THERAPEUTIC DRUG MONITORING OF DIGOXIN AND ITS MANAGEMENT

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Introduction

Digoxin, together with diuretics, constitutes the traditional approach to the treatment of congestive heart failure. However, several serious doubts have been cast in relation to the use of the drug, due to its narrow therapeutic range. Monitoring digoxin blood levels should enable the clinician to tailor the dose and produce a therapeutically-valid blood concentration. However, questions could be raised regarding how much information can be derived from serum digoxin concentrations which cannot be inferred from clinical observation alone.

Studies were carried out:

1) to assess and verify the physician's reasons for requesting serum digoxin levels
2) to investigate digoxin dosage regimens and routes of administration employed in a local health centre
3) to investigate inter- and intravariability in serum digoxin levels for a population of geriatric patients
4) to assess the predictive powers of a computerised system in determining serum digoxin levels

Methodology

Study 1: A questionnaire was issued to all house physicians, 149 in number, at St. Luke's Hospital. This consisted of a list of generally accepted indications for requesting serum digoxin concentrations. The physicians were asked to indicate those reasons which they considered valid.

Study 2: This study investigated the dosage regimens and routes of administration adopted for digoxin at Saint Vincent de Paule Residence (SVPR). All the 57 patients taking digoxin at the residence were considered. Relevant information was obtained from the patients' medical histories and through questioning of the hospital staff.

Study 3: The degree and extent of intervariability and intravariability in serum digoxin levels in a population of digitalised patients at SVPR was assessed. Information was obtained from the patients' medical histories.

a) The patients were grouped according to the current daily dose being administered, and the corresponding serum level taken, classified as sub-therapeutic, therapeutic or toxic. 52 patients out of the 57 in Study 2 were eligible for the intervariability study. Of the 5 patients considered ineligible 3 were being administered exceptional doses (2 on 0.1875mg daily, 1 on 0.125mg twice daily), whilst the other 2 patients died, and had to be omitted, since a serum digoxin had not been taken at that particular dosage strength. Of the remaining 52 participants, 14 had not had a serum digoxin level taken at the then current dose of digoxin on which day were being maintained. It was therefore, necessary to request the taking of such blood levels (these being carried out at the Pathology Department, St. Luke's Hospital,through RIA). Of the 14 requests submitted, 11 were taken, the results of which were included in the study, whilst 3 patients were non-compliant, and would not allow a blood sample to be taken for analysis.

b) To be eligible for the intravariability study, patients had to have at least 3 serum digoxin levels taken when on a particular dosage regimen. 21 patients out of the 57 in Study 2 were eligible. The serum digoxin levels for each patient were classified as sub-therapeutic, therapeutic or toxic.

Study 4: In this study, patients who (i) had undergone a change in dosage regimen and (ii) had their serum digoxin levels measured when on both regimens were considered. The patients' data were keyed into a computerised system for dosing and therapeutic drug monitoring (SIMKIN), and the predicted serum digoxin levels obtained were compared with the actual ones (i) for the first level taken and (ii) for the second level, after the system had modified the patient's volume of distribution and elimination half-life according to the first serum level.

Results

Of the 149 questionnaires issued, 56 were returned completed, 16 were returned unanswered and 77 physicians failed to answer.

Table 1: Classification of physicians' reasons for requesting serum digoxin levels

Reason	Number of physicians	
	No.	%
Routine check	10	17.8
Suspected underdigitalization	22	39.0
Suspected overdigitalization	56	100.0
Suspected clinical toxicity	6	10.7
Lack of history on digoxin use	52	93.0
Unexpected degree of response to a dose	16	28.6
Patient on unusually large or small dose	48	85.7
Suspected non-compliance	10	17.9
Suspected bioavailability problems	12	21.4
Suspected drug interactions	30	53.6
Suspected pharmacokinetic interference from concurrent disease	1	0.0
Others	0	0.0

Study 2

Table 2: Classification of dosage regimens and routes of administration at SVPR

Dosage form	Daily dose (mg/day)	Frequency of dosing	Number of patients	
			No.	%
Tablet	0.0625	once daily	9	15.8
Tablet	0.125	once daily	33	57.9
Tablet	0.1875	once daily	2	3.5
Tablet	0.25	once daily	12	21.1
Tablet	0.25	0.125 bd	1	1.8

Study 3

Table 3: Classification of intervariability of serum digoxin levels in patients on various dosage regimens

Dosage Regimen (mg/day)	No. of patients on regimen	Serum Digoxin Levels sub-therapeutic	Therapeutic	Toxic
0.0625	9	6	3	-
0.125	31	10	17	2
0.250	12	-	9	2

Table 4: Classification of intravariability of serum digoxin levels in 11 patients on various dosage regimens

Dosage Regimen (mg/day)	No. of patients on regimen	Serum Digoxin Levels sub-therapeutic	Therapeutic	Toxic
0.0625	10	6	4	-
0.0625	4	3	1	-
0.125	6	2	4	-
0.125	4	3	1	-
0.125	3	2	1	-
0.125	3	2	1	-
0.125	3	1	2	-
0.125	4	3	1	-
0.125	4	3	1	-
0.25	3	-	2	1
0.25	3	-	2	1

Study 4

When SIMKIN was run using the data collected from SVPR, it was found that for the first serum digoxin level, the actual and predicted levels were statistically different according to the student's t-test ($t_{calculated}$=2.086, $t_{tabulated}$=2.056, $p>0.05$ n=27). However, after the patient's data was adjusted by the program on the basis of the first level,

the actual and predicted levels for the second serum digoxin similar were statistically similar ($t_{calculated}$=0.0786, $t_{tabulated}$=2.086, p>0.05 n=27). Moreover, the % changes in $t_{1/2}$ and V_d needed to optimize the program to the patient were found to be greater after the first digoxin level was keyed in than after the second level was input.

Table 5: Table showing statistical difference in mean % changes in V_d and $t_{1/2}$ needed to optimize program to patient after first and second digoxin levels (n=27, p>0.05, $t_{tabulated}$=2.056)

Parameter	Point 1	Point 2	$t_{calculated}$
V_d	+32.76%	+0.159%	4.246
$t_{1/2}$	-10.60%	+1.730%	2.581

Conclusion

The reasons listed in the questionnaire have all previously been identified as important reasons for requesting serum digoxin levels. Hence, the ideal answer to this questionnaire would have been to indicate all the reasons. In actual fact, only 1 physician did so. The most notable reason which was not indicated as acceptable by local physicians was 'Suspected pharmacokinetic interference from concurrent disease'. This is in fact so important that renal function is routinely checked when a patient is on digoxin therapy.

All of the patients at SVPR were given oral therapy. 15.8% of patients were on a 0.125mg daily dosage. Since this dosage strength was not available, it was observed that it was considered preferable by hospital staff to administer half a 0.25mg tablet, rather than adopting the more accurate method of giving the patient two tablets of 0.0625mg. similarly, the 0.1875mg dose was administered by giving 3/4 of a 0.25mg tablet, rather than 3 0.0625mg tablets. Such a practice leads to a large degree of inaccuracy, and hence a loss of therapeutic efficacy.

The ultimate goal in drug therapy is to administer an appropriate dose of a drug, such that the serum levels subsequently fall within the therapeutic range, resulting in therapeutic efficacy. This also minimises adverse effects. Such a practice is not simple with digoxin, due to the

narrow therapeutic range (0.8 - 2.1ng/ml). This is attested to by the inter- and intravariability observed in serum digoxin levels. Such a fact accentuates the need for therapeutic drug monitoring of digoxin.

Computerised aids for therapeutic drug monitoring are becoming increasingly more effective, as the study with the SIMKIN program revealed. It was in fact shown that without a blood sample, the program can adequately predict expected serum concentrations though not with notable accuracy. However, following the keying in of a single blood level, and subsequently refining the patient's pharmacokinetic parameters, the program could accurately predict subsequent blood concentrations. The regular use of such a computerised pharmacokinetic aid would therefore greatly help in increasing the degree of therapeutic efficacy obtained when prescribing with digoxin.

References

Crevasse L et al: A program for optimizing drug dosage regimens: digoxin. Clinical Computing 1988 Vol. 5 No. 2 27 - 35

Hladik W.B. and Dujovne C.A.: One hundred digitalis blood levels: A utilization review. Eur. J. Clin. Pharmacol. 1979, 15, 411 - 415