Eur. J. Clin. Pharmacol. 18, 43–50 (1980)

European Journal of Clinical Pharmacology

Enteral Absorption and Bioavailability in Children in Relation to Age* **

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Summary. There is little information about enteral drug absorption during development compared to that about drug distribution, metabolism and excretion. Therefore, the bioavailablity, i. e. the amount and rate of absorption of various drugs (sulfonamides, phenobarbital, digoxin, β-methyldigoxin) and test substances (D(+)-xylose, L(+)-arabinose) was investigated in 580 children using pharmacokinetic methods. The amounts of the drugs absorbed, determined by Dost's law of corresponding areas, showed no age dependence. But the rate of absorption, k_a, calculated from the concentration time curves using a digital approximation procedure (RIP), is low at the time of birth and reaches adult values after the neonatal period. This phenomenon is identical for all of the substances tested. A prolonged gastric emptying time in the neonate does not seem to be responsible for the delayed absorption since the lagtime is not related to age. Stimulation of intestinal motility with metoclopramide increases the absorption rates, both in neonates and older children, but the age dependent differences remain. Using various dosages of L(+)-arabinose the parameters of the saturation kinetics could be determined. In neonates V_{max} values are significantly lower than in older children. Similarly, the affinity constant $\overset{*}{K}$ indicates a decreased capacity of enteral absorption in neonates compared with older children. Bioavailability data from adults cannot be accepted without further investigation since the rate of enteral drug absorption depends on age.

Key words: enteral drug absorption, development; bioavailability, neonates

There is considerable information about drug distribution, metabolism and excretion during development [7, 11, 20, 21, 26, 30, 33], but the data for enteral drug absorption during development are rather poor. It is known, that morphology and function of the gastrointestinal tract are not constant but vary from birth to senescence. These alterations may influence the fundamental process of absorption by which drugs are delivered from the sites of administration into the central circulation.

The most striking changes occur during the neonatal period. The gastric pH for instance, usually 6–8 at birth, drops within a few hours to pH values of 3 to 1. Acid secretion falls rapidly in the first 10 days of life; adult values are reached by 3 years of age [28, 33]. The gastric emptying time after milk feeding is considerably prolonged in the neonate and approaches adult values at the age of 6–8 months. Intestinal motility depends to a large extent on feeding habits and is very irregular and unpredictable; the maturation of biliary function and differences of intestinal bacterial growth may be of importance [28, 30].

These few examples indicate that drug absorption should be influenced by age. But difficulties to confirm this are obvious because the variables involved are numerous and many are interrelated.

That is why two major conditions must be fulfilled when studying drug absorption in relation to age. The first one is to keep the influence of different modifying variables as small as possible, the second one is to measure enteral absorption in terms which can be interpreted by pharmacokinetic parameters.

Methods

The enteral absorption of various drugs (sulfonamides, phenobarbital, digoxin, and β-methyldigoxin), and test substances (D(+)-xylose and L(+)-arabinose) was studied in children treated in

* Supported by the Deutsche Forschungsgemeinschaft, grants Gl 82/1–3 and He 749/2

** Presented at the International Workshop on Perinatal and Pediatric Aspects of Clinical Pharmacology, Heidelberg, Federal Republic of Germany, 27–29 February 1980

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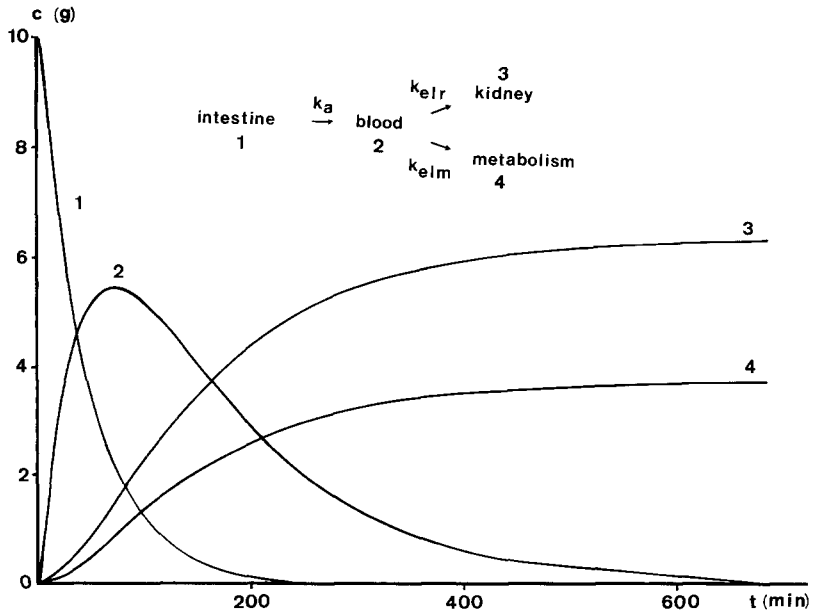

Fig. 1. Concentration time curve of D(+)-xylose after oral administration of 0.5 g per kg bodyweight in 20 children older than 2 years. The concentration in the various compartments are shown as mean values
k_a = rate constant of absorption
k_{elr} = rate constant of renal elimination
k_{elm} = rate constant of metabolism

our University Children's Hospital in 1974–1979. The drugs were given exclusively under clinical conditions: phenobarbital for treatment of convulsions and as prophylaxis against hyperbilirubinemia, digoxin for the treatment of patients with pneumonia and congenital heart defects, and sulfonamides for the treatment of urinary tract infections.

D(+)-Xylose- or L(+)-arabinose tests were performed as global function tests of enteral absorption under various clinical conditions. Since all data were derived from measurements in patients under treatment a retrospective synoptic evaluation of all clinical, chemical and bioptic parameters was necessary in order to get information about enteral absorption in relation to age. All substances were given via a feeding tube after a fasting period of 3–4 h. D(+)-Xylose and L(+)-arabinose (0.125–0.5 g/kg) were given as isotonic solutions, digoxin and β-methyldigoxin (0.02 mg/kg) as alcoholic elixirs, sulfonamides (25 mg/kg) as aqueous solutions, and phenobarbital (5–10 mg/kg) as suspended tablets. Highly sensitive analytical techniques were used so that capillary blood sampling could be performed instead of repeated venous blood sampling, which would have been unacceptable in small children. D(+)-Xylose[1] was measured in 50 µl of serum according to a method which is based on the principle of coupling D(+)-xylose with *p*-bromoaniline in an acid environment in the presence of thiourea [27]. The reproducibility of the method, expressed as standard deviation was 4.1%, the accuracy was 97.2%. A modified method was used to measure L(+)-arabinose [14]. Phenobarbital[2] was measured in 50 µl of serum using gas-liquid chromatography. The principle of the method was transformation of phenobarbital to its N,N'-dimethyl derivative using methyl iodide as methylation agent and potassium carbonate as condensing agent [15]. The yield of derivatisation was 98%. The reproducibility was 4.1%, the recovery from serum was 98.2 ± 2.8% (SD), and the minimum detectable serum concentration of phenobarbital was 0.2 µg/ml. Sulfasomidine[3] and sulfadimethyloxazole[4] were measured in 20 µl of serum as total sulfonamides using a modification [10] of the Bratton and Marshall method [3]. The reproducibility was 4.9%, and the accuracy was 98%. Digoxin[5] and β-methyldigoxin[6] were determined in 50 µl of serum using a commercial solid phase radio-immunoassay[7]. The intra-assay variation at 1 ng/ml was 0.05 ng/ml, the recovery was 98.5 ± 3.5% (SD), and the reproducibility was 6.2%.

The procedure for obtaining pharmacokinetic data was standardized. First, a pharmacokinetic model after single intravenous injection was calculated from the concentration time curve in serum and urine using a digital computer program [12]. D(+)-Xylose and L(+)-arabinose were not injected

[1] Hoffmann-LaRoche Nr. 1024, Basel, Schweiz

[2] Luminal®, Luminaletten®, Bayer Leverkusen, GFR
[3] Aristamid®, Nordmark, Hamburg, GFR
[4] Sulfono®, Nordmark, Hamburg, GFR
[5] Lanicor®, Boehringer, Mannheim, GFR
[6] Lanitop®, Boehringer, Mannheim, GFR
[7] Gammacoat ^{125}I-Digoxin RIA-Test
Clinical Assay Inc. Cambridge, Mass., USA

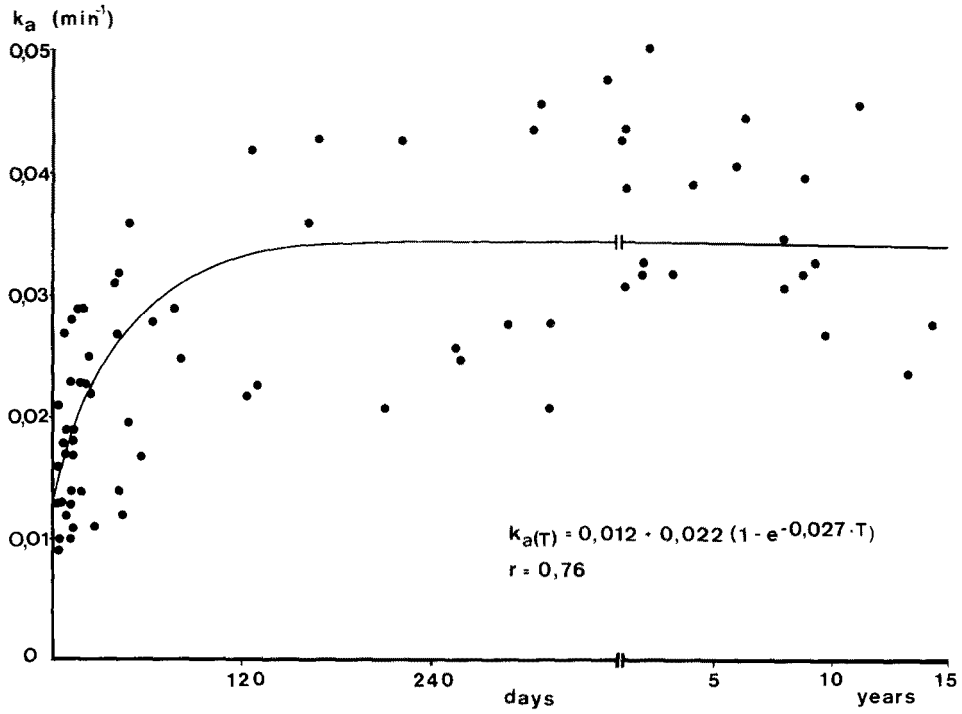

Fig. 2. Rate constant of enteral absorption (k_a) of L(+)-arabinose (0.25 g/kg) in relation to age. T = age in days

intravenously for ethical reasons, besides which sufficient data had already been published [2, 32]. Second, the amount of absorbed substances was determined using Dost's law of corresponding areas and the Wagner-Nelson method [8, 29]. The rate of absorption was calculated from concentration time curves in serum and urine.

Results

The pharmacokinetics of the test substance, D(+)-xylose, which is absorbed by an active mechanism in the upper small bowel, independent of pH values and enzymes of the gastrointestinal tract, can be described by an open multicompartment system (Fig. 1). After absorption and distribution in the extracellular fluid space, up to 50% of D(+)-xylose is metabolized in the liver the rest is eliminated unchanged by the kidneys [9, 13, 32].

The amount of D(+)-xylose absorbed after dosages of 0.3 and 0.5 g per kg bodyweight varies greatly between individuals, but is independent of age [13]. In contrast, the rate of absorption, given by the rate constant of enteral absorption, k_a, depends on age and is less in newborns and young babies than in older children. There is a non-linear correlation between k_a and age.

Similar results were obtained using the test substance L(+)-arabinose (Fig. 2). L(+)-arabinose is

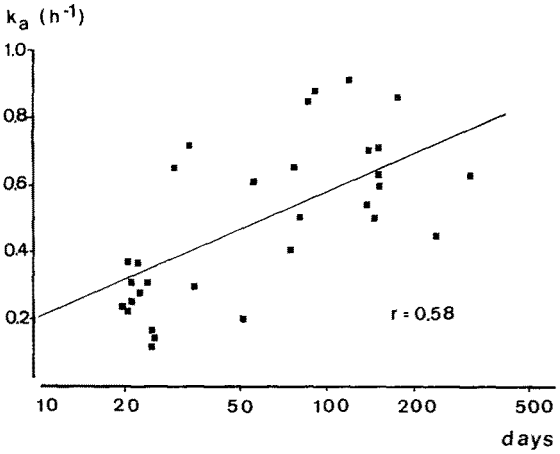

Fig. 3. Rate constant of enteral absorption (k_a) of phenobarbital in relation to age after a single oral dosage of 5–10 mg phenobarbital per kg bodyweight

absorbed by passive diffusion and has a distribution volume which corresponds to the extracellular fluid space. Sixty percent of the oral dose is eliminated by the kidneys and 40% is metabolized by the pentose-phosphate-shunt [19, 32]. Similar to the other pentose, the amount of L(+)-arabinose absorption is independent of age [13] but the rate of absorption shows a non-linear correlation between the rate constant, k_a, and age. The intestinal absorption rates in neonates, especially, are significantly reduced (Fig. 2).

Pharmacokinetic data for the enteral absorption of sulfonamides confirm that the absorption rates again are lower in neonates than in older children while there are no differences in the amount absorbed [13].

The enteral absorption of phenobarbital, digoxin and β-methyldigoxin are also similar. There are no differences in the amount absorbed, but absorption rates increase with the age of the children (Fig. 3) [13, 14].

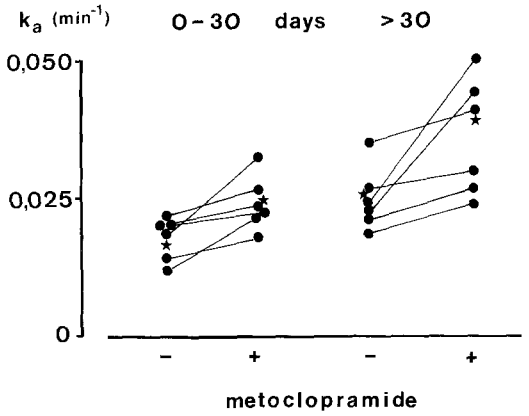

Fig. 4. Rate constant for D(+)-xylose absorption before (−) and after (+) stimulation of gastrointestinal motility with metoclopramide
k_a = rate constant of enteral absorption
⋆ = median values; significance = $2\alpha < 0.05$ in and between the age groups

Summarizing the above mentioned data, it can be said that despite the different physicochemical properties of the drugs and substances tested, there is a similar pattern of bioavailability. The amounts absorbed very greatly between individuals but are not age dependent. In contrast, the drugs and test substances are absorbed more slowly from the intestine of neonates and young babies than of older children.

The prolonged gastric emptying time and reduced intestinal motility in the neonate may be responsible for such phenomena. There is an indirect measure of gastric emptying time, the so-called "lagtime", which can be determined from the concentration-time curve. The lagtime indicates the time during which the substrate remains in the stomach until entering a region of absorption. It lasts only a few minutes for all of the substrates which were given as solutions of suspensions after a fasting period. An age dependent tendency could be excluded for every drug and test substance [13].

From these results an effect of gastric emptying on the absorption rate can be excluded for the drugs tested under the conditions mentioned above.

To examine the influence of intestinal motility, absorption studies were done before and after stimulation with metoclopramide. This drug was given to children to facilitate biopsy of the small bowel. After stimulation of the intestinal motility with metoclopramide the rate constants of absorption and the absorption rates increase both in young and older

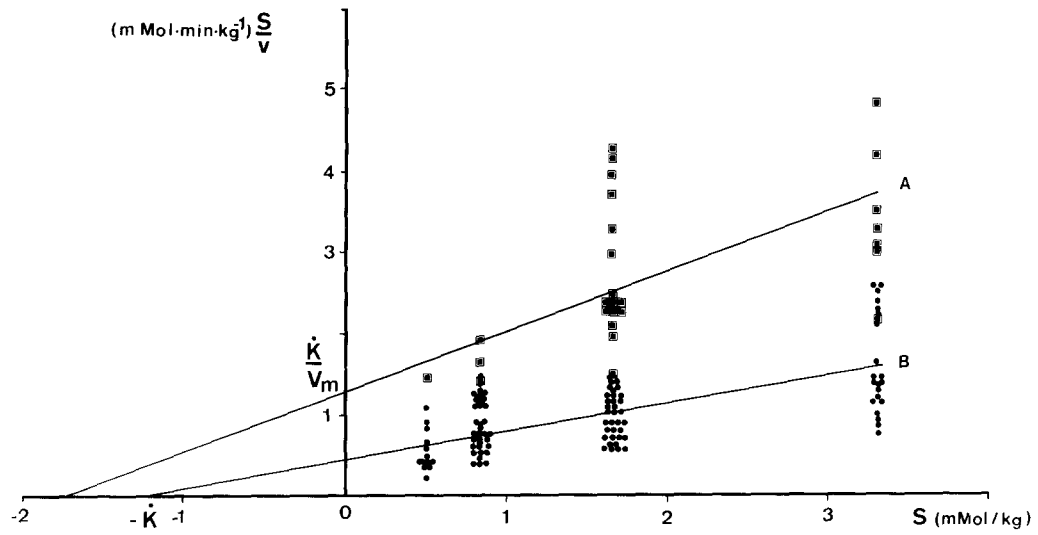

Fig. 5. Woolf-plot for determination of maximal absorption rate V_m and the affinity constant $\dot{K}$ of enteral L(+)-arabinose absorption. The median rate of enteral absorption $\bar{v}$ during a time interval of 300 min (t_0–t_{300}) is plotted against the substrate concentration. Significance $p < 0.05$ between the regression lines (A, B) and from zero.
A = newborns
B = older children

infants. But it is remarkable that the age dependent differences of the rates of absorption remain constant (Fig. 4). From these data it can be concluded that there must be factors other than gastric emptying time and intestinal motility responsible for delayed absorption in young infants.

Further information could be obtained by giving various oral dosages of L(+)-arabinose. First-order absorption kinetics only apply if the dosage does not exceed 0.25 g/kg body-weight. With increasing dosage there is no proportional increase in the amount absorbed, indicating that the enteral absorption process can be described by saturation kinetics. The maximal absorption rate, V_{max}, becomes an adequate pharmacokinetic parameter. The parameters of the Michaelis-Menten equation were determined by the method of Kübler [17]. Maximal absorption rates for various time intervals of an absorption process were determined. The transformations were done with the Woolf-plot (Fig. 5).

The maximal absorption rate, V_{max}, at the beginning of the absorption process, that is, during the first hour, is smaller in neonates (1.27 mmol/kg·min) than in infants (1.91 mmol/kg·min) (Table 1). These age dependent differences become more distinct if maximal absorption rates for L(+)-arabinose are estimated for an absorption period of 5 h. There is no significant increment in V_{max} values in neonates, but in older children the maximal absorption rate increases from 1.91 to 2.8 mmol/kg·min (Table 1). The affinity constant $\overset{\star}{K}$ of the Michaelis-Menten equation, which characterizes the absorption capacity, shows similar age dependent behaviour. In neonates the values of $\overset{\star}{K}$ are larger than those of older children, indicating that the affinity of the intestinal absorption mechanisms for L(+)-arabinose is reduced in neonates.

Table 1. Constants of the enteral saturation kinetics of L(+)-arabinose after oral administration. Maximal absorption rate, V_{max}, and the affinity constant, $\overset{\star}{K}$, of L(+)-arabinose calculated from the Woolf-plot, see regression lines. The values of V_{max} and $\overset{\star}{K}$ are given for the absorption process in the first hour (t_0-t_{60}) and in the first 5 h (t_0–t_{300})

	V_{max} (mmol/kg·min)	$\overset{\star}{K}$ (mmol/kg)	Correlation equation
Newborns (n=29)			
t_0–t_{60}	1.27	1.14	$y=0.01x+1.75$; $r=0.47$
t_0–t_{300}	1.33	1.76	$y=0.005x+1.32$; $r=0.46$
Older children (n = 101)			
t_0–t_{60}	1.91	0.45	$y=0.0033x+0.450$; $r=0.58$
t_0–t_{300}	2.80	1.16	$y=0.0023x+0.415$; $r=0.67$

Discussion

These observations in children agree to some extent with data from experimental animals. In newborn rats and mice, for instance, transport mechanisms for Ca^{++}, sulfate, hexoses, and some amino acids were present at low levels of activity throughout the neonatal period [1, 4, 16]. These mechanisms are known to be localized in different parts of the mature animal's intestine. As the animals get older the site of localisation changes from proximal to distal segments and the activity of the absorption mechanisms increases. These functional changes are related to a further morphological differentiation, that is, the brush border becomes more complex with the appearance of microvilli and pinocytotic activity increases [22].

One may speculate which mechanisms in humans are responsible for the age dependency of enteral absorption. Since gastric emptying time and intestinal motility seem to play a minor role, it may be that the permeability of the intestine, which may be understood as a global functional parameter, changes with age. From the following data speculation may be allowed.

The thickness of the "unstirred water layer phase" close to the surface area of the mucosa cells is known to be a limiting factor for the absorption rates of various substances [5, 6, 31]. The enteral absorption rate of some antibiotics is higher in adult patients suffering from sprue [23, 24]. There was no explanation for this until Read et al. [25] showed that the thickness of the unstirred layer was reduced from 643 to 442 μm in these patients. Thus, the reduced thickness of the unstirred layer phase may be responsible for the increased rate of drug absorption. While it is known that the water content in different fluid spaces and the water turnover is higher in young infants, it is not known whether the thickness of the unstirred layer phase is related to age. One may speculate that the unstirred layer phase is thicker in neonates.

What are the consequences for drug therapy?

First, it can be assumed that enteral absorption underlies age dependent changes similar to those found in drug distribution, metabolism and renal excretion. With relevance for drug therapy one may conclude, that changes of the absorption rate are of minor importance when compared to the age related differences of drug distribution and excretion. Furthermore, other interrelated factors like food intake, food composition, and colonisation of the gastrointestinal tract by various microorganisms cannot be

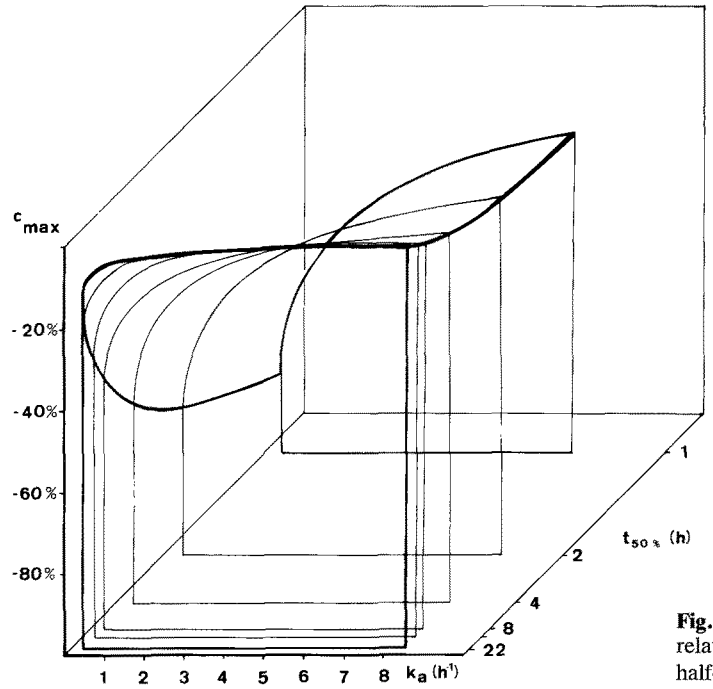

Fig. 6. Nomogram based on the Bateman-function showing the relation between rate constant of absorption, k_a, the elimination half-life, $t_{50\%}$, and the maximal concentration, c_{max}.

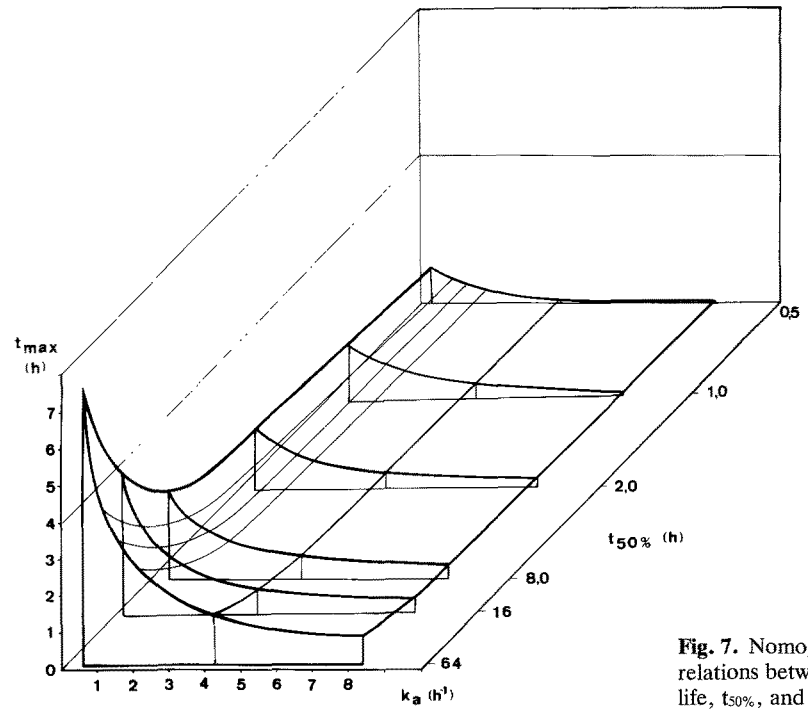

Fig. 7. Nomogram based on the Bateman-function, showing the relations between rate constant of absorption, k_a, elimination half-life, $t_{50\%}$, and the time of maximal concentration, t_{max}

neglected. There are many drugs which have a low bioavailability in adults. The lower rate of absorption in young infants can lead to an additional decrease of bioavailability. For this reason bioavailability data determined in adults should not be accepted for young infants without further investigations.

In pharmacokinetic terms, the maximal drug concentration is reached later if the absorption rate is decreased. In addition maximal drug concentration decreases the shorter the elimination half-life of the drug. These complex relationships between absorption rates and elimination rates are illustrated in the

following nomogram which is based on the Bateman-function (Fig. 6).

If the elimination half-life of a drug is short, the decrease of the maximal concnetration, c_{max}, in the central compartment becomes more distinct with lower values of the absorption rate. If the elimination half-life is relatively long, changes of absorption rates have no influence. The relation between absorption rate, elimination rate, and the time of maximal concentration, t_{max}, is demonstrated in Fig. 7.

Summarizing, it can be said that the mechanisms involved in enteral absorption vary with age. Although this effect is of minor significance for drug therapy in children compared with the effects of drug distribution and elimination, it seems to complete our knowledge in developmental pharmacology in a logical manner. For example, the metabolism of *p*-aminosalicylic acid is reduced when the enteral absorption rate increases indicating that the maximum metabolic rate has been exceeded [18]. Considering that many metabolic functions in the neonate have low activity at the time of birth, a slower enteral absorption of drugs helps to protect the limited metabolic capacity against overloading.

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Discussion

Morselli asked whether the differences in the rates of absorption, but not in the amounts absorbed, might not be due to the relatively lower blood flow of the stomach and the intestine of the newborn. *Heimann* felt that the results with different dosages to get saturation kinetics weighed against blood flow as a decisive factor.

Dillon commented that although it had been said that there was no relationship between lag time for gastric emptying and age, there did seem to be a biphasic curve with higher values in the older and the younger children and a trough in the middle. He asked if the results had been analysed by comparing groups of children to see whether the trough point was significant. *Heimann* replied that they had used regression analysis, and that there were no differences. For the substrates tested the values were four to 6 min compared with the hour required for maximal concentration.

Yaffe agreed that the data from this last neglected area of pharmacokinetics were important. Especially important in view of the pharmacist's right (in the United States) to dispense drugs on a generic basis. He asked whether similar studies had been made in older infants and children with solid dosage forms. *Heimann* replied that they had found no differences for some solid drugs given to 3 to 5 year old children, if the drugs were given before meals.

Mirkin asked whether there was any evidence of active transport for any of these drugs and, if so, could this be correlated with biological maturation. *Heimann* replied that diffusion was only one aspect of a complex mechanism. The older concepts in which ionization was of great importance did not seem appropriate. Gastric motility and emptying seemed to be more important.

Rane asked whether the rectal absorption of drugs had been studied since this was a common way of administering drugs in emergencies. *Heimann* replied that they had found no limiting effect. They had, for instance, found good absorption of phenobarbital in neonates as well as in children. It was important to have a suitable formulation.