I[st] Department of Internal Medicine of Medical Academy in Lódz, Computation Centre of the Polish Academy of Sciences in Warsaw

Application of computer techniques to the optimalization of cardiac insufficiency therapy*

Tadeusz Bogdanik, Mieczyslaw Warmus, Wlodzimierz Geraga, Stanislaw Ciechowicz, Jan Zambrzycki

Our paper presents a practical application of the mathematical model of digitalis pharmacokinetics as the first step towards the algorithmization of digitalis derivatives therapy. The paper presents the results of a computer program written for the optimalization of five digitalis derivatives (oral and intravenous therapy), based on the mathematical description of digitalis-glycoside kinetics in patients with normal and reduced renal function. We applied five derivatives, characterized by different dynamics of their resorption and excretion after oral dosage and by different metabolic, especially intrahepatic, inactivation patterns. One of the basic difficulties in therapy is connected with changing the dosage when a particular cardiac glycoside is replaced by an other one of different pharmacokinetic characteristics. This may lead to toxic reactions because the total glycoside concentration is unknown. Mathematical description of glycoside kinetics is very helpful in the management of various kinds of cardiac insufficiency.

The paper presents the time-shared computer program to formulate dosage regimens of five digitalis derivatives. The computer program takes into account five derivatives: 1. Digoxin, 2. Lanatosid C, 3. Strophantin, 4. Proscillaridin A, 5. Acetylodigitoxin. Our detailed computer program for digitalis dosage was elaborated by Krystyna Domzal and Jan Domzal in the Cybernetics and Informatics Department of the University of Lódz (Poland), based on the method described by Jelliffe (5,6) in California. Jeliffe's (5,6) computer program was based on numerous experiments and clinical observations which showed that the

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serum concentration of tritiated digoxin or digitoxin and the glycoside loss from the body were prportional to the oral dose. The half-life of tritiated glycosides is similar in liver, kidneys and myocardium after the cessation of the drug. The glycosides are then eliminated from the body in a logarithmic manner. Jeliffe (3) described that the average rate-constant for all body losses for digitoxin is 0.1155 day^{-1} and for digoxin 0.4332 day^{-1}. The value of half-time of digoxin in patients with normal renal function is 1.6 day and the total body losses rate--constant is 0.4332 day^{-1} and this is the sum of faecal losses rate--constant k_f = 0.1690 day^{-1} plus the urine losses rate-constant k_u = = 0.2642 day^{-1}. Digoxin and Lanatosid C kinetics are profoundly affected by alterations in the patient's renal function,and the average half-time of digoxin found 1.6 day by normal renal function increases to 4.1 days in anuric patients. The alteration of digitoxin urinary losses in anuric patients increases the half-time from 6.0 days in normal patients to 8.65 days in anuric patients. The value of total body losses rate-constant for digitoxin is 0.1155 and this is the sum of faecal losses rate constant k_f = 0.0801 and the urine losses rate-constant k_u = = 0.0354. The urine loss rate-constant of digoxin and digitoxin are proportional to the serum and urine concentrations and this enables to compute the half-time for digoxin and digitoxin, based on actual serum and urine concentrations. After digitoxin loading the average urine loss is 30.6 % of the daily loss, 61.6 % is the daily nonurinary loss, and 7,7 % of daily loss is dependent on the metabolic conversion of digitoxin to digoxin. On the contrary, the urine loss of digoxin is 59 %, and nonurinary loss, dependent on the enzymatic intrahepatic inactivation, is 41 % (4).

In our computer program for digitalis dosage we have incorporated the average values of digoxin resorption given by many authors (8) as 81 %, in contrast to Jelliffe's (5,6) program (85 %), and we included the average Lanatosid C resorption 42 % /omitted in the program described by Jelliffe (5,6)/. The next modification of the program was the inclusion of the values of the Acetylodigitoxin 80 % and of Proscillaridin 25 % after an oral dose. The inclusion of new drugs led to the next modification /using the values described by Krautwald (7)/, namely we have incorporated the following values of daily losses:

Acetylodigitoxin - 10 % daily losses from the total body concentration
Proscillaridin A - 50 % - " - " - " -
Strophantin - 40 % - " - " - " -
Lanatosid C - 20 % - " - " - " -

In our program we included the influence of altered renal function based on blood urea concentration and we computed total constant rate of daily digoxin losses (K) using the method of least squares:

$$K = 0.1155 - \ln 0.699 + 0.205 \frac{\ln {}^{n}/_{40}}{\ln 3}, \quad /1/$$

n = blood urea concentration.

The computer program for digitalis dosage is appropriate only for patients with normal thyroid and hepatic function and normal electrolyte balance, (especially kalium) and for patients without clinical evidence of gastrointestinal malabsorption. The patients must not be treated with drugs altering digitalis absorption or metabolism.

Enclosed we present the abbreviated printout from the Polish computer "Odra-1304". Our detailed program was written in FORTRAN. Its various applications, including the possibilities of replacing one cardiac glycoside by another, are illustrated here on a single example. A patient was given Lanatosid C parenterally followed by oral administration of digoxin in changing doses and at different intervals. The total body glycoside concentration in micrograms of glycoside per kilogramme of body weight is computed as the first part of the computer program. After the total body glycoside concentration is computed, the physician selects its optimal level comparing the former and actual state of the patient. The computer prints out statistical data about digitalis toxicity frequency, according to various levels of total body glycoside concentration. Still the next change in our program comparing to Jelliffe's (5,6) one is the lower toxicity warning threshold. Our selection of glycoside level over 13.0 mcg/kg, reminds that the toxicity risk exceeds 21 %. The computer operator must then enter the selected inputs three times, before the computer accepts them.

The last modification in our program enables us the achievement of the desired total dose in four versions: in one, two, three or four

days. Owing to this, the selection of the optimal method of the necessary body glycosides concentration can be done.

The application of computer program in digitalis therapy based on average values of five derivatives' kinetics makes the treatment more precise. Its practical value is most prominent in the reduction of digitalis toxicity frequency. In our Internal Medicine Department 29 % toxic reactions were observed before employing the computer, the number of which was then significantly reduced to 14 % (1,2). The main adventage of our program is the possibility of everyday control of total serum glycoside concentration without drawing blood after each digitalis dose. The program has also didactic values in teaching controlled digitalis therapy.

We have studied the accuracy of our program in 72 inpatients and we stated that the program enables us to have more precise digitalis therapy and reduces the frequency of toxic reactions.

We have compared in 32 patients the computed digoxin concentration to serum digoxin level determined by radioimmunoassay according to Sheiner and Rosenberg (9). The abundant literature concerning the metodologies involved with the radioimmunoassay of serum digoxin concentrations indicates that there are many problems associated with accuracy, reproducibility and comparability of results. The numerous procedural modifications alone indicate dissatisfaction among the proponents of the various methods. The various methods which have been proposed, and the conflicting data obtained in many laboratories lead to the conclusion, that when comparing the computed data to evaluated data, the data received by computer program, based on many pharmacokinetic findings are more accurate for constant control of digitalis therapy. The computed values are in close connection with patients' findings, such as heart rate, electrocardiography, blood urea concentration and magnesium and kalium plasma concentrations. The control of serum digoxin concentration could not be performed every day and the computed values can be obtained after each dose and therefore are much simpler for permenent control of digitalis therapy, taking into account five derivatives, while the radioimmunoassay method enables us to determine only digitoxin and digoxin. The isotopic methods using strontium J^{131} showed less accuracy than the radioimmunoassay method, however they might be used to determine all cardiac glycosides. In our actual experience the mathematical model of pharmacokinetics of digitalis glycoside is much more exact in everyday physician practice than the laboratory findings regarded to serum digitalis concentration in consideration of great laboratory error.

AN EXAMPLE OF PRINTOUT OF THE DIGITALIS THERAPY PROGRAM COMPUTER PROGRAM FOR DIGITALIS THERAPY

Name Number

Previous digitalis therapy? Yes.

Fixed dose? No

Body weight: 52.00

Enter number of changed doses: 22

Enter for every changed dose: dose, drug (Acetdigit, Dox, Lanat, Stroph, Proscill)

Route (oral = 0, parenteral = p),

Blood ures, hours between doses

Dose	Drug	Route	Ures	Hours
0.800	LANAT	p	49.70	24.0
0.200	LANAT	p	49.70	12.0
0.200	LANAT	p	49.70	12.0
0.200	LANAT	p	49.70	12.0
0.200	LANAT	p	49.70	12.0
0.200	LANAT	p	49.70	12.0
0.200	LANAT	p	49.70	12.0
0.250	DOX	0	49.70	24.0
0.250	DOX	0	49.70	24.0
0.250	DOX	0	103.00	24.0
0.250	DOX	0	103.00	24.0
0.250	DOX	0	103.00	24.0
0.250	DOX	0	103.00	24.0
0.250	DOX	0	103.00	24.0
0.250	DOX	0	103.00	24.0
0.250	DOX	0	103.00	24.0
0.250	DOX	0	103.00	24.0
0.250	DOX	0	103.00	24.0
0.250	DOX	0	68.00	24.0
0.250	DOX	0	68.00	24.0

CALC. BODY GLYCOSIDE CONCENTR. AT BEGINNING AND END OF EACH DOSE

Number of dose	Acetdigit beg	Acetdigit end	Lanat - Dox beg	Lanat - Dox end	Strof beg	Strof end	Proscil beg	Proscil end	Total body concent(mg) beg	Total body concent(mg) end	Total body concent mcg/kg beg	Total body concent mcg/kg end
1	0.000	0.000	0.800	0.640	0.000	0.000			0.800	0.640	15.385	12.308
2	0.000	0.000	0.840	0.751	0.000	0.000			0.840	0.751	16.154	14.448
3	0.000	0.000	0.951	0.851	0.000	0.000			0.951	0.851	18.295	16.363
4	0.000	0.000	0.051	0.940	0.000	0.000			1.051	0.940	20.209	18.076
5	0.000	0.000	1.140	1.020	0.000	0.000			1.140	1.020	21.922	19.608
6	0.000	0.000	1.220	1.091	0.000	0.000			1.200	1.091	23.455	20.978
7	0.000	0.000	1.291	1.155	0.000	0.000			1.291	1.155	24.824	22.203
8	0.000	0.000	1.357	1.049	0.000	0.000			1.357	1.049	26.097	20.183
9	0.000	0.000	1.252	0.943	0.000	0.000			1.252	0.943	24.077	18.134
10	0.000	0.000	1.145	0.891	0.000	0.000			1.145	0.891	22.028	17.137
11	0.000	0.000	1.094	0.844	0.000	0.000			1.094	0.094	21.031	16.224
12	0.000	0.000	1.046	0.801	0.000	0.000			1.046	0.801	20.119	15.410
13	0.000	0.000	1.004	0.764	0.000	0.000			1.004	0.764	19.304	14.696
14	0.000	0.000	0.967	0.732	0.000	0.000			0.967	0.732	18.590	14.079
15	0.000	0.000	0.935	0.705	0.000	0.000			0.935	0.705	17.973	13.551
16	0.000	0.000	0.907	0.681	0.000	0.000			0.907	0.681	17.445	13.103
17	0.000	0.000	0.884	0.662	0.000	0.000			0.884	0.662	16.998	12.727
18	0.000	0.000	0.864	0.645	0.000	0.000			0.864	0.645	16.621	12.412
19	0.000	0.000	0.848	0.582	0.000	0.000			0.848	0.582	16.307	11.196
20	0.000	0.000	0.785	0.537	0.000	0.000			0.785	0.537	15.090	10.329
21	0.000	0.000	0.740	0.505	0.000	0.000			0.740	0.505	14.224	9.708
22	0.000	0.000	0.707	0.482	0.000	0.000			0.707	0.482	13.603	9.260

Total glycoside concentr. at your next dose should be:
0.48 mg 9.260 mcg/kg

Note the following data:

Total body concentr. (mcg/kg)	Incidence of digit arrythmias
8.5	13 %
13.0	21 %
17.0	27 %
25.0	42 %

Concentr. over 35.0 mcg/kg may be lethal!

Enter desired concentr. (mcg/kg), Blood ures and body weight (kg)
25.0 68.00 50.00

Risk of toxicity is 42.0 %

Retype input

25.0 68.00 50.00

Retype input

25.0 68.00 50.00

Retype input

25.0 68.00 50.00

Enter drug (Acetdigit, Dox, Lanat, Stroph, Proscill), Route (0,P), Doses day

Lanat 0 2

Version 1

Desired concentration will be achieved in one day.
To achieve and maintain your selected concentration with your chosen glycoside and route, the following dose program is suggested, if renal function and electrolyte balance do not change.

Day	Number of dose	Dose in mg	Lanat Tabs of 0.25 mg Lanat	Number of drops
1	1	0.91	3.66	32.9
	2	1.21	4.84	43.6
2	1	0.38	1.51	13.6
	2	0.37	1.47	13.2
3	1	0.36	1.43	12.9
	2	0.35	1.40	12.6
4	1	0.34	1.37	12.4
	2	0.34	1.35	12.2
5	1	0.33	1.33	12.0
	2	0.33	1.32	11.9
6	1	0.33	1.31	11.7
	2	0.32	1.30	11.7
7	1	0.32	1.29	11.6
	2	0.32	1.29	11.6

Version 2 in drops

16.5, 25.4, 26.6, 27.9, 12.9, 12.6, 12.4, 12.2, 12.0, 11.9, 11.8, 11.7, 11.6, 11.6.

Version 3 in drops

11.0, 19.3, 20.0, 20.7, 21.5, 22.4, 12.4, 12.2, 12.0, 11.9, 11.8, 11.7, 11.6, 11.6.

Version 4 in drops

8.2, 16.3, 16.7, 17.1, 17.6, 18.2, 18.9, 19.5, 12.0, 11.9, 11.8, 11.7, 11.6, 11.6.

52 sec.

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