Interpretation of the Kinetics of Salicylic Acid Elimination

Sir:

Wagner (1) contends that the data relating to the elimination of salicylate can be interpreted on the basis of first-order kinetics. The present communication presents evidence which indicates that the application of Wagner's theoretical considerations to these particular aspects is not acceptable. It also reaffirms the validity and application of certain equations which Wagner (1) has claimed to be erroneous.

It was first suggested by Cummings (2) in 1963 that when the plasma salicylate level exceeds a certain value, the formation of salicyluric acid closely approaches a zero-order process. Evidence has been presented by Cummings and Martin (3–6) to support the view that the elimination of salicylate in man cannot be completely described by first-order kinetics, and that above a certain drug level its elimination can be better described in terms of simultaneous first-order and zero-order processes. It may be pointed out that Wagner makes no reference to the publication of Bedford, Cummings, and Martin (5). A similar interpretation of experimental results has been offered by Levy (7) and Nelson, Hanano, and Levy (8).

The evidence for this interpretation can be considered as follows.

1. The fraction of the dose of aspirin which is eliminated and excreted in the urine at certain specified times shortly after dosage is almost constant for doses of 160, 240, and 320 mg., but at higher dosage the fraction of the dose excreted at these times becomes progressively less (5). This is explicable on the basis that the elimination of salicylate is not first order when the dose of aspirin exceeds 320 mg., when it is assumed that the absorption step is not rate limiting.

Furthermore, the percentage of the dose which is eliminated as salicyluric acid is less after the larger doses than after the small doses (5). This suggests that the rate of formation of salicyluric acid is not always proportional to the amount of salicylic acid in the body.

2. When the decline of the serum salicylate concentration and of the rate of excretion of salicyluric acid in urine was followed for about 40 hr. after loading doses of aspirin—1 Gm. every 6 hr. for 36 hr. (5, 6): (*a*) Plots of these values against time could not be described as log-linear for 20 hr. or more after the final dose. (*b*) The rate of excretion of salicyluric acid remained almost constant between the sixth and the 17th hr. after the final dose. (*c*) These plots ultimately tended to become log-linear with a slope similar to that of corresponding plots obtained after a low single dose of aspirin. (*d*) The amount of salicylic acid remaining in the body at a time when elimination approaches a first-order rate was calculated to be 150–300 mg. (5).

If an explanation of these findings based on the continuing absorption and distribution of salicylic acid over a period of 20 hr. is not accepted, the experimental findings provide a strong indication that the formation of salicyluric acid closely approaches a zero-order rate during the period between the sixth and the 17th hr.

Wagner was able to demonstrate in his model (Example 1) that first-order kinetics can give rise to a plateau in the excretion rate plot from the third to the sixth hour. Such an explanation cannot, however, be considered sufficient to account for a plateau extending over a period of 11 hr.

3. The area under the salicylate plasma level *versus* time plot appears to be much larger when aspirin is rapidly absorbed than when the equivalent dose is slowly absorbed (3, 4), although the total urinary recovery of drug after 24 hr. is the same in both instances (9). The maximum plasma salicylate level obtained when aspirin was rapidly absorbed is almost double that obtained when aspirin was slowly absorbed, yet the maximum rates of excretion of total salicylate in urine were almost identical (3, 4). This suggests that the elimination of salicylate is relatively slower at the higher drug level which results when absorption is rapid, assuming that the total amount of aspirin absorbed within the period of the study, *viz.*, 7 hr., is the same in both instances.

4. There is a considerable difference in the maximum plasma salicylate level obtained after a single 1-Gm. dose of aspirin and after multiple 1-Gm. doses of aspirin. Thus, in a group of individuals, a single 1-Gm. dose gave an average maximum observed value of 5.1 mg./100 ml. (10), whereas after seven doses each of 1 Gm. administered six hourly, the average maximum observed value was 18.1 mg./100 ml. (4).

An attempted interpretation of salicylate elim-

ination based on first-order kinetics gives a half-life equal to 2–3 hr., as calculated from the slope of the terminal log-linear section of the plasma level plot or urinary excretion plot after a small (0.3 Gm.) dose of aspirin (5). Wagner (1) makes use of a similar value. On this basis a 6-hr. multiple-dosage schedule corresponds to a dosage interval which is equal to 2–3 half-lives of the drug, and this would give a plasma salicylate level only marginally greater than that obtained with a single dose. The plasma levels obtained, however, are at least three times greater. This suggests that the half-life of salicylate which pertains after multiple 1-Gm. doses is certainly much longer than 2–3 hr. and would appear to be nearer 10 hr.

It is submitted that the cumulative evidence refutes Wagner's (1) contention that the elimination of salicylate can be interpreted solely on the basis of a first-order kinetic model. It is considered that the experimental observations can be better described by a model based on simultaneous first-order and zero-order elimination as postulated by Cummings and Martin (3–6) and by Levy (7, 8).

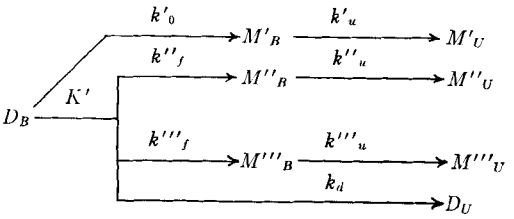
Wagner (1) also states that Cummings and Martin (11) have incorrectly used the Butler equation (12). This is not so. The considerations of Cummings and Martin (11), as those of Butler (12), were stated to apply to a substance, in this instance a metabolite, which was eliminated only by excretion, and in this case the elimination rate constant and the excretion rate constant are one and the same.

Wagner (1) states that the equation presented by Cummings, Martin, and Park (13), with respect to simultaneous first-order and zero-order drug elimination, is erroneous. The equation appears to be perfectly valid and its derivation in a more general form, is given below.

RATE OF EXCRETION OF TOTAL DRUG IN URINE WHEN ONE METABOLITE IS FORMED AT A ZERO-ORDER RATE

The kinetics of the excretion of total drug in urine is considered with respect to a model drug which is entirely eliminated by excretion in the urine and by metabolism to three metabolites (M', M'', M'''); the metabolites are eliminated solely by excretion in the urine. Thus, "total drug in urine" is defined as the sum of the amounts of drug and metabolite excreted and this will ultimately be equivalent to the amount of drug absorbed. One metabolite, M', is formed at a zero-order rate, otherwise all the processes of drug elimination and metabolite excretion are first order.

The processes of drug elimination may be represented as follows:



These processes are described by the following equations in which:

D_0	= The amount of drug in the body at a time when the process of absorption can be considered to be complete, this is designated $t = 0$
D_B	= The amount of drug in the body at time t
M_0	= The amount of metabolite in the body at a time $t = 0$
M_B	= The amount of metabolite in the body at time t
D_U	= The amount of drug excreted in the urine at time t
M_U	= The amount of metabolite excreted in the urine at time t
k'_0	= The zero-order rate constant for the formation of metabolite M'
k''_f, k'''_f	= The first-order rate constants for the formation of the metabolites M'' and M''', respectively
k_d	= The first-order rate constant for the excretion of drug
k'_u, k''_u, k'''_u	= The first-order rate constant for the excretion of the metabolites M', M'', and M''', respectively
K'	= $k_d + k''_f + k'''_f$

Thus,

$$-\frac{dD_B}{dt} = K'D_B + k'_0 \qquad \text{(Eq. 1)}$$

and integration between $t = 0$ and $t = t$ gives:

$$D_B = [D_0 + k'_0/K']e^{-K't} - k'_0/K' \qquad \text{(Eq. 2)}$$

Also,

$$M'_B = \frac{k'_0}{k'_u}[1 - e^{-k'_u t}] + M'_0 e^{-k'_u t} \qquad \text{(Eq. 3)}$$

and

$$M''_B = \frac{k''_f}{k''_u - K'}[D_0 + k'_0/K'][e^{-K't} - e^{-k''_u t}] - \frac{k''_f k'_0}{k''_u K'}[1 - e^{-k''_u t}] + M''_0 e^{-k''_u t} \qquad \text{(Eq. 4)}$$

Substitution of k'''_f and k'''_u for k''_f and k''_u in Eq. 4 gives the corresponding equation for M'''_B.

The rate of excretion of drug and of drug metabolites in urine is given by:

$$\frac{dD_u}{dt} = k_d D_B; \quad \frac{dM'_u}{dt} = k'_u M'_B; \quad \frac{dM''_u}{dt} = k''_u M''_B; \quad \frac{dM'''_u}{dt} = k'''_u M'''_B.$$

The rate of excretion of total drug in urine is ob-

tained by summing the individual rates, so that:

$$\frac{d[D_u + M_u]}{dt} = \frac{dD_u}{dt} + \frac{dM'_u}{dt} + \frac{dM''_u}{dt} + \frac{dM'''_u}{dt}$$

where

$$M_u = M'_u + M''_u + M'''_u$$

Then,

$$\frac{d[D_u + M_u]}{dt} = \left[k_d + \frac{k''_f k''_u}{k''_u - K'} + \frac{k'''_f k'''_u}{k'''_u - K'}\right] \times [D_0 + k'_0/K']e^{-K't} - \left[\frac{k''_f k''_u}{k''_u - K'} e^{-k''_u t} + \frac{k'''_f k'''_u}{k'''_u - K'} e^{-k'''_u t}\right][D_0 + k'_0/K'] + \frac{k'_0}{K'}[k''_f e^{-k''_u t} + k'''_f e^{-k'''_u t} - K'e^{-k'_u t}] - \frac{k'_0}{K'}[k_d + k''_f + k'''_f - K'] + k'_u M'_0 e^{-k'_u t} + k''_u M''_0 e^{-k''_u t} + k'''_u M'''_0 e^{-k'''_u t} \quad \text{(Eq. 5)}$$

The term $[k_d + k''_f + k'''_f - K'] = 0$, since by definition $K' = k_d + k''_f + k'''_f$, therefore only exponential terms remain.

Equation 5 is thus of the form:

$$\frac{d[D_u + M_u]}{dt} = Ae^{-K't} + Be^{-k'_u t} + Ce^{-k''_u t} + De^{-k'''_u t} \quad \text{(Eq. 6)}$$

where A, B, C, and D are constants.

When all k_u are large relative to K' and when t is large, all the $e^{-k_u t}$ terms become very small relative to the $e^{-K't}$ term and so Eq. 6 approaches:

$$\frac{d[D_u + M_u]}{dt} = Ae^{-K't} \quad \text{(Eq. 7)}$$

This equation may then be written:

$$\ln \frac{d[D_u + M_u]}{dt} = \ln [\text{const.}] - K't \quad \text{(Eq. 8)}$$

which is the equation of a straight line having a slope equal to $-K'$.

A plot of the log rate of excretion of total drug against time ultimately exhibits a linear section with a slope equal to the sum of the rate constants which govern the first-order processes of drug elimination when a zero-order process is occurring simultaneously.

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Deterioration of Nitroglycerin Tablets

Sir:

The effect of packaging and storage conditions on drug product stability is a subject of growing interest and concern (1). We wish to report here our investigations on the relationship between certain novel packaging materials and the deterioration of nitroglycerin tablets.

FDA recently found that a batch of nitroglycerin tablets sealed in aluminum foil was grossly subpotent. The faulty product had been prepared by individually wrapping 0.43-mg. ($^1/_{150}$-grain) nitroglycerin tablets in strips of aluminum foil to which a thin film of polyethylene had been laminated. Each tablet was placed between the polyethylene surfaces of two strips, and the ends were heat-sealed to provide a 25 × 15 mm. cell.

Assays of individual tablets showed that they contained 0–10% of the declared quantity of nitroglycerin (2). However, when the packaging material in one cell was extracted with isooctane, the extract contained 0.36 mg. of nitroglycerin [determined colorimetrically with phenoldisul-