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(REVIEW ARTICLE)

A new neonatal and paediatric TCI theory proposal. Second Part: Algorithm and software construction

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Abstract

The first aim of the second part of the new PK/PD software for TCI Driven Anaesthesia in Neonates, Toddlers and Elderly patients' "Proposal", is to give details about the speculative theoretical and applicative mathematical pathways that led us to develop a new algorithm and build up the applicative software.

The second aim is to explain and demonstrate the theory applicability to practical use.

The final intent is to describe the applicative software, and which is the line of speculations that lead us to choose and decide the compulsory covariate to be use in the development of the theory confirmation.

The principles of the theory proposal starts from the definition of new covariate theory values and hypothetic values of "Total Anaesthesia Live Drug Detection and Elimination " driven by a different pharmacological point of view; a new mathematical equation has been propose and the first consequence of such equation is that "Creatinine or Drug Clerance" could not to be only indexed starting from referred standard concepts , for example, to renal or hepatic elimination of anaesthetic drugs, but must be considered a much more complex event when we speculate about "Dynamic Cells Growth Systems" ,(Neonates , Toddlers, Elderly subjects), and not "Static Cells Growth Systems" as we can consider subjects ranging from 30 kgs weight up to 70 years of age, when a "Rapid Cells Decay Slope Curve" starts in compulsory mode.

Keywords: Paediatric Anaesthesia; Rapid Cells Growth Systems; Allometry; Allometric Pharmacology; Applicative TCI Software; Quantic Physic Laws

1. Introduction

1.1. New speculations that led to find different "Covariates" data to be inserted in a new software algorithm that defines the applicative anaesthetic drug delivery software

It is evident that a newer approach to speculation about variability at different ages and weight to define the real approximate clearance and pathways of general anaesthetic drugs after administrations is required. The pharmacological approach from a classical point of view is strictly related to a PK/PD relation that takes in account a few standardized variability "Constants" in the drug concentration decline curve to define the amount of drug present in the V/d at a certain time and related to administration dosage in consideration of patient weight and age:

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Our first speculation is, in our opinion, a new starting; it is better to define it as a "Postulate" that is the base of this manuscript and that is followed by a new mathematical approach. To PK/PD definition:[1] [2] [3]

"Is not possible to standardize the PK/PD of a drug, especially an anaesthetic drug, in neonates, paediatric and elderly patients starting from a stable and static point of view.[4] [5] [6]

- TCI Driven anaesthetic use is performed using software systems build up in reason of static and standard values fairly, especially in paediatrics, related to blood and plasma samples V/d concentration. This is a not direct controlled data but only a clinical response value related data. [7] [8] [9]

- The principal consequence of the first speculation is that we cannot apply, for logical reason, the same schematic software in "Rapid Dynamic Cells Growth , or Death, Systems"; this is as per definition what happens if we consider the Neonate, Toddler, Children, Adolescent, and, for opposite reason but applying the same consideration, in the "Elderly Patients Cell Growth Decay" **[4] [10] [11]**

It seemed to be clear to us that a new pharmacological approach to study the scientific question was required, and that we should must take in account something that, paradoxically was present Allometric Pharmacologic to be the fundament of modern pharmacology, but to see and study it using preset age criteria, i mean the relationship between a defined number of covariates considered from Allometric Pharmacologic Equations applied to different Ages and Weight and Related Organ Functionality and Maturation Variability considering an indispensable data " The Post Menstrual Age" of neonates.[12]

1.2. Explicative Determination

We want to point out that the basement of our speculations is to adapt old concepts to new scientific perspective: Kleiber Laws and Hill Coefficient Formulas are the bases of our speculation.[13] [14] [15]

Bayesian Mathematical analysis and Bayez Theorem application will confirm our "Thoughts" that we are not wrong to propose the realization of our software and "New Tricompartmental Equation" as "Gepts Equation" was the actual TCI software expression and theoric base.

This thought leads to a simple conclusion, we never will have the security of our act in terms of drug dosages but only an approximation to 100%. This value will never reach that percentage in our performance, but as per Quantic Physic Laws applied to Biology and Pharmacology, we only will determine its value as a function defined by approximation:

We know that it is acceptable in anaesthetic procedures an approximation effects related till 20 % to the required a desired effect from the anaesthesiologist performance and drug performance, in some paediatric cases the author described a 6% approximation to 100% but that also were not direct data measurements but clinical response related data.

Using the described new approach is, in our opinion, a very clear and adequate change in the approach of anaesthesia TCI Driven Procedures especially for very difficult patients. [16] **[46] [47] [48] [49][50] [51])**

1.2.1. Two considerations

- This is not Artificial Intelligence Guidance without control after setting up data in the software

- It always is the "Anaesthesiologist" to close the loop with his professional skills, real time decisions, led by Expertise and Valuations of the single specific patient assistance requirements.

2. Method

2.1. Creatinine Clearance: new pharmacologic relevance and determinations

We already propose in the **"Part One" [16]** of this study the new "Creatinine Clearance Formula" calculated in allometric scaling values and related per age and weight. **(Table 1-2 Bis)**

We also considered to build up our algorithm and related software inserting as covariate the **"Blood Flow Percentage Trough Defined Organs"** and consequently the **"Drug Extraction Ratio"** [17] both related to age and weight.

We found that "Drug Extraction Ratio" seemed to be Higher the less is the age and the weighing of patients, but, nevertheless, It seemed clear that it is strictly depended from and limited from the organ blood flow. (i.e. -propofol extraction values: 0,87 $^{+/-}$ 0.09 l/m^{-1} for adult patients) **(Bijorkman)** [18]

The reason why this happen seems to be the scarce muscular mass verse the body fat mass of the younger patients; this allowed us to introduce new covariates in the software development: the Fat Mass value, the Loan Mass Value, the Albumin level and the Body Mass Index (BMI) for each group of patients.

This vision is possible only if we look at the problem considering allometric exponents scaling concepts:

This postulate allowed us to program the construction of neonatal, toddler, paediatric, adolescent and, applying the same concepts but in a default inverted explication of rapid cell death, in elderly patients of a dedicated TCI software [19] [20] [21].

Renal, Hepatic, BioPhase and Plasmatic Distribution Volume and clearance where more reliable than in classical pharmacological PK/PD determinations and, finally, where dependent from a scaling program applied to Human Biology in a **"Quantic Physic Perspective". (Chidambaran et Alt)** [20]

2.1.1. The aim is to define

- E= **agonistic effect on the receptor**
- Emax = **maximal effect**
- Ec50 = **half effect**
- n= Hill **Coefficient**
- We will consider three anesthetic drugs
- **Propofol 1% and 2%**
- **Alfentanil**
- **Ketamine**

But our final speculation and desire is: the new concepts that build up a new equation coul'd be applied to every single drug.

2.2. Sequence

2.2.1. Drug Dilution

This is the first parameter to consider together with the desired "Target" parameter to reach de desired anaesthetic level.

It is necessarily a fixed parameter and is directly related to the volume in mils of drug dilution; it fixes the amount of bolus to administer, its time of administration and the speed of maintenance when the desired "Target" level is reached; in a few words we say that the infusion concentration depends on it fixing the different speeds of each drug administered.[22]

2.2.2. Let's consider "Propofol" concentration

Propofol is delivered in a 1% dilution or a 2% dilution, it is not seen to further diluted it and for trade mark reasons, but in our case a further dilution will increase the fluid administration levels that is not good in very low and restricted body V/d fluid composition, as for neonates and toddlers.

2.2.3. Let's consider "Alfentanil" concentration"

We decided that for our anaesthesiologic purpose that to set up an Alfentanil 500 mcg dosage diluted in 50 mls of 5% Dextrose gives us a reasonably good chance to give to patient a low volume bolus and a low infusion speed if we consider that the fixed range action concentration at BioPhase of Alfentanil goes from 10ng/min/L $^{-1}$ to 120 ng/L/min^{-1}

2.2.4. Let's consider "Ketamine formulation concentration"

We decided that for our anaesthesiologic purpose 400 mg of Ketamine diluted with 50 mls of Dextrose 5% where adequate to give us and maintaining a range action concentration at BioPhase of from 2 ng/L/min $^{-1}$ to 8 ng/L/min^{-1}

These are the values exposed and fixed in numerical expression settled in the software for the 3 considered drug.

2.2.5. Bolus related to desired target:

It will be ranged for each drug not considering the different ages but only considering the desired target:

Consider the effects of propofol with a correspondence on the plasmatic levels V/d at equilibrium: if my purpose is to reach a dream level, the predefined target desired will be 2 ng/L/min^{-1} level: still, if my purpose is to reach a sedation level it will rise up to 4-5 ng/L/min^{-1}, with changes in the bolus amount and infusion speed, but if my purpose is to reach and maintain anaesthetic levels that matches the surgical stimulus , my purpose can be reached in two different ways according to the clinical condition of the patient, start with a low dosage and increase it in response to monitoring and clinical levels up to a range on 10-12 ng/L/min^{-1}.

Three speculations must take in account , for each drug , first of all the knowledge by anaesthesiologist of the drag action at different V/d distribution levels at equilibrium, but, very important passage, that in a combined anaesthesia is compulsory for the anaesthesiologist to close the loop in consideration of which part of the anaesthetic levels intends to have the patient, doe's he prefer a more analgesized and anesthetised patient or less analgesized but sedated patient because anaesthetist applied a locoregional procedure or a plexus block anaesthesia?

It is a new way to consider anaesthesia, but it is already purposed from anaesthesiologists. The difference stands in the anaesthetic plan level control not referred only to data coming from clinical response monitoring or receptor ligand control, but in an "anaesthesiologist" determined anaesthesia that can be changed in real time. The more the anaesthetic drug acting level is known with an approximation to 100%, the more anaesthesia will be secure. [23] [24] [25] [26] [27]

2.3. Continuous Infusion

It will be related to the drug dilution and effective BioPhase Consumption: a" K" 0

The three compartmental anaesthetic software considers:

- A=1= VC
- B=2= VC2
- C=3=VC3

Vc3 identifies and defines a theoretical compartment where the drug reaches a coupling between what we want to have at equilibrium and the theoretic constructed artificial value of drug. The so called "Target".[28]

As already said this compartment will be constructed with the values expressed in the relate formulas presented in Part One; we will have a theoretical algorithm to equalize the drug level to the desired one taking in account in real time all the covariate values.[29] [30] [31] [32] [33]

At this point the main problem seems to be the validation of our "in vitro" theory calculation; we are not sure that than "in vitro" confirmation must be performed in a simulation program that will confirm the validity of theoretical proposal and its application "in vivo". Our proposal is that a confirmation of the validity of the process could be confirmed applying to theory the Bayesan Theorem calculation and adding the analysis of theory by defining a correct application to "Median Performance Errors" and "Absolute Median Performance Errors" data set.

2.4. Tricompartment Composition:[34] [35] [36] [37] [38] [39]

2.5. INSERT

The initial data to be considered are compulsory:

- Age

- Drug dilution
- Bolus amount related to target

The" actual result "will be The Continuous Infusion Speed

A= 1

- Size: organ maturation considering Allometric Laws
- Mass: Metabolic Power/Cells Mass
- Fat mass/Loan mass
- Albumine Value

B=2

V/d in Vc2

- aK10

aK12

- aVc ⟶ aVc2

aK21

-

- Clearance relates
- Receptorial legand : Total Ligand and--Actual ligands Concentration—Residual Ligand concentration (L2-L1)

If we consider the drug-receptor ligand laws and mathematical equations, the ligand of the drug to the receptor is, theoretically speaking, 100% when the molar equilibrium is reached: It is the plasmatic V/d concentration added to the receptor ligand

We assume that a 94% drug consumption in real time at Biophase is required to get our anesthetic purpose, and 94% 0f receptors ligand are saturate, consequentely following the receptor –ligand activity it is:

2.6. Receptorial ligand and drug acting percentage:

- Actual =100%
- Residual= 6%
- Acting = 94%
- 100%-94%=6%

The residual drug amount is 6%, that is the plasmatic concentration in V/d compartment of not acting drug.

This approximation could be considered a minus or an overload according with "**Median Performance Errors" and "Absolute Median Performance Errors" application and data calculations.**

2.6.1. MDPE

- **MEDIAN PERFORMANCE ERRORS**

$$PE\% = \frac{MC - CALCM}{CALCM} * 100$$

MC = Measured Concentration

CALCC= Calculated Concentration

2.6.2. MDAPE

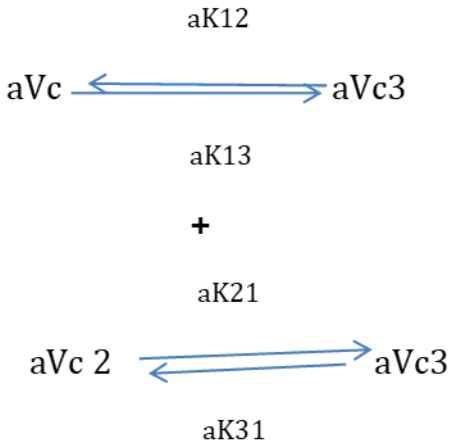
- MEDIAN ABSOLUTE PERFORMANCE ERROR
- MDAPE represents the numeric value of this percentage variation in terms of plus-minus from 100%

Then*:*

C=3 (Vc3)

Hypothetic Theory consumption at "BioPhase": It is a theoretic compartment, and it considers the mean acting consumption value of each drug when a n equilibrium between receptors and drug mole mass component related to its dilution is reached

- C= ak (L2-L1) **aK"0"**



Consumption

aVc1+aVc2+aVc3 = A + B + C at Time "ΔT" * and temperature fixed range

at Time Zero Consumption is ZERO **("0")**

("ΔT" = (t_2. t_1))

("ΔL" = (l_2 - l_1) = (37° C-34° C))

We added a new software covariate: Body Temperature

aC = A + B + C * (T0) = "0"

At different times the equation needs to be integrated

consumption at "T" (0-1-2-3-4-.....n)

$$aC = \int_{\Delta T * \Delta L}^{A+B+C} f(x)dt = \int_{\Delta T * \Delta L}^{A+B+C} (A + B + B) * \Delta T^2 * \Delta L^2$$

Finally, when we inserted all the covariates data in the software a new equation can be developed and fixed mathematically as Gepts made for his mathematic equation [40] [41] [42] [43] [44] [45] [46] [47] [48] [49] [50]

2.7. Allometric Quantistic "Conceptional" Tricomparimental Equation_Male/ Female

aConcentration = $A * e^{\alpha-(3/4)t} + B * \beta-(3/4)t + C * \gamma-(3/4)t$ * "ΔT" $(t_2 - t_1)$x "ΔL" =

$(l_2 - l_1)$

aConcentration = $A * \alpha-(3/4)t + B * \beta-(3/4)t + C * \gamma-(3/4)t$

we consider temperature and time as variables but in a fixed range:

"ΔT" = $(t_2 - t_1)$

"ΔL" = $(l_2 - l_1)$

"ΔT"= $(t_2 - t_1)$ is depending of infusion duration: we fixed a Δ range infusion time from 1 minute to 10.000 minutes. As already said "Drug Tricompartmental equation" value at Time "0" is "0"

"ΔL" = $(l_2 - l_1)$ we fixed an interval range from 37°C to 34°C degrees as per fractioned in 0,5 degrees interval. "L" value at Time "0" = 37 C°.

Its slope is regulate in 0,5 increase or decrease down to the cut off stabilized at 34 C°, this is an author's decision due to the evidence that below 34 C° it is already impossible to manage the temperature and caloric dispersion (ie.:In cardiac surgery By-Pass utilization the Emogas analysis and the temperature vale are controlled only by the differences in the assistance flow but the variables affecting these data are infinite so far.

37°; 36,5°; 36°; 35,5°; 35°; 34,5°; 34°; Celsius Degrees

aConcentration = $aA * \alpha-(1)t + aB * \beta-(1)t + aC * \gamma-(1)t$

aConcentration = $aA * \alpha-(1)t + aB * \beta-(1)t + aC * \gamma-(1)t$

aConcentration = Concentration of a drug acting at Biophase is strictly dependent from

- A, B, C, that expresses the new composition and changes in real time of a "Dynamic Rapid Cells Growth System", expressions of the components of Vc, Vc2; Vc3
- Increase and decrease of temperature "L"
- "Time" infusion duration.
- Male / female equation differs for each considered group for minimal covariate data, but it is compulsory to develop different equations. We must consider 4 male and 4 female patient groups, and we must develop a total of 8 equation when we build up the applicative software. The last speculation defines the application of these equations in elderly patients in a decremental mode sinde the cell development is a rapid death cells default
  - aConcentration = $Vc * Vc-(3/4)t + Vc_2 * Vc_2-(3/4)t + CVc_3 * Vc_3-(3/4)t$
  - aConcentration = $Vc * Vc-(1)t + Vc_2 * Vc_2-(1)t + CVc_3 * Vc_3-(1)t$
- A= Vc

- B= Vc2
- C= Vc3
- T= 1-10.000 minuts
- L= 37°C-34°C

This mathematical equation expresses better some definitions of the software algorithm equation where:

(according and reprise by Gepts 1998 "**non allometric mathematical equation**" developmental definitions

- aC= drug concentration after bolus injection
- t= Time elapsed and infusion length after drug injection
- aA.aB.aC. = (Vc, Vc2, Vc3) "Coefficients"; compartmental drug concentration (aCo = aA+aB+aC at "O" time).
- α, β, γ ="Hybrid Rate Constants". They are expressions of the drug exponential slope in each drug
    - Vc-Vc2-Vc3 = Compartments:
    - Vc= central compartment
    - Vc2= rapid or superficial compartment
    - Vc3= 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 real time. It adds to the dynamic elimination and equilibrations constants
- aK10 = central compartment elimination constant

- aK12-aK13-aK21-aK31 = intercompartmental equilibration-constants.

- aK "0" constant had been found by Shafer and Varvel in its form K"0" and is specific for each drug in TCI actual software, but in our software development it is strictly depending from the Complete Total Body Clearance new mathematical formulation and is equal for each drug [51] [52] [53] [54] [55] [56] [57] [58] [59] [60]

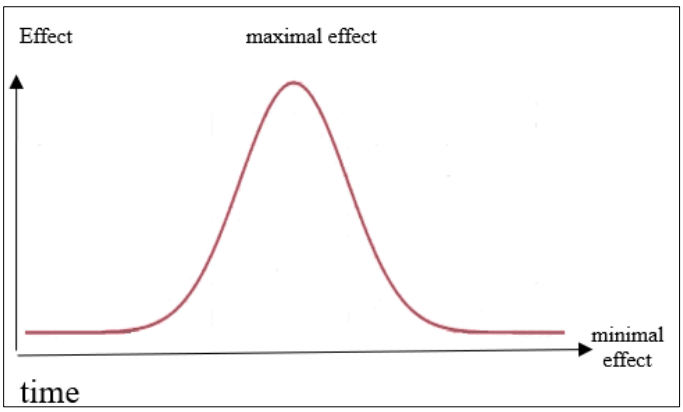


Figure 1 Actual TCI Gaussian Slope Curve [61] [62] [63] [64] [65] [66]

A Gaussian expression of a working system is much limited from a "minimum value – a maximum value – a minimum value fixed progression without any singularity "

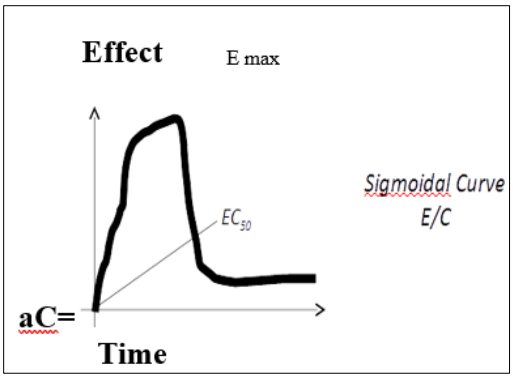


Figure 2 Anesthetic Drug Sigmoidal Slope Curve in Allometric and Quantic TCI 67

A description of the differences between the two equational curve expressions will follow Discussion chapter

2.8. New Graphic Representation of the "Software" working system

This is the visualized graph of mathematical speculations.

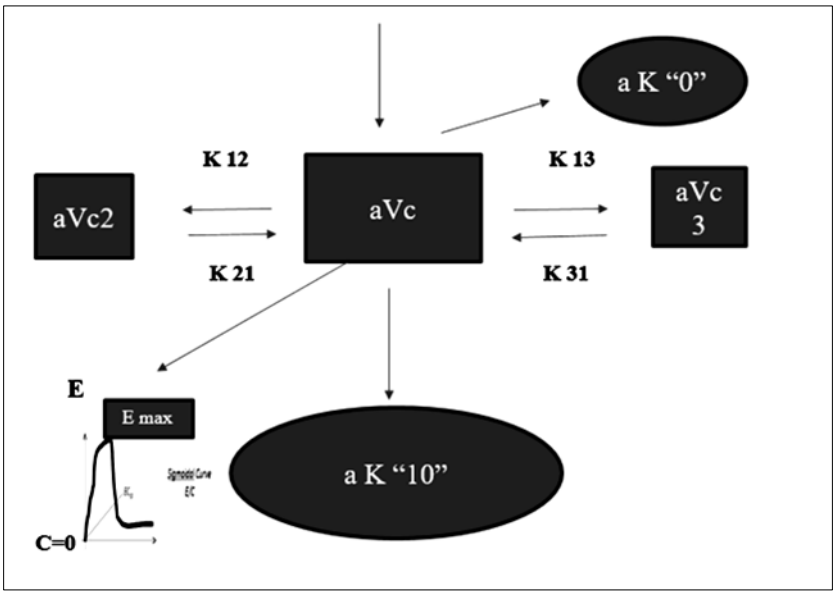


Figure 3 The new TCI Graphical Expression of Gepts original equation.

It takes in account many singularities due to the relationship between Action and real time Allometric Quantistic Variations presents in the Sigmoidal Equation drug slope. [68] [69] [70] [71] [72] [73] [74]

3. Discussion

The "Tricompatimental Equation" expresses the sigmoidal scaling and slope of a drug changes after a bolus has been administered followed by a continuous infusion in statistical approximation as per quantic laws applied to pharmacology.

The lead of result to 100% reliability is not suitable of definition because we postulated that this is a new way to look at PK/PD from a quantic physical laws and by definition we can approach the system as per statistical approximation to 100%

V/d in Vc

- aK10= 1ml/min/m2

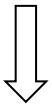
aK12

- aVc ⇌ aVc2

aK21

- clearance related
- receptor ligand: residual L2, actual L1
- concentration (L2-L1)

follows



C=3 (Vc3) Hypothetic consumption at "BioPhase"

The simulation must approximate to not less than 6 % of reliability of the residual ligand drug receptors: the direct pharmacological consequences (for every used drug) is the "on line-real time BioPhase Drug Consumption" that finally is fixed as:

aK"0"

V/d in Vc 3

- **aK10 = 1 ml/L/min**

aK12

- **aVc ⇌ aVc2**

aK21

- clearance related
- receptor ligand: residual L2, actual L1
- concentration (L2-L1)

This is the theory third compartment Vc3 that can be considered the real **"Quantic Real Time Anaesthetic Drug at "Equilibrium" - Consumption at BioPhase".**

It is a real changing point of view for the anaesthetists:

Not more "Which is the amount of drug do I have to give to the patient to reach the desired anaesthetic effect and maintain it?", but "If I want to have a prefixed theoretical approximative effect at BioPhase which are the changes in terms of Quantic Physics laws and Allometric Pharmacologic PK/PD laws the drug must have after a bolus administration and a continuous infusion administration start?

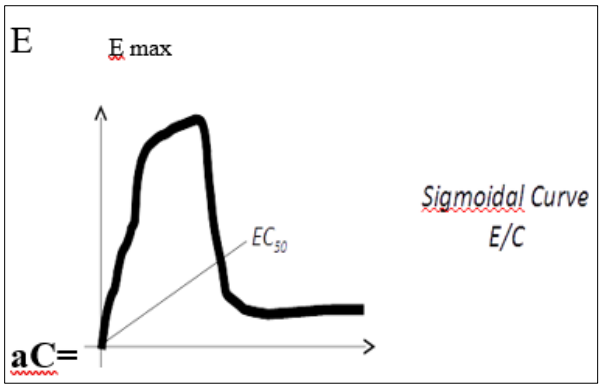


Figure 4 Anesthetic Drug Sigmoidal Slope Curve in Allometric and Quantic TC

Still, we assume that this is a new model of PK-PD drug effect related to a drug dose concentration; it is considered non a static model according with normal pharmacologic explanative laws and processes, but a dynamic system builds up with newer speculation about old pharmacologic concepts.

It is compulsory to step up that the Ec50 is not anymore considered a fixed number, as for T50 Half Time drug concentration, but follows the in time live variations in terms of the slope of exponential decay curve.

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 practical "***Cognitive status of the change in a drug effect"***; in other words, it represents "***The Translation of a Theory in Practice":***

EC= E = Emax*Cn + (Ec50)*□

Where:

- C = concentration
- E= agonistic effect on the receptor
- Emax = maximal effect
- Ec50 = half effect n= Hill Coefficient
- n= Hill Coefficient

3.1. This speculation leads us to one pratical definition of the software action:[93]

- The Rapid Growth Cell System works in a strictly relationship with the receptor capacity to be interested in a ligand with a drug , to saturate approximatively to 100% of drug—receptor complex that could be or not able to produce a response and produce an activity but it will never reach out the 100% of complex or response due to Physical Quantic Laws Limitation.

We demonstrate, hopefully, that our action drug level postulate at maximum of hypothetic +- at 6% could be better and less than the actual hypothetic level that can be acceptable in anesthesia until a 20% of clinical and pharmacological variations.

This is the core of the new software; it is the initial process about the receptor-drug ligand and effects.

It is very important to point out this speculative aspect because there is no action if there is no receptor drug ligand in enough quantity to give a clinical response. Or there could be an overload of effects that can affect the patient in a very dangerous mode.

As we know in a not precise or computer driven anaesthesia this is very simple to have, and even with a not correct use and approach of nowadays TCI use in paediatrics and elderly catastrophic events could happen.

The "Guldenberg-Waage Mass Action Law" [75] and the Michaelis–Menten Equation [76] that considers and evaluates the not linear statistical regression in concentration at Biophase of anaesthetic drugs, made possible to quantify this ligand

and made possible to transform a theoretical speculation in an active clinical acting model, quantifying how much of the drug is really working and having clinical effect.

In other words, this is the passage that leads from mathematical theory to clinical application

- To have clinical effect the first step is the receptor-drug; when an equilibrium is reached a few second transmitters effectors can start a transmission cascade that leads to a clinical response; Beta-Adenylate Cyclase, Alfa Glucuronidase, Na+ and Ca+ channels causing a Membrane Potential Electric Rising or Down Regulation Effects, ATP. cAMP and others secondary and tertiary transmitters made the clinical response active.

3.2. Hill-Langmuir equation

$$\boldsymbol{y = \frac{ymax^{\alpha}}{C + x^{\alpha}}}$$

Where

- C= system definition
- y = independent variable
- x = dependent variable
- α = coefficient (Hill)

This equation relates the drug concentration with its effect. [5] [6] [10] [12] [16] [23][25] [33] [92]

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

$$V = \frac{Vmax * S}{Km * S}$$

Where

- V = initial velocity of reaction [mol/L/s]
- Vmax = maximal reaction rate [mol/L/s]
- S = Substrate concentration [mol/L]
- Km = 1/2 match concentration [mol/l]

Thus

$$Y = \frac{ymax * \ x^{\alpha}}{c^{\alpha} + x^{\alpha}}$$

x = V

Km = y

C=Vmax

Ymax=1

A=S

Body Total Clearance: P

(This part is a necessary a reprise of the Part One (Milella 2022) [16] manuscript of this work. It was necessary to reprise it in this second part because at a next review of the former manuscript the author noticed some mathematical errors in the

equation calculations and wanted to change it representing the new correct calculations and data). (Author Note) [14] [16] [21] [58] [67] [77] [78]

P = it is related to:

- Maturation Function
- Organ function

P $_{in}$ adult is equal to P= (Pstd*Fsize*MF*OF)

We must substitute neonatal Post Menstrual Age (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 ng/L/min in consideration of the PMA of pediatric patients

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 3,83 (we consider an approximation to 3,4)

In the end, if adult standard value 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. In fact, the PMA, and consequently the already defined patient SIZE, leads us to apply the revisited mathematical formulas for Drug Clearance.

4. Results:[16]

Practically the clearance of general anesthetic drugs is defined from the relationship between all the allometric covariates **as nanogram/Liters/minute (ng/L/min**) according with the Patient Size Definitions as per allometric laws definitions and not the Patient Body Surface**. (table 1 -2 Bis**)

Please, consider that these are not the creatinine clearance renal value of drug elimination.

It should be applicable to all drugs elimination when are introduced in a rapid growth cell system and start to produce an action in response**.**

Table 1 Clearance values in allometric PK/PD Dynamic Cell Growth System

Neonatal (0-6 months) Male	CL = **0,551 ng/L/min**
Neonatal (0-6 months) female	CL = **0,654 ng/L/min**
Pediatric (6 ms-2 years) Male	CL = **0,774 ng/L/min**
Pediatric (6 ms-2 years) Female	CL = **1,344 ng/L/min**
Pediatric(2 years-5 years) Male	CL = **3,103 ng/L/min**
Pediatric (2 years-5 years) Female	CL = **4,025 ng/L/min**

Pediatric= (25-27 kg)	CL = **10,5 ng/L/min**

Table 2 Bis: Clearance values in allometric PK/PD "Dynamic Cells Growth System and Dynamic Cells Death System"

The Kleiber coefficient for Again: The Kleiber coefficient for neonatal age is 1 and not ¾ due to the immaturity of neonatal organs deputed to the clearance of the drug (Liver; Kidney)	The Kleiber coefficient for neonatal age is 1 and not ¾ due to the immaturity of neonatal organs deputed to the clearance of the drug (Liver, Kidney) The Kleiber coefficient for neonatal age is 1 and not ¾ due to the immaturity of neonatal organs deputed to the clearance of the drug (Liver, Kidney)
Consequentely: The clearance of general anesthetic drugs is defined from the relationship between all the allometry covariates: The relationship is determined by matemathic formula 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	Otherwise, the same situation can be applied in the opposite way to elderly patients. We can speculate that also elderly are suffering of loss of organ function and maturity and effective chance to work at theyr best. This is clear in terms of PK/PD relation in a "Rapid Cell Death System" **Pediatric values defined as = median height 122 cm; median weight 27,5 kg; mean Age 10; percentile mean value 0,5** **CL= Neonatal male (0 – 6 months)** **CL = /A + W/L X (W/ Percentile Growth Curve Male)(1)** **CL= Pediatric male (6 months- 2 years)** **CL = W/A + W/L X (W/ Percentile Growth Curve Male) (0,75)** **Where:** **W= weight** **A= age** **L= lenght** **(1) = Kleiber Allometric Scaling Coefficient**

4.1. Total Body Quantistic Clearance in Bayesan Analisys [80] [81] [82] [83] [94]

Our opinion at this point is that a statistical approach that differs from the past is required. We decided to analyse and evaluate our results and data applying to our clearance equation the Bayes Theorem that is a very practical way to know and understand if our speculations and software are correct and reliable.

4.1.1. Bayes Theorem is defined as

$$\boldsymbol{P(A/B)} = \frac{\mathbf{P(B/A)} * \mathbf{P(A)}}{\mathbf{P(B)}}$$

Where:

- P(A/B) = Posterior Probability of the Hypothesis given that the Evidence is True
- P(B/A) =Likelihood of the Evidence given that the Hypothesis is True
- P(A)=Prior Probability of the Hypothesis
- P(B)=Prior Probability that Evidence is True.

We apply a Bayesian statistical analisys to the already described "Sigmoidal Emax Model" data to insert in the theorem.

Question:

"Do we still need an in vivo confirmation and validation of our data?"

Examples

Let us consider the creatinine value find in Solved Creatinine Equation solution 1) ("**0**"**months** − "**6**" **months**)***male*** : **0, 551 ng/L/min**

Now let's define the terms of Bayes application:

- A event (6%)
- B event (94%)
- P= 100%
- A= 6%
- B=94%
- P= 0,33/0,517 = (0,517-0,033) X (0,033)
- 0,517
- P=0,638 = 0,015 = 0,029

Remember that by postulate the result is standardized on 6% standard deviation as target.

0,029 as Bayez result means 0,19% in absolute value and indicates that the theoretical value of equation (clearance ng/L/min) is much less than 50% (½) of the estimated value we fixed at 6% (3%) a reliable value of postulate approximation.

Let's apply the same process for paediatric male patients aged (6-2 years of age):

Creatinine theoretical equation value: 1,344 ng/L/min

Bayez Theorem calculation application:

- A event= 6%
- B event =94%

$$P(1{,}334) = \frac{1{,}344*(1{,}429-0{,}08)*0{,}08}{1{,}344*0{,}08} = 0{,}85\ \left[\frac{\frac{ng}{L}}{mom}\right]$$

Cl of 0,85 as Bayez result of P(A/B) leads to have 0,501 ng/L/min of variance that is more less than the early postulate 6% approximation theoric value.

The consequence is that if we apply the Bayez Theorem to our already solved equations for creatinine clearance, we will find approximation values under the acceptable 6%postulate values in every calculation.

This condition defines our correct determination that P(A/B) is the Posterior Probability of the Hypothesis given that the Evidence is True.

In a few words: a theoretical allometric quantic laws mathematical approach in PK/PD estimation is validate from a mathematical confirmation; and the validation leads to results of a much more reliable values than the postulate 6%

The subsequent step of our speculation must consider the Real Amount of drug acting and the sequence of triggering a receptor response at the Biophase (the so defined aK"0") in real time, its consumpion , its legand with receptors, its quantity in plasma at real time as residual value .

- Let's reconsider and complete the thoughts about the Waage and Gulderberg [75] law constant of dissociation at equilibrium called Kd.

Kd =[L/M] [LM]

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

Y = ratio of molecule that reached the receptor: Y = [LM][LM] + [L]

If we substitute [LM] with Kd the equation looks like: Y = [M]Kd + [M]

Thus: $C = \frac{Kd}{\alpha} = 1$

Furthermore, the mass equation at equilibrium is:

K1→ nL + R LnR K2← $[LnR] = [Ro]2\ x\ [L]n = [\ Ro\ x\ [L]n\ ]\ [L]n + Kd\ [L]n + [KA]n$ L

Where:

L = ligand variable concentration (always > 1)

LnR = ligand receptor complex

Ro= receptor number (total concentration)

L = total concentration of ligand

K1= association constant

K2 = dissociation constant

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

KA = ligand concentration at 50%; like α/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

- Effect Site Involvement Sequence

(Second messenger ⇨ Enzymatic Hynibition ⇨ ionic channels modulation)

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. [84] [85] [91]

- Black and Leff [86] in 1983 described an operative model of the receptor mechanism of action:

K1→ mA + mR + ε mAR + ARmEK2←

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 =
- Agonist−Receptor Effector complex [85] [86] [91]
- AR = complex receptor activity
- ARmE = agonist receptor complex = Action Effect $K'1 \rightarrow AR\ AR * K'2 \leftarrow$

This relationship takes into consideration the number of receptors that can develop an effect, and it is named De Castillo −Katz law [84]:

- AR = active complex
- AR* = inactive complex.

This represents the aK"0" at Biophase [85

4.2. Applicative New "aTCI" Algorithm

4.2.1. Initial Data Input

- Age:
- Weight:
- Sex: M o F
- Temperature:
- High:
- Anesthetic drug (Propofol 1%-Propofol 2%-Ketamine-Alfentanil):
- Anesthetic drug Dilution: Each drug is diluted in a propr parameter of drug amount and liquid solution:
- Target. It is the predefined objective in terms of acting real time drug, consumption, clearance and receptor ligand the anesthesiologist aim to fix and reach out:
- Postulate: "There will be a double choice of settled calculated initial drug bolus and the bolus speed will be, according with the clinical condition of the patient and the age of it decided from the operator: 300 mm/hg/hr bolus speed or 600 mm/hg/hr bolus speed

4.2.2. Subsequent Derivated Data

The aim of the subsequent drug action and changes is the filling up of the central compartment, the so "aVC" identified compartment.

Initial Bolus

Propofol:

Dilution: 10 mg in 1 ml (1%) or 20 mg in 1 ml (2%)

Target: from 1 ng//L/min $^{-1}$ to 12 ng/L/min^{-1}

Alfentanil:

Dilution: 500 mcg diluited in 50 ml of Glucose 5%.

Target: from 10 ng/L/min^{-1} to 120 ng/L/min^{-1}

Ketamine:

Dilution: 400 mg diluited in 50 mls of Glucoe 5%

Target: from 2 ng/L/min^{-1} to 8 ng/L/min^{-1}

4.3. Flow

It is strictly dependent from the different organ specific flow related to Age and Weight.[8]

It is extremely proportional in the different ages and specific clinical condition.

Those are two covariates are the "aVc" that will be led to equilibrium with "aVc1" and finally at equilibrium with "aVc2" that represents the theoretical compartment

5. AVc composition

5.1. Body Composition (BC)

The legend is as follow:

Fat Free Mass = FFM

Loan Mass = LM

Albumin level = AL

Protein level = PL

$\boldsymbol{BC = \frac{FFT+LM}{AL+PL}}$ *[12] [70] [86] [87] [88]*

Fat Free Mass can be calculated using weight and height. It is correlated to the PWR coefficient which is assumed to be 1 instead of ¾ in neonates as above mentioned.[20]

Protein level: 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.

5.2. Fat Free Mass (FFM)

This is the second fundamental not fixed covariate:

$$FFM = WHS_{max} * H^2 * \left[\frac{W}{(WHS_{50} * H^2 + W)}\right]$$

5.2.1. Male Values

$$WHS_{max} = 49{,}2\ {}^{Kg}/_{m^2}\ WHS_{50} = 30{,}93\ {}^{Kg}/_{m^2}$$

5.2.2. Female values:

$$WHS_{max} = 37{,}99\ {}^{Kg}/_{m^2}\ WHS_{50} = 35{,}98\ {}^{Kg}/_{m^2}$$

= Weight, Age,

Where (3/4) scaling coefficient relates equation to Kleiber Laws of "Rapid Growth Cell Dynamic System" [12] [15] [20]

These two concepts will be explained in a wide and complete mode further on in this manuscript

5.3. Pharmacokinetic Parameter Calculation:

$$\boldsymbol{P = a * w^b = \frac{w}{Ht} * A * w}$$

We define "Half Time" drug action not as the "Drug "half time = t_{50} " but as the result of the Sigmoidal Consumption and Quantic Clearance is a fix data obtained from the already explained equation.

D = half of the Drug infusion at the time T=0 $[\frac{ng}{\frac{L}{min^{-1}}}]$

t = the time when the Drug concentration in the V1 compartment is halved

Calculate

HT = $\boldsymbol{D\ x\ T^2 x}$ (***Receptorial Agonistic Effect realted to the Receptor interaction at Biophase***

It Changes in relation to the covariate's changes. 89-90-91-92-93-94

6. Applicative software

aConcentration = Concentration of a drug acting at Biophase is strictly dependent from

- *A, B, C, that expresses the new composition and changes in real time of a "Dynamic Rapid Cells Growth System", expressions of the components of Vc, Vc2; Vc3*
- *Increase and decrease of temperature "t"*
- *"Time" infusion duration.*
  - aConcentration = aVc * Vc-(3/4) t + aVc2 * Vc2-(3/4)t + aCVc3* Vc3(3/4)t
  - aConcentration = aVc * Vc-(1)t + aVc2 * Vc2-(1)t + aCVc3* Vc3-(1)t
  - A= Vc
  - B= Vc2
  - C= Vc3
  - T= 1-10.000 minutes
  - L= 37°C-34°C

This mathematical equation expresses better some definitions of the software algorithm equation.

6.1. Mathematic operative data

Vc; Vc2, Vc3; K10; K12; K13; k21; K31; K"0"

Filling up of central compartment "Vc"

- Age: Male (0 mons-6 mons)[1]; (6 mons-2 years)[2]; (2 years-5 years)[3]; (5 years-15 years)[4]
- Age: Female (0 mons-6 mons); (6 mons-2 years); (2 years-5 years); (5 years-15 years)
- Sex: Male-Female
- Weight: Male (3.3)[1];(7.5)[2]; (12.4)[3]; (25)[4];
- Weight: Female (3.7)[1];(79)[2]; (12.9)[3]; (27)[4]
- Hight: Male (50 cm)[1];(85 cm)[2]; (95 cm)[3]; (95 cm)[4];

- Hight: Female (50 cm)[1];(85 cm)[2]; (95 cm)[3]; (122 cm)
- Basal metabolic rate Male: -Male (0-6 month== 122.685 kg/cal/die[1]; Male (6 months-2 years=553.5145 kg/cal/die)2; Male (2 years-5 years=639,0656 kg/cal/die)[3]; --Male (5 years-14 years=831.3605 kg/cal/die)[4];
- Basal metabolic rate Female: Male (0-6 month=447.618 kg/cal/die)[1]; Male (6 months-2 years=543.867 kg/cal/die)[2]; Male (2 years-5 years=845 kg/cal/die)[3]; --Male (5 years-14 years=1279 kg/cal/die)[4].
- Fat mass-Loan mass: (Fat mass= Male: (11)[1] ; (11.01)[2] ; (11.03)[3] ; (11.04)[4] ;-- Female: (11)[1] ; (11.02)[2] ; (11.05)[3] ; (11.19)[4] ;
- Loane mass kg: Male- (2.8)[1]; (6)[2]; (9.6)[3]; (21.68)[4]; -- Female: (2.78)[1]; (6.32)[2]; (9.76)[3]; (22)[4];
- BMI- kg= Male: (14)[1] ; (10.38)[2] ; (13.7)[3] ; (14.25)[4] ; -- Female: (14.8)[1] ; (10.45)[2] ; (13.29)[3] ; (18.58)[4]
- Albumin values mean legand levels in mg/dcl = (K= 0.33 in premature-neonates-elderly)[1]; (K=0,45 from birth to 30 days of age)[2]; (K=0.45 from 1 to 12 months)[3]; (K=0.37 from 12 to 21 months)[4]
- Temperature: Time lapse from 37.0 to 34 .0 C° with 0.5 degree lowered or increased value
- Drug dilution- Propofol: Dilution: 10 mg in 1 ml (1%) or 20 mg in 1 ml (2%)
- Drug dilution- Alfentanil: Dilution: 500 mcg diluted in 50 ml of Glucose 5%.
- Drug dilution-Ketamine: Dilution: 400 mg diluted in 50 mls of Glucose 5%
- Desired target levels by 1.0 change unit per concentration levels: Ketamine: from 2 ng/L/min^{-1} to 8 ng/L/min^{-1}

- Infusion speed (600 mm/Hg/h) (1200 mm/Hg/Hr)

- Time lapse (From Time “0” at “10000 minutes”)

- Time lapses control every “1” minute

Vc2

- Vc2: drug level Range maximum and minimum:
- Distribution volume 1 ml/L /min^{-1}(a”K”10)
- Drug receptor value total: 100% at Time
- Drug receptor value eliminated 4 % At time 1.000-
- Drug receptor value acting 96 % at time from 1 to 10000 every minute
- Clearance new equations levels (8 different levels): Male: (0.551 ng/L/min)[1]; (0.774 ng/L/min)[2]; (3.103 ng/L/min)[3] ; (10.5 ng/L/min)[4] ; -- Female: (0.654 ng/L/min)[1] ; (1.344 ng/L/min)[2] ; (4.025 ng/L/min)[3] ; (10.75 ng/L/min)[4] ;
- Organ flow x weight: Neonates-Ped—Elderly: liver 20 %-brain 44% heart 45 Kidney 7% Muscles 5% (Holliday 1991)
- Consider a flow of 90 ml/Kg in neonates, 65 % in toddlers; 60 % in adolescents; 50,5 In elderly without any consistent difference between sex, we have:
- Flow ml/min: (270 ml)[1]; (480 ml)[2]; (854)[3] ; (3.450)[4]
- Organ maturation Index: (weight x 1.5 / Height) = Male (3.5 x 1.5 / 0,5)1 ; (7.5 x 1.5 / 85)2 (12.2 x 1..5) / 953 ; (25.1 x 1.5 / 122)4 ; Female : (3.7 x 1..5 / 0.5)1 ; (7.9 x 1.5 / 85)2 ; (12.9 x 1.5 / 95)3 ; (27.5 x 1.5/ 122)4 ;

- Termic dispersion coefficient (temperature-time lapse: 10 % x (37 C°-1 C°

Vc3

- Drug level at equilibration time at biophase at equilibrium (desired target at a “K”0)
- Desired target levels by 1.0 change unit per concentration levels: Propofol: from 1 ng//L/min-1 to 12 ng/L/min^{-1}
- Desired target levels by 1.0 change unit per concentration levels: Alfentanil: from 10 ng/L/min 1to 120 ng/L/min^{-1}
- Desired target levels by 1.0 change unit per concentration levels: Ketamine: from 2 ng/L/min-1 to 8 ng/L/min^{-1}.
- EC50 time slope desired values and minimum target value I range from maximum target and time stop of infusion: it is a mean value Male: Propofol 1%: (6.5 ng/L/min $^{-1}$) ; Alfentanil : (65 ng/L/min^{-1})1 ; Ketamine : (4 ng/L/min^{-1})

7. Basal Metabolic Rate Calculation Male Formula

7.1. Male: 88.362+(13.397x weight in Kg) +(4.799x height in cm) -(5.677 x age in years

7.1.1. Male (0-6 months)[1]

88.362+ (9.247 x 3.5) +(84.799 x 50) -(5.677 x 0.5) =

121.0765+4.239-2.8375=125.35-2,837= 122.685 kg/cal/die

7.1.2. Male (6 months-2 years)2

88.362+(9.247 x 7.5) +(4.799x 85) -(5.677 x 1,5 mean age in years)

88.362+(65.3925) +(407.915) -(8.155) =157.7545+319.915) = 561.6695-(8.155)= 553.5145 kg/cal/die

7.1.3. Male (2 years-5 years)3

88.362+(9.247 x 12,4) +(4.799x 95) -(5.677 x 3,5 mean age in years)

88.362+(114.6628) +(455.905) -(19.8695) = 639,0656 kg/cal/die

7.1.4. Male (5 years-14 years)4

88.362+(9.247 x 25) +(4.799 x 122) -(5.677 x 8.5 mean age in years)

88.362+(231.175) +(585.578) -(73.7545) = 831.3605 kg/cal/die

7.2. Basal Metabolic Rate Female Calculation Formula:

Female: 447.593+ (9.247 x weight in Kg) + (3.098 x height in cm) -(4.330 x age in years)

7.2.1. Female (0-6 months)1

447.593+ (9.247 x 3.7) +(3.098 x 50) -(4.330 x 0.5) =

447.593+(34,9) +(154.19) -(2.165) = 447.618 kg/cal/die

7.2.2. Female (6 months-2 years)2

447.593+ (9.247 x 7,9) +(3.098 x 85) -(4.330 x1,5 mean age in years) =

447,593+(73,51) -(6,495) = 543.867 kg/cal/die

7.2.3. Female (2 years-5 years)3

447.593+(9.247 x 12,9) +(3.098 x 95) -(4.330 x 3,5 mean age in years)

447.593+(119.280) +(294.31) -(15.550) = 845 kg/cal/die

7.2.4. Female (5 years-14 years)4

447.593+(9.247 x 30) +(4.799 x 122) -(4,330 x 8.5 mean age in years)

447.593+(282,81) +(585.578) -(36,805) = 1279 kg/cal/die

7.3. This amount ad consume of kg/calories required every day to consent :

- Heart beating
- Cell production
- Autonomic Respiration
- Body temperature
- Blood Vessel Circulation

- Nutrient fasting metabolism
- Exercise
- Anesthetic Status

We speculate that Anesthesia processing and procedures can be not considered a dispersion action except for complicate and very long procedures, but that anesthesia produces a reduction in BMR and we also postulate no effect on body calory consumption at equilibrium.

7.4. Fat Mass and Loane Mass:

The human body is composed of several different tonometry metabolic and working systems.

What is different in a rapid cell growth system and cell dead system is the great difference in the body composition

We can have a delta between fat free mass and loan mass that is near 80% in neonates and decreases up to 14 years of age; and a totally diverted result in elderly patients where there is a inverted delta: more loan mass respect to fat mass up to 90% of difference.

In this algorithm that is trying to define a new pharmacodynamic -pharmacokinetic for a Quantic Allometric TCI, it is compulsory for us to insert these differences. Nowadays working for static systems of driven anesthesia cannot be applied to allometric Quantic Anesthesia TCI driven in rapid cell growth systems.

We can say that the loan mass is defined to be the 20% of our body composition.

If we look at a 70 kg patient, we can define the Loan Mass as:

(70 Kg x 0.2) equal to 56 kg of Loan Mass and 14 kg of ipotetic Fatt Mass. (70-14=56)

This is correct, for static and well condition patients.

We can ’t speculates in such a way in the presence of rapid growth cell systems.

7.5. Total Body Fat Mass:

In literature, but more in practical medical activity, many ways to define numerically the Fatt Mass value are present.

In our speculation we will furthe proceed in applying the Wilmoore and Behnke formulas.

Anf we will apply it for eacho group af patients and with separation between male and female finally data.

7.6. Male Fatt Mass Calculation:

Male FM (%) = 495 / [1.0324-0.19077] x [logarithmic value for neck and waist mesure)]+0.15456 x height-450

Female FM (%) =: 495 / [1.29579-0.35004 x [logarithmic value for waist-neck-flanks)]-450

Male FM (%) = 495 / [1.0324-0.19077] x [[logarithmic value for neck and waist measure] +0.15456 x [logarithmic value Height]-450

7.6.1. Male (0-6 months)1

495 / [1.0324-0.19077] x [logarithmic value for neck and waist measure]+0.15456] x [logarithmic value Height]-450

495 / [1.0324-0.19077] x [0.025+0.1546]x [0.05] -450 =

495 / [0.841] x [0.1796] x [0,05] -450 =

495 / [0.15104] x [0.05] -450=

495/ -449.993= 11%

7.6.2. Male (6 months-2 years)2

495 / [1.0324-0.19077]x [logarithmic value for neck and waist measure)]+0.15456 x [(logarithmic value Height]-450

495 / [1.0324-0.19077] x [0,03+0.1546]x [0.085] -450 =

495 / [0.841] x [0.1846] x [0.085] -450

495 / [0.1551] x [0,085] -450=

495 / -449.498 = 11,01 %

7.6.3. Male (2 years-5 years)3

495 / [1.0324-0.19077(logarithmic value for neck and waist measure)]+0.15456 (height)-450

495 / [1.0324-0.19077] x [0,033+0.1546]x [0.095] -450 =

495 / [0.841] x [0.1876] x [0.095] -450

495 / [0.1577] x [0,095] -450=

495 / 449.985 =11,03 %

7.6.4. Male (5 years-14 years)4

495 / [1.0324-0.19077(logarithmic value for neck and waist measure)]+0.15456 (height)-450

495 / [1.0324-0.19077] x [0,035+0.1546]x [0.0122] -450 =

495 / [0.841] x [0.189] x [0.0122] -450

495 / [0.1589] x [0,0122] -450=

495 / 449.998=11,04%

7.7. Female Fatt Mass Calculation

495 / [1.29579-0.35004] +0.1546 x [(logarithmic value for waist-neck-flanks)]-450

7.7.1. Female (0-6 months)1

495 / [1.29579-0.19077] x[logarithmic value for neck and waist measure]+0.15456] x [logarithmic value Height]-450

495 / [1.29579-0.19077] x [0.027+0.1546]x [0.05] -450 =

495 / [1.1050] x [0.1816] x [0,05] -450 =

495 / [0.1906] x [0.05] -450=

495/ -449.994= 11%

7.7.2. Female (6 months-2 years)2

495 / [1.29579-0.35004 X [logarithmic value for waist-neck-flanks)]+ 0.15456 x [height]-450

495 / [1.29579-0.19077] x [0,032+0.1546]x [0.085] -450 =

495 / [1.1050] x [0.1846] x [0.085] -450

495 / [0.2006] x [0,085] -450=

495 / -449.498 = 11,02 %

7.7.3. Female (2 years-5 years)3

495 / [1.29579-0.35004 (logarithmic value for waist-neck-flanks)]-450

495 / [1.29579-0.35004] x [0,035+0.1546]x [0.095] -450 =

495 / [1.1050] x [0.1910] x [0.095] -450

495 / [0.2110] x [0,095] -450=

495 / 449.985 =11,05 %

7.7.4. Female (5 years-14 years)4

495 / [1.29579-0.35004 (logarithmic value for waist-neck-flanks)]+ [0.0122]-450

495 / [1.0324-0.19077] x [0,037+0.1546]x [0.0122] -450 =

495 / [1.1050] x [0.583] x [0.0122] -450

495 / [0.644] x [0,0122]

495 / 449.998=11,19 %

Loane Mass Calculatuion Formula:

LM= (weight—20%) = kg

7.7.5. Male: (0 -6 months)1

LM= (3.5 x 0.2) = (3.5-0,7) = **2.8 kg**

7.7.6. Male (6 months-2 years)2

LM= (7.5 x 0.2) = (7.5-1.5) = 6 **kg**

7.7.7. Male (2 years-5 years)3

LM= (12.4 x 0.2) = (12.- 2.48) = **9.6 kg**

7.7.8. Male (5 years-14 years)4

LM= (27.1 x 0.2) = (27.1- 5.42) = **21.68 kg**

7.7.9. Female (0-6 months)1

LM= (3.7 x 0.2) = (3.7- 0.740) = **2.78 kg**

7.7.10. Female (6 months-2 years)2

LM= (7.9 x 0.2) = (7.9-1.58) = 6.32 **kg**

7.7.11. Female (2 years-5 years)3

LM= (12.9 x 0.2) = (12.9-2.44) = 9.76 kg

7.7.12. Female (5 years-14 years)4

LM= (27.5 x 0.2) = (27.5-5.5) = 22 kg

These are results absolutely in line with the fact that the increase of the age increases, in normal rapid cell growth, the delta between FFM and LM

8. BMI Calculation Formulas

8.1. BMI is the acronyms for Body Mass Index:

We decided to introduce il the algorithm this value even in the FFM and the Laon Mass are more precise than simple BM, but it has been done for a confirmation about the correctness of our speculation:

We confirm that all the variables' data are introduced according with Whitehous-Tanner **formulas**

MBI Formula= (weight: height ^{2}) / the result

Weight is expressed in kgs and height in meters

8.1.1. Male

Male: (0 -6 months)[1]

BMI = (3.5: 0.5^2) = (3.5: 0,25) = 14

Male (6 months-2 years)[2]

MBI= (7.5: 0,85^2) = (7.5: 0.7225) = 10,338

Male (2 years-5 years)[3]

MBI= (12.4: 0.95^2) = (12.4-0.9025) = 13.7

Male (5 years-14 years)[4]

MBI= (27.1 x 1,22) = (27.1: 1.48) = 14,25

8.1.2. Female

Female (0-6 months)[1]

BMI= (3.7: 0.5^2) = (3.7: 0.25) = **14.8**

Female (6 months-2 years)[2]

BMI= (7.9 x 0.85^2) = (7.9: 0.7225) = 10.45 **Female (2 years-5 years)[3]**

BMI= (12.9 x 0.95^2) = (12.9: 0.9025) = **14.293**

Female (5 years-14 years)[4]

MBI= (27.5 X1.222) = (27.5: 1,48) = 10.

Table 3 Body Mass Index (BMI)

BMI Formula= (weight: height 2) / the result **Weight is expressed in kgs and height in meters**
Male: (0 -6 months)1 BMI = (3.5: 0.52) = (3.5: 0,25) = 14
Male (6 months-2 years)2 MBI= (7.5: 0,852) = (7.5: 0.7225) = 10,338
Male (2 years-5 years)3 MBI= (12.4: 0.952) = (12.4-0.9025) = 13.7

Male (5 years-14 years)4 MBI= (27.1 x 1,22) = (27.1: 1.48) = 14,25
Female (0-6 months)1 BMI= (3.7: 0.52) = (3.7: 0.25) = 14.8
Female (6 months-2 years)2 BMI= (7.9 x 0.852) = (7.9: 0.7225) = 10.45

Table 4 Metabolic Rate Value Male

Basal Metbolic rate value in Male patients
Male: 88.362+(13.397x weight in Kg) +(4.799x height in cm) -(5.677 x age in years
Male (0-6 months)1 88.362+ (9.247 x 3.5) +(84.799 x 50) -(5.677 x 0.5) = 121.0765+4.239-2.8375=125.35-2,837= 122.685 kg/cal/die
Male (6 months-2 years)2 88.362+(9.247 x 7.5) +(4.799x 85) -(5.677 x 1,5 mean age in years) 88.362+(65.3925) +(407.915) -(8.155) =157.7545+319.915) = 561.6695-(8.155)= 553.5145 kg/cal/die
Male (2 years-5 years)3 88.362+(9.247 x 12,4) +(4.799x 95) -(5.677 x 3,5 mean age in years) 88.362+(114.6628) +(455.905) -(19.8695) = 639,0656 kg/cal/die
Male (5 years-14 years)4 88.362+(9.247 x 25) +(4.799 x 122) -(5.677 x 8.5 mean age in years) 88.362+(231.175) +(585.578) -(73.7545)= 831.3605 kg/cal/die
• Heart beating • Cell production • Blood Vessel Circulation • Nutrient fasting metabolism • Autonomic Respiration • Body temperature • Blood Vessel Circulation • Exercise • Anaesthetic Status

Table 5 Metabolic Rate Value Female

Basal Metabolic rate value in Female Patients
Female: 447.593+ (9.247 x weight in Kg) + (3.098 x height in cm)-(4.330 x age in years)
Female (0-6 months)[1] 447.593+ (9.247 x 3.7) +(3.098 x 50) -(4.330 x 0.5) = 447.593+(34,9) +(154.19) -(2.165) = 447.618 kg/cal/die
Female (6 months-2 years)[2] 447.593+ (9.247 x 7,9) +(3.098 x 85) -(4.330 x1,5 mean age in years) = 447,593+(73,51) -(6,495) = 543.867 kg/cal/die

Female (2 years-5 years)[3] 447.593+(9.247 x 12,9) +(3.098 x 95) -(4.330 x 3,5 mean age in years) 447.593+(119.280) +(294.31) -(15.550) = 845 kkg/cal/die
Female (5 years-14 years)[4] 447.593+(9.247 x 30) +(4.799 x 122) -(4,330 x 8.5 mean age in years) 447.593+(282,81) +(585.578) -(36,805) = 1279 kag/cal/die
• Heart beating • Cell production • Blood Vessel Circulation • Nutrient fasting metabolism • Autonomic Respiration • Body temperature • Blood Vessel Circulation- Exercise • Anaesthetic Status

8.2. Software

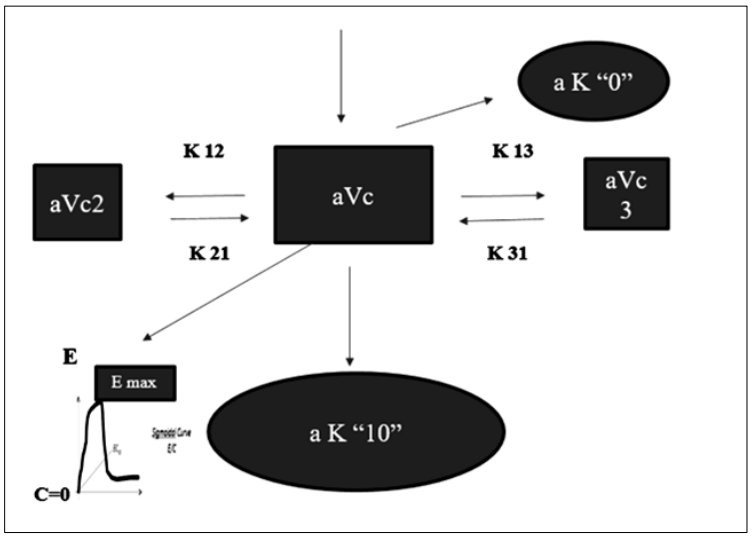


Figure 5 The New Three Compartment Pharmacokinetic model

As extensively shown in this article, each" K" is a function of the new Covariants shown below. The calculations are carried out by allocating the patient in one of the four identified ranges. The input parameters of the SW, as regards the Patient, are three. Age, weight, height and temperature which must be between 34-37 degrees centigrade. Depending on the age (expressed in months) the patient is allocated to one of the following four ranges

8.2.1. Age ranges [AGE] (age always expressed in months)

Range 1 = 0-6 months
Range 2 = 6m – 24m
Range 3 = 24m – 60m
Range 4 =60m – 180m

Depending on the range, the values of the covariants are established, determining the average reference values, which are shown hereinafter.

8.2.2. Medium Weight Male [W]

Range 1 = 3,3 [kg]

Range 2 = 7,5 [kg]

Range 3 = 12,4 [kg]

Range 4 = 25 [kg]

8.2.3. Medium Weight Female [W]

Range 1 = 3,7 [kg]

Range 2 = 7,9 [kg]

Range 3 = 12,9 [kg]

Range 4 = 27 [kg]

8.2.4. Medium Height (Male & Female) [H]

Range 1 = 0,50 [m]

Range 2 = 0,85 [m]

Range 3 = 0,95 [m]

Range 4 = 1,22 [m]

8.2.5. Basal Metabolic Rate Male [BMR]

Range 1 = 122,685 [Kcal/die]

Range 2 = 553,5145 [Kcal/die]

Range 3 = 639,0656 [Kcal/die]

Range 4 = 831,3605 [Kcal/die]

8.2.6. Basal Metabolic Rate Female [BMR]

Range 1 = 447,618 [Kcal/die]

Range 2 = 543,867 [Kcal/die]

Range 3 = 849,017 [Kcal/die]

Range 4 = 1279,07 [Kcal/die]

8.2.7. Fat Mass Male [FM]

Range 1 = 11

Range 2 = 11,01

Range 3 = 11,03

Range 4 = 11,04

8.2.8. Fat Mass Female [FM]

Range 1 = 11

Range 2 = 11,02

Range 3 = 11,05

Range 4 = 11,19

8.2.9. Loan Mass Male [LM]

Range 1 = 2,8

Range 2 = 6

Range 3 = 9,6

Range 4 = 21,68

8.2.10. Loan Mass Female [LM]

Range 1 = 2,78

Range 2 = 6,32

Range 3 = 9,76

Range 4 = 22

8.2.11. BMI Male

Range 1 = 14

Range 2 = 10,38

Range 3 = 13,7

Range 4 = 14,25

8.2.12. BMI Female

Range 1 = 14,8

Range 2 = 10,45

Range 3 = 13,29

Range 4 = 18,58

In the case of albumin, the SW violates the Range rule and to determine the K value to use in the calculations we start from the patient's age.

8.2.13. Albumin Value [AV] (Male &Female)

K = 0,45 (from 0 to 12m)

K = 0,37 (from 12m to 21m)

K = 0,58 (> 21m)

8.2.14. Organ Flow [OF] (Male & Female)

Range 1 = 270 [ml/min]

Range 2 = 480 [ml/min]

Range 3 = 854 [ml/min]

Range 4 = 3450 [ml/min]

*8.2.15. Organ Maturation index [OM] Male ((weight * 1,5)/height)*

Range 1 = (3,3*1,5)/0,5 =9,9

Range 2 = (7,5*1,5)/0,85 = 13,235

Range 3 = (12,4*1,5)/0,95 = 19,578

Range 4 = (25*1,5)/1,22 = 30,373

*8.2.16. Organ Maturation index [OM] Female ((weight * 1,5)/height)*

Range 1 = (3,7*1,5)/0,5 =11,1

Range 2 = (7,9*1,5)/0,85 = 13,941

Range 3 = (12,9*1,5)/0,95 = 20,368

Range 4 = (27*1,5)/1,22 = 41,72

The following clearance values are applied in case the patient temperature is equal to 37 degrees centigrade

8.2.17. Clearance Male [CL]

Range 1 = 0,551 $[\frac{nl}{min}/m^2]$

Range 2 = 0,774 $[\frac{nl}{min}/m^2]$

Range 3 = 3,103 $[\frac{nl}{min}/m^2]$

Range 4 = 10,5 $[\frac{nl}{min}/m^2]$

8.2.18. Clearance Female [CL]

Range 1 = 0,664 $[\frac{nl}{min}/m^2]$

Range 2 = 1,344 $[\frac{nl}{min}/m^2]$

Range 3 = 4,025 $[\frac{nl}{min}/m^2]$

Range 4 = 10,75 $[\frac{nl}{min}/m^2]$

The micro-rate constants for the three-compartment model are shown in Figure .

The differential equations describing the rate of change for the number of drugs in compartments 1,2 and 3 follows directly from micro rate constants.

In this case the differential equations are:

$$\frac{dx1}{dt} = I + x2 * K21 + x3 * K31 - x1 * K10 - x1 * k12 - x1 * K13 =$$

$$= I + x2 * K21 + x3 * K31 - x1(K10 + K12 + K13) \text{ Equation 1}$$

$\frac{dx2}{dt} = x1 * K12 - x2 * K21$ *Equation 2*

$\frac{dx3}{dt} = x1 * K13 - x3 * K31$ *Equation 3*

Where I is the rate of drug input, x is the amount of drug for a specific compartments and K is the micro-rate constants.

To solve the previous differential equations, we used Euler's method.

Euler's method is a straightforward numerical approach for solving **ordinary differential equations (ODEs)**. It estimates the solution by iteratively calculating future values of the function based on its current value and its rate of change (the derivative).

The update rule is:

$Y(n+1) = Y(n) + f(tn,Y(n)) * \Delta t$

Where:

- *Y(n):* the current value of the function,
- $f(tn,Y(n))$: the derivative of the function (rate of change),
- Δt: the time step (increment in time).

At each time step Δt, Euler's method updates the concentrations as follows:

$x_1^{n+1} = x_1^n + \Delta t * \frac{dx1}{dt}$

$x_2^{n+1} = x_2^n + \Delta t * \frac{dx2}{dt}$

$x_3^{n+1} = x_3^n + \Delta t * \frac{dx3}{dt}$

The SW that solves the differential equations requires the calculation of the Volume of Distribution of the central compartment along with all the micro-rate constants:

Vc Composition: Male-Female

Basal metabolic rate, Fat loan mass, Fat mass, BMI index, Albumin value, Continuous infusion speed as drug concentration level value, Organ Flow, Organ Maturation Index , Body drug clearance, Age in months, Weight, Height in meter fractions.termic dispertion slope value. K10 as Vd compulsory drug elimination after bolus.

8.2.19. Vc Male

(BMR M) / (Fat Loan Mass M + Fat mass M) / BMI M x (Albumin value) x (Organ maturation M) – (Termic Dispersion) x (Continuous infusion drug concentration value) x (Organ Flow in minutes)- Body Drug Clearance / (Age in months) x (Weight in Kg x Height) in meter fractions - 3% drug slope at biophase.

8.2.20. Vc Female

(BMR M) / (Fat Loan Mass M + Fat mass M) / BMI M x (Albumin value) x (Organ maturation M) – (Termic Dispersion) x (Continuous infusion drug concentration value) x (Organ Flow in minuts)- Body Drug Clearance / (Age in months) x (Weight in Kg x Height) in meter fractions - 3% drug slope at biophase.

8.2.21. K12 Male-Female

Vc final value, - (BMR M) / (Fat Loan Mass M + Fat mass M) / BMI M x (Albumin value) x (Organ maturation M) – (Termic Dispersion) x (Continuous infusion drug concentration value) x (Organ Flow in minutes)- Body Drug Clearance / (Age in months) x (Weight in Kg x Height) in meter fractions - 3% drug slope at biophase.

8.2.22. K21 Male-Female:

K12 final value, - (BMR M) / (Fat Loan Mass M + Fat mass M) / BMI M x (Albumin value) x (Organ maturation M) – (Termic Dispersion) x (Continuous infusion drug concentration value) x (Organ Flow in minutes)- Body Drug Clearance / (Age in months) x (Weight in Kg x Height) in meter fractions - 3% drug slope at biophase.

8.2.23. K13 Male-Female

K21 final value, - (BMR M) / (Fat Loan Mass M + Fat mass M) / BMI M x (Albumin value) x (Organ maturation M) – (Termic Dispersion) x (Continuous infusion drug concentration value) x (Organ Flow in minutes)- Body Drug Clearance / (Age in months) x (Weight in Kg x Height) in meter fractions - 3% drug slope at biophase.

8.2.24. K31 Male-Female

k13 value - (BMR M) / (Fat Loan Mass M + Fat mass M) / BMI M x (Albumin value) x (Organ maturation M) – (Termic Dispersion) x (Continuous infusion drug concentration value) x (Organ Flow in minutes)- Body Drug Clearance / (Age in months) x (Weight in Kg x Height) in meter fractions - 3% drug slope at biophase.

8.3. SIMULATION

8.3.1. Vc Male

(BMR M) / (Fat Loan Mass M + Fat mass M) / BMI M x (Albumin value) x (Organ maturation M) – (Termic Dispersion) x (Continuous infusion drug concentration value) x (Organ Flow in minutes)- Body Drug Clearance / (Age in months) x (Weight in Kg x Height) in meter fractions - 3% drug slope at biophase.

8.3.2. Age ranges [AGE] (age always expressed in months)

Range 1 = 0-6 months

8.3.3. Medium Weight Male [W]

Range 1 = 3,3 [kg]

8.3.4. Medium Height (Male & Female) [H]

Range 1 = 0,50 [m]

8.3.5. Basal Metabolic Rate Male [BMR]

Range 1 = 122,685 [Kcal/die]

8.3.6. Fat Mass Male [FM]

Range 1 = 11

8.3.7. Loan Mass Male [LM]

Range 1 = 2,8

8.3.8. BMI Male

Range 1 = 14

8.3.9. Albumine Value [AV] (Male &Female)

K = 0,45 (da 0 a 12m)

8.3.10. Organ Flow [OF] (Male & Female)

Range 1 = 270 [ml/min]

*8.3.11. Organ Maturation index [OM] Female ((weight * 1,5)/height)*

Range 1 = (3,7*1,5)/0,5 =11,1

8.3.12. Clearance Male [CL]

Range 1 = 0,551 [$\frac{nl}{min}/m^2$]

8.3.13. Termic dispersion

1% C every 1 ° C degree

Infusion Speed as per desired Target (mean)

K10 =10 ng/L/min

- **Propofol**: from 1 ng/L/ min^{-1} 12 ng/L/min^{-1} minus K31 value

  Desired target levels by 1.0 change unit per concentration levels

- **Alfentanil:** from 10 ng/L/min^{-1} to 120 ng/L/min^{-1}Desired target levels by 1.0 change unit x concentration levels:

- **Ketamine**: from 2 ng/L/min^{-1} to 8 ng/L/min^{-1};

8.4. Simulation

Vc Popofol ng/L/min in male; 0-6 monts

122,685 / (13,8) / (6,3) x (11,1) – (1,2) x (6,5) x (270) -(0,551) /59,4 =

427-128 (3% drug slope)

299

K12=

299/ (13,8) / (6,3) x (11,1) – (1,2) x (6,5) x (270) -(0551) /59,4

1.092-327

2869-860 (3%drug slope)

200,9

K13=

200,9/ (13,8) / (6,3) x (11,1) – (1,2) x (6,5) x (270) -(0551) /59,4

4757-1427(3% drug slope9

332,7

K21

332,7/ (13,8) / (6,3) x (11,1) – (1,2) x (6,5) x (270) -(0551) /59,4

12.514-3754 (3% drug slope)

876,0

K31=

876,0/ (13,8) / (6,3) x (11,1) – (1,2) x (6,5) x (270) -(0551) /59,4

20665-6199 (3% dug slope)

1444,6

8.5. Practically

Vc3 is define as= K31 value minus (-) EC50 time slope desired values and minimum target values it ranges from maximum target and time stop of infusion x total drug level concentration and infusion drug level value: we postulated a 3% sigmoidal slope value

it is a mean value Male-(Female):

Propofol 1%: (6.5 ng/L/min $^{-1}$); Alfentanil: (65 ng/L/min $^{-1}$); Ketamine: (4 ng/L/min^{-1});

8.6. The final number is "K"0 value

The "K" 0 value must be not more or less than 6% of final value as we postulated to define in the algorithm and software and defines the effective value of drug acting in real time at BioPhase.

9. Conclusion

It is very complex and difficult to try to write reliable conclusions to this two parts manuscript; we speculated about the chance to change some aspects of anesthesia that are very cloudy and sometimes seems to act like a never-ending calculation. We felt like we were only pioneering in a far Galactic Field.

But few aspects of the question are very clear to me:

- Many of the readers of the two manuscript wil find large number of very speculative questions to ask for an answer, and chances to arguing against what we wanted to explain and made concrete tryng to apply Mathematical theory concepts to human body expression and functions. And "vice versa", many times we had to do the exact opposite speculation and apply a human body expression and function in a mathematic mode. That is the reason why we wanted to refer our work to the "Quantistic Physics Laws "applied to human body.

  Our opinion is that if we look with clear intension and predisposition it has to be like we try to say

  Especially in anesthesia practice it is very difficult , if not impossible , to reach the 100 % of the desired result because we can't, and maybe we will never be able, have a total complete knowledge of the brain and hormonal and receptor response to an exogen stimulus , we will can activate our innate and not consciousness response,; it might be that we will arrive to get the complete result further up on the road of our tentative but…..a minimal acknowledgement there ever will be present. And we will be more precise in what we do only if we change our way of looking at anesthesia. And this is what nowadays it happens when we try to explain the Universe using Quantic Physical Laws.

- Consequently, we realized and understood that nowadays neonatal and pediatric or elderly patients anesthetic procedures are still not clearly classified and safely solve and/or controlled in many of their technical aspects. But we can get very close to give the patient a more safe and correct anesthesia if we decide not to control it only through the aspects of the clinical response to anesthetic drugs, but priorly giving the patients a computerized pathway, s very close statistically to the 100% of what we want the drug , every drug, has to do , and then we know the the drug action result with the control of clinical levels response, that is exactly the opposit way we perform anesthesia today.

Let's remember what one of the most extraordinary Physics Scientist of all time, Prof Richard Feynman, was used to say: "……a theory is only a theory until it is not validated and demonstrated by a mathematical equation….".

The attempt to hypothetically create the software described in this "two parts" manuscript follows Prof Richard Feynman's words. But also is the consequence and follows more than 44 years that one of the author spent in his

professional life in the research of a control over the patients safety and wellness during anesthesia; it had been done treating premature patients, having very low weight and birth Post Menstrual Age Time , most of them affected from the worst human disease that are, for sure, the congenital cardiac disease, and also supporting very elderly patients , in all clinical surgical and ICU fields.

In the end, please, let me say my deep intimal conviction as a doctor and as an anesthesiologist and Human: "It will always be the Anesthetist to close the loop and not a machine to decide when to do it". [60] [61] [62] [63] [64] [89] [90]

We will be honored if there will be only one chance that we had open a new way to approach to anesthesia conception.

And and how great we are to be an expression of the Universe in our role of "Humans".

Compliance with ethical standards

Ethic Involvement

The authors Disclaim all eventual "Ethic Involvement" in the manuscript purpose and text exposure.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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