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sulfonamide

Pharmacokinetic Studies with a Long-Acting Sulfonamide in Subjects of Different Ages

A Modern Approach to Drug Dosage Problems in Developmental Pharmacology

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Extract

The principal aims of this paper are to discuss the striking differences in sulfonamides pharmacokinetics which can be observed when comparing groups of subjects at very different stages of development and to demonstrate the practical value of investigations to establish the correct dosage of a drug in infants and children. The sulfonamide compound used for this study was 2-sulfa-3-methoxy-pyrazine.

The first series of investigations concerned the determination of all the biological constants needed to establish the optimal dosage of the drug for five groups: newborns, infants, children, adults and elderly subjects. The values measured included protein-binding and pharmacokinetic constants. The second series of studies investigated the application of the Krüger-Thiemer pharmacokinetic theory in the five age groups.

When compared with adult values, the drug concentration in plasma water at half saturation binding is higher in newborn and elderly subjects, while it is rather low in children (table II). The maximum binding capacity of the plasma did not differ in a significant way among all groups studied, with the exception of the elderly subjects in whom high values were found. As a result of the relatively marked changes with age of these two constants, the minimum concentration of free sulfonamide in plasma was found to be much higher in newborns than in all other groups.

In table III, pharmacokinetic constants are reported. The rate constant of absorption was found to decrease from high values in newborns and in infants to low values in children; the lowest values were found in adults, whereas in elderly subjects the constant was again high. The rate constant of elimination was very low in newborns, higher in infants and children, slightly lower in adults and was very low again in elderly subjects. As was expected, an inverse trend was observed when the time of half elimination (biological half-life) was calculated, being highest in newborns, lower and approximately equal in infants, children and adults and very significantly elevated in elderly subjects. The coefficient of distribution of 2-sulfa-3-methoxy-pyrazine was found to be very high in newborns, high in infants, low and about equal in children and adults and again high in elderly subjects.

When the theoretical maintenance dose and the ratio between initial and maintenance dose were calculated from the pharmacokinetic constants and from the protein-binding constants, values characteristic of each state of development were obtained (tables III and IV). Relative maintenance dose was found to be very low in newborns, high in infants and children and lower in adults and elderly subjects. The initial to maintenance dose ratio was found, on the contrary, to be very high in newborns and elderly subjects and about equal in infants, children and adults, the children showing the lowest values.

The practical value of the Krüger-Thiemer method for calculating an optimal dosage regimen was tested by measuring plasma concentrations of sulfonamide in subjects of different ages treated for prolonged periods of time. A remarkably constant minimum blood concentration was found in each instance, thus indicating that the theoretic treatment of the variables had permitted prediction of optimal drug dosage (figs. 4 and 5).

Speculation

The Krüger-Thiemer method was found very useful to calculate the optimal drug dosage regimen in subjects of different ages, from birth through senescence. This same type of experimental approach could be used in the future, with profit, to calculate optimal dosages of other drugs for which the therapeutic effect depends chiefly upon the maintenance of a relatively constant plasma concentration.

Introduction

Among the numerous problems which are still discussed in the broad field of developmental pharmacology, one of the most important concerns the correct method to calculate the dosage of a drug, in order to obtain comparable blood levels in subjects of different ages.

For certain types of drugs which are usually administered for relatively long periods of time, and of which the therapeutic effect is mainly bacteriostatic, sulfonamides, for example, rapid attainment and maintenance of a relatively constant plasma level is essential. This level should be between a properly calculated minimum and maximum [2].

Attempts to use a single parameter to calculate drug dosages in patients in the pediatric age group have been essentially unsuccessful [17], mainly because too many factors changing rapidly during development play important roles in determining the concentration of drugs in blood.

A pharmacokinetic approach offers the possibility of solving the problem of drug dosage in subjects of different ages and sizes. This approach will of necessity demand specific and individual solutions for each series of drugs.

KRÜGER-THIEMER [8, 9] has published a theory with a pharmacokinetic basis which allows successful achievement of constant blood levels of sulfonamides in adults. It is the purpose of the investigations described in this present report to try to apply the Krüger-Thiemer pharmacokinetic theory to subjects of various ages.

The principal aims of this report are to discuss the sharp differences in sulfonamides pharmacokinetics observed among groups of subjects at very different stages of development and, furthermore, to demonstrate the practical value of this approach for the establishment of correct drug dosage for infants and children.

General Scheme of the Research Materials and Methods

The sulfonamide used throughout our investigations was 2-sulfa-3-methoxy-pyrazine (Kelfizina®). In contrast to other long-acting sulfonamides, this agent is bound particularly poorly to plasma proteins and has a relatively long biological half-life [1]. These characteristics, together with the fact that the pharmacokinetic peculiarities of this compound in adults are already well known [1], led us to select it for the present study in developmental pharmacology. The research included two series of investigations.

First series of investigations. These concerned the determination of all the biological constants needed to establish the optimal dosage of the drug in newborns, infants, children, adults and elderly subjects. These, together with a general indication of the method used to calculate each, are summarized in table I.

The biological constants can be divided in two groups. The first group includes the protein-binding constants of the sulfonamide for plasma proteins; the second lists all the pharmacokinetic constants.

Protein-binding constants. The drug concentration in plasma water at half saturation binding (dissociation constant, K_β) and the maximum specific binding capacity of the plasma proteins for the sulfonamide (β) have been calculated as intercept and angular coefficient, respectively, of the Langmuir adsorption isotherm on pools of plasma drawn from ten newborn infants and from at least five subjects in each of the other age groups. One pool for each age group was considered. On the same plasma samples, water content of the plasma (ml/ml) and protein content (g/l) were also measured; the minimum percentage of free sulfonamide in plasma (f_{min}) was then calculated (table II).

Pharmacokinetic constants. The rate constant of absorption, the rate constant of elimination, the half-life and the volume of distribution were all calculated from mathematical analysis of plasma concentration curves after a single oral dose of the drugs. These were performed on a limited number of subjects of each age group. All the calculations were carried out both on the IBM 7040 computer of the University of Milan and on the Electrologica computer of the University of Kiel. The former processed a program issued by WIEGAND and SANDERS [16] and translated by us from FORTRAN 0 to FORTRAN IV, the latter a program written by KRÜGER-THIEMER [10] in ALGOL 60. The programs utilized two different methods of calculation, but the results obtained agree very well.

Table I. Definitions and determinations of the biological constants necessary for the calculation of the dosage schedules of sulfa drugs (from KRÜGER-THIEMER)

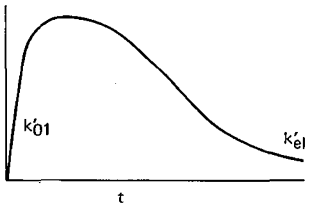
No.	Biological constants	Symbol	Unit	Experimental methods of determinations
1	Rate constant of absorption	k'_{01}	h^{-1}	Evaluation of the curve of blood content in blood plasma of humans. 
2	Rate constant of elimination	k'_{el}	h^{-1}	
	Time of half elimination (Biological half-life)	$t'_{50\,\%}$	h	
3	Coefficient of distribution relative to the blood plasma	Δ'	ml/g	
4	Drug concentration in plasma water at half saturation binding	K_β	µmol/l	Evaluation of bound and free drug in human blood plasma by ultrafiltration, dialysis or ultracentrifugation. Calculation by the law of mass action.
5	Maximum specific binding capacity of the plasma proteins	β	µmol/g	
6	Minimal inhibitory concentration	µ	µmol/l	Evaluation of µ against *E.coli* or other pathogenic bacteria in a medium free of antagonists.
7	Proportionality constant between µ and c_{min} (minimal free sulfonamide concentration) for a therapeutical effect of 95 percent	σ	—	In analogy calculated from the dosage schedules of other clinically effective sulfa drugs.

Table II. Protein-binding constants

Subjects	w[1]	p[2]	K_β µmol/l	β µmol/g	No. of points	EMS[3,4]	f_{min}[5] (%)
Newborns (2–3 days)	0.92	5.8	513.25	10.63	5	67.62	43.36
Infants (1–12 months)	0.95	6.1	293.76	12.00	6	27.53	27.60
Children (4–9 years)	0.92	6.5	199.74	10.12	5	32.86	21.84
Adults	0.95	7.0	347.85	12.53	23	84.87	27.37
Aged (> 70 years)	0.95	7.0	507.92	17.32	16	100.42	28.47

[1] water content of blood plasma (ml/ml)

[2] plasma total proteins (g %)

[3] Error Mean Square

[4] This is the error about regression; this is to be understood as a measurement of the technical error and not of the biological variability.

[5] $f_{min} = \dfrac{w}{w + \dfrac{\beta\, p}{K_\beta}} \times 100 =$ minimum concentration of free sulfonamide in plasma

Data reported on table III are those obtained working with an Electrologica computer. For each subject, the following variables were calculated:

1. Pharmacokinetics constants: k'_{01} (rate constant of absorption), k'_{el} (rate constant of elimination) and Δ' (plasma distribution coefficient) with 95 % confidence limits.
2. Half-life: $t'_{50\%}$ with 95 % confidence limits.
3. Ratio between the initial dose and the maintenance dose (R*).
4. Relative maintenance dose to be administered every 24 hours (D/G).

Table IV contains mean values and standard errors of the three pharmacokinetics constants. It is important to point out that while the standard errors used in table III are estimates of 'goodness of fit' of the theoretical model to plasma levels, the corresponding values in table IV are estimates of the dispersion to be expected when the experiment is repeated in other subjects of the same age group.

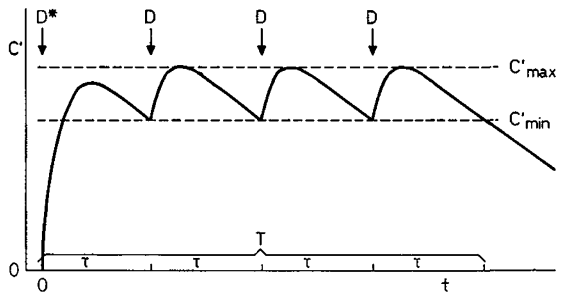
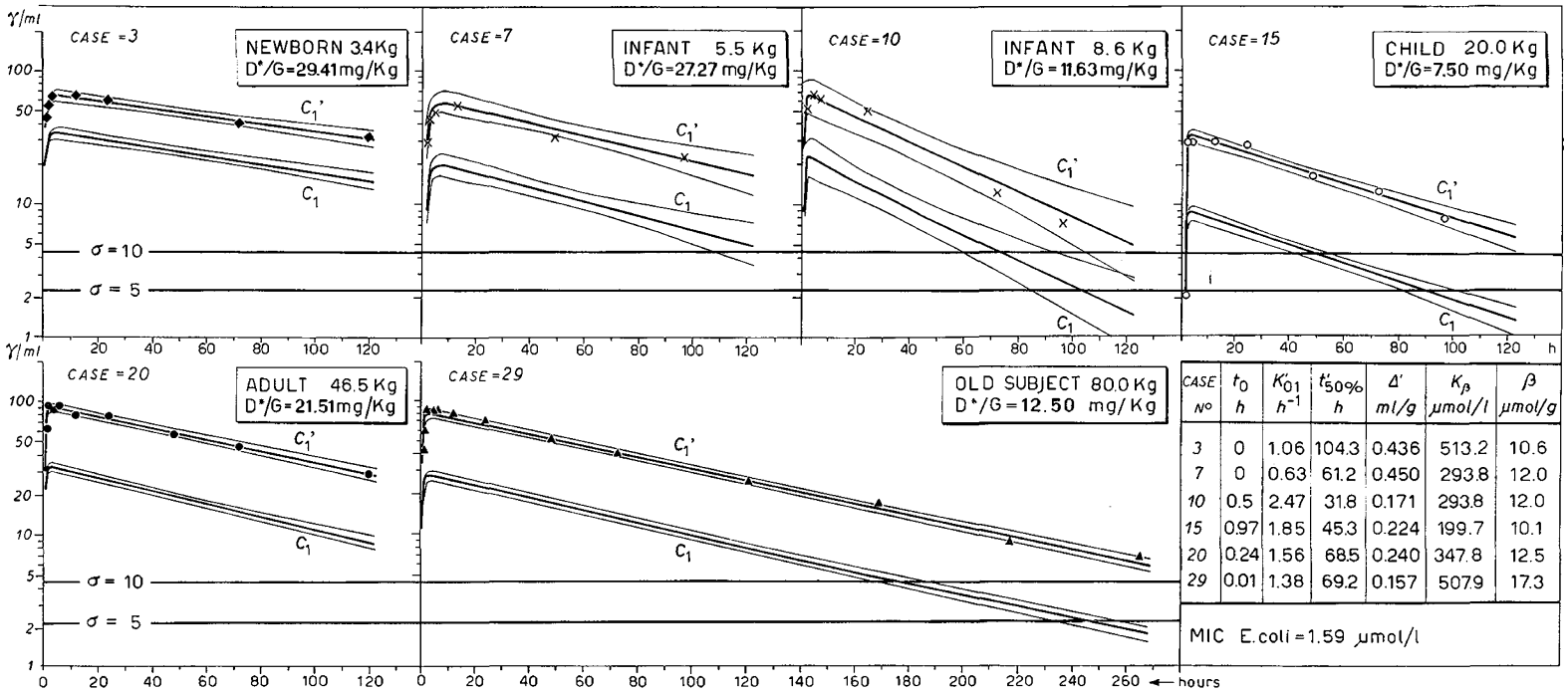


Fig. 1. Ideal type of plasma concentration curve of a sulfonamide according with KRÜGER-THIEMER [9]. D* = initial dose; D = maintenance dose; C'_{max} = maximal plasma concentration of free sulfonamide. C'_{min} = minimal plasma concentration of free sulfonamide; τ = interval of time between each single dose administration.

Fig. 2. Examples of plasma concentration curves of 2-sulfa-3-methoxy-pyrazine (with 95% confidence limits) after a single administration in subjects of different ages.
C_1' = concentration of drug in plasma; C_1 = calculated concentration of the drug in plasma water.



CASE No	t_0 h	K'_{01} h^{-1}	$t'_{50\%}$ h	A' ml/g	K_β µmol/l	β µmol/g
3	0	1.06	104.3	0.436	513.2	10.6
7	0	0.63	61.2	0.450	293.8	12.0
10	0.5	2.47	31.8	0.171	293.8	12.0
15	0.97	1.85	45.3	0.224	199.7	10.1
20	0.24	1.56	68.5	0.240	347.8	12.5
29	0.01	1.38	69.2	0.157	507.9	17.3

MIC E.coli = 1.59 µmol/l

Table III. Pharmacokinetic constants of 2-sulfanilamido-3-methoxy-pyrazine

Patient	No.	Age	Body weight G kg	Dose D mg	Relat. dose D/G mg/kg	Number of points N/N_2[1]	Zero time shift t_0^0 h	Rate constant for absorption: k'_{01} h^{-1}	Rate constant for elim.: k'_{el} h^{-1}	Apparent biological half-life: $t'_{50\%}$ h	Plasma-distribution coefficient: A' ml/g	Dose ratio $R^* = D^*/D$	Relative maintenance dose D/G $\tau = 24$ h mg/kg
		Newborns days											
ME	1	2	2.90	100	34.48	7/4	0.000	0.35 (0.27–0.47)	0.008504	81.5 (60.4–109.9)	0.434 (0.375–0.502)	5.42	0.90 (0.73–1.12)
BE	2	2	3.08	100	32.47	7/3	0.5	3.01 (ibm)	0.003135	221.1 (126.6–386.0)	0.531 (0.484–0.583)	13.80	0.39 (0.23–0.66)
GD	3	3	3.40	100	29.41	7/4	0.000	1.06 (0.75–1.50)	0.006645	104.3 (80.8–134.6)	0.436 (0.392–0.484)	6.78	0.70 (0.57–0.87)
		Infants months											
RS	4	2	3.40	150	44.12	7/6	0.5	1.43 (ibm)	0.012844	54.0 (52.1–55.9)	0.383 (0.375–0.392)	3.77	2.02 (1.96–2.08)
BM	5	1	3.40	150	44.12	6/4	0.5	1.17 (ibm)	0.008571	80.9 (69.6–93.9)	0.585 (0.547–0.625)	5.38	1.95 (1.72–2.22)
OM	6	2	3.65	150	41.10	8/6	0.5	2.39 (ibm)	0.010794	64.2 (45.7–90.2)	0.479 (0.405–0.567)	4.38	2.08 (1.55–2.79)
TD	7	3	5.50	150	27.27	8/5	0.000	0.63 (0.38–1.05)	0.011327	61.2 (42.4–88.3)	0.450 (0.360–0.562)	4.20	2.03 (1.57–2.64)
LR	8	5	6.40	150	23.44	7/6	0.5	4.05 (ibm)	0.010096	68.6 (52.5–89.8)	0.375 (0.342–0.411)	4.65	1.51 (1.18–1.94)
NE	9	10	8.30	100	12.05	8/6	0.5	1.83 (ibm)	0.025710	27.0 (15.3–47.4)	0.224 (0.115–0.436)	2.17	2.77 (1.57–4.90)
NP	10	11	8.60	100	11.63	7/5	0.5	2.47 (0.63–9.59)	0.021763	31.8 (23.4–43.4)	0.171 (0.122–0.240)	2.46	1.71 (1.28–2.30)
AM	11	10	9.70	100	10.31	8/6	0.5	1.72 (0.32–9.14)	0.015904	43.6 (22.4–84.8)	0.234 (0.137–0.401)	3.15	1.59 (0.95–2.66)
		Children years											
TO	12	4	16.0	150	9.38	7/5	0.903	1.74 (1.21–2.51)	0.006356	109.0 (64.8–183.4)	0.234 (0.195–0.281)	7.07	0.68 (0.44–1.06)
BI	13	4	18.0	150	8.33	7/4	0.5	0.41 (0.06–2.96)	0.028071	24.7 (11.2–54.2)	0.174 (0.050–0.604)	2.04	2.77 (1.37–5.61)
CP	14	8	20.0	150	7.50	8/6	0.525	1.74 (0.66–4.56)	0.011316	61.2 (35.5–105.8)	0.208 (0.152–0.286)	4.20	1.15 (0.75–1.76)
AN	15	9	20.0	150	7.50	8/5	0.967	1.85 (1.41–2.43)	0.015288	45.3 (38.1–53.9)	0.224 (0.196–0.256)	3.26	1.75 (1.53–2.00)
AC	16	9	20.5	150	7.32	7/5	0.863	1.55 (0.93–2.59)	0.013180	52.6 (36.8–75.1)	0.200 (0.154–0.260)	3.69	1.31 (1.02–1.69)
CC	17	7	23.5	150	6.38	7/4	0.5	1.45 (0.70–2.99)	0.025086	27.6 (22.7–33.7)	0.167 (0.128–0.220)	2.21	2.42 (2.02–2.89)
PL	18	8	26.6	150	5.64	8/7	0.5	4.20 (ibm)	0.018949	36.6 (27.5–48.6)	0.179 (0.139–0.229)	2.74	1.82 (1.41–2.35)
		Adults											
BU	19	27	43.3	1000	23.10	13/8	0.403	0.33 (0.23–0.46)	0.011259	61.6 (53.8–70.4)	0.225 (0.184–0.275)	4.23	1.00 (0.88–1.15)
BAM	20	16	46.5	1000	21.51	10/6	0.245	1.56 (1.32–1.84)	0.010125	68.5 (60.8–77.1)	0.240 (0.225–0.256)	4.64	0.98 (0.89–1.08)
SM	21	29	47.2	2000	42.37	9/6	0.982	0.41 (0.24–0.71)	0.009573	72.4 (41.4–126.5)	0.239 (0.173–0.329)	4.87	0.90 (0.60–1.35)
BL	22	37	64.5	1000	15.50	12/9	0.912	0.50 (0.29–0.89)	0.013613	50.9 (43.5–59.7)	0.183 (0.138–0.243)	3.59	1.03 (0.84–1.25)
		Elderly subjects											
PR	23	> 70	52.0	2500	48.08	13/11	0.000	2.66 (2.21–3.20)	0.007515	92.2 (88.8–95.8)	0.326 (0.315–0.337)	6.06	0.93 (0.90–0.96)
LS	24	> 70	57.0	2500	43.86	14/13	0.5	4.76 (ibm)	0.005618	123.4 (116.5–130.6)	0.280 (0.269–0.291)	7.93	0.58 (0.56–0.61)
SG	25	> 70	67.0	2500	37.31	13/10	0.333	1.86 (1.64–2.11)	0.006127	113.1 (106.6–120.1)	0.292 (0.280–0.306)	7.31	0.67 (0.64–0.70)
FS	26	> 70	68.0	2500	36.77	14/12	0.924	0.66 (0.47–0.92)	0.007730	89.7 (81.2–99.0)	0.276 (0.251–0.304)	5.91	0.81 (0.75–0.86)
RL	27	> 70	68.5	2500	36.50	13/12	0.021	3.21 (2.61–3.95)	0.006820	101.6 (97.6–105.8)	0.247 (0.239–0.255)	6.62	0.63 (0.61–0.65)
GA	28	> 70	80.0	1000	12.50	13/11	0.012	1.38 (1.08–1.77)	0.010009	69.2 (65.1–73.7)	0.157 (0.145–0.169)	4.68	0.61 (0.58–0.65)

[1] N = total number of points
N_2 = number of points on the descending branch
[2] In the absence of measured points on the ascending branch of the curve the arbitrary value 0.5 has been chosen. The value 0.000 means that the calculation originally resulted in a negative to
[3] For (ibm) means: initial branch method, for detailed explanations see KRÜGER-THIEMER (to be published 1967)

The comparison between data from groups of subjects of different ages, insofar as the rate constant of absorption, the biological half-life and the volume of distribution are concerned, was performed with the one-way analysis of variance (ANOVA). The Sheffé test [12] was used to make multiple comparisons. It must be noted that R* (the ratio of the initial dose to the maintenance dose) and D (the maintenance dose) are complex functions of the above-mentioned variables. Special cautions, therefore, were taken when R* and D values were compared in different age groups, even if they were in accord with the ANOVA results. For these reasons, conclusions concerning the constants R* and D must be considered as merely indicative.

Second series of investigations. These concerned the evaluation of the practical value of the Krüger-Thiemer pharmacokinetic theory in all age groups studied. Knowledge of the biological constants for each age group enabled us to calculate, in each instance, the appropriate sulfonamide dosage to be given in order to maintain both a constant and an optimal drug concentration in plasma. Subjects studied had the following age characteristics: full-term infants, 2–3 days; infants, 3–12 months; children, 4–11 years; and elderly subjects, older than 70 years.

Data on minimum drug concentration in plasma obtained in adults have been previously reported by BOSCHI *et al.* [3] and are included in this paper only for comparative purposes.

An ideal plasma concentration curve is presented in figure 1, where D* is the initial dose, τ is the interval between each dose (24 hours in our case), and D is the maintenance dose. It may be observed that the plasma sulfonamide concentration never falls below a minimum value [9] and never exceeds a maximum one.

Plasma sulfonamide concentration was determined by the technique of BRATTON and MARSHALL [4]. Total serum protein levels were measured by the biuret reaction [11]. Minimal inhibitory concentration, evaluated *in vitro* against *E. coli* in a medium free of antagonists, was considered to be 1.59 μg/ml, as suggested by KRÜGER-THIEMER and BUNGER [9].

Results

Protein-Binding Constants

Listed in table II are the constants for protein binding as obtained through direct measurement, together with the calculated standard errors about the regression for each value.

When compared with the adult values, the drug concentration in plasma water at half saturation binding (K_β) was higher in newborn and elderly subjects and lower in children. In contrast, the maximum binding capacity of the plasma (β), with the exception of the elderly subjects in whom high values were found, did not differ significantly among all the groups we considered. As a result of the relatively marked change of these two constants with age, the minimum concentration of free sulfonamide in plasma (f_{min}) was much higher in the newborn group than in all the other groups. This finding has important implications. In the newborn, it is likely that a relatively low total plasma concentration of sulfonamide results in a satisfactory level of free sulfonamide; this is the only significant fraction from a therapeutic viewpoint [5]. It appears probably that the lower sulfonamide plasma protein-binding constants found in the newborns are related to at least two factors: (1) lower plasma protein concentration, and (2) higher serum bilirubin levels.

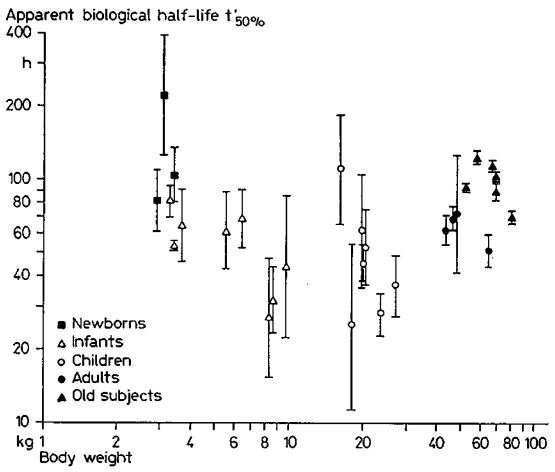


Fig. 3. Correlation between the apparent biological half-life of 2-sulfa-3-methoxy-pyrazine and the body weight of subjects of different ages.

Pharmacokinetic Constants

Plasma concentration values of all single oral load curves were recorded. These were obtained in order to establish the pharmacokinetic constants in all age groups.

In figure 2, some of these curves are shown. Included are both the measured concentration in plasma (c'_1) and the calculated concentration in plasma water (c_1). It should be noted that the slopes of the curves are very different in each age group, with a much slower decrease in concentration values in the newborn and elderly subjects and with a faster decrease in children and older infants.

Some of the pharmacokinetic constants show discrete

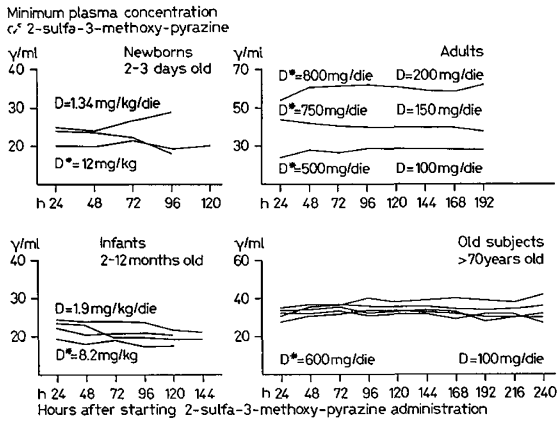


Fig. 4.

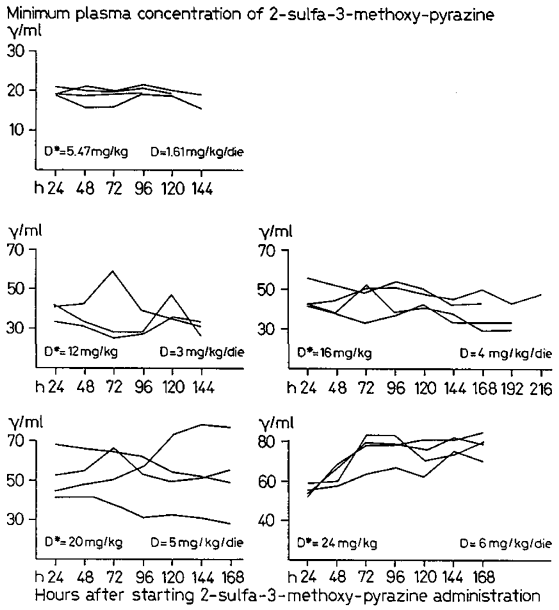


Fig. 5. Plasma 2-sulfa-3-methoxy-pyrazine, minimum concentrations (γ/ml) in different groups of children (4–11 years old) treated with various dosage regimens.

age-dependent differences. In table III, the mean kinetic values and their ranges are reported in detail, together with the age and weight of the subjects from which they were calculated. Our results may be summarized as follows:

Rate Constant of Absorption (k'_{01})

Although the lowest values were found in adults, statistical evaluation of the data shows no significant variations between various age groups.

Time of Half Elimination (Biological Half-Life, $t'_{50\%}$) and Rate Constant of Elimination (k'_{el})

The biological half-life was found to be much higher in newborns than in infants, children or adults. When the first age group was compared with all the other groups, a statistically significant difference was always obtained. Elderly subjects had an average biological half-life for 2-sulfa-3-methoxy-pyrazine intermediate between that of newborns and that of all the other groups. Figure 3 correlates the biological half-life values with the body weight of the subjects. It may be observed that values for smaller infants approach those of newborns, whereas those for larger infants are essentially the same as those of children. As was expected, a reverse trend was observed for the rate constant of elimination, with much lower values for newborns than for infants, children and adults.

Coefficient of Distribution

This constant was found to be very high in newborns, with statistically significant differences from values obtained in children, adults and elderly subjects. Infants also had values significantly higher than children, whereas no clear-cut differences were observed when values for infants were compared with those found in newborns.

Relative Maintenance Dose and Dose Ratio Values in all Groups of Subjects Studied

When the theoretical maintenance dose and the ratio between initial and maintenance dose were calculated from pharmacokinetic constants and protein-binding constants, very different values were found for subjects in different stages of development (table III).

Relative maintenance dose seemed to be rather low in newborns, higher in infants and children and lower in adults and elderly subjects.

The initial/maintenance dose ratio (R*) found was, on the contrary, very high in newborns and elderly subjects and about equal in infants, children and adults, the children showing the lowest values.

These findings are not susceptible to a statistical test of significance (vide supra).

Minimum Drug Levels in all Groups Treated for Several Days with a Calculated Dosage Regimen

To estimate the practicality and validity of the Krüger-Thiemer theory, minimum sulfonamide plasma levels (i. e. the drug concentration at the end of the interval period of time between each dose) were determined during prolonged drug administration. The results from all groups are reported on figures 4 and 5.

Table IV. Pharmacokinetic constants[1]

Age groups	k'_{01} h^{-1}		k'_{el} h^{-1}		$t'_{50\%}$ h		Δ' ml/g	
	Avg.	SE	Avg.	SE	Avg.	SE	Avg.	SE
Newborns	1.47	0.795	0.0061	0.00157	135.6	43.238	0.47	0.0319
Infants	1.96	0.368	0.0146	0.00216	53.9	6.587	0.36	0.0507
Children	1.85	0.433	0.0169	0.00291	51.0	10.855	0.20	0.0096
Adults	0.70	0.289	0.0111	0.00089	63.3	4.712	0.22	0.0133
Elderly subjects	2.42	0.596	0.0073	0.00063	98.2	7.786	0.26	0.0236

[1] See table I for abbreviations

Because of the potential danger of administering sulfa drugs to newborns [13] and the difficulty in drawing blood samples over a period of many days, only three full-term newborns were studied. The amount of drug given was the lowest that could give minimum therapeutic concentration in plasma. As may be seen from data reported in figure 4, a remarkably constant minimum blood concentration was found in all the newborns.

The same constancy in minimum blood concentration was found in infants and elderly subjects, despite the very different initial/maintenance (R*) dose ratio which was used.

The scheme of the drug level evaluation experiments in children was much more complex. A total of 19 children were studied; they were divided in five groups. All received an initial/maintenance dose ratio of 4, but each received very different maintenance doses (1.47, 3, 4, 5 mg/kg/day). It may be observed from figure 5 that a satisfactory constancy of minimum plasma concentration levels was obtained in all groups, except in children treated with the highest dosage (6 mg/kg/day). It is unknown why very high doses of sulfonamides give a plasma concentration curve which has a clear trend to increase after a few days of administration.

Furthermore it should be noted that the D*/D ratio given to children was, for practical reasons, a little higher than the theoretical one (4.0 instead of 3.6).

Finally, in figure 4, data obtained from adults are also reported. These data were published recently by BOSCHI *et al.* [3]. As in younger subjects, there was a remarkable constancy of plasma concentration, even following administration of maintenance doses which were very different.

Discussion and Conclusions

It appears, from an overall evaluation of the series of investigations reported on the various age groups, that large differences characterize the kinetics of a long-acting sulfonamide at various stages of development.

The possibility of obtaining very high sulfonamide plasma levels after identical drug intake, both in newborns when compared with children [14] and in elderly subjects when compared with adults, is already known [2]. However, as far as we know, no complete comparative pharmacokinetic study has been previously performed for a single sulfa compound in various age groups.

Developmental pharmacology must not be considered merely as the pharmacology of immature subjects [17, 18]; rather, the discipline includes a continuous evaluation of drugs from birth through senescence. As a part of drug evaluation, it is necessary to define safe and effective dosages of specific agent. Our experimentation with 2-sulfa-3-methoxy-pyrazine illustrates the age dependency of effective drug dosages.

Most of the pharmacokinetic constants which were calculated were found to be very different when comparing newborns to children and to adults. This is particularly true for the time of half elimination and for the coefficient of distribution, probably as a consequence of the very low glomerular filtration rate and the large extracellular fluid volumes present in the neonatal period of life [6, 11, 15].

Furthermore, it is interesting to observe that some of the pharmacokinetic constants (time of half elimination, coefficient of distribution) are quantitatively similar in newborns and elderly subjects. Even if the reasons for these findings are obviously very different, from the standpoint of practicality, the results are very similar; to maintain minimum constant plasma concentrations, a very high initial/maintenance dose ratio has to be given.

Unfortunately, no general rules can be drawn from any series of investigations on pharmacokinetics of drugs at different ages. For any single series of compounds to be used in pediatrics if a rational dosage regimen is to be established, researches must be performed on human subjects to determine all pertinent kinetic constants.

Summary

A complete pharmacokinetic study of a long-acting sulfonamide was performed in subjects of various age groups, i.e., newborns, infants, children, adults and elderly persons.

In each of these groups, the optimal dosage regimen was thereafter determined following the method first described by KRÜGER-THIEMER. The practical value of these studies was verified by prolonged administrations of the dose of the drug calculated to be correct. The results show that very different amounts of sulfonamide must be administered at various ages if comparable and constant, minimum, effective plasma concentrations of the drug are to be obtained.

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