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KINETICS OF SERUM AMINOSALICYLIC ACID LEVELS

BY

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A mathematical model, involving three consecutive first order reactions, has been applied to already existing experimental material in order to explain the hourly variation in serum levels obtained after administration of varying repeated doses of different preparations of *p*-aminosalicylic acid to human volunteers. The model closely agrees with the experimental data for all the orally administered preparations concerned, and the differences in blood levels for different preparations can be explained in terms of the values attributed to the parameters involved in the model. The same model adequately describes the elimination of aminosalicylic acid from the blood after a single intravenous infusion provided that the initial blood level attained does not exceed about 11 mg/100 ml., but fails at higher values. In the latter instance a second order model gives a good fit to the experimental curves. The increase in serum levels found experimentally for the same subjects during the first weeks of prolonged treatment with phenyl-*p*-aminosalicylate corresponds to a change in the values of the parameters for the elimination from the blood only.

First order reactions have previously been proposed to explain the elimination of various drugs from the blood stream, and a combination of two consecutive first order processes has been used to account for the absorption into and subsequent elimination from the blood of orally administered preparations. Wiegand & Taylor (1960) have developed formulae for the combination of three consecutive first order reactions in order to explain the effects of sustained-release tablets.

Various methods for estimating the rate constants in the first order reactions involved have been described in the literature. Dominguez & Pomerene (1945), using a model not specifying the absorption process, determined the rate constant for elimination from that part of the experimental curve where absorption has become negligible, and calculated the absorption rate from the fitted curves for blood level and excretion rate as found by urine determinations. Nelson (1960), using a similar model calculated the absorption rate from urine values only, while Wiegand & Taylor (1960) determined the rate constant for the sustained-release process from *in vitro* experiments.

METHODS

In the present study none of these methods were applicable because the already existing experimental material did not include urinary determinations or *in vitro* experiments for the sustained-release process; moreover the scheme involving three doses per day prevented the elimination process from becoming dominant for a sufficiently long time to obtain a reasonably good estimate of the elimination rate constant. Therefore, it was decided to obtain direct estimates of the three rate constants and the apparent distribution volume by nonlinear regression techniques, using an iterative procedure developed by Jørgensen & Vestergaard (1960) for use in a digital computer.

The formula, when adapted to the conditions of the experimental material (three doses per day, given at the same times each day), reads as follows:

$$g(t)=d\mu\times\frac{100b}{V}\left[\frac{p_\mu}{(p_\mu-m_\mu)(p_\mu-b)}\times\frac{\sum_h e^{-(t-t_h)/p\mu}}{1-e^{-24/p\mu}}-\frac{m_\mu}{(p_\mu-m_\mu)(m_\mu-b)}\times\frac{\sum_h e^{-(t-t_h)/m_\mu}}{1-e^{-24/m_\mu}}\right.$$

$$\left.+\frac{b}{(p_\mu-b)(m_\mu-b)}\times\frac{\sum_h e^{-(t-t_h)/b}}{1-e^{-24/b}}\right]$$

$g(t)$ =blood level in mg/100 ml. at time t;

t =time in hours after midnight;

$d\mu$ =size of dose for the preparation μ expressed as aminosalicylic acid and corrected for nonabsorbed material (effective dose);

V =apparent distribution volume in litres;

b =reciprocal rate constant for the elimination process expressed in hours;

p_μ =reciprocal rate constant for the sustained-release process expressed in hours;

m_μ =reciprocal rate constant for absorption from the gastrointestinal tract expressed in hours;

t_h =hour of day for the administration of the preparation.

The expression for the summation Σ is valid for $t \geqslant t_h$. For $t<t_{hh}$ the formula should read $\sum_h e^{-(24+t-t_h\, p_\mu)}$ etc. Applied to the beginning of the treatment the divisor $1-e^{-24/p_\mu}$ etc. should be omitted. For mixtures of two or more preparations the resulting g(t) is the sum of terms calculated for each of the preparations involved. In the form given the formula remains valid for oral administration of solutions by putting $p=o$, and for intravenous infusions by putting $p=m=o$.

The assumptions made in the above formula are that each of the three processes, release from the preparation into the gastrointestinal tract, absorption into the blood stream, and elimination from the blood, may be represented by a first order reaction. This places no restriction on the ways of elimination, whether by urinary excretion or by biotransformation, provided only that each of these paths is followed at a rate proportional to the amount of the drug remaining in the blood. Two or more such parallel paths result in a process characterized by a constant half-life, and so constitute a first order reaction with rate constant $/b=\Sigma 1/b_i$.

In order to calculate values for the various parameters from the present experimental material some further assumptions are needed:

V is assumed to be the same for all persons involved;

b is allowed a separate value for each group;

m_μ is common to all groups involving the drug μ, while

p_μ takes on different values for different preparations of the same drug (coated or uncoated aminosalicylic acid).

Drugs

Oral preparations used were: aminosalicylic acid (PAS), a coated granulate of it (Pasido), sodium aminosalicylate (Na-PAS), phenyl-*p*-aminosalicylate (Tebamin), and mixtures of aminosalicylic acid and phenylaminosalicylate (three parts of phenylaminosalicylate and one part of aminosalicylic acid: Dantyl (Great Britain and Eire) or Tebanyl Comp.). Sodium aminosalicylate was also given by intravenous infusion (Aminacyl ad infusionem "Wander").

Experimental

The experimental material available consisted of results from 1,170 blood samples from subjects treated orally with aminosalicylic acid and its derivatives as listed in the first five columns of Table 1, and results from 112 blood samples from those receiving intravenous infusion of sodium aminosalicylate, the experimental means of which are listed in Table 5.

Oral treatments. It has previously been shown that the daily maximum blood level during a course of treatment with phenylaminosalicylate rises in the first 2 weeks (Frederiksen, Jensen, Mørch & Tybring, 1957). Therefore, the subjects of the experiment were treated for a considerable period, up to 43 days, with the single doses given in Table 1, administered at the times of the principal meals, at 8 a.m., noon and 6 p.m. About three times a week blood samples were taken about 2 hr after administration of the second dose at a time when the daily blood level had reached its maximum.

The content of free aminosalicylic acid in the serum was determined colorimetrically by Lehmann's method (1951). This also determines the content of *p*-aminosalicyluric acid (Lehmann, 1953), but microbiological determinations in 394 of the serum samples showed the *p*-aminosalicyluric acid content to be less than 5% of that of free aminosalicylic acid. When the maximum had stopped rising blood samples were taken before the administration of the three single doses, and also at other times of the day.

The absorption of the sparingly soluble phenylaminosalicylate depends to a great extent on the particle size. Consequently, in the calculation of the effective dose allowance is made for the amount of unabsorbed compound, measured in the faeces. Group G represents a coarse grain product with an 80% absorption, whereas H showed 89% absorption.

In groups A, E, F, I, and J samples were taken again after a few days, so that each subject in these groups appears twice.

Intravenous treatments. A single dose of sodium aminosalicylate (18.5 g; equivalent to 13.5 g of aminosalicylic acid) was given intravenously in the course of 1 hr to two female and three male volunteers, once before and once after at least 2 weeks of treatment with phenylaminosalicylate (4 g. three times a day).

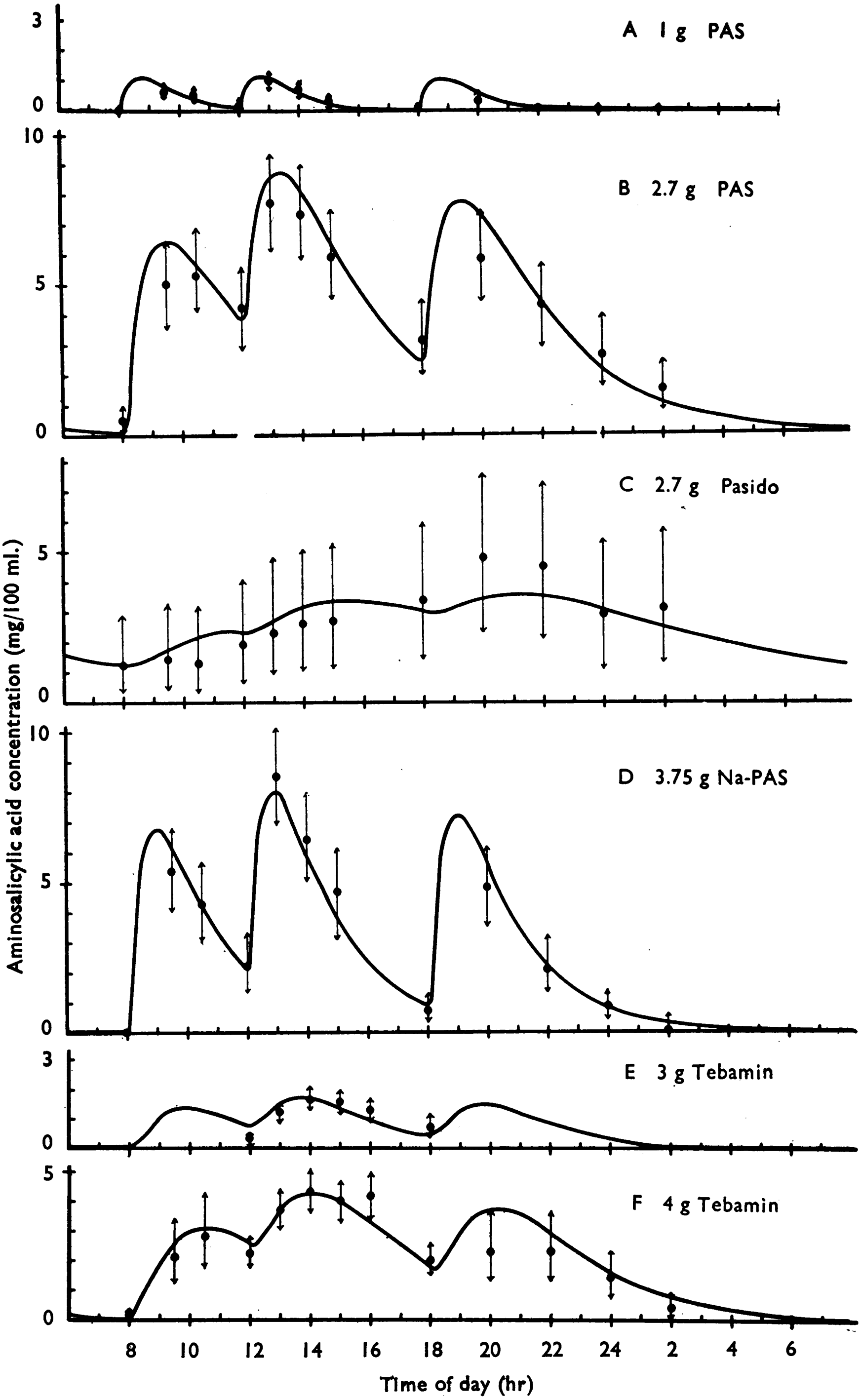
RESULTS

The results from the oral treatments were used by the "Regnecentralen," Copenhagen, to obtain the best estimates for the eighteen unknown parameters:

V, $p_{(PAS)}$, $p_{(Pasido)}$, $p_{(Na\text{-}PAS)}$, $p_{(Tebamin)}$, $m_{(PAS)}$, $m_{(Na\text{-}PAS)}$, $m_{(Tebamin)}$, and b_A—b_J. These estimates are listed in Table 1.

The calculations were performed according to the method of Jørgensen & Vestergaard (1960). This is a least squares procedure, valid for normally distributed variables with constant variance. The variable $g(t)$ does not fulfil this condition, but the transformed variable $y=(1/k)\times\log_e[1+k(g-3)]$, $k=0.27$ for $g<3$, $k=0.05$ for $g>3$, is satisfactory and has been used in the above calculations and in the statistical part of this work.

From the parameter values the theoretical values for the blood level have been calculated for every 30 min throughout the 24 hr of the day, and the agreement of the mathematical formula with the experimental material can consequently be estimated, partly graphically, partly by a statistical estimate of the deviations between the theoretical values and the average of the experimental values. In Fig. 1 the theoretical curves are depicted, as well as the average values of the levels found, calculated via the transformed variable with statement of 95% confidence limits.


A 1 g PAS
B 2.7 g PAS
C 2.7 g Pasido
D 3.75 g Na-PAS
E 3 g Tebamin
F 4 g Tebamin
Aminosalicylic acid concentration (mg/100 ml.)
Time of day (hr)
0
3
5
10
8
10
12
14
16
18
20
22
24
2
4
6

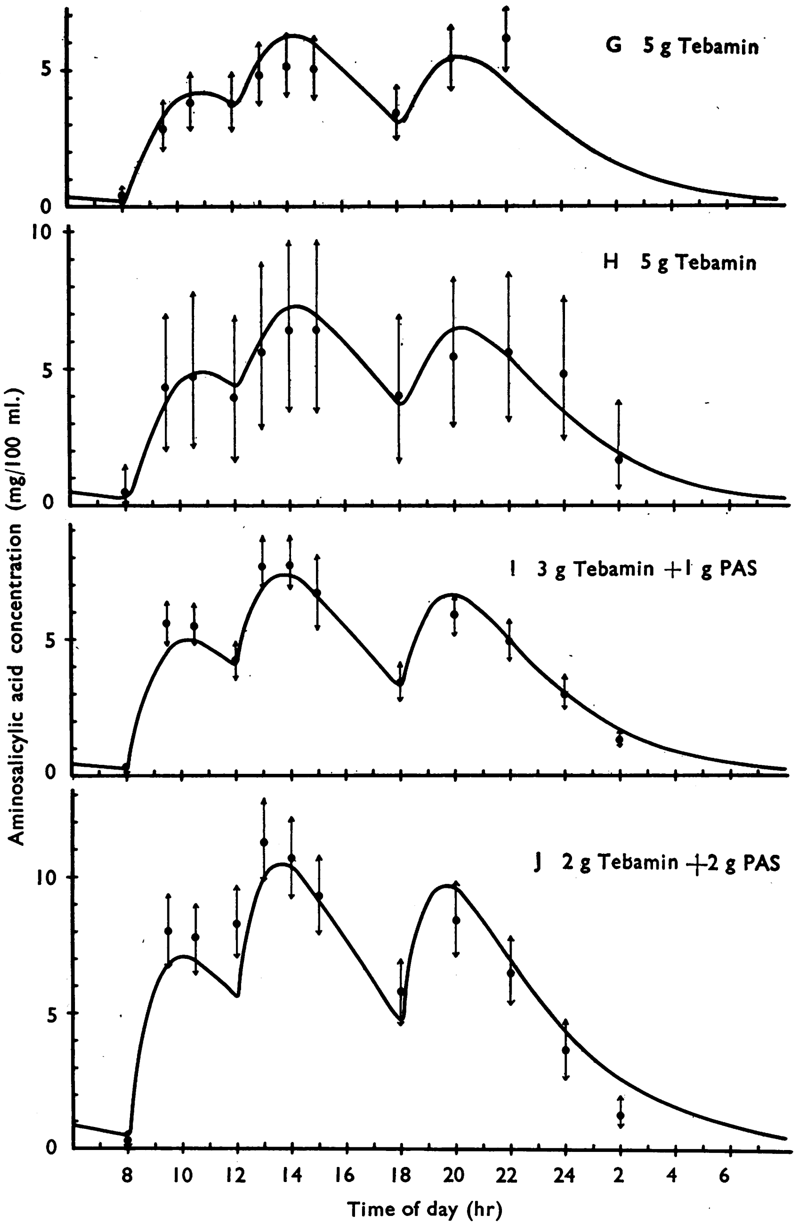


Fig. 1. Blood levels after continued oral treatment with aminosalicylic acid preparations. The stated doses were given at 8 a.m., 12 noon, and 6 p.m. The graphs show experimentally determined means with 95% confidence limits, and curves calculated from the first order model. PAS=aminosalicylic acid; Pasido=coated granulate of PAS; Tebamin=phenylaminosalicylate.

TABLE 1

ORAL TREATMENTS

PAS=aminosalicylic acid; Pasido=coated granulate of PAS; Tebamin=phenylaminosalicylate

					Calculated parameters			
						Half-life (hr) for the first order process involved		
Group	No. of subjects	Preparation	Single dose (g)	Effective single dose (g PAS)	V (l.)	p $\log_e 2$	m $\log_e 2$	b $\log_e 2$
A	10	PAS	1	1·00	24·3	0·00	0·65	0·38
B	5	PAS	2·7	2·70	24·3	0·00	0.65	1·91
C	5	Pasido	2·7	2·70	24·3	5·48	0·65	1·30
D	5	Na-PAS	3·75	2·72	24·3	0·00	0·40	1·37
E	20	Tebamin	3	1·70	24·3	0·34	1·44	0·56
F	23	Tebamin	4	2·27	24·3	0·34	1·44	1·23
G	9	Tebamin	5	2·67	24·3	0·34	1·44	1·61
H	5	Tebamin	5	2·97	24·3	0·34	1·44	1·72
I	30	Tebamin +PAS	3 +1	2·70	24·3	0·34 0·00	1·44 0·65	1·87
J	10	Tebamin +PAS	2 +2	3·13	24·3	0·34 0·00	1·44 0·65	2·36

Bartlett's test as listed in Table 2 shows that the variances for temporal subgroups within a group are identical, and that the variances vary significantly from group to group. Accordingly, the estimates relevant to the different groups have been used for the *t*-tests listed in Table 3. In making multiple *t*-tests such as those of Table 3, one would expect approximately 5% of the calculated values to exceed the 95% limits, and even a *t*-value as large as 3.30 (group J at 2 a.m.) has a 13.5% chance of occurring, so that no statistical significance should be attached to any recorded *t*-values except those of group E at noon, and group J at noon. These two values merit a more thorough investigation:

TABLE 2

COMPARISON OF VARIANCES FOR THE TRANSFORMED VARIABLE Y

The first rows give a comparison of variance estimates for temporal subgroups within groups, and the lowest row gives a comparison of mean squares for groups

			Bartlett's test		
Group	Mean square for group S^2 (y)	Degrees of freedom	χ^2	df	P (%)
A	1·20	72	9·43	7	80
B	2·20	47	9·94	11	50
C	7·38	48	4·20	11	4
D	1·94	44	8·80	10	45
E	2·26	104	12·1	5	96
F	2·78	164	25·4	12	99
G	2·40	80	2·68	9	2·5
H	6·99	42	12·7	11	70
I	3·47	308	23·4	11	98
J	2·90	108	18·6	11	93
	3·13	1,017	82·4	9	$>>$99·95

(1) Group E, t=*4.56.* This group includes twenty single determinations, six of which are <0.5 mg/100 ml., and this is conventionally recorded as zero. Taking

TABLE 3

DEVIATION OF THE EXPERIMENTAL MEANS FROM THE CALCULATED CURVES EXPRESSED AS *t*-VALUES

The *t*-values have been calculated for the transformed variable y using the variance estimates listed in Table 2

	Group									
Time	A	B	C	D	E	F	G	H	I	J
8	0·00	−1·91	0·06	0·11	—	0·09	−1·66	−0·69	0·94	1·24
9.30	1·70	1·97	0·47	1·25	—	0·79	0·85	−0·47	−2·71	−1·77
10.30	−1·87	0·50	1·06	−0·10	—	0·36	0·68	0·06	−1·56	−1·20
12	−1·85	−0·63	0·49	−0·24	4·56	1·21	−0·08	0·37	−0·35	−4·28
13	0·69	1·08	0·33	−0·61	1·85	0·12	0·70	0·33	−1·76	−1·79
14	−0·81	0·87	0·46	−0·56	0·06	0·12	1·93	0·56	−0·79	−0·46
15	−0·98	0·50	0·53	−1·30	−1·37	0·00	1·57	0·39	−0·14	−0·24
16	—	—	—	—	−2·51	−2·45	—	—	—	—
18	0·14	−1·29	−0·35	0·53	−2·41	−1·04	−0·60	−0·16	−0·44	−1·83
20	1·73	1·85	−1·05	1·04	—	2·07	0·15	0·75	1·91	1·68
22	0·29	0·02	−0·76	0·14	—	0·91	−2·68	−0·14	−0·06	0·78
24	0·14	−0·84	0·17	−0·05	—	0·40	—	−1·13	−0·12	1·22
02	0·00	−1·06	−0·55	0·35	—	1·52	—	0·25	1·62	3·30

the true value of the mean of the " zeros " to be 0.25 mg/100 ml. the overall mean of the group changes from 0.28 to 0.41 mg/100 ml. against the theoretical value of 0.75 mg/100 ml. This leads to a *t*-value of 3.02, which is acceptable.

(2) Group J, t= *−4.28.* The mean and six of the ten sample values composing it are recorded as higher than the corresponding values for the two preceding determinations, even though no dose has been given to the subjects in the intervening time. This is obviously wrong, and one might suspect that in this case the noon dose has been given not after, but before the taking of blood samples. Disregarding the two above-mentioned *t*-values, and bearing in mind that the values in succeeding subgroups are not truly independent, one may take Table 3 as a proof that the experimental material available is adequately described by the proposed mathematical model.

Plotting the results from the intravenous experiments on semi-log paper shows that in this case the elimination cannot be explained as a combination of first order processes. According to the literature (Way, Smith, Howie, Weiss & Swanson, 1948 ; Lehmann, 1953 ; Lauener, Hodler, Favez, Dettwiler & Hadorn, 1957) the elimination of aminosalicylic acid occurs in three different ways: by biotransformation into the biologically inactive derivatives *N*-acetyl-*p*-aminosalicylic acid and *p*-aminosalicyluric acid, and by direct renal excretion of free acid. The ratio between free acid and inactive derivatives found in the urine varies with the size of dose, the relative amount of *N*-acetyl-*p*-aminosalicylic acid being considerably lower at higher blood levels of aminosalicylic acid. Strict adherence to the first order mechanism would lead to a constant ratio between free acid and the derivatives independent of the blood level, so that the first order reaction must fail for *N*-acetyl-*p*-aminosalicylic acid.

If the change in concentration of the biotransforming factor is taken into consideration, a second order reaction results. Denoting by g and z the concentrations of free acid and the biotransforming factor respectively, and assuming a constant supply rate k for z for the limited time-interval during which the serum level of aminosalicylic acid drops to zero, the following equations apply:

$$dg/dt = -Kgz$$
$$dz/dt = k + dg/dt$$
$$z = g + kt - (g_0 - z_0)$$
$$dg/dt = K(g_0 - z_0 - kt)g - Kg^2$$

By changing the independent variable t to:

$$x = \sqrt{K/k}[kt - (g_0 - z_0)]$$

the solution becomes:

$$g(x) = \frac{\varphi(x)}{\sqrt{K/k}\int \varphi(x)\,dx + A}$$

where $\varphi(x)$ denotes the normal curve of error which is found tabulated together with its integral in most statistical works.

For specified values of K, k, z_0, and g_0 the constant A may be calculated from the above formula by putting

$$g(x) = g_0 \text{ for } x = -(g_0 - z_0)\sqrt{K/k},$$

and so g is given in terms of t, K, k and $(g_0 - z_0)$, the difference in levels between g and z at time zero.

The above formula would apply if the biotransformation into *N*-acetyl-*p*-aminosalicylic acid were the dominant process, but combination of a second order reaction with two or more reactions of either first or second order leads to very complicated differential equations with solutions containing more parameters than could reasonably be determined from the available experimental values. It was therefore decided to investigate whether this simple formula alone would adequately describe the experimental material. Imposing the restriction that K be the same for all four groups, estimates were obtained for the parameters. These are listed in Table 4. In order to obtain these estimates, fifth degree polynomials were fitted to the four sets of experimental points, according to the method of Birge & Shea (Birge &

TABLE 4

ESTIMATES FOR THE PARAMETERS IN THE SECOND ORDER MODEL

a, before, and *b*, after 2 weeks' treatment with phenylaminosalicylate. K is expressed as equivalents of aminosalicylic acid

		K (mg/100 ml. × hr)$^{-1}$	k (mg/100 ml./hr)	$(g_0 - z_0)$ (mg/100 ml.)
Female	*a*	$6 \cdot 02 \times 10^{-2}$	5·95	36·5
	b	$6 \cdot 02 \times 10^{-2}$	4·50	37·8
Male	*a*	$6 \cdot 02 \times 10^{-2}$	7·09	31·3
	b	$6 \cdot 02 \times 10^{-2}$	3·80	32·0

Weinberg, 1947). The polynomials were then introduced into the differential equation

$$dg/dt = K(g_0 - z_0 - kt)g - Kg^2$$

and the equation was solved by integration, and put in the form

$$g - g_0 - K(g_0 - z_0)\int_0^t gdt + Kk\int_0^t gtdt + K\int_0^t g^2dt = 0$$

The square of this expression, when integrated between the relevant limits for t, gives a sort of squares of deviations, which can be minimized by suitably choosing the values for K, Kk, and $K(g_0 - z_0)$. The values so obtained were then used as initial values for an iteration process using the formula

$$g(x) = \frac{\varphi(x)}{\sqrt{K/k}\int\varphi(x)dx + A}$$

Table 5 and Fig. 2 show the experimental and calculated values for the serum levels as from the termination of the infusion (t = o). The standard deviation of the experimental values ranges from 4.5 to 1.9 for women, and from 3.2 to 1.5 for men (high values for high blood levels), and so the model is applicable as an extrapolation formula. It appears that the initial level is higher for women than for men when the same dose is administered, presumably because of a smaller volume of distribution in women. If the estimate of the average apparent volume of distribution of 24.3 l., previously found, is applied, an initial concentration of 55.6 mg/100 ml. is obtained, provided that the intravenous dose was administered momentarily. If it is taken into consideration that this condition has not been fulfilled as the administration is stretched over 1 hr, and that the estimate of 24.3 l. is an average for women and men, a reasonable agreement is present.

TABLE 5

SERUM LEVELS AFTER INTRAVENOUS INFUSION OF 18.5 g OF SODIUM AMINOSALICYLATE (EQUIVALENT TO 13.5 g OF AMINOSALICYLIC ACID)

Experimental results and values were calculated from the second order formula using the parameters listed in Table 4. Means are for two female and three male subjects. *a*, before, and *b*, after, 2 weeks' treatment with phenylaminosalicylate. Calc. = calculated; Expt. = experimental; * approximate

Time after infusion (hr)	Female				Male			
	a (mg/100 ml.)		*b* (mg/100 ml.)		*a* (mg/100 ml.)		*b* (mg/100 ml.)	
	Calc.	Expt.	Calc.	Expt.	Calc.	Expt.	Calc.	Expt.
0	—	52·4	—	52·4	—	42·2	—	49·4
1	34·1	35·2	40*	38·8	28·8	29·6	32*	32·4
2	27·8	27·8	32*	—	21·9	21·9	27*	27·1
3	22·7	22·9	26·6	25·6	15·9	15·8	23·0	22·5
4	17·4	16·5	22·8	—	10·6	10·2	19·7	19·1
5	12·7	12·1	18·7	17·5	6·2	6·2	16·3	15·4
6	8·5	9·6	14·9	—	3·0	3·3	13·1	12·0
7	5·1	5·2	11·4	10·0	1·1	1·2	10·1	9·8
8	2·5	2·9	8·1	—	0·3	0·3	7·3	8·3
9	1·0	—	5·3	6·0	0·0	—	5·0	—

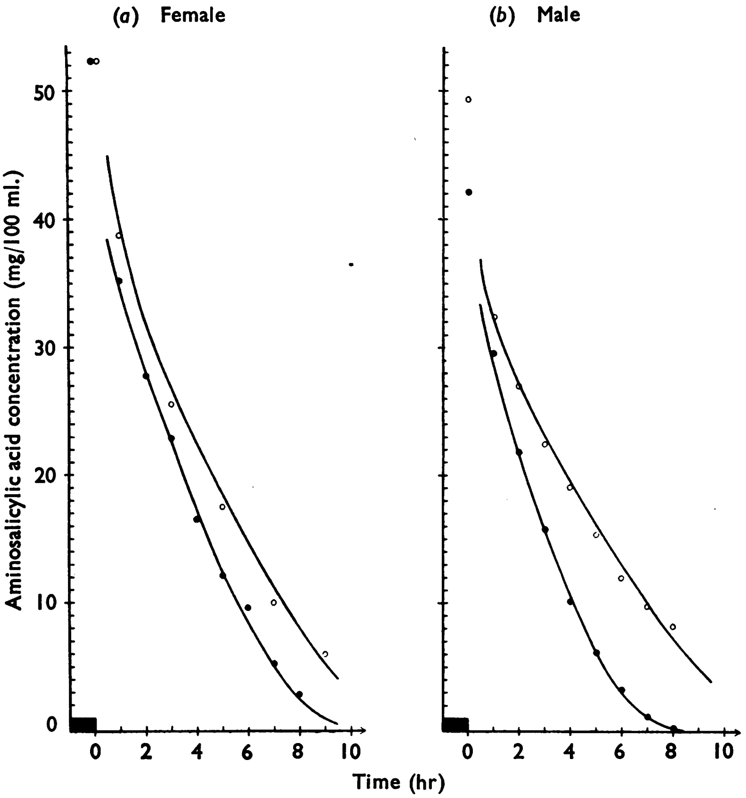


Fig. 2. Blood levels after a single intravenous infusion (during black rectangles) of 18.5 g of sodium aminosalicylate. Points are experimentally determined means before (●) and after (○) 2 weeks of oral treatment with phenylaminosalicylate oral (4 g, three times a day), and curves are calculated from the second order model. (*a*), female, and (*b*), male subjects.

DISCUSSION

The failure of a first order model to account for the elimination rate at high initial serum levels raises the question of the size of the systematic error introduced by using such a model at the serum levels found in the first part of our experimental material. The highest serum level attained, that of group J at 1 p.m., is a little less than 11 mg/100 ml. Using the value for the apparent distribution volume previously estimated (24.3 l.) this serum level would be obtained by intravenous infusion of 4.10 g of sodium aminosalicylate (equivalent to 3.00 g of aminosalicylic acid). A theoretical curve for serum levels resulting from such an infusion has been calculated by means of the second order model, using the values for K and k found for male subjects after treatment with phenylaminosalicylate and a value of 6.4 for $(z-g)_0$. In Table 6 equally spaced points for this curve have been tabulated together with their logarithms to the base 10.

Now imagine that these six values were experimentally determined means from thirty subjects. The usual procedure would be to try to fit a straight line through

TABLE 6

THEORETICAL FIRST ORDER AND SECOND ORDER RELATIONS FOLLOWING INTRAVENOUS INFUSION OF 4·10 G OF SODIUM AMINOSALICYLATE

The second order curve was calculated for $K=6{\cdot}02\times10^{-2}$, $k=3{\cdot}80$ and $(z-g)^0=6{\cdot}4$. The first order curve was calculated taking the values listed in column three as experimental points, and $b=1{\cdot}02$ (a half-life of 0·71 hr). L.s.d.=least significant difference for the group including thirty subjects

Time after infusion (hr)	Second order		First order			
	g	$\log_{10}g$	g	$\log_{10}g$	Δg	L.s.d.
0	11·00	1·04	11·10	1·045	0·10	1·7
1	4·36	0·64	4·17	0·62	−0·19	1·4
2	1·77	0·25	1·59	0·20	−0·18	1·2
3	0·64	−0·19	0·60	−0·22	−0·04	1·1
4	0·19	−0·72	0·22	−0·66	0·03	0·5
5	0·05	−1·30	0·08	−1·08	0·03	0·3

the points (t, log g) and to compare the deviations beween that line and the experimental points with the standard deviations for the experimental means. If this comparison proved favourable, one would conclude that a first order reaction accounted satisfactorily for the elimination process. In Table 6 such a straight line has been computed, taking into account that the different experimental points have different standard deviations. The calculated values for log g have been transformed into values for g, and these have been compared with the values calculated for the second order model. It follows that for experimental values involving thirty subjects or less, and subjected to a variance of the same order as found in our material, it is meaningless to differentiate between a first order and a second order model for initial serum levels below 11 mg/100 ml.

As previously shown the daily maximum in blood level rises during treatment with phenylaminosalicylate in the first week. The total daily excretion of aminosalicylic acid and its derivatives is constant, and the blood level reaches zero before next morning, so accumulation is out of the question (Frederiksen *et al.*, 1957). The same consideration applies to other aminosalicylic acid preparations, though to a lesser extent.

If sodium aminosalicylate is administered intravenously after 2 weeks of oral treatment with phenylaminosalicylate the same initial level is obtained as when the infusion is given before the phenylaminosalicylate (Fig. 2). As the blood levels, however, do not decrease so fast when the infusion is administered after treatment with phenylaminosalicylate the elimination must be slower. This corresponds to a lower value for k as indicated in Table 4.

In the model for the course of the blood level after oral dosage the parameter b is a function of k ; therefore, a change of b during a treatment must be expected whereas the other parameters V, p, and m can be assumed to remain unaffected during the treatment. This phenomenon is least pronounced for small doses, for example 1 g of aminosalicylic acid three times a day, when the resulting rise in blood level and consequently in b is very slight. If the model for the oral administration is applied to the first day of the treatment, agreement with the results of the experiments is obtained if the values listed in Table 1 for the parameters V, p, and m are employed, together with an initial value for b which corresponds to the b-value for 1 g of aminosalicylic acid, and which is allowed to rise gradually during the first week. The rise in b is furthermore less pronounced for sodium aminosalicylate, which gives high but short-lived levels, than for the acid and phenylaminosalicylate which give more retarded levels. .

It seems that to obtain a rise in b, aminosalicylic acid must be present in the blood for as long a time as possible. If, for instance, only one dose is omitted the blood level will on the following day be below the average values for the hour in question.

To compare levels and durations of the various aminosalicylic acid preparations, the areas, that is the products of time and level for 24 hr periods, are listed in Table 7. The column area/effective 24 hr dose gives an idea of the difference in the utilization of preparations, and shows besides that large doses are better utilized than small ones.

TABLE 7

COMPARISON BETWEEN VARIOUS AMINOSALICYLIC ACID PREPARATIONS AS REGARDS LEVELS AND DURATION

PAS=aminosalicylic acid; Pasido=coated granulate of PAS; Tebamin=phenylaminosalicylate All doses were oral, except for Na-PAS in the lower part of the table, which was intravenous, The area (columns five and six) equals the product of time and level summed over 24 hr. *a*, before. and *b*, after, 2 weeks' treatment with phenylaminosalicylate.

Group	Preparation	Single dose (g)	Effective 24 hr dose (g)	Area (mg/100 ml. × hr)	Area/g effective 24 hr dose (mg/100 ml. × hr/g)
A	PAS	1	3 × 1·00	7·1	2·4
B	PAS	2·7	3 × 2·70	92·7	11·4
C	Pasido	2·7	3 × 2·70	62·2	7·7
D	Na-PAS	3·75	3 × 2·72	26·3	3·2
E	Tebamin	3	3 × 1·70	17·0	3·3
F	Tebamin	4	3 × 2·27	50·1	7·4
G	Tebamin	5	3 × 2·67	76·6	9·6
H	Tebamin	5	3 × 2·97	91·1	10·2
I	Tebamin +PAS	3 +1	3 × 2·70	90·5	11·2
J	Tebamin +PAS	2 +2	3 × 3·13	132·3	14·1
	Na-PAS	18·5	1 × 13·5	—	—
	Female *a*			150	11·1
	Female *b*			189	14·0
	Male *a*			105	7·8
	Male *b*			164	12·2

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