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THE USE OF CLINICAL PHARMACOKINETICS IN THE DESIGN AND CONTROL OF MEDICAL PRESCRIPTION

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ABSTRACT

The study was done in 14 patients hospitalized in Tijuana Baja California, State Hospital. Creatinine clearance and renal function were determined using the Crockfort-Gault nomogram. The half-life of gentamycin and dosage were obtained with the Fuller-Goldman method. This method presents an enormous advantage for calculating and obtaining doses which can be used to reach ideal plasmatic concentrations. This allowed us to readjust doses in an analytical way. Analyzing the data obtained of the plasmatic concentrations in a stationary state we found that 65% of the patients had serum concentrations that fell within recommended levels (2 – 4.9 mcg/ml) for the pathologies encounter in the study. In these cases the patients had a volume of distribution between 12 to 16.3L/Kg. This pharmacokinetic method is an excellent guide for the designing of individual regimen of dosification in a scientific way. Its predictive power is very acceptable for pharmacologic agents that have a very narrow therapeutical window. 35% of the cases did not reach plasmatic concentrations in stationary state because they presented an atypical pharmacokinetic parameter (obesity). Pharmacokinetics methods area beneficial for administrating pharmacologic doses in patients, they provide a scientific alternative to this procedure. Especially in pharmacologic agents that have a high potential for producing toxic side effects.

KEYWORDS: Pharmacokinetics parameters, Fuller-Goldman Method, Crockfort-Gault nomogram.

INTRODUCTION

This work presents an alternate form of dosage of a aminoglycoside (gentamicin) in safer and more effective form, based on the use of the Fuller-Goldman kinetic method, which is very useful for the design of dosing regimens in drugs that have a high potential for the development of adverse reactions and a narrow therapeutic window. The study was carried out in patients admitted to the State Hospital of Tijuana, who were admitted to the services of internal medicine, surgery, and genecology which included in its therapeutic handling gentamicin. Individualized dose of this aminoglycoside were obtained through the determination of a couple of plasma concentrations, in patients with infectious pathology due to Gram negative[14,15,29] obtaining kinetic parameters. Gentamicin is in the basic table of pharmacologic products for the State Health Department and prescribed in inpatients as well as outpatients, however it is common that it administered similarly in all patients, reason for which this contributes to the therapeutic inefficiency and other toxicity data.

Through the implementation of a kinetic method in the design of dosing regimens one of the objectives is to optimized the use of the pharmacologic agent.[1,2] The main source of variability in the response of many aminoglycosides is the volume of distribution , which is why this parameters was determined in each patient. The effective concentration of the drug according to the etiological agent was also considered.[4,5,6] Thus the estimating of the dose was also considered by the afore mentioned kinetic method.

We assess prospectively pharmacotherapy in hospitalized patients who received gentamicin. Adjust dose and therapeutic ranges through the monitoring of plasma levels and calculated the dose by the kinetic method of Fuller-Goldman.

This gave place to the following.

1. The use of a kinetic method.
2. Validate an analytical method to be used in the analysis of the sample.
3. Kinetic studies on patients and individualize therapy. Creation of its Individual therapeutic regimen.
4. Obtain kinetic parameters for aminoglycosides in Mexican patients.

The need in the health sector for individualize doses of certain pharmacological agents with a narrow therapeutic window is well known.[1,8,38] This has been proven through research with several drugs, aminoglycosides are pharmacologic agents that cause adverse effects such as

ototoxicity[41] and Nephrotoxicity.[43] The goal of this work was to find by plasma monitoring individualized kinetic parameters for the calculation of doses in patients with Gram negative[18,45] Pseudomonas[26], e. coli, Enterobacter, etc.) pathologies, which allowed for the adjustment of dose and thus avoid the empirical use of this aminoglycoside, decreasing the potential toxicity of this drug.[1,10,12,24]

The following concepts have been established

Serum concentrations correlate better with antibacterial activity.[21, 22, 23] Concentration depends on the volume of distribution and the speed of elimination.

These factors are influenced by the form of administration and extracellular fluid volume.[5]

1. Aminoglycosides presents a narrow therapeutic range.[16,19,21,27,33,36]
2. Patients with inadequate renal function should be monitored[27,28], the smallest decline in renal function[13,20] produces accumulation of the drug. There are patients with atypical kinetic parameters asobese[6,7,8,34,39], ascetics[3], burn[32,37], cardiac patients, febrile[31], preterm infants[30,35] requiring even greater monitoring and adjustment of dose.[6, 7, 8, 9]
3. The therapeutic efficacy and the reduction of toxicity should be based with the monitoring and control of plasma concentrations[5, 8, 17]

BACKGROUND

Aminoglycosides were among the most antimicrobial used pharmacological agents. The beginning of Pharmacotherapy with these was in 1957 with the introduction of kanamycin, they have evolved to the passage of the years[1316,25] They are considered bactericidal showing increased activity at alkaline PH, and present amino group and sugar. All you get as an amorphous hydrated solid without a characteristic melting point or absorption by chromatographic separation, UV has demonstrated that gentamicin consists of three components designated as C1, C2 and C1a.[11] Each one of the three components has five basic amine groups with different molecular weights. Common sugar is called garosamine and dissimilar them 2.6 - diamine sugars have been called A, B and C for gentamicin C1, C2, C1a respectively.[11]

The active ingredient is gentamycin sulphate which is a white hygroscopic, odorless powder. Biological activity is expressed in mcg of gentamicin by mg sulfate based on a power of 1000mcg mg (dry Base). It is very stable when stored in a tightly closed container at ambient temperature for at least five years with regard to its strength, specific rotation and PH Determination of gentamicin in bodily fluids.

We used a immunoassay method (EMIT) which is a homogeneous technique, its principle is based on the competence of the drug with the enzyme glucose-6-Phosphatase dehydrogenase by antibody binding sites. The activity of the enzyme Nicotine Adenine Dinucleotide oxidized in Nicotine Adenine Dinucleotide reduced results in the change in the absorbance which is measured spectrophotometrically.

Mechanism of action

Bactericidal agents that pass through the cell wall and join the 30S Ribosome, therefore inhibit protein synthesis. They are polar, have poor passive diffusion and require active transport to penetrate the bacterial cell wall, this transport depends on the pressure of oxygen and PH resistance from this drug is by plasmids, which stimulate the bacteria to produce enzymes that bind to the bacterial wall which inactivate gentamycin through adenilation, acetylation and phosphorylation groups hydroxyl and amine.[40,42]

Pharmacokinetics

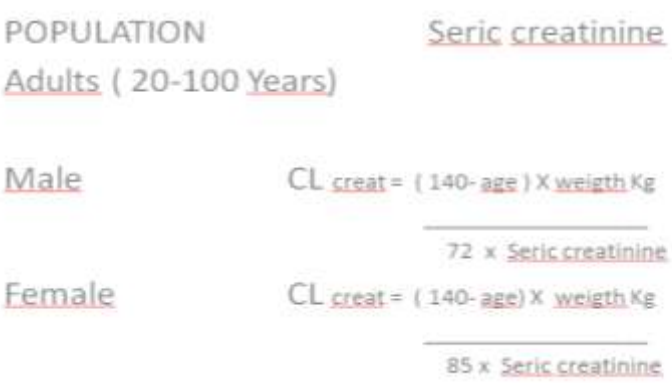
he half-life in gentamicin is highly variable, they reported 2-3 hours, a purge of 0. 82 ml/min, volume of distribution of 0. 31L/Kg. By its polar nature are largely excluded the majority of cells, central nervous system and eyeball. The volume of apparent distribution of this drug is 25% of lean body weight. There are patient with atypical pharmacokinetic parameters as obese patients which presented a large volume of adipose tissue, preterm infants who have one larger volume of Extracellular Fluid spaces and not fully developed glomerular function such patients must be monitored very closely.[40,44]

The plasma concentration of this drug similar to the rest of the aminoglycosides is produced by the initial dosage or loading depends only on the volume of distribution of the drug. Eliminating relies almost entirely by the kidney; there is a linear relationship between the concentration of creatinine and the half-life of all the amino glycosides in patients with moderate renal compromise. These drugs are highly soluble in water only if administered parenterally the serum levels achieved by intramuscular route are lower than intravenously. Reason why in acute pathologies IM administration is not recommended. Their volume of distribution approximates the extracellular fluid, protein-binding in not significant. They cannot be absorbed by the gastrointestinal tract or mucous membranes by the polarity presented. They penetrate easily into joints, pleura, pericardium and peritoneum. The Elimination of these agents relies almost entirely on kidney (filtration glomerular reaching

concentrations of 50 to 200 mcg/ml). When there is normal kidney 60% of all aminoglycosides are excreted in the first two hours after parenteral administration, and the 85% is excreted within 24 hours. Accumulated in renal cortex drug is excreted slowly in the next 10 to 20 days after the last administration. The smaller decline in kidney function produces accumulation of the drug, the lengthening of the half-life in these drugs is approximately linear, reaching up to 40 to 50 hours half-lives in anuric patients.

The estimation of renal function was based on the determination of creatinine, endogenous substance produced by muscle catabolism and almost in its entirety is excreted unchanged. The usefulness of this renal parameter is that is in direct proportion with the clearance of many drugs. We use the nomograph Cockcroft-Gault equation for the calculation. (Figure 1).

Figure 1
Nomogram Crockcroft-Gault



Maximum plasma concentrations of 2 to 3 mcg/ml are reached after the administration of 1 mg/Kg. The maximum concentrations of 12 mcg/ml should be avoided for long periods. We found that adequate serum must take into account the sensitivity of the etiological agent, the severity of the infectious process and the condition of the patient. We found that maintaining serum concentrations between 4 to 10 mcg/ml was controlled most of the infectious diseases studied in research.

MATERIALS AND METHODS

The study was carried out in hospitalized patients of the state hospital of Tijuana with a state of mind that allows them to understand and gave valid informed consent for participating in the study. Clinical trials should be in terms of respect for fundamental human rights and the

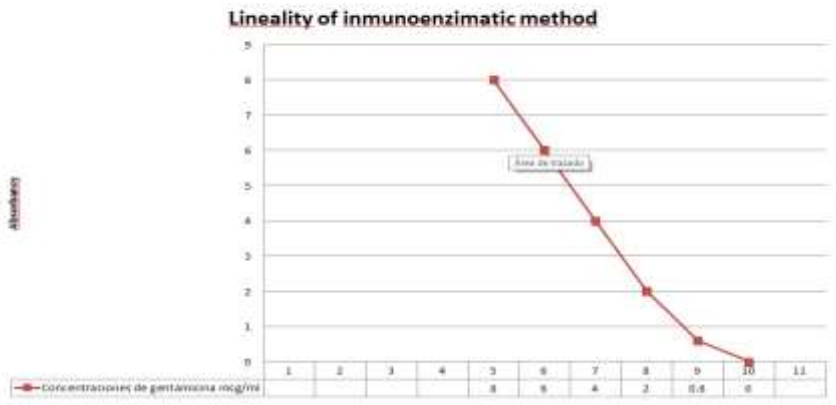
ethical postulates that affect the biomedical research with human beings, according to these effects the contents of the Declaration of Helsinki, the initial in Helsinki (1964) and subsequent updates in Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996) and Edinburgh (2000). This pilot[10] study protocol was approved by the Committee of bioethics in the Faculty of medicine and psychology from the Universidad Autónoma de Baja California, confidentiality protocols of the data were established and followed. The study was divided into.

a. study In-Vitro: The analytical method to quantify gentamicin in blood samples was an immunoassay (EMIT), with the analyzer Express Plus 6500 by Cyva-Corning which was validated (Table1). This method quantifies up to 6 mcg/ml, samples above these figures above these figures are diluted and tested again to obtain accurate results. This has an analytical control analyzing three standard curves by day and under the same conditions, through the use of low level controls, medium and high when samples are analyzed. For concentrations of 0.6 to 6 mcg/ml it presents a linearity of Y = 21.08 X + 774.41, presents an intraday C.V 2.41 to 5.74% accuracy.(Table 1 and figure 2)

Table 1. Precision intra-day Absorbance.

Mcg/ml	I	II	III	X	OF	C.V.%
0.6	759	762	800	773.66	18.66	2.41
2	801	850	842	831	21.46	2.58
4	890	901	915	866.15	39.27	4.53
6	975	909	950	892.55	51.31	5.74

Figure 2



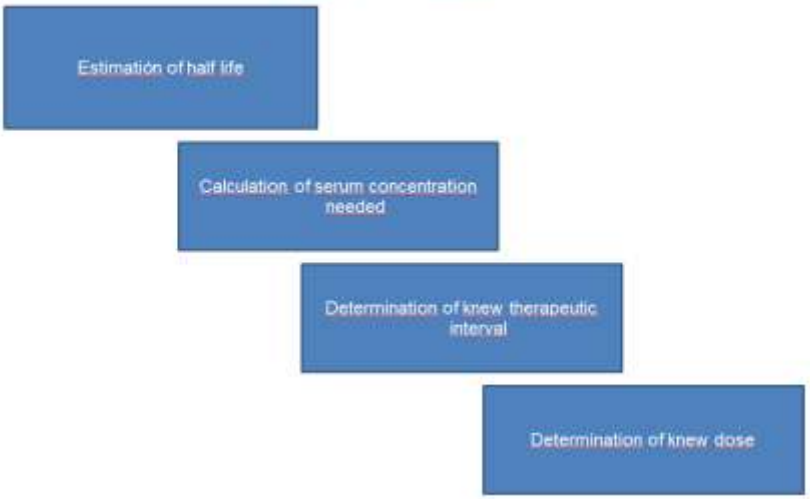
a In-Vivo Study: determination of the drug in patients using the kinetic method selected (Fuller-Goldman) and proposal for the individual therapeutic scheme. The design of the study was prospective, experimental involving patients that entered hospitalization services in the areas of internal medicine, surgery and genecology of the State Hospital in Tijuana. The selection of these took place in the review of income notes as well as the therapeutic indications which included in its management gentamycin. Renal assessment is carried out through the application of laboratory for the determination of urea/creatinine and the implementation of the nomograph of Cockcroft-Gault. The study is carried out in 14 adult patients, 11 female and 3 male characteristics and diagnosis are presented in table 2.

Table 2. Study group.

AGE	PATIENT IDENTIFICATION	WEIGHT (Kg)	SEX	DIAGNOSTICS	SERVICE
34 a	001	86	F	Bartholinitis	Gineco
18 a	002	57	F	Subacute gastroenteritis	M.int.
47 a	003	108	M	Acute gastroenteritis	M.int.
47 a	004	78	F	Urinary tract infection	Gineco
61 a	005	86.7	M	Staphylococcal Dermatitis	M.int.
33 a	006	134	F	Chronic vaginitis	Gineco
32 a	007	60	F	Acute abdomen	Surgery
27 a	008	57.4	F	Urinary tract infection	Gineco
26 a	009	82	F	Urinary tract infection	Gineco
28 a	010	79.8	F	Urinary tract infection	Gineco
63 a	011	62	F	Colpoplastia	Gineco
66 a	012	85	F	Acute otitis	M.int.
53 a	013	72	F	Urinary tract infection	Gineco
52	014	107	M	Acute gastroenteritis	M.int.

The drug was administered through bag infusion in an interval of 30 minutes. The first 3 ml of blood sample is taken at 30 minutes post infusion, the second sample takes 5 minutes before the second administration of it. Pharmacokinetic Parameters obtained T1/2, were calculated using the kinetic method of Fuller-Goldman (Figure 3), dose, dosing interval, reason for dose and dose standardized to 8 hours for each patient.

Figure 3
Fuller-Goldman Method



The average weight of the Group was 77.94 Kg, the median administered dose of 88.63 mg and the therapeutic range of 9.78 hours. (Table 3) Calculations are made for plasma concentrations at steady state of the adjusted dose (table 5) and therapeutic individual Schemes are obtained and presented to the treating physician.

RESULTS AND DISCUSSION

The EMIT immunoassay is used as the analytical method to quantify gentamicin in blood samples, using the analyzer Express Plus 6500 by Cyva-Corning. This method quantifies up to 6 mcg/ml, samples above these figures are diluted and tested again to obtain accurate results. This presents an analytical control analyzing three standard curves by day and under the same conditions, by the use of low level controls, medium and high whenever samples are analyzed. For concentrations of 0.6 to 6 mcg/ml present a linearity of Y = 21.08 X + 774.41, C.V 2.41 to 5.74% intra-day accuracy (Table1). The study group was formed by convenience since you couldn't predict the number of patients who would be hospitalized. The study was carried out in 14 adult patients, 11 female and 3 male, characteristics and diagnosis are mention in table 2. 57.14% were admitted to the genecology ward, 35.71% to internal medicine and 7.14% to surgery. The predominant Diagnose was of urinary tract infection. A relationship between the volume of distribution and rates obtained using the kinetic methods of Fuller - Goldman and a classical Kinetic equation is found. There is a concordance of dose when the kinetic parameter volume of distribution is between 12 to 16.38 L/Kg, the difference of dosage in in both methods is between 0.9 to 7.5 mg.

We found marked differences in doses between Fuller-Goldman and equations when the volume of distribution is above 16. 38 L/Kg, here figures range from 16.7 to 28.1 mg.

Below 12 L/Kg the difference is 11.9mg. Comparing volumes of distribution in the interval between 16.39 at 22.68 L/Kg we perceived differences in doses obtained by the method of Fuller-Goldman and the kinetics classic equations (mathematical method) ranging from 16 to 84.2 (Table 3), in this range of volume of distribution there are obese patients with atypical kinetic parameters. The weight of patients in the study tilted from 79.8 to 134 Kg, which corresponds on average 18% above the preferred weight for the entire study group.

Analyzing the 14 patients studied the average dose calculated by the kinetic method of Fuller-Goldman was 88.63 mg (Table 3), whereas for the mathematical kinetic method was 107.13 mg, this gives us a difference in dose of 18.5 mg, which corresponds to a 17.26% difference between both methods. Doses calculated for each patient in the study by the method of Fuller-Goldman was 0.76 to 1.76 mg/Kg, with a speed of infusion of 6.8 to 15.1 mg/Hr. The same parameter calculated by the method of classical kinetic mathematical equations was 1.04 to 1.66 mg/Kg, with a speed of 21.4 infusion of 8.4 mg/Hr.

Table 3. Adjustment of aminoglycosides doses.

VD L/Kg	Patient identification	Dose (mg)	Interval (Hr.)	Dose mg/Kg		RO mg/Hr		Dose mg/8 Hr
		FG	FG	FG	EFC	FG	EFC	
18	001	80	9	.93	1.11	8.8	12	70
11.9	002	60	8.7	1.05	1.33	6.8	9.5	55
22.6	003	87.2	7.9	.80	1.58	11	21.4	88
16.3	004	108.6	9.6	1.39	1.43	11.3	14	90
18.2	005	67.2	7.3	.77	1.04	9.2	11.3	74
28.1	006	215	14.7	1.60	1.26	14.6	21.2	117
13.8	007	105.8	7	1.76	1.66	15.1	12.5	120
12	008	80	9	1.39	1.40	8.8	10.1	70
17.2	009	65.7	8.2	.80	1.21	8	12.4	64
16.7	010	62.9	8.3	.78	1.44	7.5	14.1	60
13	011	72.7	7.2	1.17	1.09	8.4	10	80
17.8	012	69	9.9	.81	1.07	6.9	11.4	55
15.1	013	84.5	12	1.17	1.27	7	11.5	56
22.4	014	82.2	12	.76	1.26	6.8	16.8	55
N = 14								
Weight	77.94 kg	OF = 14.41 Kg						
Dose X	88.63 mg	OF = 37.77 mg						

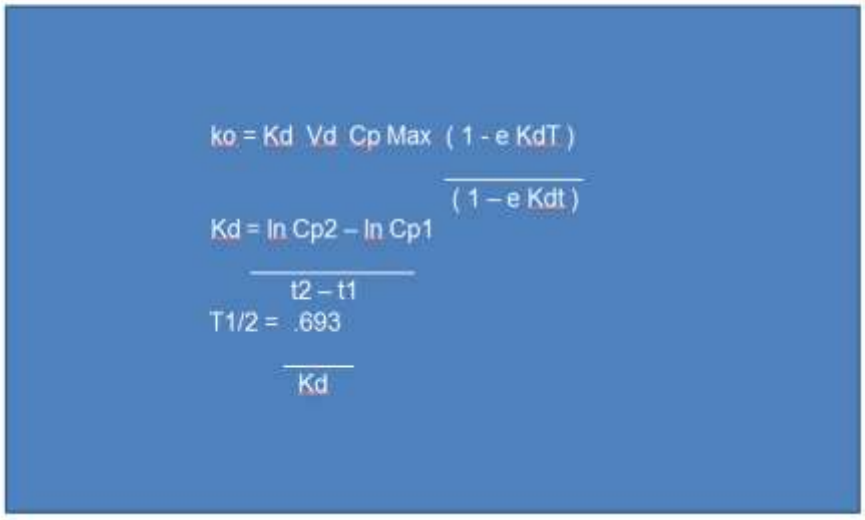
Inter.D	9.78 Hr	OF = 1.25 Hr	
VD X	17.36 l/Kg	OF = 4.36 L/Kg	

FG = kinetic method of Fuller-Goldman.

EFC = kinetic method of classical mathematical equations.

An analysis of variance was performed between the reasons of dosing (Ro) obtained and doses, between kinetic method of Fuller-Goldman (Figure 3) and the classical kinetic mathematical equations (Figure 4) not finding any statistical difference, the value of significance was 0.05, half-life times calculated between the two methods analysis gave us a difference of 0. 17Hr.

Figure 4
Pharmacokinetic Equations



In table 4 are the different plasma concentrations in patients in the study, the parameters of renal function were monitor by BUN, serum creatinine and the calculus of kidney function by the Cockcroft-Gault nomogram. Table 5 shows the results obtained by the method of Fuller-Goldman of the individual kinetic parameters. All found pathologies were handled according to plasma concentrations suggested for each Etiologic Agent. By calculating kinetic parameters using the Fuller-Goldman method we obtained Plasmatic concentrations at steady state in each patient. Therapeutic schemes calculated and presented to the medical staff,. Only 14.28% apply the Individual therapeutic scheme (ITS) with the specified doses and dosing interval.

Table 4. Plasma concentration at steady state.

Patient identification	Ro	CL	CP EE	CP Max	CP Min
	Mg/Hr	Ml/Min	Mcg/ml	Mcg/Ml	Mcg/Ml
001	8.8	4.2	2.09	4.99	0.54
002	6.8	2.93	2.32	5.66	0.92
003	11	6.42	1.71	4.31	0.45
004	11.3	3.63	3.11	7.53	0.89
005	9.2	3.6	2.55	4.82	1.13
006	14.6	4.53	3.22	6.21	1.99
007	15.1	2.58	8.85	8.49	2.28
008	8.8	2.85	3.08	5.8	0.86
009	8	3.04	2.63	6.1	3.81
010	7.5	4.53	1.66	4.18	0.43
011	10	2.83	3.53	5.5	0.86
012	6.9	3.81	1.81	4.4	0.52
013	7	2.86	2.44	4.75	1.03
014	6.8	5.03	1.36	3.94	0.27

Table 5. Pharmacokinetic parameters.

Patient identification	t1/2	VD	Dose	RO	Interv.Dosif.	Dose
	HR	L/Kg	Mg	Mg/Hr	HR	Mg / 8 Hr
001	3	18	80	8.8	9	70
002	2.9	11.9	60	6.8	8.7	55
003	2.6	22.6	87.2	11	7.9	88
004	3.2	16.3	108.6	11.3	9.6	90
005	3.6	18.2	67.2	11.3	7.3	74
006	4.9	28.1	215	14.6	14.7	117
007	3.5	13.8	105.8	15.1	7	120
008	3	12	80	8.8	9	70
009	4.1	17.2	65.7	8	8.2	64
010	2.7	16.7	62.9	7.5	8.3	60
011	3.3	13	72.7	10	9.9	80
012	3.3	17.8	69	6.9	9.9	55
013	4	15.1	84.5	7	12	56
014	4	22.4	82.2	6.8	11.1	55

CONCLUSIONS

The kinetic method of Fuller-Goldman presents a huge advantage to calculate the dose required to obtain ideal plasma concentrations. It allows us to analyze and adjust doses in an analytic way. It is an excellent guide for the design of individual dosing regimens and no

longer in an empirical form. Their predictive power is very acceptable for drugs with a narrow therapeutic window and where the volume of distribution oscillates between 12 a16.3 L/Kg. Analyzing the data obtained from the plasmatic concentrations at steady state calculated for gentamycin, shows that 65% of patients the values obtained where the ideal therapeutic ranges for the diseases found in patients in the study, which were Bartholinitis, subacute Gastroenteritis, urinary tract infection and Staphylococcal Dermatitis. We obtained a 80% success rate in the patients in whom they used the Individual therapeutic scheme.

In 35% of the cases we could not obtain a steady state plasma concentration for the ideal therapeutic range, there are a set of factors and atypical kinetic parameters in obese, preterm infants, and burn patients which contributes to this, the non-obtaining of the ideal dose. This kinetic method used presents a very viable and effective alternative for the administration of pharmacological agents that present a narrow therapeutic range and with a high potential for adverse reactions and toxic side effects.

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