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(REVIEW ARTICLE)

Pediatric TCI: A new pharmacokinetic-pharmacodynamic theory proposal-part one

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Abstract

New theoretical research of pharmacokinetic-pharmacodynamics constants for anaesthetic drugs are discussed in this report. Our study aims to set up a new algorithm to be validate and eventually insert in a new theoretical software. The algorithm will be installed in a new Target Controlled Infusion (TCI) System dedicated to neonatal and paediatric anaesthesia and especially for patients weighing less than 30 kgs, so for dynamics rapid cells growth and or elderly patients suffering of rapid dynamic death cells.

TCI systems used for the management of paediatric and neonatal anaesthesia, i.e. Paedfusor TCI by Absalom-Lal-Kenny et al (2005), needed further investigation for their use in younger patients.

There is a lack of body functioning and pharmacological data in the paediatric and neonatal population that need to be integrated in a new program to be installed in computer-driven anaesthesia systems.

A new theoretical pathway and speculation about the approach to applied pharmacology is compulsory.

But as new theoretical "pharmacodynamics-pharmacokinetic" (PK/PD) concept and covariates choices are required to be settled in the systems; a new scientific approach is required.

Our theoretical speculations and practical mathematical proposal takes into consideration different covariate factors and is based not only on the theoretical consideration that drove to "Gepts thricompartimental equation" concept, but would like to considers the aid of "allometry" growth pharmacological laws and equations and insert the concepts in a sort of "Quantic Pharmacology" new research pathway.

We want to argue if the way we look at such a complex approach is correct, and if it could be applicable, and better defines and use novel data to improve the "Gepts" equation related to the neonatal-paediatric-elderly age range.

Keywords: Target Controlled Infusion; Pediatric TCI; allometry laws; Pediatric allometry covariates; Pediatric quantic algorithm;

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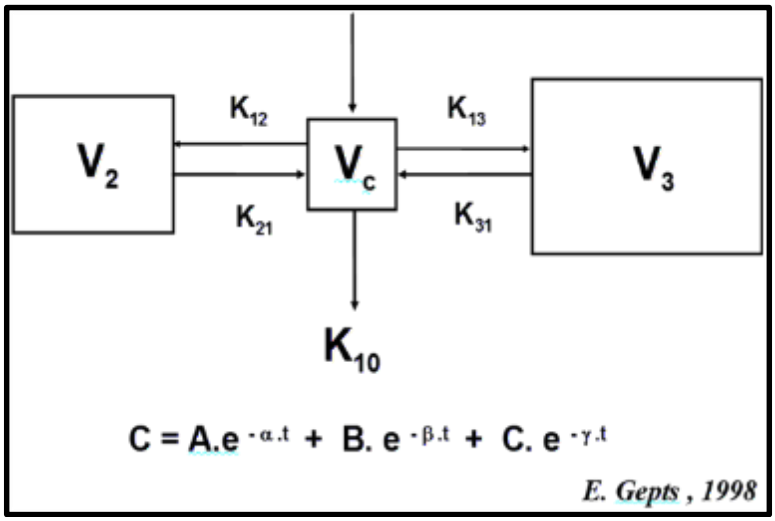
1. Introduction

1.1. Pediatric Target Controlled Infusion (TCI)

Target controlled infusion (TCI) systems are based on the theoretical pharmacological compartmental equilibrium concept in a thricompartimental set up for the use in dedicated pumps driving a presented anaesthetic drugs delivery and their titration during anaesthesia.[1]

The algorithm that defines the third "theoretical" compartment is based on the "Gepts Equation". This algorithm defines many covariables involved in the anaesthetic drug changes in the organism after a bolus dose is injected followed by a continuous infusion. The objective is to introduce the exact amount of drug that gives anaesthesiologists a predefined anaesthetic level with a good approximation (from 15 to 20 % or, hopefully, less than 6% of variation from the theoretical value) [2] [3]



$C = A.e^{-\alpha.t} + B.e^{-\beta.t} + C.e^{-\gamma.t}$

Figure 1 Gepts Thricompartimental Equation

This mathematical structured graphic figure expresses an algorithm equation where:

- *C= drug concentration after bolus injection*
- *T= Time lapse after drug injection*
- *A.B.C. = "Coefficients"; compartmental drug concentration (Co = A+B+C at "O" time).*
- *α,β,γ ="Hybrid Rate Constants". They are expressions of the drug exponential slope in each drug*
- *e= log10*

- Vc-V2-V3 = Compartments:
- Vc= central compartment
- V2=rapid or superficial compartment
- V3=remote or deep compartment (theoretical compartment; at equilibration time it considers the K"0" elimination constant as the half time elimination drug at the Biophase. In reale time.) [4]

It adds to the dynamics elimination and equilibrations constants [Fig.2] Fig.3]:

- K10 = central compartment elimination constant
- K12-K13-K21-K31 intercompartimental equilibration constants.
- K "0" constant has been found by Shafer and Varvel and is specific for each drug.

This type of algorithm works very well upon "pharmacodynamic-pharmacokinetic" studies that involve adults or children weighting more than 30 kg. [4] [5]

It is difficult to adapt these studies in paediatric patients, especially neonates, but also in elderly patients, due to the lack of many valuable, required and necessary covariates in the Gepts equation algorithm.

Here we propose the use of different pharmacological variables and covariate factors for our patients' setting.

Hybrid Rate Constants for α, β, γ derived drug slope curve needs to be changed and recalculated taking into consideration allometry pharmacological growth curve laws and parameters.

Our aim is to rewrite and propose a new third theoretical compartment algorithm.

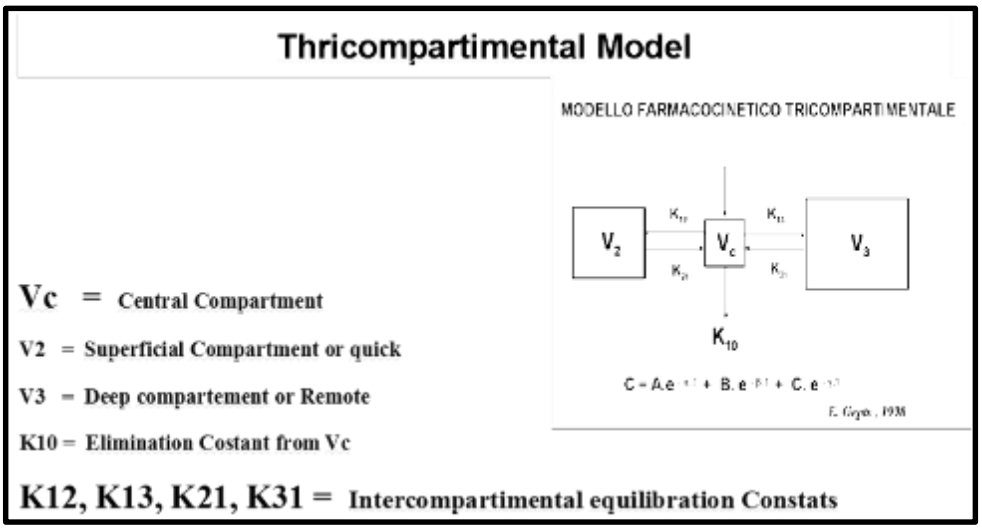


Figure 2 Thricompartimental Model

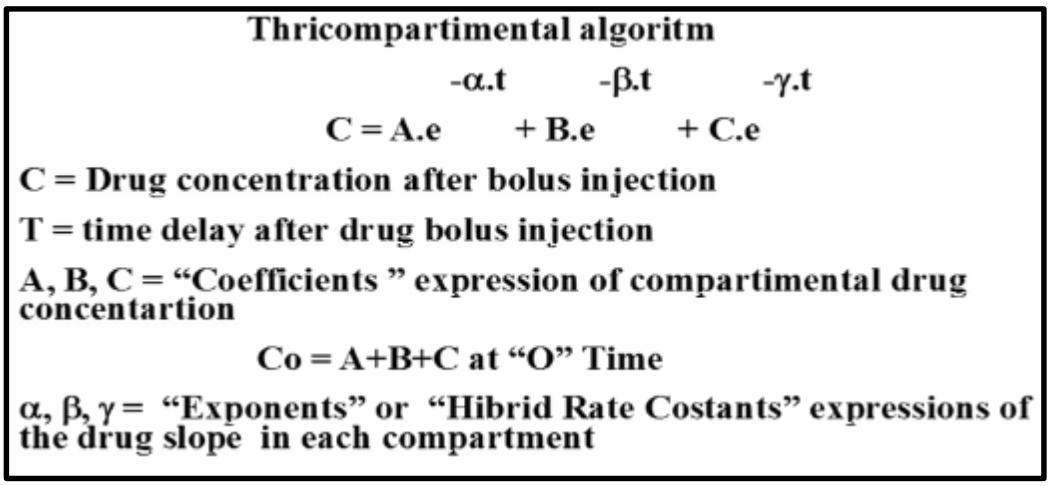


Figure 3 Thricompartimental algoritm

In a second step the algorithm will be validated *in vitro* using a drug PK/PD pharmacological simulation program, and finally we will confirm the statistical probity of the new software applying the statistical validation mode of performances Errors and Absolute Performances errors. Thus, in a secure way, the program will be validated *in vivo* in our patient cohorts previously described.

The "Pedfusor" PK/PD pediatric variables had been used in pediatric anaesthesia procedures until now. (Fig 4)

Comparison of the original Marsh, Short, Paedfusor and final Schüttler pharmacokinetic variables

	Marsh (adult)	Marsh (paediatric)	Short	Paedfusor (20 kg)	Schüttler (20 kg, 5 yr)
Vc (ml kg–1)	228	343	432	458	384
K10 (min–1)	0.119	0.1	0.0967	0.062	0.073
K12 (min–1)	0.112	0.0855	0.1431	0.114	0.135
K13 (min–1)	0.042	0.021	0.0392	0.042	0.06
K21 (min–1)	0.055	0.033	0.1092	0.055	0.05
K31 (min–1)	0.0033	0.0033	0.0049	0.0033	0.00174

Figure 4 Pedfusor propofol pharmacokinetic variables [6]

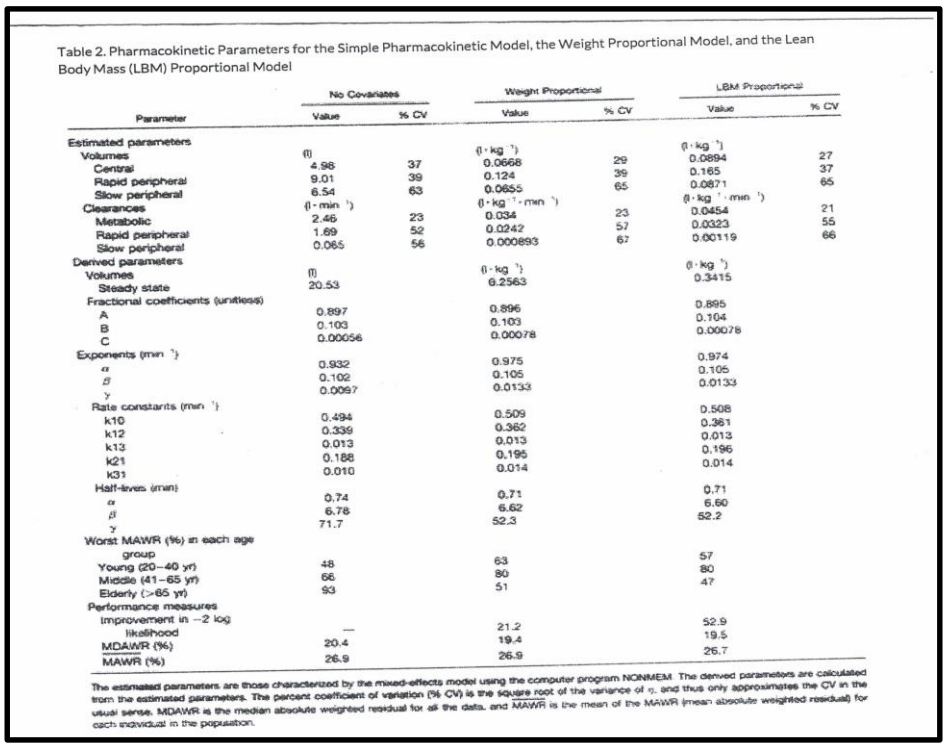


Table 2. Pharmacokinetic Parameters for the Simple Pharmacokinetic Model, the Weight Proportional Model, and the Lean Body Mass (LBM) Proportional Model

Parameter	No Covariates Value	No Covariates % CV	Weight Proportional Value	Weight Proportional % CV	LBM Proportional Value	LBM Proportional % CV
Estimated parameters						
Volumes	(l)		(l · kg $^{-1}$)		(l · kg $^{-1}$)	
Central	4.98	37	0.0668	29	0.0894	27
Rapid peripheral	9.01	39	0.124	39	0.165	37
Slow peripheral	6.54	63	0.0655	65	0.0871	65
Clearances	(l · min $^{-1}$)		(l · kg $^{-1}$ · min $^{-1}$)		(l · kg $^{-1}$ · min $^{-1}$)	
Metabolic	2.46	23	0.034	23	0.0454	21
Rapid peripheral	1.69	52	0.0242	57	0.0323	55
Slow peripheral	0.065	56	0.000893	67	0.00119	66
Derived parameters						
Volumes	(l)		(l · kg $^{-1}$)		(l · kg $^{-1}$)	
Steady state	20.53		0.2563		0.3415	
Fractional coefficients (unitless)						
A	0.897		0.896		0.895	
B	0.103		0.103		0.104	
C	0.00056		0.00078		0.00078	
Exponents (min $^{-1}$)						
α	0.932		0.975		0.974	
β	0.102		0.105		0.105	
γ	0.0097		0.0133		0.0133	
Rate constants (min $^{-1}$)						
k10	0.494		0.509		0.508	
k12	0.339		0.362		0.361	
k13	0.013		0.013		0.013	
k21	0.188		0.195		0.196	
k31	0.010		0.014		0.014	
Half-lives (min)						
α	0.74		0.71		0.71	
β	6.78		6.62		6.60	
γ	71.7		52.3		52.2	
Worst MAWR (%) in each age group						
Young (20–40 yr)	48		63		57	
Middle (41–65 yr)	66		80		80	
Elderly (>65 yr)	93		51		47	
Performance measures						
Improvement in −2 log likelihood	—		21.2		52.9	
MDAWR (%)	20.4		19.4		19.5	
MAWR (%)	26.9		26.9		26.7	

The estimated parameters are those characterized by the mixed-effects model using the computer program NONMEM. The derived parameters are calculated from the estimated parameters. The percent coefficient of variation (% CV) is the square root of the variance of η, and thus only approximates the CV in the usual sense. MDAWR is the median absolute weighted residual for all the data, and MAWR is the mean of the MAWR (mean absolute weighted residual) for each individual in the population.

Figure 5 Minto Pedfusor Pharmacokinetics [4]

Also Minto's alfentanil PK/PD values, as shown in Fig 5 , and Kataria's PK/PD expecially for ketamine Pedfusor driven administrations in pediatrics had been used (Fig 7)

As already said this application of differents pharmacokinetics-pharmacodynamics variable settled in Pedfusor program or in any other anesthetic drugs infusional device in my personal opinion is not complete in terms of scientific speculation and accuracy of the effective amount of administered drug to a patient that must be considered as a "Rapid Cells Dynamics Growth System" as we must consider a neonate , an infant, a toddler, either than in a "Rapid Cells Death System" as we consider elderly patients [1] [2] [3] [4].

Many authors recognize that it is acceptable only if we take as a postulate that in anaesthetic conduct, variation within the 20% of physiological data are to be considered acceptable.

My concern is about the concept that, in nature, and at in our case at biophase during anaesthesia, we can consider it acceptable in a "Static System" or "Long Term Cells Developmental System" as it has to be considered a mean age adult patient weighing and aging in a range from 30 kgs to 70 years must be considered [8][9] [10] [11].

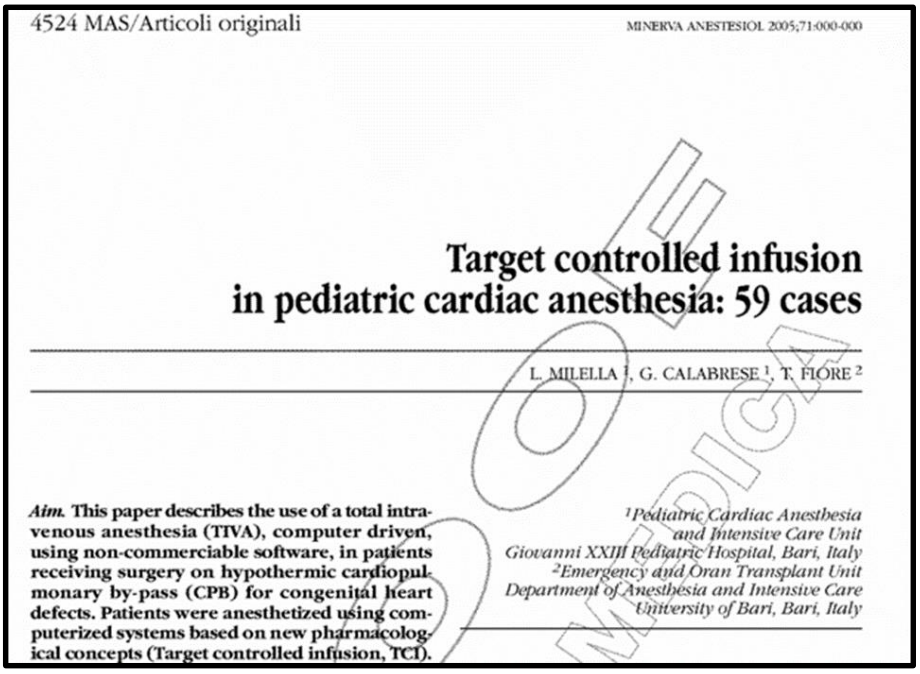
This opinion came in my scientific speculations since a personal author practical first application of a sperimental pediatric TCI was applied routinarely in pediatric patients starting in 1995 by the author and Prof Gavin NGC Kenny in Glasgow [12].

The author worked on data coming from almost 30 cardiac procedures and other general anaesthesia procedures.

Then, this sperimental process was continued in Italy for a few years [13] [14] [15] [16], but was discontinued for personal health problems.

The analysis of data showed that using the experimental TCI system (Anesthesia Technology Ltd-New Forest Farm-Walshford-wetherby_LS22 5JJ- UK; in our availability from 1997- Autorized Application from Italian National Research Center--CNR) programmed with 12 PK/PD drugs variables and a applicability range from "0" age and 100 years age, and "1" kg and "150" kgs , in a correct way , adapting the filling up bolus infusion to the clinical condition of the patient and adapting the target titrate to the correct surgical matching time there were optimal results in terms of hypnosis, cardiovascular parameters stability and reprise of spontaneous breathing [14] [15] [16].

In terms of statistical attendance and standard deviation, performance errors and absolute performance errors were calculated and the system showed a deviation from baseline in data over-prediction and under-prediction not more than 6% of variations from the baselines, that obviously is a much better value respect at the acceptable 20% of variations as acceptable value changes from baseline [14] [15] [16] [17].



4524 MAS/Articoli originali

MINERVA ANESTESIOL 2005;71:000-000

Target controlled infusion in pediatric cardiac anesthesia: 59 cases

L. MILELLA [1], G. CALABRESE [1], T. FIORE [2]

Aim. This paper describes the use of a total intravenous anesthesia (TIVA), computer driven, using non-commerciable software, in patients receiving surgery on hypothermic cardiopulmonary by-pass (CPB) for congenital heart defects. Patients were anesthetized using computerized systems based on new pharmacological concepts (Target controlled infusion, TCI).

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[2]*Emergency and Oran Transplant Unit Department of Anesthesia and Intensive Care University of Bari, Bari, Italy*

Figure 6 Never published data [17]

At this point a few explanation words about Reference [17] are compulsory.

Figure 6 shows the first printed page of a manuscript submitted for review by the author (and alt.), to Minerva Anestesiologica EDS in October 2003. This manuscript has been never reviewed until July 2005, without explanation even neither there was any response to legal letters requiring a formal position from EDS about the manuscript.

In the end, the "galley proof" after acceptation for publications were mailed to the author by EDS in July 2005, as you can see in fig 6, but in the meanwhile Absalom, Lal, Kenny published a paper showing most recent pedfusor application data in pediatric cardiac surgery and cardiac catheterization laboratory procedures, with the unaceptable consequence that author's data had become obsolete.

The author's decision was not to publish the article very early and pioneer data because before they had been already presented at different congress lectures; this can be controlled trough observation of data analysis written in presented reference [13] [14] [15] [16].

KATARIA

Kataria 5	Marsh 21 and Gepts 22	Parameter	Paedfusor 23	Short 85	Schuttler 79	Rigby-Jones 24	Murat 86	Saint Maurice 87	Coppens 49
10.4	4.66	V1 (L)	9.16	8.64	7.68	11.68	20.6	14.44	3.48
20.2	9.28	V2 (L)	18.96	10.8	20.74	26.68	19.4	35.6	4.68
164	58.04	V3 (L)	116.58	69.4	284.82	225.86	121.74	188	19.02
0.66	0.542	CL1 (L/min)	0.568	0.836	0.56	0.444	0.98	0.62	0.76
1.16	0.51	CL2 (L/min)	1.044	1.22	1.036	0.32	1.34	1.24	2.04
0.62	0.192	CL3 (L/min)	0.384	0.34	0.46	0.268	0.4	0.22	0.66

Figure 7 Kataria Pedfusor Pharmacokinetics [7]

Furthermore, according with subsequent application of anaesthetic procedure applying TIVA in the age from 2005 and 2021 performed in premature babies, infants, toddlers, convinced that the early years impression that Pedfusor and related infusional pumps using pharmacokinetics-pharmacodinamic models constructed by the author already proposed was inadequate to give to pediatric patients a correct anaesthesia level from many points of view [18] [19] [20] [21] [22].

Data analysis from these procedures confirmed us that there was not enough correlation between age, weight, target level of anaesthetic drugs [18] [19][20] and we were having the impression that the less was weighing the patients and was the patient aged the more amount of drug was required for a correct anaesthesia level, controlled with Neural analysis system (ANI) Bispectral Index (BIS) and cerebral saturation levels and O_2 consumption Near Infrared Spettroscopy (NIRS) [20][21] [22].

Thus, was speculated that we had to split up the verified application of TIVA and TIVA_TCI performed until that moment related to normal pharmacological evaluation to new pharmacokinetic-pharmacodynamic covariate describing the evolution of the anaesthetic drugs in a "Dynamic Rapid Cells Growth or Rapid Cells Death System", from a "Static Cells Growth System".

Our decision was to try to change the covariate for the less 30 kgs using new pharmacological approach and a sort of Quantistic Pharmacology [22] [23].

According with other authors [23][25] [26] [27] we were convinced that Allometric Pharmacological variable could work better and a correct scaling pharmacokinetic-pharmacodynamic approach could be found even for anaesthetic procedures in very rapid changing organism.

But the scaling program presented from these authors, in our opinion, was not complete, and more variables must be inserted in the program to define the correct scaling of working of a" Dynamic Rapid Cells Growth System".[28] [29] [30] [31]

The aim of our work is to construct a new Thricompartimental Equation utilizing allometry Scale Laws and different covariate factors than GEPTS ones. Patient cohorts will include neonates (0 to 6 month), toddlers (6 months to 2 years of age) and paediatric patients (2 to 5 years of age), weighing 0/2 kg to 30 kg.

The new Vc-V2 pharmacological compartments and the theoretical V3 compartment must be constructed and developed applying different pharmacological concepts, including quantum cellular physiology applicability to very fast cell growth, metabolic power and organ function.

In nature we have two types of cells with a very rapid growth rate: cancer cells and cells of premature newborns and neonates in the first order, toddlers in second order. In addition, elderly cells display a similar pattern in terms of growth rate since their functionality decreases very rapidly over time although an increase in their number is not observed. Thus, the use of our new algorithm will also be evaluated in anaesthetic procedures in elderly patients.

We will verify the feasibility of our new algorithm using theoretical "K" constants and novel covariates.

The algorithm will then be validated "in vitro" (simulating Pharmacological Program Application) in our patient cohorts previously described.

Finally a statistical probity of the new software will be proved with simulation program.

1.2. Allometry

Allometry is a term to describe the nonlinear relationship between the size and the function of an organ at different age timepoints (fig 8):

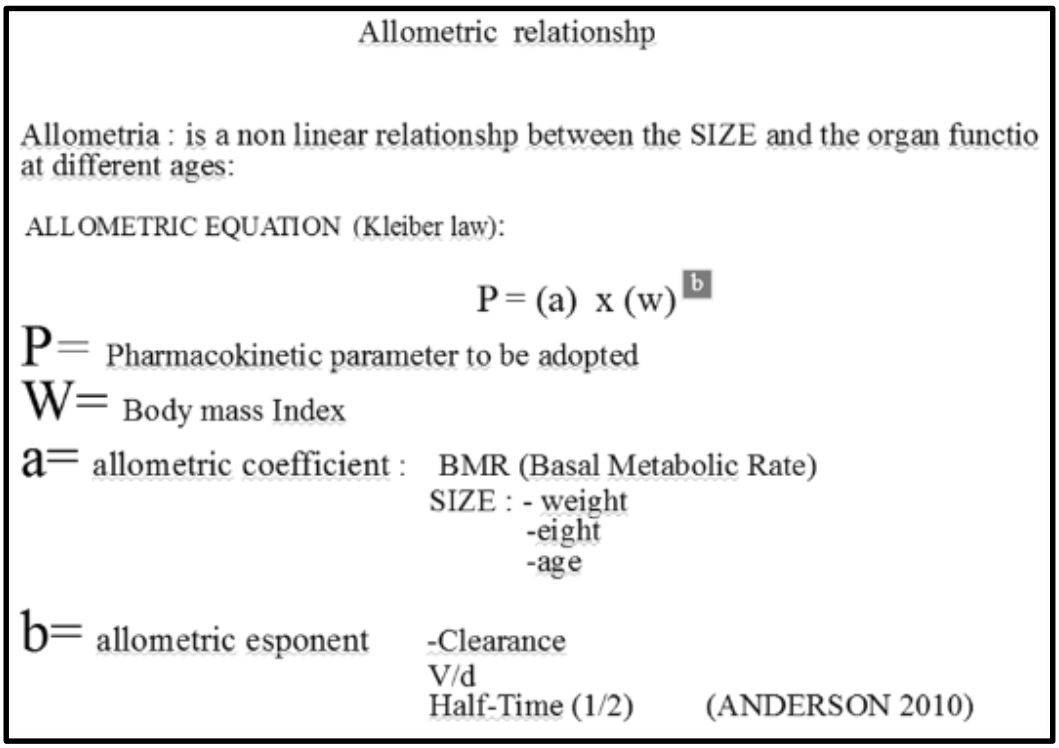


Figure 8 Kleiber Laws Descriptive Approach [23] [24]

This is a very simple definition of allometry, but it opens up into a broad array of relations between the organic metabolic rate and what concerns the maturation of the organs appointed to define functional parameters in vivo.

It is no longer just a matter of weight, age, height, drugs action to define the control of PK-PD, but also a more complex process which involves many others covariates, the theoretical development of organic function and its application to anaesthetic drugs control.

Knowing the amount of drug to be administered to the patient is no longer sufficient to obtain a result. Many other factors need to be considered including the peculiarity of neonatal cellular growth and maturation over time, drug changes in the body, the amount of drug needed for a site effect, how it is removed from the biophase and the time needed to be cleared out.

Briefly, the definition of a correct distribution value is mandatory in order to reach the desired target using a theoretical algorithm that defines new equilibration constants at the biophase.

Hence, we aim to define a new theoretical biophase.

2. Material and methods

2.1. Developmental Points-sections 1 to 8

Covariates that will be pointed out considered for a new equation algorithm calculation are described in this paragraph.

2.1.1. Kleiber laws (1932)

Kleiber law considered the need of a more accurate PK-PD parameter in order to define the body size in a not conformistic way. Its mathemathical formula expresses this new vision.

$$P = (a) * (w)b$$

- P = Pharmacokinetic parameter to be define and adopted
- W = Body mass index

2.1.2. Clearance (Pharmacokinetic-pharmacodynamic of the drug in use = K"0" at Biophase

2.1.3. V/d (Distribution volume)

2.1.4. Rapid Growth Organ Maturation

2.1.5. Organ Function

2.1.6. Half-Time (1/2)

We will consider the Hughes Context sensitive and not the D50. The slope curve is a component of the thricompartimental equation.

2.1.7. Body Fat/Body Proteins

2.1.8. Temperature and Calorimetric Dispersion Coefficient

2.2. Kleiber Allometric growth coefficient definition

Allometry variations as a function of Body Dimension [23] [24] [25] [26] [27] [28] [29] [30] [31]

Figure 9 shows how, as per definition of allometry relation with weight, height, maturation, in biology there is not a direct correlation between dimension and growth of an organism, neither between body weight and organ maturation expecially in newborn and neonates.

These dynamics are very impedimental in the research of a standard algorithm, in terms of driven pharmacodynamic and pharmacokinetic pump program setting, to apply at dynamic and rapid body growth, and rapid cells changing system

But, nevertheless, there is a direct correlation between a progress (y) to dimension (x) if we consider the presence of a Regression Coefficient that defines an "Allometry Costant" (b) only when b = 1.

This assumption defines a direct relationship between body weight and organ maturation when b ≠1.

This last dynamic defines that we are in presence of a direct Allometric Correlation and not an Isometric Relationship.

This correlation is directly related to the composition of the Dynamic System we are defining and from the scaling coefficient identified by Kleiber Laws: [24] [25] [26]

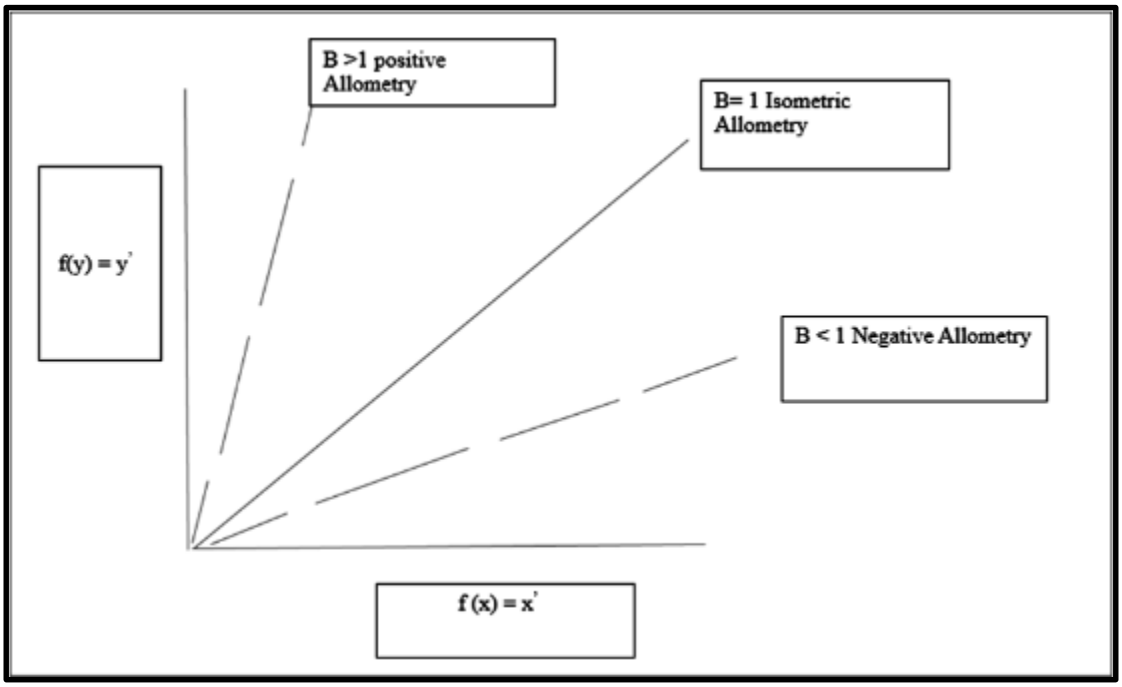


Figure 9 Allometry Ergonomic Pattern

If we analyze this postulate step by step we will define:

---Value of scaling coefficient:

Allometric relationshp

Allometria : is a non linear relationshp between the SIZE and the organ functio at different ages:

ALLOMETRIC EQUATION (Kleiber law):

$$P = (a) \times (w)^{b}$$

P= Pharmacokinetic parameter to be adopted

W= Body mass Index

a= allometric coefficient : BMR (Basal Metabolic Rate)
SIZE : - weight
-eight
-age

b= allometric esponent -Clearance
V/d
Half-Time (1/2) (ANDERSON 2010)

$$Y = (\alpha + bx)$$

2.3. BMR (Basal Metabolic Rate)

(Not linear relationship)

$$\text{Size} = \left\{ \begin{matrix} \text{a) Height} \\ \text{b) Function} - \text{ age} \\ \text{c) Weight} \end{matrix} \right\} \quad \text{SIZE/FUNCTION}$$

This coefficient (a) is a definition of Metabolic Power/Body Mass Index related to organ function:

$$\text{Kleiber Law} = \frac{\text{Metabolic Power}^{[24]}}{\text{Cells Mass}}$$

$P = B\ x\ M\ ¾$

B = Taxonomy constant related to species: $\begin{cases} Neonate \\ Elderly \end{cases}$

M = Species Mass

It is defined as **y=** a * Body Mass **(PWR)**

Kleiber: y = t * Metabolic Power = PWR = ¾ BMI

W = Body Mass Index (BMI)

- Metabolic Power Law = y(x)= $a.x^{(k)}$

$$\begin{cases} a = \text{proportionality constant} \\ k = \text{power law exponent} \end{cases} \qquad log\ Y(x) = log\ (a) + K log\ (x)$$

Scale Invariance: $y(cx) = a(ck)^K = c^k y^{(x)}$

As per its definition allometry represents the relationship among attributes of a living system.

This relationship is expressed as a Power law: the metabolic rate scales to the ¾ power of the mass [25] [26][28] [29] [30] [31].

-PWR = ¾ or ¼

This process can also be related to **Ontogenesis** which represents the evolutive changes that occur in an organism since birth:

A = exponential type growth

B= deceleration until a complete saturation of the system

- *Initial organization phase*
- *Initial exponential growth phase*
- *Saturation phase (decelerating phase or redaction of the earn) due to the increasing of density of the system*

$\frac{dl}{dt} = \alpha l - \beta l2 \rightarrow \frac{dm}{dt} = \alpha ma - \beta m$

This is the expression of the mass growth of an organism (Von Bartalannffy Law)

a and b are *indeterminate exponents* and depend on the type of species observed.

According to Kleiber the power needed for the mass growth is related as follows:

$$P = \Sigma \begin{cases} P - \text{deputed to manage the already existing organ cells} \\ P - \text{deputed to construct the others cell of the organ cells} \end{cases}$$

P = Metabolic Power$Pb = Bc + Ec \frac{dm}{dt}$

$$Pb = Bc\,(nmc);\ m = nmc$$

Ec = energy required to construct a single cell with **mass/mc**

N= total number of cells constituting the total mass "m"

P = Metabolic Power

Follows:

$$\frac{dm}{dt} = \alpha m3/4 - Bm;\ \alpha = \frac{B0ma}{Ec};\ \beta = \frac{Bc}{Ec}$$

$$\text{Saturation Mass} = M = \frac{dm}{dt} = 0 \rightarrow \left(\frac{B0mc}{Bc}\right)4$$

If we consider the mass incremental time we have:

$$M(t) = M\,[4\sqrt{\frac{m"0"}{M}}a^{-\mathrm{T}/\tau 1} + 1 - c^{-t/\tau 1}$$

$$1 = \frac{4Ec}{Bc}$$

In mammals it is equal to:

$$Ec \backsimeq 2{,}1\ x\ 10\ -5\ ;\ mc = 3{,}10\ x\ 10\ -9\ g\ ;\ a = 0{,}25\ \frac{8^{-1/4}}{day}\ ;\ B0 = 1{,}9\ x\ 10\ -2w$$

If we want to express the equation as a not dimensional curve it looks like:

$$2 = \frac{m}{M}\ ;\ \tau = \frac{t}{\tau 1}\ t\ ;\ \tau = \text{duration in time (days)}$$

When we consider Basal Metabolism we drive:

Basal Metabolism (metabolic rate) = B

$$B = kM\,\gamma$$

The evolution equation considers:

B(M) = allometry coefficient 1 and non ¾

But we must also consider the temperature of the system that means: [29]

$$B(-M,T)\ \alpha\ M^{¾}\ a^{-Ei/kt}$$

Where:

Ei = Process activation energy

We must consider the relationship between embryonic mass, temperature and evolution time

T = Absolute temperature

$$4^{t}\sqrt{m} = 4\_; \quad \frac{\alpha(T)}{\mathrm{A(T)}} = \alpha\ \frac{(T_0)\exp(-\mathrm{E}T_0^1)}{\mathrm{K}T_0^2}; \quad T_0^1 = \frac{T}{1+\mathrm{T/T}_0}$$

T_0 = freezing point of water as reference temperature. In our algorithm we will use a "T range" between 35 and 37 C° degrees scaling of 0,1 degrees interval.

Table 1 Metabolic rate in adults and neonate organs (3.5 kg-70 kg)

Organs	Weight (kg)	Adults			Neonates		
		MR/24h kJ(kcal)	MR/kg/24h kJ(kcal)	% total MR	Wt (kg)	MR/24h kJ(kcal)	% total MR
Liver	1.6	2018 (482)	1261 (301)	27	0.14	177 (42)	20
Brain	1.4	1414 (338)	1010 (241)	19	0.35	354 (84)	44
Heart	0.32	512 (122)	1600 (382)	7	0.02	32 (8)	4
Kidney	0.29	783 (187)	2700 (645)	10	0.024	65 (15)	7
Muscles	30.00	1356 (324)	45 (11)	18	0.8	37 (9)	5
Others body components							
Total	70.00	7530 (1800)	108 (26)	100	3.5	750 (180)	100

(Holliday 1982)[32]

BMI is the very first complicated data to consider in this age population.

We must approach to the Weight/Height curve from a different point of view, adding other variables and dividing it in male data and female data.

When utilizing allometry PK-PD laws it is compulsory to consider the Kleiber concept of SIZE. (Section 1)

2.4. Clearance

When considering drug clearance from the Kleiber laws point of view we need to take into account the continuous dynamic organ maturation process and organ function.

Maturation and organ function are strictly correlated.

The Hill model best describes the maturation curve and the maturation process:[33]

$$MF = PMA^{Hill}\ MF = \frac{1}{1} + \left[\frac{PMA}{TM_{50}}\right] \rightarrow TM^{Hill} + PMA_{50}^{Hill}$$

TM_{50} is maturation half-time;

Hill coefficient relates to the slope of the maturation profile

$$MF = PMA^{Hill}\ MF = \frac{1}{(1)} + \left[\frac{PMA}{TM_{50}}\right]\ ; \rightarrow TM^{Hill} + PMA^{Hill}$$

$$MF = MF = \frac{1}{(1)} + \delta\left[\frac{PMA}{TM_{50}}\right]^{-Hill\ 1/8}$$

This is equation defines an asymmetric organ development.

It is related to the function of Cytochrome P450.

- **Tanner-Whitehose Growth Percentile Curves**

Tanner-Whitehouse Growth Percentile Curve is based on: 1) Weight and Age; 2) Weight and Height. (Length) needs to be considered in order to integrate the BMI and the metabolic power relationship to the clearance and slope decay curve of the anesthetic drugs [34] [35] [36].

PK-PD in neonates depends on SIZE, Organ Maturation and Organ Function

-SIZE

$$P = \begin{cases} -\text{Organ maturation} \\ -\text{ Organ Function} \end{cases}$$

P in adult is equal to P= Pstd x Fsize x MF x OF

In this way we can introduce a new concept af calculating DRUG CLEARANCE considering different SIZE EXPRESSION (as for Kleiber definition) [40] [41] [42] [43] [44] [45] [46] [47] [48] [49]

Adults. $CL = CL\ std\ \frac{x(W)^{¾}}{70}$

This is the renal elimination of a drug:

$GFR = 121\ nL\ /min/\ 70\ kg$

$TM50 = 47{,}7\ nl/min/70$

We must substitute neonatal PMA in weeks to adult's 70/kg value

GFR at 1 year of age is 90% of adults while in neonates at 40 weeks of age GFR is equal to:

$GFR = PWR = 0{,}632\ nL/min/PMA$

It is strictly dependent on the Creatinine Production Rate (CPR).

In accordance with the Hill equation, we reconstruct a sigmoidal PMA curve showing that clearance at 54,6 weeks of age is equal to 50% of the real value.

Hill coefficient is equal to 3,83

We also consider that albumin levels become normal after 5 months of age and albumin legand levels become normal at 1 year of age and the elimination coefficient follows as:

- K = 0,33 in premature and neonates
- K = 0,45 in term infants to 30 days of age
- K = 0,45 1-12 months of age
- K = 0,7 13-21-months

In the end, if adult standard value (std) is constant, we must consider different parameters for neonate and pediatric patients due to the different growth curve in compliance with the Tanner-Whitehouse curve for weight(W), Age (A), Length (L) and sex (male-female).

This is easily understandable because we postulated that we are in presence of a "PMA"

According with a mathematical practical equation development we describe clearance calculation in different ages and weight as for:

$$\text{Neonatal male } (0-6 \text{ months}) \text{ CL} = \text{CL}\frac{W}{A}+\frac{\text{W}}{\text{L}}\ x\ \left\{\frac{W}{(\text{Percentile Growth Curve Male})}\right\}^{(1)}$$

$$\text{Neonatal female } (0-6 \text{ months}) \text{ CL} = \text{CL}\frac{W}{A}+\frac{\text{W}}{\text{L}}\ x\ \left\{\frac{W}{(\text{Percentile Growth Curve Female})}\right\}^{(1)}$$

The Kleiber coefficient for this age is 1 and not ¾ due to the immaturity of neonatal organs deputed to the clearance of the drug (Liver; Kidney)

$$\text{Pediatric male } (6 \text{ ms}-2 \text{ years}) \text{ CL} = \text{CL}\frac{W}{A}+\frac{\text{W}}{\text{L}}\ x\ \left\{\frac{W}{(\text{Percentile Growth Curve Male})}\right\}^{(3/4)}$$

$$\text{Pediatric female } (6 \text{ ms}-2 \text{ years}) \text{ CL} = \text{CL}\frac{W}{A}+\frac{\text{W}}{\text{L}}\ x\ \left\{\frac{W}{(\text{Percentile Growth Curve Female})}\right\}^{(3/4)}$$

$$\text{Pediatric male } (2 \text{ years}-5 \text{ years}) \text{ CL} = \text{CL}\frac{W}{A}+\frac{\text{W}}{\text{L}}\ x\ \left\{\frac{W}{(\text{Percentile Growth Curve Male})}\right\}^{(3/4)}$$

0

$$\text{Pediatric female } (2 \text{ years}-5 \text{ years}) \text{ CL} = \text{CL}\frac{W}{A}+\frac{\text{W}}{\text{L}}\ x\ \left\{\frac{W}{(\text{Percentile Growth Curve Female})}\right\}^{(3/4)}$$

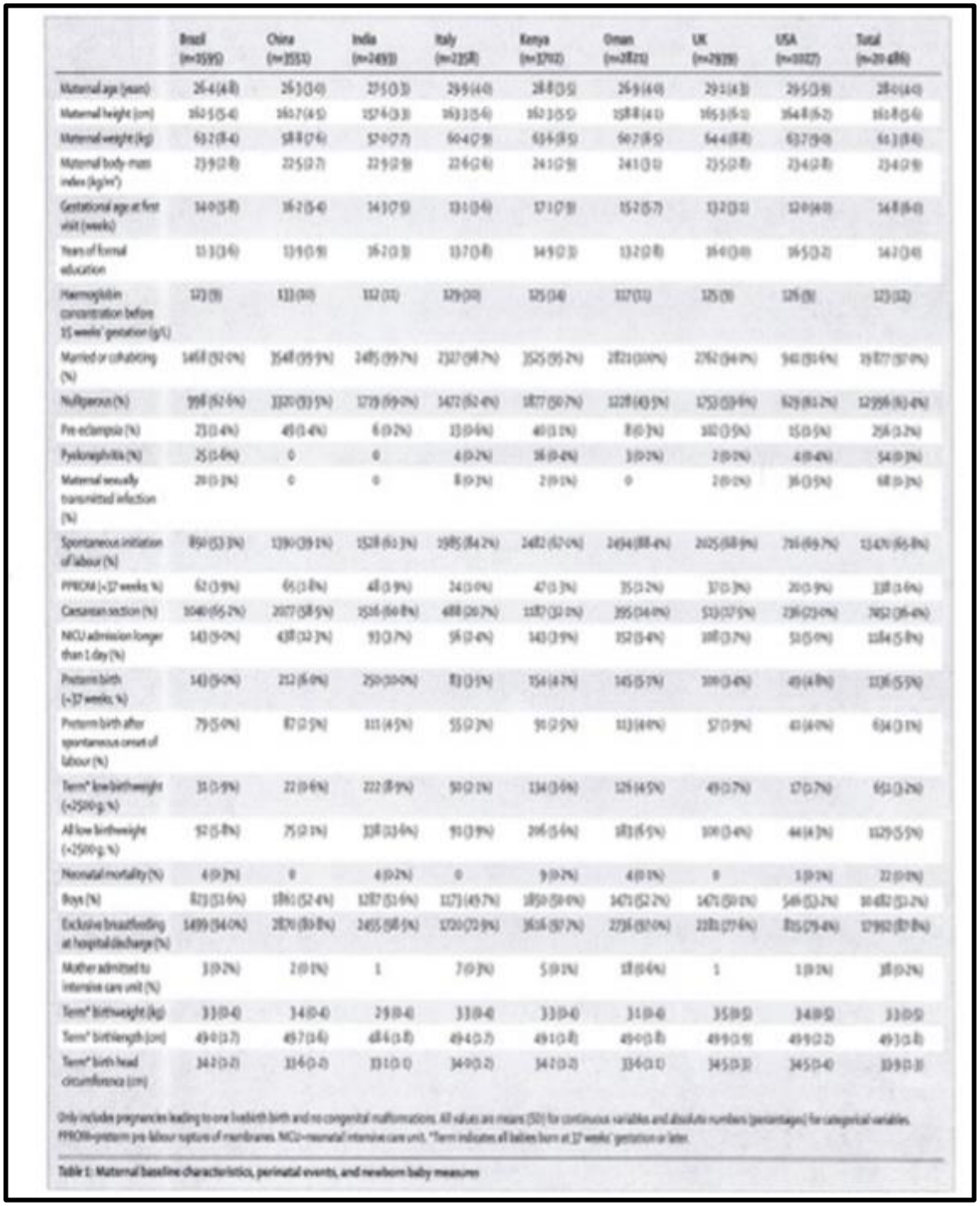
$$\text{Pediatric} = (25 \text{ kg}-30\text{Kg})\frac{\text{CL}}{70}\ \text{CL stdvx } (\text{W})^{3/4}$$

A very interesting study about population gender differences in the Percentile Growth curve has been developed and applied It is the "International standards for newborn weight, length, and head circumference by gestational age and sex: the newborn Cross-sectional Study for the Intergrowth-21 Project" -Josè villar, Lelia Cheick Ismail, Cesar G victoria et alt; *for the 21thcentury INTERGROWTH-21-the lancet vol 384 september 6 2014* [49]

It seems to be more accurate especially in terms of racial and gender differences but it is more complicated to transfer its enormous amount of data into the software algorithm

This can be easily verified if we analyze Tables 8-9-10.

--- 44 weeks of age as cut-off represents another limit for its use in our model. Thus, the Tanner-Whitehose percentile curve represents the best choice for our new algorithm.

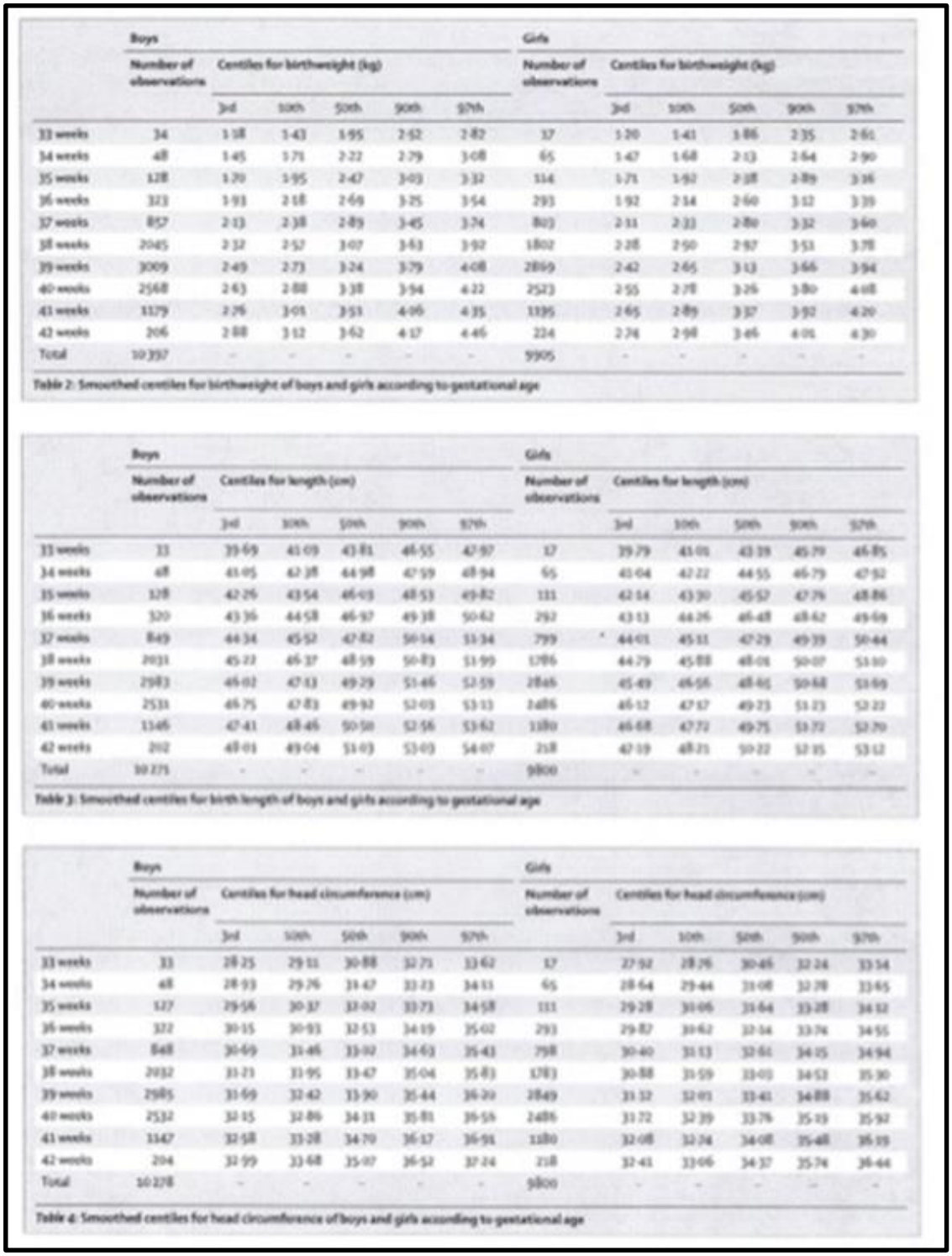


	Brazil (n=5595)	China (n=3551)	India (n=2493)	Italy (n=2358)	Kenya (n=3702)	Oman (n=2823)	UK (n=2979)	USA (n=1037)	Total (n=20 486)
Maternal age (years)	26·4 (6·0)	26·3 (5·0)	27·5 (5·3)	29·9 (4·0)	26·8 (5·5)	26·9 (4·0)	29·1 (4·3)	29·5 (5·9)	28·0 (4·4)
Maternal height (cm)	160·5 (5·4)	160·7 (4·5)	157·4 (5·3)	163·3 (5·4)	160·2 (5·5)	158·8 (4·1)	165·3 (5·1)	164·8 (6·2)	161·8 (5·6)
Maternal weight (kg)	63·2 (13·4)	58·8 (7·6)	57·0 (7·7)	60·4 (7·9)	63·6 (13·5)	56·7 (8·5)	64·4 (13·8)	63·7 (14·0)	61·1 (11·4)
Maternal body-mass index (kg/m²)	23·9 (2·8)	22·5 (2·7)	22·9 (2·9)	22·6 (2·6)	24·1 (2·9)	24·1 (3·1)	23·5 (2·8)	23·4 (2·8)	23·4 (2·9)
Gestational age at first visit (weeks)	14·9 (5·8)	16·2 (5·4)	14·1 (7·1)	13·1 (3·6)	17·1 (7·3)	15·2 (5·7)	13·2 (3·1)	12·9 (4·0)	14·8 (6·0)
Years of formal education	11·3 (3·6)	13·9 (3·5)	16·2 (3·3)	13·7 (3·8)	14·9 (3·3)	13·2 (3·8)	16·4 (3·0)	16·5 (3·2)	14·1 (3·4)
Haemoglobin concentration before 15 weeks' gestation (g/L)	123 (13)	133 (10)	112 (11)	129 (10)	125 (14)	117 (11)	125 (13)	126 (13)	123 (12)
Married or cohabiting (%)	5468 (97·8%)	3548 (99·9%)	2485 (99·7%)	2327 (98·7%)	3525 (95·2%)	2821 (100%)	2762 (94·9%)	940 (91·6%)	19 877 (97·9%)
Nulliparous (%)	2398 (42·6%)	1320 (37·5%)	1278 (51·9%)	1477 (62·9%)	1877 (50·7%)	1228 (43·5%)	1753 (59·4%)	629 (61·2%)	12 956 (63·4%)
Pre-eclampsia (%)	23 (0·4%)	49 (1·4%)	6 (0·2%)	13 (0·6%)	40 (1·1%)	8 (0·3%)	102 (3·5%)	15 (1·5%)	256 (1·2%)
Pyelonephritis (%)	25 (0·4%)	0	0	4 (0·2%)	16 (0·4%)	3 (0·1%)	2 (0·1%)	4 (0·4%)	54 (0·3%)
Maternal sexually transmitted infection (%)	20 (0·3%)	0	0	8 (0·3%)	2 (0·1%)	0	2 (0·1%)	36 (3·5%)	68 (0·3%)
Spontaneous initiation of labour (%)	850 (15·3%)	1396 (39·9%)	1528 (61·3%)	1985 (84·2%)	2482 (67·0%)	2494 (88·4%)	2025 (68·9%)	716 (69·7%)	13 476 (65·8%)
PPROM (<37 weeks, %)	62 (1·9%)	65 (1·8%)	48 (1·9%)	24 (1·0%)	47 (1·3%)	35 (1·2%)	37 (1·3%)	20 (1·9%)	338 (1·6%)
Caesarean section (%)	1040 (55·2%)	2077 (58·5%)	1516 (60·8%)	488 (20·7%)	1187 (32·1%)	995 (34·9%)	533 (17·5%)	236 (23·0%)	7492 (36·4%)
NICU admission longer than 1 day (%)	143 (5·0%)	438 (12·3%)	93 (3·7%)	56 (2·4%)	140 (3·9%)	152 (5·4%)	108 (3·7%)	51 (5·0%)	1264 (5·8%)
Preterm birth (<37 weeks, %)	143 (5·0%)	212 (6·0%)	250 (10·0%)	83 (3·5%)	154 (4·3%)	145 (5·1%)	109 (3·4%)	49 (4·8%)	1136 (5·5%)
Preterm birth after spontaneous onset of labour (%)	79 (5·0%)	87 (2·5%)	111 (4·5%)	55 (2·3%)	91 (2·5%)	113 (4·0%)	57 (1·9%)	43 (4·0%)	636 (3·1%)
Term* low birthweight (<2500 g, %)	31 (1·9%)	22 (0·6%)	222 (8·9%)	50 (2·1%)	134 (3·6%)	125 (4·5%)	49 (1·7%)	17 (1·7%)	651 (3·2%)
All low birthweight (<2500 g, %)	92 (5·8%)	75 (2·1%)	338 (13·6%)	93 (3·9%)	296 (8·0%)	183 (6·5%)	109 (3·4%)	44 (4·3%)	1129 (5·5%)
Neonatal mortality (%)	6 (0·3%)	0	6 (0·2%)	0	9 (0·2%)	4 (0·1%)	0	3 (0·2%)	22 (0·1%)
Boys (%)	823 (51·6%)	1861 (52·4%)	1287 (51·6%)	1173 (49·7%)	1859 (50·6%)	1471 (52·2%)	1471 (50·1%)	549 (53·2%)	10 452 (51·2%)
Exclusive breastfeeding at hospital discharge (%)	1499 (34·0%)	2870 (80·8%)	2455 (98·5%)	1720 (72·9%)	3516 (97·7%)	2726 (97·0%)	2318 (77·6%)	815 (79·4%)	17 902 (87·8%)
Mother admitted to intensive care unit (%)	3 (0·2%)	2 (0·1%)	1	7 (0·3%)	5 (0·1%)	18 (0·6%)	1	1 (0·1%)	38 (0·2%)
Term* birthweight (kg)	3·3 (0·4)	3·4 (0·4)	2·9 (0·4)	3·3 (0·4)	3·3 (0·4)	3·1 (0·4)	3·5 (0·5)	3·4 (0·5)	3·3 (0·5)
Term* birthlength (cm)	49·4 (1·7)	49·7 (1·6)	48·4 (1·8)	49·4 (1·7)	49·1 (1·8)	49·4 (1·8)	49·9 (1·9)	49·9 (2·1)	49·3 (1·8)
Term* birth head circumference (cm)	34·2 (1·2)	33·6 (1·2)	33·1 (1·3)	34·9 (1·2)	34·1 (1·2)	33·6 (1·1)	34·5 (1·3)	34·5 (1·4)	33·9 (1·3)

Only includes pregnancies leading to one liveborn birth and no congenital malformations. All values are means (SD) for continuous variables and absolute numbers (percentages) for categorical variables. PPROM=preterm pre-labour rupture of membranes. NICU=neonatal intensive care unit. *Term indicates all babies born at 37 weeks' gestation or later.

Table 1: Maternal baseline characteristics, perinatal events, and newborn baby measures

Figure 10 Oxford Intergrowth gender variables tables 1



	Boys						Girls					
	Number of observations	Centiles for birthweight (kg)					Number of observations	Centiles for birthweight (kg)				
		3rd	10th	50th	90th	97th		3rd	10th	50th	90th	97th
33 weeks	34	1·58	1·43	1·95	2·52	2·82	37	1·20	1·41	1·86	2·35	2·61
34 weeks	48	1·45	1·71	2·22	2·79	3·08	65	1·47	1·68	2·13	2·64	2·90
35 weeks	128	1·70	1·95	2·47	3·03	3·32	114	1·71	1·92	2·38	2·89	3·16
36 weeks	323	1·93	2·18	2·69	3·25	3·54	293	1·92	2·14	2·60	3·12	3·39
37 weeks	857	2·13	2·38	2·89	3·45	3·74	803	2·11	2·33	2·80	3·32	3·60
38 weeks	2045	2·32	2·57	3·07	3·63	3·92	1802	2·28	2·50	2·97	3·51	3·78
39 weeks	3009	2·49	2·73	3·24	3·79	4·08	2859	2·42	2·65	3·13	3·66	3·94
40 weeks	2568	2·63	2·88	3·38	3·94	4·22	2523	2·55	2·78	3·26	3·80	4·08
41 weeks	1379	2·76	3·01	3·51	4·06	4·35	1335	2·65	2·89	3·37	3·92	4·20
42 weeks	206	2·88	3·12	3·62	4·17	4·46	224	2·74	2·98	3·46	4·01	4·30
Total	10 397	-	-	-	-	-	9905	-	-	-	-	-

Table 2: Smoothed centiles for birthweight of boys and girls according to gestational age

	Boys						Girls					
	Number of observations	Centiles for length (cm)					Number of observations	Centiles for length (cm)				
		3rd	10th	50th	90th	97th		3rd	10th	50th	90th	97th
33 weeks	33	39·69	41·09	43·81	46·55	47·97	37	39·79	41·01	43·39	45·79	46·85
34 weeks	68	41·05	42·38	44·98	47·59	48·94	65	41·04	42·22	44·55	46·79	47·92
35 weeks	128	42·26	43·54	46·03	48·53	49·82	111	42·14	43·30	45·57	47·76	48·86
36 weeks	320	43·36	44·58	46·97	49·38	50·62	292	43·13	44·26	46·48	48·62	49·69
37 weeks	849	44·34	45·52	47·82	50·14	51·34	799	44·01	45·11	47·29	49·39	50·44
38 weeks	2031	45·22	46·37	48·59	50·83	51·99	1786	44·79	45·88	48·01	50·07	51·10
39 weeks	2983	46·02	47·13	49·29	51·46	52·59	2846	45·49	46·56	48·65	50·68	51·69
40 weeks	2531	46·75	47·83	49·92	52·03	53·13	2486	46·12	47·17	49·23	51·23	52·22
41 weeks	1346	47·41	48·46	50·50	52·56	53·62	1180	46·68	47·72	49·75	51·72	52·70
42 weeks	202	48·01	49·04	51·03	53·03	54·07	218	47·19	48·21	50·22	52·15	53·12
Total	10 275	-	-	-	-	-	9800	-	-	-	-	-

Table 3: Smoothed centiles for birth length of boys and girls according to gestational age

	Boys						Girls					
	Number of observations	Centiles for head circumference (cm)					Number of observations	Centiles for head circumference (cm)				
		3rd	10th	50th	90th	97th		3rd	10th	50th	90th	97th
33 weeks	33	28·25	29·11	30·88	32·71	33·62	37	27·92	28·76	30·45	32·24	33·14
34 weeks	68	28·93	29·76	31·47	33·23	34·11	65	28·64	29·44	31·08	32·78	33·65
35 weeks	127	29·56	30·37	32·02	33·73	34·58	111	29·28	30·06	31·64	33·28	34·12
36 weeks	322	30·15	30·93	32·53	34·19	35·02	293	29·87	30·62	32·14	33·74	34·55
37 weeks	848	30·69	31·46	33·02	34·63	35·43	798	30·40	31·13	32·61	34·15	34·94
38 weeks	2032	31·21	31·95	33·47	35·04	35·83	1783	30·88	31·59	33·03	34·52	35·30
39 weeks	2985	31·69	32·42	33·90	35·44	36·22	2849	31·32	32·01	33·41	34·88	35·62
40 weeks	2532	32·15	32·86	34·33	35·81	36·56	2486	31·72	32·39	33·76	35·19	35·92
41 weeks	1347	32·58	33·28	34·70	36·17	36·91	1180	32·08	32·74	34·08	35·48	36·19
42 weeks	204	32·99	33·68	35·07	36·52	37·24	218	32·41	33·06	34·37	35·74	36·44
Total	10 278	-	-	-	-	-	9800	-	-	-	-	-

Table 4: Smoothed centiles for head circumference of boys and girls according to gestational age

Figure 11 Oxford Intergrowth age variables tables 2

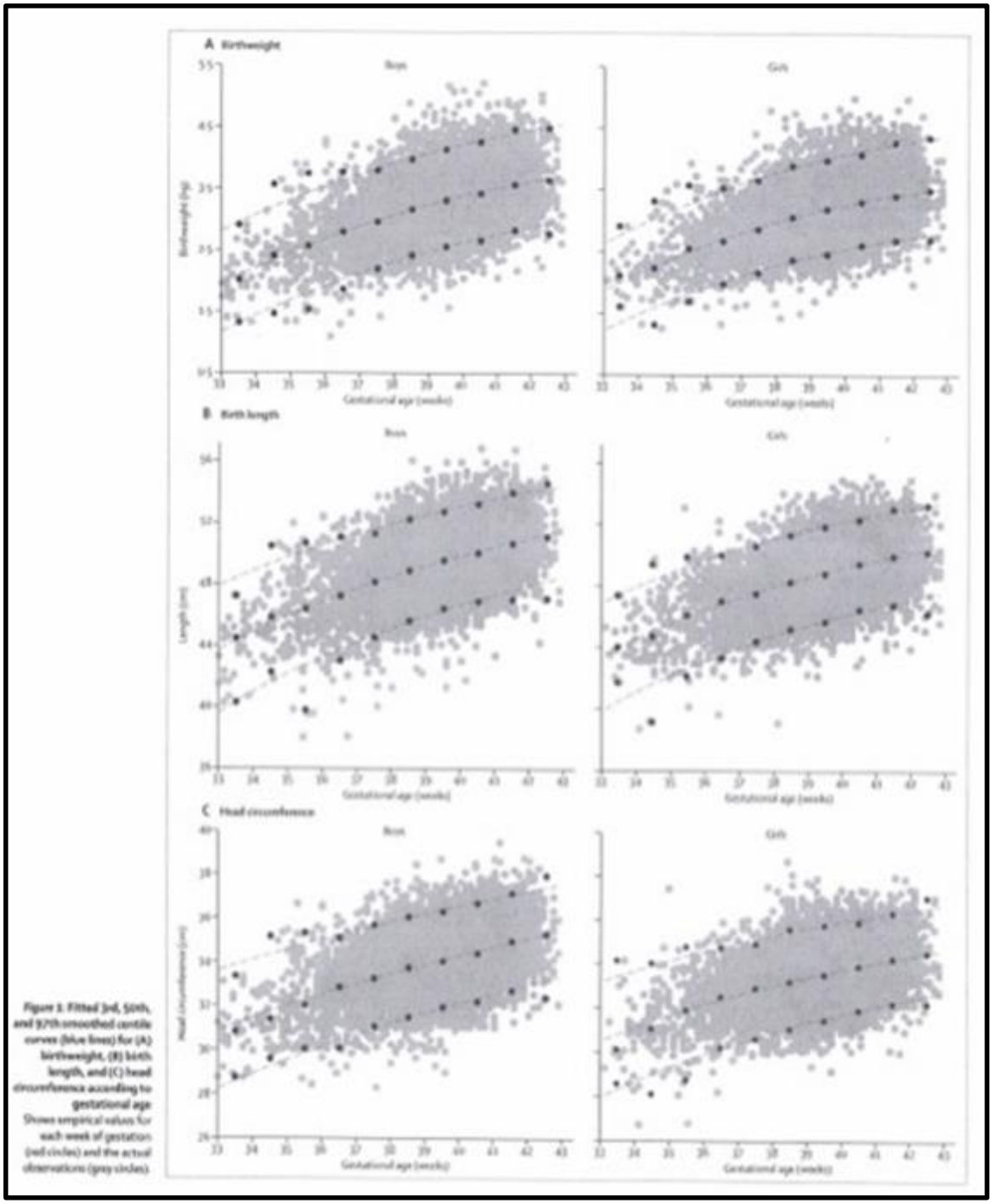


Figure 12 Oxford Intergrowth percentiles variables tables 3

New covariates that take into account not only weight and length but also the actual age of the neonate will be added to the normal clearance equation, following an allometry PK-PD pathway to practically build up a new thricompartimental equation.

The real problem is that following the value results relate to gender constitution variability as expression of living locality, obliges to introduce an enormous number of covariates in the TCI program

This is too much difficult to do and this is why we too apply the formulas to Tanner-Whitehouse Percentile Growth Index..

2.4.1. Practical mathematical equation and Clearnce variability at different ages and weight as a consequence of allometric variables applications

The clearance of general anesthetic drugs is defined from the relationship between all the allometry covariates:

Neonatal male$(0-6$ months$)\mathrm{CL} = 0{,}632 \ \frac{3{,}3}{50}+\frac{3{,}3}{0{,}4}\ x\ \left\{\frac{3{,}3}{0{,}5}\right\}^{(1)}$

$$\mathrm{CL} = \mathrm{CL} = 0{,}632 \ \frac{3{,}3}{50}+\frac{3{,}3}{0{,}4}\ x\ \left\{\frac{3{,}3}{0{,}5}\right\}^{(1)} = 0{,}632 \text{ x } 1{,}036 = \mathbf{0{,}654\ mL/min/m2}$$

Neonatal female$(0-6$ months$)\mathrm{CL} = 0{,}632 \ \frac{3{,}7}{50}+\frac{3{,}7}{0{,}4}\ x\ \left\{\frac{3{,}7}{0{,}5}\right\}^{(1)}$

$$\mathrm{CL} = \mathrm{CL} = 0{,}632 \ \frac{3{,}7}{50}+\frac{3{,}7}{0{,}4}\ x\ \left\{\frac{3{,}7}{0{,}5}\right\}^{(1)} = 0{,}14\ x\ 6{,}6 = 0{,}632 \text{ x } 0{,}858 = \mathbf{0{,}54\ mL/min/m2}$$

The Kleiber coefficient for this age is 1 and not ¾ due to the immaturity of neonatal organs deputed to the clearance of the drug (Liver; Kidney)

Pediatric male$(6$ ms $-$ 2 years$)\ \mathrm{CL} = 0{,}632 \ \frac{7{,}5}{85}+\frac{7{,}5}{1{,}4}\ x\ \left\{\frac{7{,}5}{0{,}5}\right\}^{(\frac{3}{4})}$

$$\mathrm{CL} = \mathrm{CL} = 0{,}632 \ \frac{7{,}5}{85}+\frac{7{,}5}{1{,}4}\ x\ \left\{\frac{7{,}5}{0{,}5}\right\}^{0{,}75} = 0{,}17\ x\ 11{,}12 = 0{,}632 \text{ x } 1{,}912 = \mathbf{1{,}208\ mL/min/m2}$$

Pediatric female$(6$ ms $-$ 2 years$)\ \mathrm{CL} = 0{,}632 \ \frac{9{,}4}{85}+\frac{9{,}4}{1{,}4}\ x\ \left\{\frac{9{,}4}{0{,}5}\right\}^{(\frac{3}{4})}$

$$\mathrm{CL} = \mathrm{CL} = 0{,}632 \ \frac{9{,}4}{85}+\frac{9{,}4}{1{,}4}\ x\ \left\{\frac{9{,}4}{0{,}5}\right\}^{0{,}75} = 0{,}217\ x\ 14{,}1 = 0{,}632 \text{ x } 3{,}05 = \mathbf{2{,}12\ mL/min/m2}$$

Pediatric male$(2$ years $-$ 5 years$)\ \mathrm{CL} = 0{,}632 \ \frac{12{,}4}{95}+\frac{12{,}4}{3{,}1}\ x\ \left\{\frac{12{,}4}{0{,}5}\right\}^{(0{,}75)}$

$$\mathrm{CL} = \mathrm{CL} = 0{,}632 \ \frac{12{,}4}{95}+\frac{12{,}4}{3{,}1}\ x\ \left\{\frac{12{,}4}{0{,}5}\right\}^{0{,}75} = 0{,}25\ x\ 18{,}6 = 0{,}632 \text{ x } 6{,}5 = \mathbf{2{,}9388\ mL/min/m2}$$

3Pediatric female$(2$ years $-$ 5 years$)\ \mathrm{CL} = 0{,}632 \ \frac{15{,}7}{95}+\frac{15{,}7}{3{,}1}\ x\ \left\{\frac{w}{0{,}5}\right\}^{(0{,}75)}$

$$\mathrm{CL} = \mathrm{CL} = 0{,}632 \ \frac{15{,}7}{95}+\frac{15{,}7}{3{,}1}\ x\ \left\{\frac{15{,}7}{0{,}5}\right\}^{0{,}75} = 0{,}32\ x\ 23{,}15 = 0{,}632 \text{ x } 7{,}40 = \mathbf{4{,}59\ mL/min/m^2}$$

$$\text{Pediatric } (25-30 \text{ Kg}) = \mathrm{CL} = 0{,}632 \ \frac{27{,}5}{122}+\frac{27{,}5}{10}\ x\ \frac{(27{,}5)^{0{,}75}}{0{,}5} = 3{,}2\ x\ 41{,}25 = 0{,}6732 \text{ x } 132 = \mathbf{83{,}42\ mL/min/m^2}$$

(Median height 122 cm; median weight 27,5 kg; mean Age 10; percentile mean value 0,5);

The principal objection to these equations is that "Drug Clearance "is not only related to renal elimination but many variables play an import role in the process:

Just for example if we consider the hepatic extraction and inactivation of a drug it has a very huge effect in the clearance process; the "Drug Extraction Ratio is very High. For propofol utilization in standard weighing patients it is 0,87 $^{+/-}$ 0.09 l/m^{-1}, but, nevertheless, it is strictly depended from and limited from the organ blood flow. (Bijorkman)

That is why we are strongly convinced that allometry exponents scaling concepts and program costruction in neonatal, pediatric and elderly patients has a more correct appliability for Renal, Hepatic,Biophase and distribution volume than classical pharmacological PK/PD covariates.(Chidambaran et Alt)

2.5. Distribution Volume (V/d)-Maturation-Organ Function [50] [51] [52][53] [54] [55] [56]

The V/D is defined as the amount of volume in which a drug is diluted and from which is removed starting immediately after the injection.

It defines an elimination rate constant named K"10" that is specific for each drug.

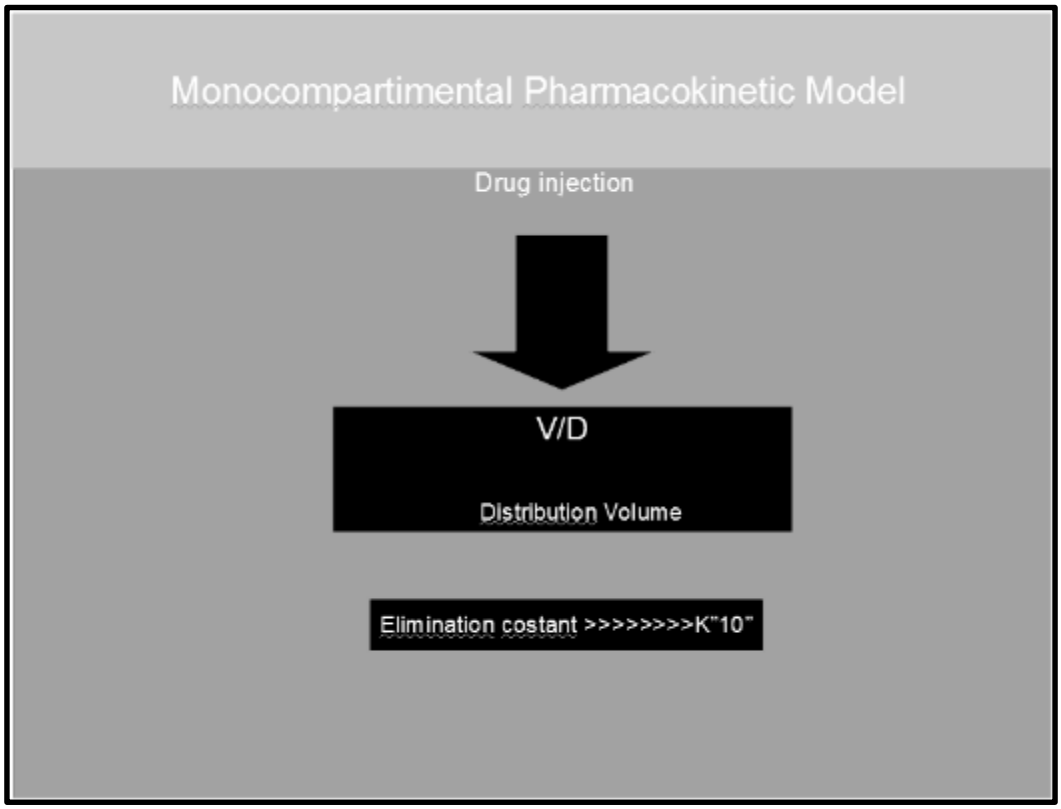


Figure 13 Monocompartmental Pharmacokinetic Model

The relationship between drug bolus and continuous infusion represents the basis of the volume of distribution in the plasma and at biophase.

It also depends on many covariate factors and needs to be reconsidered taking into account the pathway of each anesthetic drug from the point of view of concentration slope curve.

It is strictly related to K10; K"0"….K"n" constants.

V/d seems to be not sufficient anymore to define the distribution of the drug in the various compartments, especially at biophase. Therefore, the introduction of the concept of Therapeutic Drug Concentration which is a much more accurate value that takes into consideration changes in the drug effects and distribution pathways after a bolus injection immediately followed by continuous infusion.

The receptor-ligand binding also needs to be considered.

The Hill-Langmuir law describes the metabolic pathway of a drug, quantifying the ligand-receptor interaction. It is strictly related to the mass action law of Guldenberg-Waage [57] and the Michaelis –Menten [58] [59] equation.

Hill-Langmuir equation:

$$y = \frac{y\,max^{\alpha}}{C + x^{\alpha}}$$

Where:

- C0 system definition
- y = independent variable
- x = dipendent variable
- α = coefficient

This equation relates the drug concentration with its effect.

For example, if we consider the relationship between Hb and Po2 the equation looks like:

$$y1 = \frac{100\,K\,x^{\alpha}}{1 + K\,x^{\alpha}}$$

Where:

y = O2 percentage; x = po2; k-α = parameters

$$y2 = \lambda \frac{k_2 x^{2}}{1 + k_2 x^{2}} + (100 - \lambda)\frac{k1^{x}}{1 + k1^{x}}$$

Where:

y = O2 %; x = paO2 in mmHg; λ = Hb_2 %; (100-λ) ; k_1 and k_2 = Hill equilibration Constants

$$y3 = \sum_{r=1}^{n} \lambda r \frac{krx^{r}}{1 + kr^{r}} \text{ with } \sum_{r=1} \lambda r = 100;$$

For the practical application of these equations Michaeliss and Menten described a simple model as follows:

$$V = \frac{Vmax\,[S]}{Vmax\,[S]}$$

Where:

- V = initial velocity of reaction (mol/L/s)
- V_{max} = maximal reaction rate (mol/L/s)
- S = Substrate concentration (mol/L)
- K_m = 1/2 match concentration (mol/l)

Thus:

$$\mathbf{Y} = \frac{\mathbf{y\,max\,x^{\alpha}}}{\mathbf{c^{\alpha} + x^{\alpha}}}$$

x = V;

K_m = y,

$C = V_{max}$;

$Y_{max} = 1$;

$\alpha = S$

This equation describes a model of PK-PD drug effect related to a drug dose concentration. It is no longer considered as a number or a numeric point as Half time decay or T_{50} concentration but as a slope of exponential decay curve.

The curve describes a "Sigmoidal E_{max} Model"

$$E = \frac{E_{max}\, C^{\alpha}}{EC^{\alpha}50 + C^{\alpha}}$$

E = predicted effect of the drug

E_{max} = maximum effect of the drug

EC_{50} = ½ time effect

α = Hill Sigmoidal Effect

The Waage and Gulderberg law expresses the mass action defining a constant of dissociation at equilibrium called Kd.

$$Kd = \frac{[L/M]}{[LM]}$$

L; M; LM are the molar concentration of the drug.

Y = ratio of molecule that reached the receptor:

$$Y = \frac{[LM]}{[LM] + [L]}$$

If we substitute [LM] with Kd the equation looks like:

$$Y = \frac{[M]}{Kd + [M]}$$

Thus:

$$C = Kd^{1/\alpha}\alpha = 1$$

Furthermore, the mass equation at equilibrium is:

$$nL + R \underset{K2}{\overset{K1}{\rightleftarrows}} LnR$$

$$[LnR] = [Ro]^{k2}\, x\, [L]^n = [\, Ro\, x\, [L]^n\,]$$

$$[L]^n + Kd\,[L]^n + [K_A]^n$$

Where:

- L = ligand variable concentration
- R = Receptor - costant – (always > 1)

- [LnR] = ligand receptor complex
- [Ro]= receptor number (total concentration)
- [L] = total concentration of ligand
- K1= association constant
- K2 = dissociation constant

Kd $= \frac{K2}{K1}$ represents the equilibrium value between ligands and total complex legand-receptors

$[K_A]$ = ligand concentration at 50%; similar to $\alpha/2$, if n = 1 then n =Kd

N = Receptor site number.

This is called Receptor Occupation Theory which takes into consideration two of the receptor components and characteristics:

Signal recognition

Signal transduction

As pointed out earlier, the Hill sigmoidal curve of slope that considers the concentration-response relationship (E/C) needs to be translated into an operative model substituting E/C with LnR and Ro values.

Black and Leff in 1983 described an operative model of the receptor mechanism of action:

$$mA + mR + \varepsilon \underset{\leftarrow K2}{\overset{K1}{\rightarrow}} mAR + ARm^{E}$$

Where:

A = Agonist

R = receptor

ε = effector with great affinity for AR complex

m = AR complex, number of complex necessary to product an effect (Operational Slope Factor)

K1 and K2 = Associative and dissociative constants of receptor

K′1 and K′2= Associative and dissociative constants of receptor $= \frac{\text{Agonist}-\text{Receptor}}{\text{Effector complex}}$

AR = complex receptor activity

$AR_m{}^E$ = agonist receptor complex $= \frac{\text{Action}}{\text{Effect}}$

$$AR \underset{K'2}{\overset{K'1}{\rightleftarrows}} AR^{*}$$

This relationship takes into consideration the number of receptors that are able to develop an effect and it is named De Castillo –Katz law.[60] [61]

AR = active complex

AR* = inactive complex.

This is the concentration-effect relationship that is developed in the slope curve E/C with E/C AGONIST-CONCENTRATION SLOPE CURVE.

This relationship represents the cognitive status of the change in a drug effect; and the translation of a theory in practice

$$\frac{E}{C} = E = Emax \frac{C^n}{C^n + (Ec_{50})^n}$$

Where:

- C = concentration
- E= agonistic effect on the receptor
- E_{max} = maximal effect
- E_{c50} = half effect
- n= Hill Coefficient

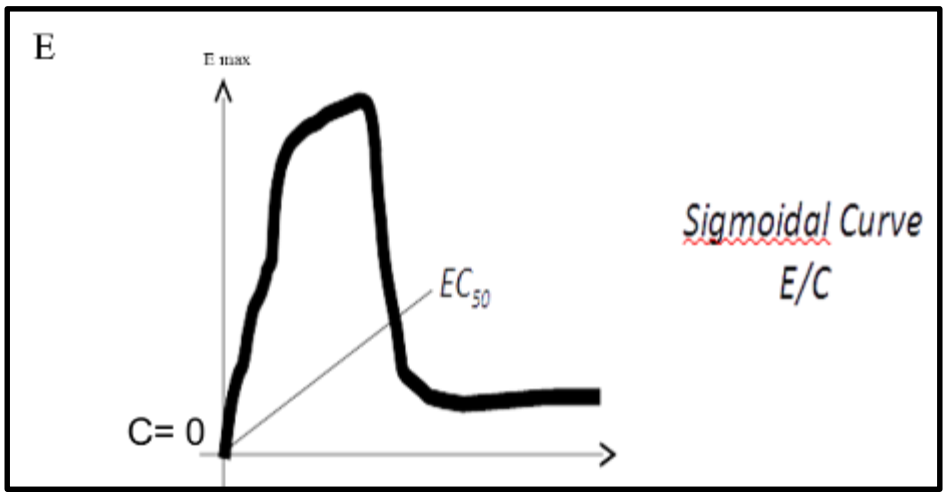


Figure 14 E/C curve

$E \neq 0$ e $C = 0$

That means: time ”0” - concentration”0”- effect “0” As per definition of the trhicompartimental equation.

When we want to develop a control over a biological activity it is advised to construct the E/C curve in a first instance and then to apply the Hill equation, thus developing a numerical applicability.

This is due to the Hill equation that can anticipate in a aprioristic way only the symmetric value of the concentration receptor–agonist (being the anesthetic drug the ligand acting drug at the receptor site).

It is compulsory to define it as a slope curve and the E/C slope curve best satisfies the conditions to create a new PK-PD model.

According with the Gulderberg-Waage mass action law,

when an equilibrium is reached the relationship between molar concentrations remains constant. (once the target point is reached the value remains constant as it is guided from the algorithm covariables data)

$$\mathbf{aA + bB} \underset{\mathbf{cC + dD}}{\rightleftharpoons}$$

$$K = \frac{[C]^c \times [D]^d}{[A]^a + [B]^b}$$

Maturation and organ function are strictly related.

The Hill model can describe the maturation curve and the maturation process:

$$MF = \frac{PMA^{Hill}}{TM_{50}{}^{Hill} + PMA^{Hill}}$$

TM_{50} is maturation half-time;

It is related to the function of Cytochrome P450

3. Discussion

3.1. Therapeutic Concentration and half-time in TCI programs and the Hysteresis concept component [62] [63] [64] [65] [66] [67] 68] [69] [70+ [71]

- When we consider a drug administration, expecially in case of anesthesia drugs, the pharmacological concepts related to concentration, distribution volume and clearance follows first and second PK/PD relations (Therapeutic Concentration)
- When there is a repetead bolus drug administration or a continuous infusion administration we can continue to applie first and second order PD/PK pharmacological concepts, but when we start an infusional regimen there is the beed to add the concept of drug elimination in time
- This process is called compensation and avoids the so called “No Valley Anestesia Phenomenon” and the “Awareness Phenomenon “during the “Lucid Time “interval due to patient thecnication matching the surgical procedure before surgery starting.
  - Therapeutic Concentration (TC) =Bolus dose/ V.d
  - INFUSION = Therapeutic Concentration x Clearance

This concepts, are not exhaustive of a correct drug administration. They expose the patient to: lack of drugs and or overdose of drug.

This is because we do not consider other factors acting on the drug during time after injections.

The need for a new PK/PD thierd orders pharmacological concept is required

And this is at the basis of TCI Idea.

- COMPENSATION (equilibration at V3 Theoretical Compartment)
- (TCI)

When considering such a speculation, the calculation of how the drug changes in the body after injection is far more important than the quantity thea is administered to reach a not predictable result (Target).

If we consider the Gepts theoretical compartment (V3) we need to consider that the distribution volume (V/d) value has to be completed with another covariate value according with the practical pharmacodynamic concept defined as ”Hysteresis”.

Hysteresis defines the amount of drug that effectively arrives at the biophase after a bolus injection and after an infusion.

This value does not represent the same value that we decide to give to the patients but it takes into account the consumption of the drug due to many clearance covariate actions previously described. (See figures 12 and 13)

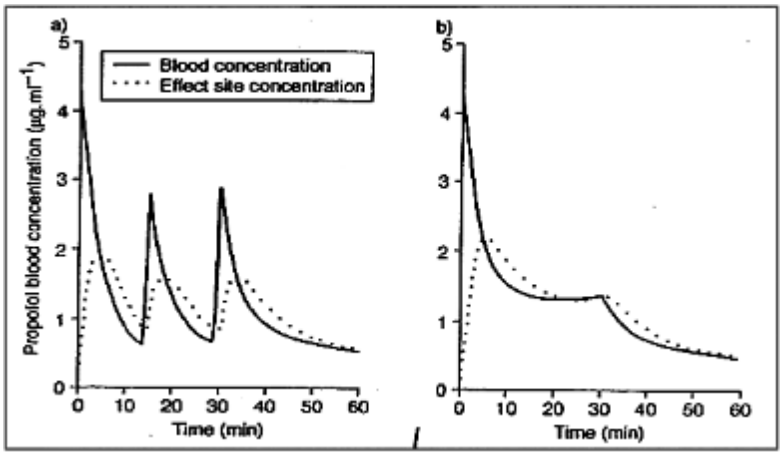


Figure 15 Drug consumption after bolus (E Gepts 1998)

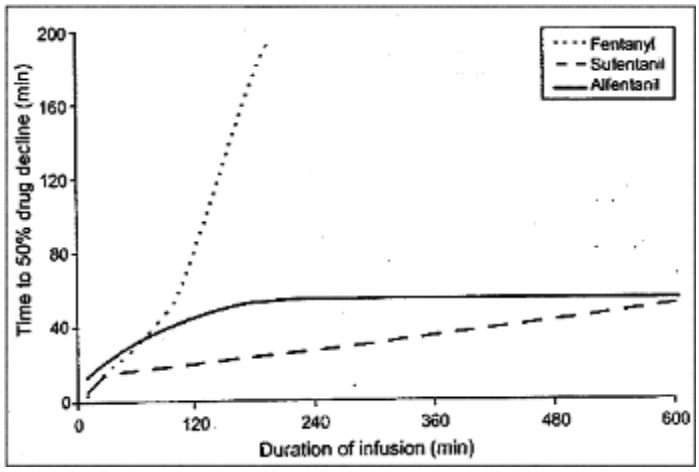


Figure 16 Drug consumption slope curve after infusion time delay (E Gepts: !998)

Consequently, the half time (D50) concept cannot be used to calculate the decay of the drug, whereas the slope curve represents the first step for a new pharmacokinetic- pharmacodynamics pathway as shown below.

Half-Time (1/2) new concept [72] [73] [74] [75] [76] [77]78] [79] [80] [81] [82] [83] [84]

Half-Time (1/2) is defined as the time that takes for the concentration of the drug to be reduced by 50% at its V/d.

Its number is no longer sufficient while the slope decay curve of the drug is needed and we must consider this slope as a value of each component of the area under the slope curve measured with a Fast Fourier Analysis.

We must build up an allometry theoretical concepts:

Hughes "Context Sensitive Half-Time" considers a slope curve for each drug. It defines the time required for the plasma drug concentration to decline by 50% after terminating each infusion.

Bailey "Mean Effect Time" considers the chance of a drug to produce a site effect, a statistical concept represented by the linear regression of the possibility for a drug to produce an effect: it can be considered the opposite of Context.

Varvel and Shafer "Effect Site Equilibration Time" is the "K0" value of elimination costant at biophase. It defines the amount of drug effectively eliminated at the biophase in real time. Being a theoretical value, it is necessary to evaluate it in vivo by analyzing the drug concentration.

Subsequently, a statistical analysis of the concentration must be performed using the calculation of Median Performance Errors and the Absolute Median Performances Errors: standard deviation of the value (MDPE) and its value (AMDPE) that must be less than 20% as until now accepted, but we can say that our aim is to demonstrate that applying new allometric concepts this variation is of 6% at most.

This is the simplest way to detect infusion errors.

$$\text{IE} = \frac{\text{Balance Volume} - \text{Ideal Volume}}{\text{Ideal Volume}} \; x\; 100$$

Practically:

$$\text{IE} > \text{MDPE} = \frac{\text{Cm} - \text{Ccalc}}{\text{CCalc}} \text{ x } 100$$

A further precisation must be done from the practical point of view:

If we consider all the speculation previously explicate, a scheme is required to reassume in a simplistic way how TCI works and how it represents a important change in anesthesia use of drug but in anesthetist approach to anesthesia.

Tackley formulated a very simple schema that defines both the questions:

It formulated a protocol that explains very quickly the TCI application philosophy and that works as follows:

Bolus

Elimination

Transfer

The so called “BET SCHEME”.

(Tackley 1999)

3.1.1. Body fat/Body Proteins [85] [86]

It is difficult to obtain the accurate value of Body Fat, body proteins and water in neonates and paediatric patients, especially when a disease occurs.

For anesthetic drugs we must consider different pharmacokinetics pathways depending from lipophilicity or idrofillicity of the drug, and also the protein bindings.

We believe that we need to consider a median ligand value for all drugs.

Two fat components are described in the body: Normal Fat Mass; Fat Free Mass.

Normal fat Mass (NFM)

NFM depends from:

NFM(Flat) = (W minus FFM)

Flat value is = 0,21

NFM (kg) = FFM + F (Flat)x (W-FFM)

$$\text{F}_{\text{size}} = \left\{\frac{\text{NFM}}{\text{Wstd}}\right\}^{\text{PWR}}$$

PWR equal to 1 or ¾ represents the drug clearance.

F_{size} is an allometric parameter that correlates in a not linear fashion NFM to PWR as NFM^{PWR} and is strictly related to the normal weight according with percentile tables.

We must consider NFM in accordance with the previously described clearance formulas, attributing NFM the supposed age, weight and length related value.

If F_{size} is equal to "0" we must insert in the algorithmic formula related to Body fat the FFM value. (0,21)

3.1.2. Fat Free Mass (FFM)

Fat Free Mass can be calculated utilizing weight and height (weight and length in neonates).

It is correlated to the PWR coefficient which is assumed to be 1 instead of ¾ in neonates as above mentioned.

$FFM= WHS_{max} \times H^2 \times [W/(WHS_{50} \times H^2 + W)]$

Male:

$WHS_{max} = 49,2\ Kg/m^2$

$WHS_{50} = 30,93\ kg/m^2$

Female:

$WHS_{max} = 37,99\ Kg/m^2$

$WHS_{50} = 35,98\ kg/m^2$

3.1.3. Body proteins

The value of body proteins is assumed to be normal or in a range that needs to be decided for each Tanner-Whitehouse curve. We also consider albumin levels normal after 5 months of age and albumin ligand levels normal at 1 year of age.

Albumin percentage levels and action power is set by age and sex as follows:

- K = 0,33 in premature and neonates
- K = 0,45 in term infants to 30 days of age
- K = 0,45 1-12 months of age
- K = 0,7 13-21-months

In addition, we must consider the total value of proteins as a standard value of 5 g/l.

3.1.4. Body Composition [87] [88] [89]

We can now define the body composition:

FFM is the value that practically correlates the structure to the function;

TWT is related to Height and Sex

NFWT = FFM +FFAT x (TWT-FFM)

Where: NFWT is the free water transport in the considered Dynamic System related to white and tannauser data (TWT)

$$F_{\text{size std70 kg}} = \frac{(\text{NFWT})^{3/4}}{(\text{NFWT}_{\text{std}})}$$

1 = (0-6 months)

¾ = (6 month -5 years)

$F_{\text{size std (kg)}} = \underline{(NFWT)}$

$$\text{Age } (NFWT_{std}) = \frac{\text{Weight}}{\text{Age}}$$

Whrere (3/4) scaling coefficetn relates equation to Kleiber Laws of "Rapid Growth Cell Dinamyc System")

3.2. Body Temperature and Calorimetric Dispersion: [90]

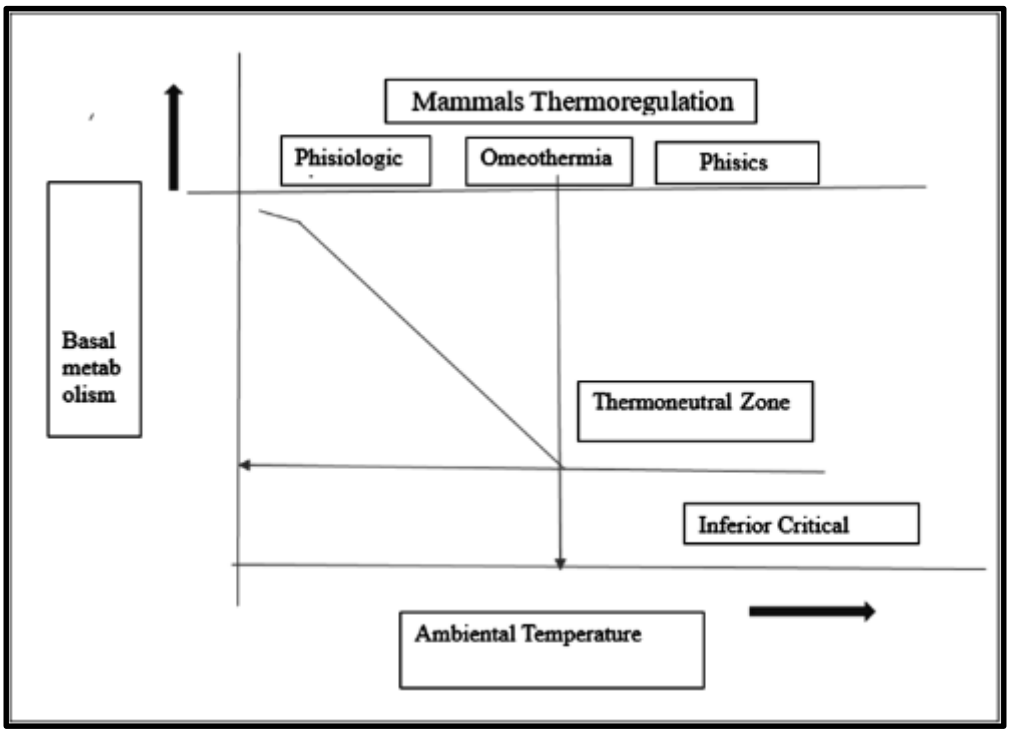


Figure 17 Mammals Thermoregulation

3.3. Thermoregulation

It well known that mammals spend a large part of their energy to keep stable body temperature.

Al the enzymes and catalytic systems leading to have an action require a range of temperature adequate to start and finalize it with a very low variation tolerance; you can see in figure 11 how to mateine omothermia is compulsory to mantein a correct basal metabolism, and how body functions are expressed at best in a so called thermoneutral zone.

Consistent change in this state, coming from ambiental temperature or uncorrected omeothermic sustaining process, can create problems.

But, it is acceptable that in very particular situations we can need to low down artificially temperature to a critical inferior zone, and sometimes overtake this zone.

Let's point out this speculation whit a practical example: we low down body temperature when we perform cardiac surgery, to reduce oxygen consumption in a situation of not correct oxygen delivery or disponibility.

An extreme position in this sense is applied in surgery performed, especially for congenital pediatric cardiac procedures, in deep "Hypothermic Circulatory Arrest" at 14-16 degrees of temperature with no heart beating, no lung breathing and no blood in the body.

This scenario, not in so extreme situations, obliges us to consider anesthetic drug changing from metabolic and receptorial action point of view. In our opinion when the cell cytoplasmatic passage from "sol status" to "gel status" is not reached, and it happens about at 23-24 Celsius degrees, a difference of three degrees is equal to 12 degree difference in changing metabolism and drug action. In order to consider this speculation very important, in our opinion it Is necessary we define, apply and insert a covariate for temperature mean variations in the algorithm and mathematic formula.

These two Parameters, (maximal temperature and minimal temperature), can be set as a continue slope range variation in Celsius degrees by 0, 1 slow down slope:

3.4. Celsius Degree range (34> Range <37)

In case of wider changes in body temperature we assume that changes are acceptable but the loop of changing target infusion is closed by anesthesiologist decision to increase or reduce infusion

3.4.1. "Point of view explicitation" by the author

In the last decade from 2010 ahead, many authors look after to pediatric TCI with concerns that the application of adult derived PK/PD/ of drugs was not enough correct, and most of them tried to apply new pharmacological concepts in order to better define why we called this process in this manuscript "Rapid Cells Growth Dynamic System" or" Dynamic Cells Rapid Death in elderly.

The researcher aim was try to create a more reliable program to perform Computer Driven Anesthesia in neonatal and Pediatric Patients but also in elderly patients [69] 70] [71] [72] [85]86] [87] [88] [89].

In my opinion the first step was to understand what identify as a Rapid Cells Growth Dynamic System, how many are there in humans, how it works but, I'm strongly convinced that the change should be greater than this. We must speculate about a new mathematical vision of matter functioning and developing in such a system that can't be studied using normal pharmacological application but, reasonably, has to be applied in a Quantic Mode, and with the term "Quantic" I refer to "Physics mathematical" definition of Quantistic Mechanical laws not only applied to infinitesimal atomic structures and laws, but also to every single system whose is impossible to exactly define in real time in absolute exact mode but only in terms of possibility of time, position and activity at is target.

The concept at the basis of this personal speculation is that in such a System we'll never have the perfect, definitive and defined data and result but we only can assume that there is a Probabilistic Result changing very quickly.

That the reason why I talk of "Quantic Pharmacological Definition of a new TCI program for pediatrics and elderly":

The rapid cell growth systems in nature are:

- Premature and neonate cells
- Low weight Low Age Neonate cells
- Infant cells
- Cancer and Tumoral cells
- Blood cells, but we must consider Blood as a tissue and a specific organ and not only a vehicle.

At the age of 70 the cells death is unarrestable, and this is because older patient's require a rapid Death cell Dynamic vision of their functional purpose.

- The first application with "Diprifusor" started in 2010 when Anderson realized that allometric scaling laws application to PK/PD could be realiable if not necessary to study pediatric TCI dedicated Programs.[23] [24]
- In 2011 Wa-Hu Yang et al. thought that it was not correct to apply adult TCI programs to pediatric patients. It studied 31 patients having TCI Diprifusor anesthesia, and he obtained an acceptable result in term of MPDE and AMPDA not overruling or underuling for more than 15 to 20%.[70]
- This acceptable result brought to the author that different program organized per gender was necessary for Chinese population and he applied is speculation to SLOG/-III-TCI system development.
- And this is what we already pointed out talking about the about Tanner-Whitehouse Percentile application or, much more difficult to do, the perspective to apply the INTERGROWT PROGRAM Percentile Growth Results.[35]

[36] [37]

- Is the pump functioning in a correct way? doe's the mechanical functioning of pump affects the amount of infusion altering the amount of drug? This question has been solved by Il Do et alt in 2019 [70] that demonstrate there was an acceptable deviation from expected dosage and funded amount of drug from point of view of a Median Performance Errors and absolute Median Pe4rformancies Errors that resulted in not more that 10% over or under prediction [69].

I want to remember that such analysis had already been done by author since 1997 and the value where established to be not more than 6% in Pedfusor program application [12] [13] [14] [15] [16] [17].

3.4.2. New thricompartimental diagram

We can say that not a great difference in the diagram of "Thricompartimental Gepts Equation" must be done but we need to expose he allometry pathway followed to construct the new "third compartment at biophase equilibrium" equation as follows:

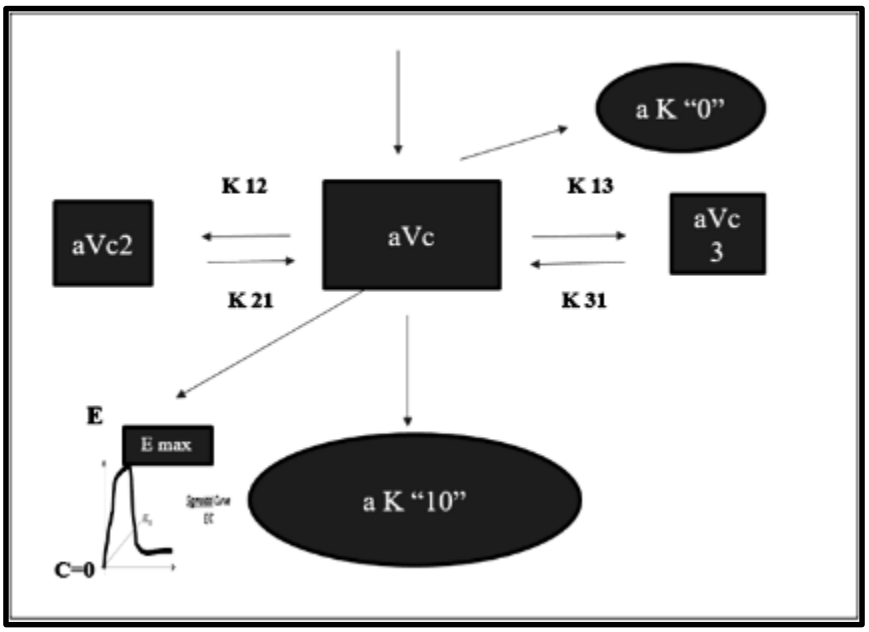


Figure 18 Sigmoidal Slope Curve and allometry Thricompartimental PK/PD Model

As a consequence of this assumption this diagram identifies:

- Vc-V2-V3 = Compartments:
  - Vc= central compartment
  - V2=rapid or superficial compartment
  - V3=remote or deep compartment (theoretical compartment; at equilibration time it considers the aK"0" elimination constant as the half time elimination drug at the Biophase. In real time.)
- aK10 = central compartment elimination constant
- K12-K13-K21-K31 intercompartimental equilibration constants.
- aK "0" constant that is a direct consequence of the allometric laws applications to PK/PD and requires confirmation *in vitro* and in vivo and leads to substitute the Shfafer and Varvel application data results and is also is specific for each drug.

The mathematical equation that results in the diagram formulation becomes:

$-\alpha t -\beta t -\gamma t$

$C= a A.e + aB.e + aC.e$

- C= drug concentration after bolus injection

- T= Time lapse after drug injection
- aA.aBa.aC. = "Allometric Coefficients"; compartmental drug concentration (Co =a A+aB+aC at "O" time).
- α,β,γ ="Hybrid Rate Constants". They are expressions of the drug exponential slope in each drug
- e= $\log_{10}$

In the end you can see the New Algorithm Diagram in fig 15.

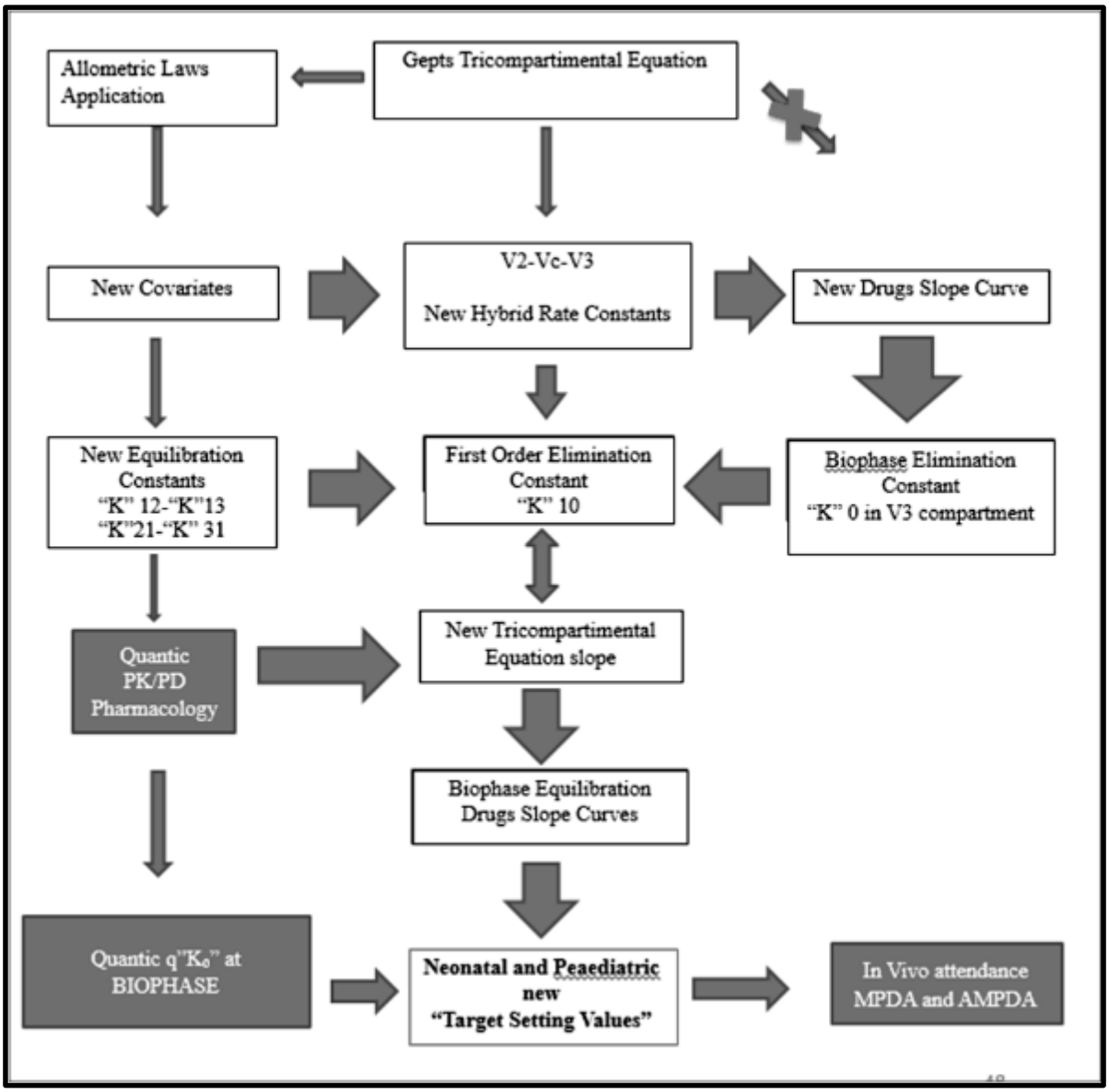


Figure 19 Algorithm Flow Diagram

4. Conclusion

This article is the first step of a program that aims to study a new "Pediatric TCI Program".

This first part has been dedicated to a mathematical explanation of new pharmacological biological application concepts expressed and new speculations about anesthesia in neonates, infants and elderly.

The Theorical Phisics and Nobel Prize in the late 80's, Richard Feynman, was used to say: "…It doesn't matter how beautiful your theory is, it doesn't matter how smart you are, if it doesn't agree with experiment , it is wrong……"

The aim of the author is to try to demonstrate his theory first in an "*in vitro*" sperimentation with the use of simulations PK/PD pharmacological programs, and then possibly reproduce it in "in vivo"

This is the reason why the author decided to divide his manuscript in two different parts.

Compliance with ethical standards

Acknowledgments

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Statement of conflict of interest

No Conflict of Interest.

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