A new formula to calculate the medicine dosage in function of the weight

Uma nova fórmula para calcular a dosagem de medicamentos em função do peso

Una nueva fórmula para calcular la dosis del medicamento en función del peso

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Abstract
A problem in relation to medicine concentration is linked to difference of age of the patients when the medicine was formulated for a pattern age, for instance, for adults. The use of this kind of medicine for children must be calculate correctly and some formulas based in the empirical mathematical methods were suggested and they are used nowadays; however, patients form a same pattern age but with different weight shows a different biotype and requires a different concentration of medicines, as well as the children and the elderly people. According, in this work, based on the mechanical mathematical model using the relation area/volume, a more exact calculus including the metabolism, was proposed to generate a more accuracy formula to calculate the medicine concentration for children and for people of different weight.
Keywords: Drug dosage calculations; Relation área/volume; Mathematics model.

Resumo
Um problema em relação à concentração do medicamento está relacionado à diferença de idade dos pacientes quando o medicamento foi formulado para uma idade padrão, por exemplo, para adultos. O uso deste tipo de medicamento para crianças deve ser calculado corretamente e algumas fórmulas baseadas nos métodos matemáticos empíricos foram sugeridas e são utilizadas atualmente; entretanto, pacientes com um mesmo padrão de idade, mas com peso diferente, apresentam biótipo diferente e requerem concentração de medicamentos diferente, assim como crianças e idosos. Nesse sentido, neste trabalho, com base no modelo matemático mecânico utilizando a relação área / volume, um cálculo mais exato incluindo o metabolismo, foi proposto para gerar uma fórmula mais acurada para calcular a concentração do medicamento para crianças e para pessoas de diferentes pesos.
Palavras-chave: Cálculos da dosagem de medicamento; Relação área/volume; Modelo matemático.

Resumen
Un problema con la concentración del fármaco está relacionado con la diferencia de edad de los pacientes cuando el fármaco se formuló a una edad estándar, por ejemplo, para adultos. El uso de este tipo de medicamentos para niños debe calcularse correctamente y se han sugerido y se utilizan actualmente algunas fórmulas basadas en métodos matemáticos empíricos; sin embargo, los pacientes con el mismo patrón de edad, pero con diferente peso, tienen un biotipo diferente y requieren diferentes concentraciones de fármaco, así como los niños y los ancianos. En este sentido, en este trabajo, a partir del modelo matemático mecánico utilizando la relación área / volumen, se propuso un cálculo más preciso que incluye el metabolismo, para generar una fórmula más precisa para calcular la concentración del fármaco para niños y personas de diferentes pesos.
Palabras clave: Cálculo de dosificación de drogas; Relación área/volumen; Modelo matemático.

1. Introduction

Notwithstanding the valorous action of the medicine in the corporal metabolism, there is an important restriction regarding the ability to obtain the correct effective concentration, especially for use in children (Lesar, 1998; Ernest, 2007; Ivanovska et al., 2014; Walsh, 2016).

Many studies on the dosing of medicines have been performed and continue to be carried out, mainly due to difficulties in determining the optimum concentration of the active compound for use in adult, paediatric (Balakrishan et al., 2006a; Salunke et al., 2017; Preis and Breikreutz, 2017) and geriatric (Liu et al., 2014) patients.

Indeed, errors associated with the dosage of medicine for children, adults and elderly patient represent the most common reasons for adverse drugs events in healthcare situations (Lesar, 1998). In addition, the misuse of medicines is an important issue in the health science field (Andrade et al., 2020).

Some articles have cited dosage errors in the use of medicines designed for adults in children (Balakrishan et al., 2006a; Balakrishan et al., 2006b; Liu et al., 2014; Salunke et al., 2017; Preis & Breikreutz, 2017). Determining the correct adjustment of the medicine dosage is a complex problem, as physicians must also consider aspects such as metabolic, physiological and weight differences among individuals (Lesar, Briceland and Stein 1997) and the polarity of drugs (Aversi-Ferreira, 2014). Furthermore, an increase in the production of a number of the drugs could generate additional problems regarding toxicology (Silva, Jesus & Branco, 2020).

There seems to be no consensus on how to solve this important aspect of medicine use (Bates et al., 1995), mainly in relation to the performance of standardised tests by physicians (Bates et al., 1995; Lesar, 1998). On the other hand, paediatricians use tables to determine the correct drug dosage for children; however, adverse outcomes were found to arise from the incorrect use of equations (Bates et al., 1995) in about 15% of studies (Lesar, 1998).

For a long time, researchers have been trying to solve problems associated with the dosage of medicines for children (Lack & Stuart-Taylor, 1991). However, problems related to weight differences among adult patients have been little explored.

For children, many empirical formulas have been used to determine medicine concentrations; for instance, the Salisbury, body surface area (BSA) (Lack & Stuart-Taylor, 1991), Young, Martinet and Cowling rules (Brasil, 2008).

Several critical studies have identified problems with the use of these formulas and suggested modifications (Lack & Stuart-Taylor, 1991). In fact, weight, body surface, metabolism and height have been proposed as the basis for calculating medicine concentrations for children (Ernest et al., 2007).

One problem related to the use of formulas for medicine dosage calculations is whether to use a direct mathematic relationship or an exponential one (Lack & Stuart-Taylor, 1991).

In fact, the relationship between area and volume was studied by Galileo (1638), who discussed differences in the weight (weight is directly proportional to volume for the same material) of animals and objects such as ships and bones and discovered that weight increases to a greater extent than the area for the same object.

In this way, a mock-up been increased for a real size, for instance, a boat would sink because the weight increase raised to third power and the area increase raised to second power, then the relationship between the area to volume is raised to 2/3 power.

Thus, the relationship between area and weight has been known since the time of Galileo. Hypothetically, this relationship could be used to generate a mathematic function for the concentration of medicines, such as in allometric studies of inter- and intraspecies differences (Gould, 1969).

Therefore, the aim of this study was to compare existing drug concentration formulas with one based on the area/volume relationship for weight differences between adults and differences in drug concentrations between children and adults.

2. Methodology

A literature search was performed with the terms "*medicine concentration*", "*medicine concentration calculus*" and "*pediatric medicine concentration calculus*". From the literature, formulas for calculating paediatric medicine concentration were found for medicines that were made only for adults, not for children. These formulas were empirical; therefore, they were based on available data and used the patient's age as the basis for the calculation. Only one paper considered the superficial body area of children to determine the medicine concentration (i.e., a mechanical approach into the rigors mathematical model) (Rodman, 1994).

Non-paper articles were found by searching the PubMed, Elsevier, Scielo and Scopus databases for articles on different concentrations of medicines considering weight variations of people in different phases of life, such as in infancy, adulthood and late adulthood (i.e., linked to aging).

A relationship between the weight was obtained in function of the mass variation power to 2/3 because the variation of the weight occurred according to the increase/decrease of the power 2 for area and power 3 for weight.

It is important to consider that mass is directly proportional to volume. Then, we adequate the area/volume formula to calculate the medicine concentration for the aging linked to weight and, it comes from the relation:

$$\frac{Subject\ dosage}{Pattern\ purpose\ medicine} = \frac{(weight\ of\ the\ subject)^{2/3}}{(weight\ of\ the\ pattern\ purpose\ medicine)^{2/3}}$$

Data for the concentrations of many medicines for children were compared using the empirical formulas and the formula proposed in this article.

We studied the differences and similarities between these formulas for calculating the medicine dosage for children in order to test our formula. Subsequently, the reliability of the proposed area/volume formula was determined.

StatPlus:mac (AnalystSoft Inc., 2020) software was used to calculate the coefficient of correlation at $p < 0.05$ (Figure 1).

3. Results

The Young, Cowley and Martinet formulas (Elias and Mariano, 2004; Brasil, 2008) are as follows:

Young

$$pediatric\ dose: \frac{child's\ age}{child's\ age\ +\ 12}\ x\ adult\ dose$$

Cowling

$$X: \frac{child's\ age\ +\ 1}{24}\ x\ adult\ dose$$

X: number of times that the paediatric dose is lower than the adult dose

Martinet

$$Y = \frac{child'sage\ +\ 1}{20}\ x\ 100$$

Y: percentage of adult dose.

These formulas are empirical, and they use the child's age to determine the paediatric dosage. In this work, we used the metabolic approach linked to the area/volume relationship to propose a new formula, as follows:

$$subject\ dosage = \frac{medicine\ dose\ x\ (weight\ of\ the\ subject)^{2/3}}{(weight\ of\ the\ pattern\ purpose\ medicine)^{2/3}}$$

To verify the reliability of these formulas, we tested 150 medicines designed for adults, 50 of which are shown in Table 1, to compare the results obtained between the commonly used empirical formulas and the area/volume formula proposed in the current article. The medicine concentrations are made for a healthy adult weighing 70 kg and 1.70 m tall. The adult medicine concentrations were used to calculate the concentration of the same medicine for a child aged 10 years old.

Table 1: Comparative data among the empirical formulas and the mechanical formula proposed in this article. Note: * MAD= maximum adult dose. *MPD= maximum pediatric dose. *AW= adult weight. *PW= pediatric weight. *CA= child's age. *FC= Cowling's Formula. *FY= Young's Formula. *FM= Martinet's Formula. *FT= Formula Test. *//= there were no studies. *- = was not specified in the package leaflet.

Medicamento	MAD	MPD	AW	PW	CA	FC	FY	FM	FT
	(mg)	(mg)	(kg)	(kg)	(years old)	(mg)	(mg)	(mg)	(mg)
Atenolol	100	//	70	31	10	45,83	41,67	55	58,09
Diazepan	20	//	70	31	10	9,167	9,09	11	11,62
Azithromycin	500	300	70	31	10	229,167	227,27	275	290,5
Cephalexin	4000	1500	70	31	10	1833,33	1818,18	2200	2324
Ibuprofen	3200	800	70	31	10	1466,67	1454,54	1760	1859,2
Dipyrone	4000	3000	70	31	10	1833,33	1818,18	2200	2323,99
Codeine phosphate	360	60	70	31	10	165	163,63	198	209,16
Acetylsalicylic acid	500	100	70	31	10	229,17	227,27	275	292,71
Captopril	150	//	70	31	10	68,75	68,18	82,5	40,99
Sertraline	200	50	70	31	10	91,66	90,91	110	116,19
Amoxicilin	6000	4650	70	31	10	2750	2727,27	3300	3560
Simethicone	500	-	70	31	10	229,17	227,27	275	296,72
Dexamethasone	15	-	70	31	10	6,875	6,82	8,25	8,9
Acetominophen	4000	2325	70	31	10	1833,333	1818,182	2200	1093,245
Dimenhydrinate	400	150	70	31	10	183,333	181,818	220	109,325
Domperidone	40	35	70	31	10	18,333	18,182	22	10,932
Fluoxetine	80	-	70	31	10	36,667	36,364	44	21,865
Nimodipine	90	-	70	31	10	41,250	40,909	49,5	24,598
Atorvastatin	80	20	70	31	10	36,667	36,364	44	21,865
Losartan	100	-	70	31	10	45,833	45,455	55	27,331
Omeprazole	120	40	70	31	10	55,000	54,545	66	32,797
Nimesulide	200	77,5	70	31	10	91,667	90,909	110	54,662

Ketoprofen	300	-	70	31	10	137,500	136,364	165	81,993
Betametashone	8	7,75	70	31	10	3,667	3,636	4,4	2,186
Prednisone	60	62	70	31	10	27,500	27,273	33	16,399
Scopolamine	100	100	70	31	10	45,833	45,455	55	27,331
Loratadine	10	10	70	31	10	4,583	4,545	5,5	733,000
Ciprofloxacin	1500	1500	70	31	10	687,500	681,818	825	409,967
Levofloxacin	1000	-	70	31	10	458,333	454,545	550	273,311
Fexofenadine	180	60	70	31	10	82,500	81,818	99	49,196
Carbamazepine	2000	1000	70	31	10	916,667	909,091	1100	546,623
Risperidone	16	-	70	31	10	7,333	7,273	8,8	4,373
Zidovudine	300	160	70	31	10	137,500	136,364	165	81,993
Oseltamivir	150	120	70	31	10	68,750	68,182	82,5	40,997
Fluconazole	400	372	70	31	10	183,333	181,818	220	109,325
Albendazole	400	400	70	31	10	183,333	181,181	220	109,325
Metronidazole	2000	697,5	70	31	10	916,667	909,091	1100	546,623
Diclofenac	200	_	70	31	10	91,667	90,909	110	54,662
Piroxicam	40	_	70	31	10	18,333	18,182	22	10,932
Etoricoxib	90	_	70	31	10	41,250	40,909	49,5	24,598
Metformin	2550	2000	70	31	10	1168,750	1159,091	1402,5	696,944
Pioglitazone	45	_	70	31	10	20,625	20,455	24,75	12,299
Furosemide	80	40	70	31	10	36,667	36,364	44	21,865
Methyldopa	3000	_	70	31	10	1375,000	1363,636	1650	819,934
Chlortalidone	200	50	70	31	10	91,667	90,909	110	54,662
Acetylcysteine	600	400	70	31	10	275,000	272,727	330	163,987
Digoxin	1,5	0,775	70	31	10	0,688	0,682	0,825	0,410
Clopidogrel	300	_	70	31	10	137,500	136,364	165	81,993
Ciprofibrate	100	_	70	31	10	45,833	45,455	55	27,331
Cimetidine	2400	930	70	31	10	1100,000	1090,909	1320	655,947

Source: Authors.

A regression test was performed to compare all formulas to each other. The correlation coefficient (R^2) indicates a strong correlation between the empirical formulas and the mechanical one described here (Figure 1).

Figure 1: Graphics and coefficient of correlation values (R^2) for each formula compared two by two to verify the reliability of the empirical formulas each other and them with the mechanical formula proposed in this article. FC= Cowling Formula, FY= Young Formula, FM= Martinet Formula, FT= Formula Test.
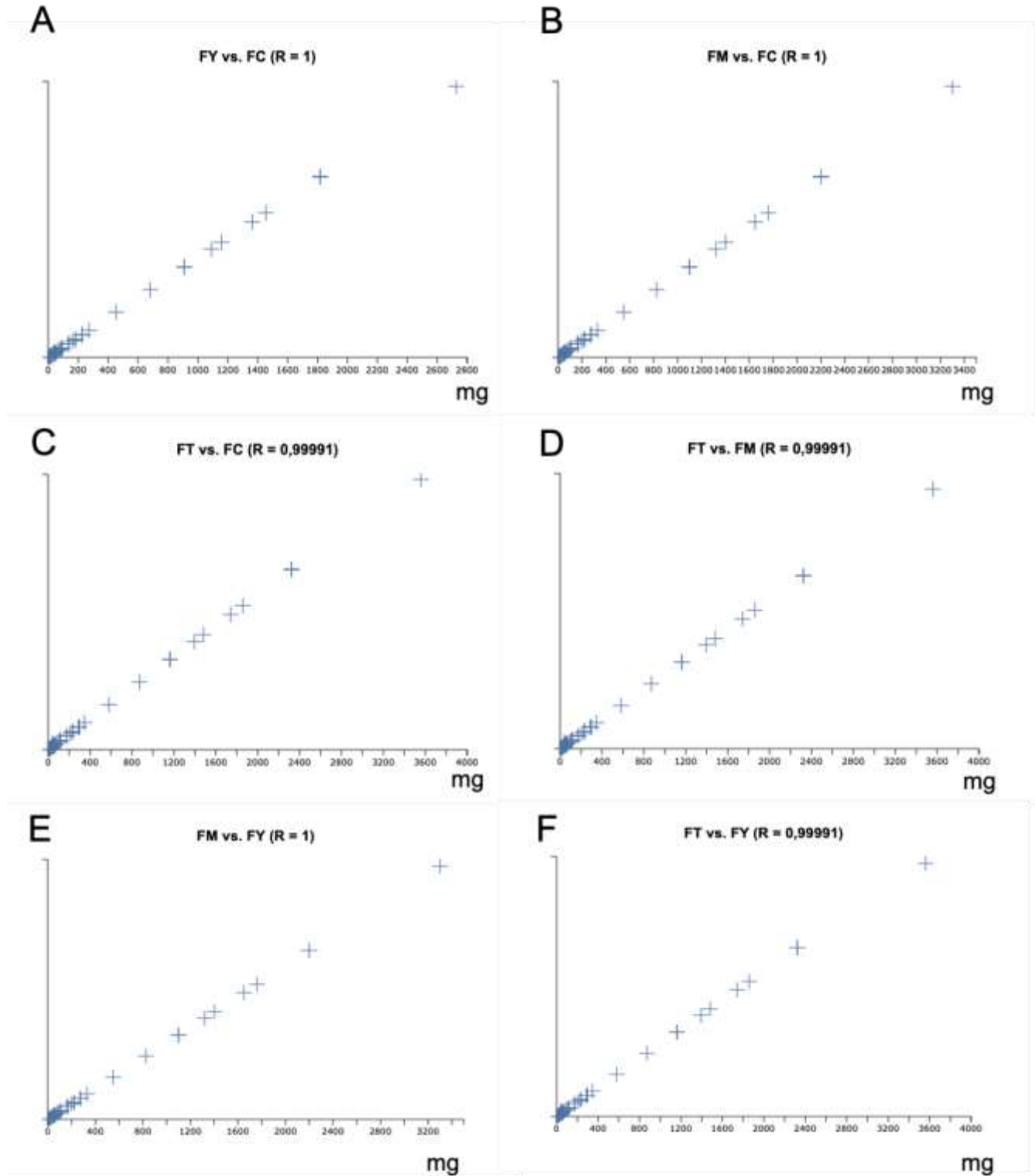
Source: Authors.

4. Discussion

According, the area/volume analysis targeted to metabolism study, was adapted to associate difference of the medicine concentration, obviously considering the rate area/volume between the bodies mass.

Until now, the formulas used to calculate the medicine dosage for children were derived from an empirical mathematical model based on data not necessarily associated with metabolism. Metabolism is the basis of medicine formulations for patients; therefore, the age of children and adults and were conveniently used to fit to empirical data should not be used for adults of different weights, as they will have different metabolisms.

A mechanical formula considering the metabolism and area/volume relationship could be used to determine the dosage of medicines designed for adults but used in children, for children of different weights, and for adults and elderly adults with a different metabolism and/or bodyweight.

Indeed, the relationship between area and volume is the basis for metabolism studies for investigating animal evolution and metabolism in terms of ecology, but it could also be used for the same species at different stages of development in a direct mathematical and physiological sense.

For a long time, formulas from empirical models have been used to adapt the concentration of medicines for children, and our mechanical formula shows an identical R^2 to previously cited formulas (Table 1 and Figure 1) for adapting medicines for children. As our mechanical formula uses metabolic data, one strength is that it could be used for adults of different weights, in addition to children and elderly people.

However, for elderly patients, there is an additional problem that must be considered. Some cases present an increase in bodyweight along with a decrease in metabolism, representing a physiological discrepancy in the formula.

The solution to this problem is to insert the correction factor (Δ) into the formula (see equation below); however, this correction factor must be based on experimental data from continuous studies of the effects of medicines in elderly patients, which was not performed in this work.

$$\frac{Subject\ dosage}{Pattern\ purpose\ medicine} = \frac{(weight\ of\ the\ subject)^{\frac{2}{3}} \cdot \Delta}{(weight\ of\ the\ pattern\ purpose\ medicine)^{2/3}}$$

Accordingly, the correction factor must be less than 1 for elderly patients because their metabolism is slower than that of adults. However, for children and adults with normal, excess or slightly increased bodyweight, our formula considers those variations.

5. Conclusion

The mechanical formula proposed in the current study can be used to obtain the optimal drug concentration for children and adults, with adjustments for the elderly and adults of any age. This formula represents a reliable basis for the general use of drugs in individuals who do not fit the specifications for the standard adult dose specified by the manufacturer. It is important to state that the mechanical formula proposed here is based on metabolic data, i.e., the area/volume correlation, and the fit of the graphs, shown by the correlation coefficient, indicates the reliability of this formula for use in people other than children, but also children with abnormal weight as adult with abnormal weight.

Other studies are necessary to (1) verify the details for variations in the use of our formula, (2) verify the correction factor (Δ) for elderly people, and (3) verify discrepancies among individuals based on their unique characteristics.

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