Mathematical Model for Reducing the Concentration of a Chemical Substance Applicable in the Procedures of Plasmatic Treatment

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The objective was to study the correlation between the mathematical form of a chemical that we want to lower its initial concentration by the regressive method and the purging of the body's toxic present chemicals that need to be eliminated. We developed a chemical model, by which, to a given volume, with a certain (X - concentration %) dissolved substance in a container, the initial solvent, without solvit, is added (concentration 0%) with an equal rhythm to the one that is lost from the used container. The solution that will be lost will contain less and less concentrations of solvit, compared to the initial value X%. At the same time, the concentration of our chemical model will decrease. We applied a regressive mathematical formula to this model in order to calculate the concentration in the container in each moment. At the same time, we conducted treatment sessions in patients in which certain substances need to be eliminated, a procedure that complies with the described chemical model. We have demonstrated that at the same volume of 0% solvit wash, the substance purging with X% concentration is more effective, if the procedure starts with an initial loss of concentrated substance, with ulterior volume replacement. Laboratory data confirms the mathematical model in patients who started the procedure with plasma loss. The developed chemical model demonstrates that the initial loss of substance, hastens the decrease of the initial concentration, especially as the loss is higher at the beginning of the procedure if we use the same replacement volume without the substance in the initial solution. This model can be applied in plasma treatment methods in order to study the patient's safety and the amount of plasma the patient can lose at the beginning.

Keywords: mathematical model, TPE (therapeutical plasma exchange), volume replacement, plasma purge

In most cases, the substitution solutions used in plasma purification techniques, by plasmapheresis, are represented by freshly frozen plasma (FFP) and albumin [1-3]. These solutions are used in TPE (therapeutical plasma exchange), representing the treatment of over 100 pathologies.

Over the past 20 years, this type of treatment has been increasingly used, targeting new indications the field of neurology, nephrology, haematology, and especially in pathologies with immunological substrate [4, 5].

Their lack in sufficient quantities and their high cost requires efficient use. Note that for an adult of 70 kg in a single TPE session, about 15 FFP bags are required, the recommendation advocating 4-7 sessions. The use of a lower number of bags with the same effectiveness is a desideratum that we are trying to achieve [5].

In these procedures it is desirable to remove from organism chemicals or products that are in elevated concentrations: autoantibodies that are fixed by the links of H_2N-antigens, bilirubin - $C_{33}H_{36}N_4O_6$, triglycerides - $C_{55}H_{98}O_6$, heavy metals (Hg, Pb etc.), alpha amanitin - $C_{39}H_{54}N_{10}O_{14}S$, creatinine - $C_4H_2N_3O_5$, and ureea - CH_4N_2O [6, 7].

Experimental part

In our study, we used a heterogeneous lot of 18 adult patients to whom we applied a procedure of plasma drawdown. There were patients with autoimmune neurological pathologies, myasthenia gravis and polyradiculoneuritis.

The chemical model of elevated plasma concentrations of these substances could be extremely easily lowered in vitro. If we consider the plasma volume a 3L container with a concentration of substance that we want to lower, we would throw the entire container and put 3L of clean plasma (0% concentration of the substance we want to eliminate) (fig.1).

The plasma purge procedure involves the elimination of dirty plasma drop by drop (with high concentration of toxic substance) and replacing it at the same rhythm with pure plasma.

Our in vitro model implies calculating at every moment of the procedure the concentration in the container according to their placement volume, used until that time.

For this calculation we use a mathematical function exported to Excel, where the drop's place is taken by an arbitrary volume of 100 mL, the container will have 3000

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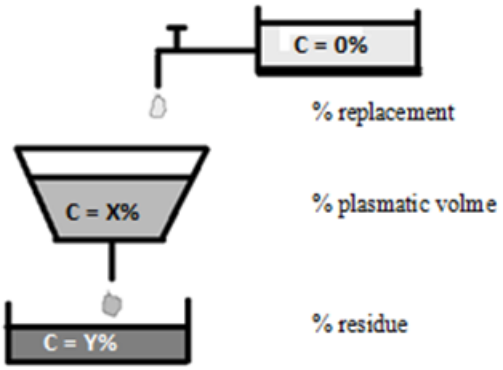

Fig. 1. Scheme of a plasmatic treatment procedure

mL and the replacement volume will also count 3000 mL. The literature considers the 1:1 ratio, as minimally required for an effective session. Thus, we will initially have 3000 mL replacement volume, 3000 mL plasma volume and 0 mL residue. In the middle of the session, there placement will be equal to the residue (1500 mL), and the plasma volume will be 3000 mL constant. At the end of the session the replacement will be 0 mL, 3000 mL residue and 3000 mL constant plasma volume.

Results and discussions

We consider a chemical substance plasma concentration of 10% and we eliminate 100 mL of plasma volume with a concentration of 10% and add 100 mL of replacement with 0% concentration.

Thus, in the central container we have 10% of 3000 mL, the equivalent of 300 g. Eliminating 100 mL of 10%, the equivalent of 10 g and adding 100 mL 0%, in the container we will have 290 g that represent a concentration of 9.66%. Continuing this pattern until the end of the procedure, we will have 30 steps that we import from an Excel table where we apply the following mathematical regression function [8-14].

In A column we have the remaining in the container solvit in grams, and in C column, its concentration in solution at a certain time (table 1).

According to data presented in table 1, we will have the following plasma concentrations:

C1: 300 mg/3000 mL = 10%

C2: (300 mg -300 mg x 100 mL/3000 mL)/3000 mL = 290 mg/3000 mL = 9.67%

C3: (290 mg-290 mg x 100 mL/3000 mL)/3000 mL = 280.33 mg/3000 mL = 9.34%

C9: 7.37%

C20: 5.25%

C30: 3.74%

Using this mathematical calculation at the end of the given process, we will have a 3.74% concentration of the chemical in the container that from a medical point of view represents a cleaning of 62.6%.

This calculation corresponds to the literature data [15-17], alleging that the use of a replacement volume equal to the plasma volume achieves a 63% purging (table 2).

Next we will try to calculate what happens if we remove an arbitrary volume of 1000 mL from the container, replace it with 1000 mL of 0% solution, and further proceed with the elimination of 100 mL while replacing with other clean 100 mL. We will remove 100 mg of substance and start the process with another 20 steps (10 we consider: 1000 mL = 100 x 10 steps). The new calculated purged percentage will be 66.1%, 5% higher than 63%, the percentage calculated in the previous paragraph.

This demonstrates that any loss, at any time, increases the effectiveness of the purge even if the replacement is used immediately after, which corresponds to literature data [18-23] (table 3).

The next aspect we aim to demonstrate is what happens to the whole process in terms of purging if this initial loss (from 100 mL to 1000 mL) is not replaced. We will apply the same chemical model in which, of the 3000 mL, were move a variable quantity that we no longer replace, following the steps model, with a loss of 100 mL from the container and replacement of 100 mL with 0% concentration, and in the end, we add the lost quantity (table 4). In this case we will have even greater effectiveness of the process. At 300 mL loss, we will have a purge of 69% (100% - 97.45/3L), at a 500 mL loss we will have a purge of 70.2% (100% - 90.09/3L) and at a stop of

=SUM(A1-A1*100/3000)

	A	B
1	300	0.1
2	290	0.0967
3	280.333	0.0934
4	270.989	0.0903
5	261.956	0.0873
6	253.224	0.0844
7	244.783	0.0816
8	236.624	0.0789
9	228.736	0.0762
10	221.112	0.0737
20	157.536	0.0525
21	152.285	0.0508
22	147.208	0.0491
23	142.302	0.0474
24	137.558	0.0459
25	132.973	0.0443
26	128.54	0.0428
27	124.256	0.0414
28	120.114	0.04
29	116.11	0.0387
30	112.24	0.0374
31	108.5	0.036

Table 1
THE REMAINING IN THE CONTAINER SOLVIT IN GRAMS - A COLUMN

X times plasma changed	Cf/Ci	Clearance (1 - Cf/Ci)
0.8	0.508	0.492
1.0	**0.368**	**0.632**
1.2	0.301	0.699
1.3	0.272	0.727
1.4	0.247	0.753
1.6	0.202	0.798
1.7	0.182	0.818
1.8	0.165	0.835
2.0	0.135	0.865

Table 2
ELIMINATION ACCORDING TO PLASMA CHANGED, THE RATIO BETWEEN THE FINAL (Cf) AND THE INITIAL (Ci) CONCENTRATION

=SUM(C1-C1*100/3000)

	C	D
1	200	0.066667
2	193.333	0.064444
3	186.889	0.062296
4	180.659	0.06022
5	174.637	0.058212
6	168.816	0.056272
7	163.189	0.054396
8	157.749	0.052583
9	152.491	0.05083
10	147.408	0.049136
20	105.024	0.035008
21	101.523	0.033841
22		

Table 3
CONCENTRATIONS AFTER IMMEDIATE LOSS AND 1000 mL REPLACE

1000 mL, a purge of 76% (100% - 71.68/3L), which corresponds to literature data [24-26].

This calculation demonstrates that any loss from the container at the beginning of the procedure, increases the effectiveness of the purge and that this is even greater as higher is the loss, in accord to literature [27, 28].

If we consider the container in the experiment the plasma volume of approximately 3000 mL for an adult of 70 kg, as shown in the literature [29-31], in the process of plasma purification any loss of plasma at the beginning of the procedure increases its effectiveness.

This process is even more important when the plasma loss is higher at the beginning of the procedure, than if this loss is replaced, until the end of the procedure, by fewer volumes.

If we consider the high costs of FFP or albumin, and the reduced FFP quantities availability in the territorial transfusion centers, effective TPE sessions can be done with the same results if we apply the presented plasma loss chemical model [32, 33].

In order to verify the practical applicability of the theory that we have demonstrated, we have used this procedure in patients. Because the plasma volume of a patient does not behave exactly as a container model, we have closely monitorized the hemodynamic impact that the plasma clearance can have. When the patient's' clinical condition allowed the plasma loss (hemodynamically stable patients, water retention patients), we started the procedure of plasma loss (between 700 and 1000 mL). Being hospitalized to Intensive Care, the hemodynamic impact has been closely monitorized. When tension decrease becomes important, plasma loss is stopped immediately, and 10% to 500 mL albumin replenishing is progressively performed, while the process continues with a standard TPE procedure where the draw down is equal step by step with the replacement [29, 32].

We monitored the hemodynamic effect in plasma loss and followed the clinically effect of the procedure. In 10 sessions in patients with myasthenia gravis we measured acetylcholine receptors antibodies at the beginning of a session and at the end of it (table 5).

The decrease in antibody titer was similar to that predicted theoretically in our chemical experiment and much higher than in the medical literature current data on the amount of replacement used. Clinical efficacy was also present in all cases at 24-48 h after the treatment was performed [31, 33].

If we try to calculate the quantities of replacements we save in order to have the same purification effectiveness, we will get the following results.

For a replacement of:

200 mL we will save 350 mL (1.5 FFP bags)

500 mL we will save 750 mL (3 FFP bags)

700 mL we will save 900 mL (4.5 FFP bags)

1000 mL we will save 1400 mL (7 FFP bags) - 7x150 EUR = approx. 1000 EUR.

=SUM(I1-I1*100/2000)

	G	H	I
1	270	250	200
2	260	240	190
3	250.3704	230.4	180.5
4	241.0974	221.184	171.475
5	232.1679	212.3366	162.9013
6	223.5691	203.8432	154.7562
7	215.2887	195.6894	147.0184
8	207.3151	187.8619	139.6675
9	199.6367	180.3474	132.6841
10	192.2428	173.1335	126.0499
20	131.8092	115.1048	75.47072
21	126.9274	110.5006	71.69718
22	122.2264	106.0806	
23	117.6995	101.8374	
24	113.3403	97.76387	
25	109.1425	93.85331	
26	105.1002	90.09918	
27	101.2076		
28	97.45913		

Table 4
CONCENTRATIONS AFTER LOSS WITHOUT REPLACE

No	Weight	Hematocrit	Patient estimated plasma volume (mL)	Ac nmol/liter		Clearance Protocol
				Before	After	
1	76	36	3040	9.128	2.241	75%
2	75	35	3000	5.547	1.181	80%
3	92	32	3680	0.978	0.147	85%
4	74	39	2860	4.814	1.145	77%
5	72	37	2880	2.509	0.552	78%
6	72	35	2920	2.091	0.504	76%
7	85	34	3400	10.415	3.233	70%
8	85	31	3440	3.369	1.28	66%
9	55	41	2470	0.394	0.100	75%
10	55	39	2510	0.367	0.070	81%

Table 5
THE VALUE OF ANTIBODIES (FOR ACETYLCHOLINE RECEPTORS) BEFORE AND AFTER THE SESSION OF TPE THROUGH THE PROTOCOL WITH THE INITIAL LOSS OF 100 mL OF PLASMA

Conclusions

If we have a container with a chemical diluted volume, in a given concentration, above which we add the same solvent without chemical substance, with a flow equal to that by which the substance is leaking from the container, the chemical substance purging process is even greater, as at the beginning of the process we have a bigger loss, and the replacement is later. If we extrapolate the chemical dilution process into a therapeutic plasma exchange session (TPE), the effectiveness of a TPE session is seven greater, as the plasma loss is more important at the beginning of the session, and the longer there placement is added, so that the patient's plasma volume does not undergo any significant changes. The plasma loss process should be performed under full hemodynamic monitoring in the Intensive Care Unit.

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