ is a function of t_{sai}, and Eq. 16 as

$$S_i = A_{oi}\varphi_i (t_{si}) \quad \text{(Eq. 18)}$$

Substituting $A_{oi} = F_i D_i / V_{di}$ and rearranging, Eq. 17 becomes

$$D_i = \frac{V_{di} S_{ai}}{F_i f_i (t_{sai})} \quad \text{(Eq. 19)}$$

and Eq. 18 becomes

$$D_i = \frac{V_{di} S_i}{F_i \varphi_i (t_{si})} \quad \text{(Eq. 20)}$$

[1] Model 2 for sulfonamides does not include discrete steps for tubular reabsorption or protein binding since the problem only requires characterization of how rapidly the drug concentrates in the urine. All the estimated rate constants are really composite values representing several processes since all models are only approximations for what is really taking place *in vivo*. According to the principle of microscopic reversibility, each step in a mechanism should be reversible, but experimental techniques are not sophisticated enough to determine all discrete rate constants, only "overall" macroconstants are available. The value for k_4 characterizes how fast the sulfonamide is eliminated, and it includes effects from several processes as tubular reabsorption, the distribution of drug into various tissues according to their perfusion and partition characteristics, protein binding in these various tissues and blood as well as the discrete elimination process.
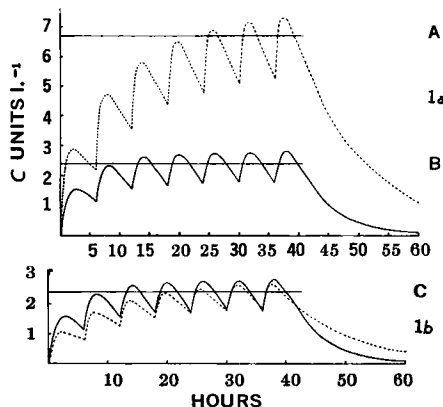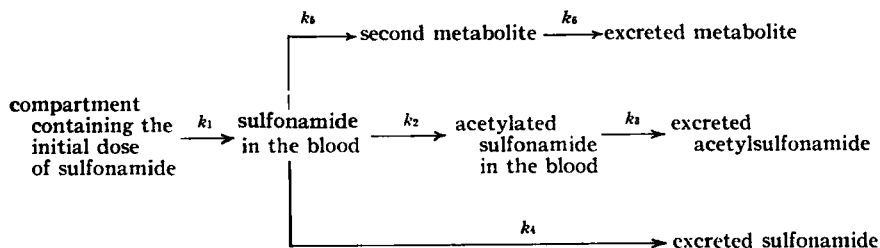
The total dose of sulfonamides, D_T, must equal the sum of the doses of the individual sulfonamides, ΣD_i. For a mixture of three
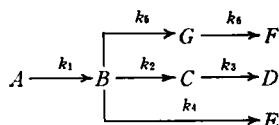
$$D_T = D_1 + D_2 + D_3 \quad \text{(Eq. 21)}$$

and three equations can be written for Eq. 19 and three for Eq. 20.

Since the parent compound and the acetylated derivative have to be considered for each sulfonamide, eight possibilities exist for Eq. 21; that is, all the possible combinations of the six equations corresponding to Eqs. 19 and 20.

$$
\begin{array}{c}
\xrightarrow{\ k_5\ } \text{second metabolite} \xrightarrow{\ k_6\ } \text{excreted metabolite} \\
\end{array}
$$

$$
\begin{array}{l}
\text{compartment} \\
\text{containing the} \xrightarrow{\ k_1\ } \text{sulfonamide} \xrightarrow{\ k_2\ } \text{acetylated} \xrightarrow{\ k_3\ } \text{excreted} \\
\text{initial dose} \qquad \text{in the blood} \qquad \text{sulfonamide} \qquad \text{acetylsulfonamide} \\
\text{of sulfonamide} \qquad\qquad\qquad\qquad \text{in the blood}
\end{array}
$$

$$
\xrightarrow{\qquad\qquad k_4 \qquad\qquad} \text{excreted sulfonamide}
$$

in simple notation

$$
A \xrightarrow{\ k_1\ } B \begin{array}{c} \xrightarrow{\ k_5\ } G \xrightarrow{\ k_6\ } F \\ \xrightarrow{\ k_2\ } C \xrightarrow{\ k_3\ } D \\ \xrightarrow{\ k_4\ } E \end{array} \qquad\qquad\text{(Model 2)}
$$

Case A: $D_T = \dfrac{V_{d1} S_{a1}}{F_1 f_1 (t_{sa1})} + \dfrac{V_{d2} S_{a2}}{F_2 f_2 (t_{sa2})} + \dfrac{V_{d3} S_{a3}}{F_3 f_3 (t_{sa3})}$

Case B: $D_T = \dfrac{V_{d1} S_{a1}}{F_1 f_1 (t_{sa1})} + \dfrac{V_{d2} S_{a2}}{F_2 f_2 (t_{sa2})} + \dfrac{V_{d3} S_3}{F_3 \varphi_3 (t_{s3})}$

Case C: $D_T = \dfrac{V_{d1} S_{a1}}{F_1 f_1 (t_{sa1})} + \dfrac{V_{d2} S_2}{F_2 \varphi_2 (t_{s2})} + \dfrac{V_{d3} S_3}{F_3 \varphi_3 (t_{s3})}$

Case D: $D_T = \dfrac{V_{d1} S_{a1}}{F_1 f_1 (t_{sa1})} + \dfrac{V_{d2} S_2}{F_2 \varphi_2 (t_{s2})} + \dfrac{V_{d3} S_{a3}}{F_3 f_3 (t_{sa3})}$

Case E: $D_T = \dfrac{V_{d1} S_1}{F_1 \varphi_1 (t_{s1})} + \dfrac{V_{d2} S_{a2}}{F_2 f_2 (t_{sa2})} + \dfrac{V_{d3} S_{a3}}{F_3 f_3 (t_{sa3})}$

Case F: $D_T = \dfrac{V_{d1} S_1}{F_1 \varphi_1 (t_{s1})} + \dfrac{V_{d2} S_{a2}}{F_2 f_2 (t_{sa2})} + \dfrac{V_{d3} S_3}{F_3 \varphi_3 (t_{s3})}$

Case G: $D_T = \dfrac{V_{d1} S_1}{F_1 \varphi_1 (t_{s1})} + \dfrac{V_{d2} S_2}{F_2 \varphi_2 (t_{s2})} + \dfrac{V_{d3} S_3}{F_3 \varphi_3 (t_{s3})}$

Case H: $D_T = \dfrac{V_{d1} S_1}{F_1 \varphi_1 (t_{s1})} + \dfrac{V_{d2} S_2}{F_2 \varphi_2 (t_{s2})} + \dfrac{V_{d3} S_{a3}}{F_3 f_3 (t_{sa3})}$
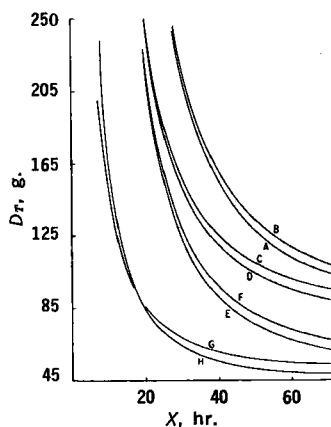
Fig. 2—Plot of D_T versus X for the 8 cases, A–H.

The kinetic constants and solubilities used for the sulfonamides under consideration are listed in Table I and were taken from the indicated literature.

To have the least chance for crystalluria the time of saturation for each drug has to be the same; that is, the times of saturation in each of the individual cases (A through H) have to be equal (for Case A, $t_{sa1} = t_{sa2} = t_{sa3} = X_A$). The case which gives the minimum total dose, D_T, for saturation will be the limiting case, and the ratio of the terms

in the summation will be the best ratio for the drugs in the formulation.

The values of D_T for various X_j's are plotted in Fig. 2 for the eight different cases (A through H). A digital computer was used to calculate the values. For a given D_T greater than the minimum asymptotic D_T for Case H either Case H or Case G will be limiting. Since Case H is limiting at lower values of the total dose, D_T, Case H is the one of interest. The fact that Case H is limiting means that for sulfadiazine and sulfamerazine the parent compounds will cause crystalluria if the dose is

TABLE I—KINETIC CONSTANTS AND SOLUBILITIES FOR THE TRIPLE SULFAS

Parameter	Sulfadiazine, $i = 1$	Sulfamerazine, $i = 2$	Sulfamethazine, $i = 3$
$S_i{}^a$ mg. ml.$^{-1}$	0.16	0.34	0.62
$S_{ai}{}^b$ mg. ml.$^{-1}$	0.33	0.35	0.74
k_{1i} hr.$^{-1}$	0.65[c]	0.60[d]	0.66[e]
$k_{2i} + k_{4i} + k_{5i}$ hr.$^{-1}$	0.0414	0.0295	0.095
$k_{2i}{}^f$ hr.$^{-1}$	0.15(0.0414) = 0.0062	0.35(0.0295) = 0.0103	0.6(0.095) = 0.057
$k_{4i}{}^f$ hr.$^{-1}$	0.85(0.0414) = 0.0352	0.45(0.0295) = 0.0133	0.4(0.095) = 0.038
k_{3i} hr.$^{-1}$	0.06	0.04	0.20
V_{di}/F_i ml.	30,000	23,000	18,000

^{a} Sulfadiazine equivalent solubilities at 37° and pH = 6 for the sulfas. Taken from *Reference 3*. ^{b} Sulfadiazine equivalent solubilities at 37° and pH = 6 for the acetylated sulfas. Taken from *Reference 3*. ^{c} V_{d1}/F_1 and k_{31} were estimated from Fig. 1a of *Reference 6*. The other kinetic constants for sulfadiazine are from Table II of *Reference 5*. ^{d} V_{d2}/F_2 and k_{32} were estimated from Fig. 1 of *Reference 4*. The other kinetic constants for sulfamerazine are from Table II of *Reference 4*. ^{e} The kinetic constants for sulfamethazine are calculated from data in *Reference 4*. ^{f} The kinetic constants k_{2i} and k_{4i} were estimated by multiplying the overall elimination rate constant, $k_{2i} + k_{4i} + k_{5i}$, by the fraction of the sulfonamide excreted as the acetylsulfonamide or the unchanged sulfonamide, respectively. The values used for these fractions were taken from Table IV of *Reference 7*.

large enough, while for sulfamethazine the acetyl derivative will cause crystalluria (this can be seen from the equation for Case *H*). In order to have the largest total concentration of sulfonamides without crystalluria, the ratio of sulfadiazine–sulfamerazine–sulfamethazine should be 1:3.1:3.9 (on a sulfadiazine equivalent). This is the ratio of the terms in the equation for Case *H* when $t_{s1} = t_{s2} = t_{sa3} = \infty$. The ratio in terms of the individual compounds instead of the sulfadiazine equivalent is sulfadiazine–sulfamerazine–sulfamethazine = 1:3.2:4.3. On the average this ratio should have the least chance for crystalluria, if the kinetic constants are the best average ones. Since the kinetic constants in some cases were only estimated from blood level curves in the literature, they may not be the best.

It should be noted in Fig. 2 that the numerical values for D_T are large. This is a result of using the best ratio of sulfas for the given set of conditions and equations which assume a constant urine volume. The effect of varying urine volume or flow rate was not considered because the objective was only to calculate the best ratio of triple sulfas which gives the least chance of crystalluria. Case *H* will always be limiting whatever the flow rate.

The solubilities of the sulfonamides depend on pH. Above pH 7 the solubilities increase rapidly. The solubilities at pH = 6 of the three sulfonamides in question were chosen because this approaches the normal human urine pH, and the ratio of the solubilities of the three sulfonamides is almost constant over the pH range 5.6–6.5 (3). Therefore, the calculated ratio of 1:3.2:4.3 for the three sulfonamides should be the best ratio over the pH range 5.6 to 6.5.

As the solubility and/or the biological half-life of a drug increases, the incidence for crystalluria will become less. If the three sulfonamides in a combination have similar long biological half-lives,

similar half-lives of acetylated derivative production and elimination, and similar fractions absorbed and volumes of distribution, then the ratio of the sulfonamides in the formulation should be the ratio of their solubilities.

The calculations indicate that kinetic aspects can be important in the simultaneous administration of drugs. The triple sulfas was used as an example for the application of kinetics and limiting solubilities to obtain a formulation with the best margin of safety. To show this increased margin of safety, a large-scale clinical test would be needed.

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⌐⊶⇒ *Keyphrases*

Drugs, simultaneous administration—kinetics

Sulfadiazine-sulfamerazine-sulfamethazine—co-administration

Absorption-elimination rates—simultaneous administration

Solubility, drug—simultaneous administration

Kinetic equations—multiple drug dosage forms

Griseofulvin Absorption in Man After Single and Repeated Treatments and Its Correlation with Dissolution Rates

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Absorption of griseofulvin from six different preparations was studied in man. Plasma levels were followed for 1 day after a single oral 500-mg. dose, and for 7 days after daily 500-mg. doses. A high correlation was found between dissolution rates in simulated intestinal fluid and absorption during 0–25 hr., 49–173 hr., and 0–173 hr.

G riseofulvin is widely used for treating fungal infections in man and animals. Its rela-

tively high dose and meager water solubility (15 mcg./ml. at 37°) might contribute to its poor and variable absorption. Because certain minimal drug-plasma levels are needed for an effective cure (1–3), griseofulvin preparations must be carefully designed to ensure maximum absorption.

The authors have shown previously (4) that