Clinical Topics

Use and misuse of a digoxin assay service

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Abstract

In a study of the use of a digoxin assay service and its influence on clinical management 285 assay requests were audited over 12 weeks. For 67 (24%) there was no clear clinical indication for the request and for 140 the period between the last dose of digoxin being given and the blood sample being taken was either unknown or inappropriate. Treatment in 64 patients (22%) was changed either while awaiting the assay result or after receiving it; 24 of these changes bore no relation to the original clinical indication for requesting the assay, suggesting that such changes were based on the assay result alone. Of samples collected within six hours after the last dose, 15 of 69 (22%) led to a reduction in treatment compared with 10 of 116 (9%) taken after six hours ($p<0.025$), thereby highlighting the danger that incorrectly timed samples may lead to inappropriate clinical decisions.

Introduction

The need for a critical assessment of the value of therapeutic drug monitoring services has recently been emphasised.[1-3] The most extensively monitored drug is digoxin because of its widespread clinical use, difficulty in interpreting clinical response, and the ready availability of simple analytical techniques. There is, however, considerable overlap between therapeutic and toxic plasma digoxin concentrations[4] making it difficult, if not unwise, to base decisions about treatment on these measurements alone.

We performed an audit of the digoxin assay service in Freeman Hospital, Newcastle upon Tyne, to assess the clinical indications for assay requests and the role of the assay in clinical management.

Methods

Freeman Hospital is a general hospital with 800 beds and includes a regional cardiology unit. The laboratory provides a daily digoxin assay service for several hospitals and general practitioners throughout the Northern region. Our investigation, however, included only requests originating within the hospital over 12 weeks. Two weeks before the start of the study a circular indicating its purpose and giving relevant practical guidance was sent to all medical staff in the hospital.

When requesting a digoxin assay doctors were asked to complete a short questionnaire giving details of the patient's age, digoxin dosage, time elapsed between the last dose being given and the blood sample being taken, and the reason for using digoxin. Reasons for making the request were sought under the headings of suspected toxicity, subtherapeutic response, impaired renal function, and change in drug treatment likely to lead to interaction with digoxin. The requesting doctor was also asked to indicate whether a change in digoxin treatment would be made while awaiting the assay result and about the nature of any such change. When a request for a digoxin assay was received in the laboratory without these details the analysis was performed as usual and the result returned directly to the requesting doctor with a questionnaire for retrospective completion. Prospectively and retrospectively completed questionnaires were treated separately in the subsequent analysis of the data.

A second questionnaire was included with all assay report forms, seeking information on any intended changes in the patient's digoxin treatment in the light of the assay result and asking whether the doctor had found the result useful in patient management.

Digoxin assays were performed with the Serono MAIA radioimmunoassay kit (Serono Diagnostics, Woking), and potassium and creatinine concentrations were measured on a Beckman Astra (Beckman, USA).

Results

GENERAL AUDIT STATISTICS

During the 12 weeks 623 digoxin assays were performed, of which 358 arose from requests from within the hospital and were included in the audit. Both questionnaires were returned for 285 (80%) of the analysis requests audited and, of these, the first questionnaire was completed prospectively in 128 cases (45%). Eighty eight requests (31%) were received from outpatient clinics. Two hundred and seventeen patients (76%) were aged over 60, 23 (8%) had plasma potassium concentrations of less than 3·5 mmol(mEq)/l, and 94 (33%) had plasma creatinine concentrations greater than the laboratory upper reference limit of 125 μmol/l (1·41 mg/100 ml).

TABLE I—*Clinical indications for digoxin assay requests*

Clinical indication	No (%)* of questionnaire responses: Prospective (n=128)	Retrospective (n=157)
Suspected toxicity	35 (27)	43 (27)
Subtherapeutic	34 (27)	32 (20)
Toxic or subtherapeutic	6 (5)	22 (14)
Renal impairment	17 (13)	51 (32)
Possible interactions	22 (17)	14 (9)
No stated reason	33 (26)	34 (22)

* Multiple responses were permissible so the total stated indications exceed 100%.

REASONS FOR ASSAY REQUESTS

Table I shows the stated reasons for requesting the drug assay. The categorisation used was based on individual clinical judgments rather than on a standardised protocol. χ^2 Analysis of these data indicates significant differences between the overall prospective and retrospective responses ($p<0.001$). In particular, a higher proportion of the requests with retrospective responses were attributed to renal impairment and toxic or subtherapeutic effects. This difference could be partly due to the availability

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of additional information on renal function but could also be explained by differences among clinical units in the prospective completion of questionnaires. These reasons also seem the most likely to be chosen retrospectively in the absence of a clear justification for the assay.

A further difference between the groups was the greater number of possible interactions in the prospective responses, but it is unclear why this should be so. Sixty seven requests (24%) were made without any apparent clinical reason. Some may have been directed at assessing compliance, but only one specifically identified this as the reason for the request.

TIME OF BLOOD SAMPLING

Figure 1 shows the mean digoxin concentrations and the time of blood sampling relative to the last dose of digoxin. Sampling times were quoted in 225 responses (79%). In the remaining questionnaires sampling times were not stated and presumed to be unknown. In 80 cases blood samples were drawn within six hours after the last dose of digoxin before drug absorption and distribution were complete. Mean digoxin concentrations varied with respect to time of sampling, being highest between two and four hours after the last dose. Individual digoxin concentrations varied widely, with a large proportion of high concentrations occurring shortly after the last dose. Of the 80 samples drawn before six hours, 25 (31%) had a digoxin concentration equal to or greater than 2·56 μmol/l (2·0 μg/l). In contrast, of 121 samples drawn from six to 24 hours after the last dose, 20 (17%) reached this concentration ($p<0·025$, χ^2 test).

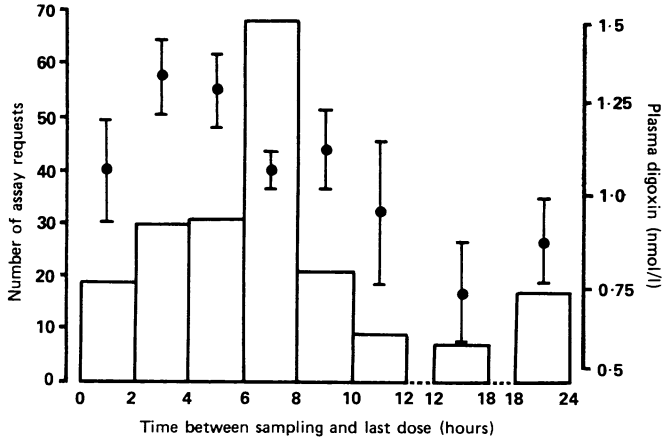

FIG 1—Relation between No of assay requests and mean (SD) plasma digoxin concentrations with respect to time between sampling and last dose.
Conversion: SI to traditional units—Digoxin: 1 μmol/l≈1·3 μg/l.

Comparison of outpatient and inpatient groups showed a greater proportion of requests occurring within six hours in the outpatients (31 (35%) *v* 49 (25%)). The proportion of requests with unknown timing in the two groups was similar (23 (26%) and 37 (19%) respectively).

CLINICAL DECISIONS

A distinction was drawn between alterations in treatment made on requesting an assay, alterations made while awaiting the result, and subsequent alterations made due to the result of the assay (fig 2). In 64 patients (22%) the assay result led to a change in treatment.

Table II shows the details of the initial assessment of patients whose treatment was changed only after the assay without preceding changes on clinical grounds alone. In many cases the change in treatment was consistent with the original clinical assessment, but some changes were at variance with that assessment or were made in the absence of any original clinical indication for requesting an assay, suggesting that these changes were based on the assay result alone.

Many changes in treatment were based on results from inappropriately timed blood samples. Excluding patients whose treatment was changed while awaiting the assay result 34 of the 55 changes (62%) in digoxin treatment were based on samples drawn within six hours of the last dose or at an unknown time (table II). These inappropriately timed samples seemed to influence clinical management because, of 69 samples taken within six hours after the last dose (without a preceding change in treatment), 15 (22%) resulted in digoxin being decreased or stopped, whereas of 116 samples drawn at six hours or later, only 10 (9%) resulted in digoxin being decreased or stopped ($p<0·025$). These results imply inadequate recognition of the dangers of early sampling. This was further highlighted by the fact that 134 samples (96%) collected within six hours after the last dose or at an unstated time were thought by the requesting doctors to have been helpful in patient management.

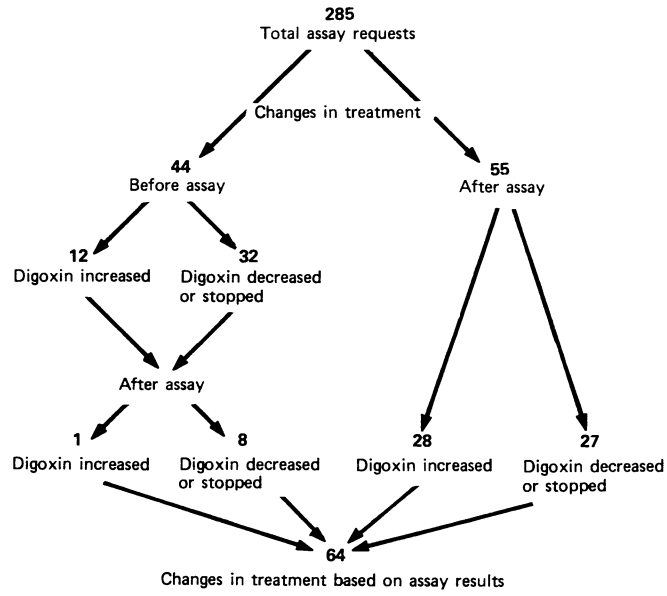

FIG 2—Alterations in treatment before and after digoxin assay results.

TABLE II—*Clinical indications and time between sampling and last dose in patients whose treatment was changed only after assay (figures are numbers (percentages) of patients)*

	Digoxin increased	Digoxin decreased or stopped
Clinical indication:		
Suspected toxicity	8 (29)	9 (33)
Subtherapeutic	16 (57)	3 (11)
Toxic or subtherapeutic	1 (4)	2 (7)
Renal impairment	0	3 (11)
No specific indication	3 (11)	10 (37)
Time between sampling and last dose:		
<6 hours	7 (25)	15 (56)
>6 hours	11 (39)	10 (37)
Unknown	10 (36)	2 (7)

Discussion

Digoxin assays should be undertaken only when there is a definite clinical indication. The fact that the patient is taking digoxin is not in itself sufficient justification for requesting an assay in the absence of other clinical indications. Appropriate indications include suspected toxicity, subtherapeutic clinical response or suspected poor compliance, changing renal function, potential drug interactions, and assessment of the need for continuing treatment.[5] About three quarters of the assays in this study were justified: half to resolve questions of suspected toxicity or subtherapeutic response and a quarter on other adequate clinical grounds. Previous surveys of digoxin assay services have shown that many requests amounting to 82·5% in one series[6] and 49% in another,[7] are made without any clear clinical justification, but unjustified requests amounted to only 67 (24%) in this study. Awareness by doctors that an audit was in progress might possibly have favourably influenced this figure, though the request rate during the study (358 in 12 weeks) was

within 10% of that expected (385 in 12 weeks) from the average digoxin request rate for this hospital.

The importance of the timing of blood sampling in relation to the last dose has been emphasised, and blood digoxin concentrations may more than double in the first few hours after the last dose.[8 9] Samples should not be drawn within six hours after the last dose; indeed, some have argued that this should be extended to 11 hours.[8] The proportion of samples taken within these six hours in this study is a considerable cause for concern, as they showed an increased prevalence of high digoxin concentrations. Moreover, early sampling leading to high concentrations seemed to influence management, as it was associated with a greater likelihood of digoxin being decreased or stopped. If daily doses of digoxin were taken in the evening the problems of early sampling seen in this study would be largely alleviated. The effect of such a practice on the relation between digoxin pharmacodynamics and therapeutic requirements during the sleep-wake cycle, however, are unclear. Of additional concern was the substantial proportion of requests in which the doctor did not seem to know when the blood sample was taken with respect to the last dose of digoxin. Interpretation of an assay result in these circumstances is extremely unwise.

The lack of correlation between digoxin concentrations and clinical assessment of therapeutic effects and toxicity has often been emphasised.[1 4 10] Interpretation of assay results should not be based solely on the limits defined in any "therapeutic range"; due consideration must be given to the patient's age, history, drug treatment, renal function, and plasma potassium concentration.[4] From the available data in this study on some of these aspects old age and renal functional impairment were more commonly encountered than hypokalaemia. We believe that digoxin assay request forms should be designed to elicit this information to encourage doctors to consider these additional factors.

We do not have the detailed clinical knowledge of the patients in this audit that would enable us to assess individual management decisions. None the less, our data suggest that assay results played a major part in determining clinical management, as in many instances decisions were taken that bore no clear relation to the indication originally stated for undertaking the assay.

Assays that are inappropriate, for whatever reason, waste time and money.[11] Based on the most recent costings of biochemical services in this hospital each digoxin request costs £3·57 to analyse and report. This includes all direct and indirect consumable and labour expenditure. The total cost of providing the assay to all hospitals served by this laboratory in 1985 was £9500, and extrapolation of our results based on the misuses of the assay in this hospital, which we identify as early or unknown sampling times and requests made without apparent clinical justification, indicates a waste of about £6000 a year. This is greater than the true potential saving, as many of the improperly timed samples would still be indicated on clinical grounds if correctly timed. Elimination of those requests lacking clinical justification, even if appropriately timed, would produce savings.

We conclude that this audit has shown a need for closer collaboration between the doctor and the laboratory to ensure optimal clinical and economical use of digoxin assays.

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Epidemiology

Report from the PHLS Communicable Disease Surveillance Centre

In July two cases of postoperative tetanus were reported from one hospital and a single case from another hospital. A small outbreak of three cases of legionnaires' disease occurred in travellers who had visited the same hotel in the Netherlands. Reports of the acquired immune deficiency syndrome (AIDS) to the Communicable Disease Surveillance Centre increased to 76 in July, the highest monthly total so far recorded, bringing the cumulative total of cases to 465 since surveillance began.

Tetanus

During July two cases of postoperative tetanus in Blackpool received wide publicity. Both patients were women, one aged 63 and the other aged 55, and both had undergone cholecystectomy. Case searching at the hospital revealed two other possible cases, one after a coronary bypass operation and the other after pinning and plating of a fractured neck of femur, but on further investigation the diagnoses of tetanus seemed unlikely. All four patients had been operated on in one or other of a pair of theatres with a common ventilating system. *Clostridium tetani* was isolated from the air intake filters but this did not imply that the infection in the patients was airborne because the organism is ubiquitous and can often be isolated from the environment; indeed, in surveys up to 10% of environmental samples in hospitals have proved positive for *C tetani*.

A further case was reported in another hospital, also in July, and this followed choledochoduodenostomy. So far no relevant common factor between the operations in the two hospitals has been identified. Similar cases after gall bladder surgery have been reported, two in a hospital in Northumberland in October 1981 and June 1982, two in different hospitals in Manchester in November 1979 and November 1983, and one in a hospital in Brussels. But again no common factors between these patients were identified to suggest the source and mode of spread of the infection.

Tetanus is now very rare in the United Kingdom. Between 1930 and 1959 there were estimated to be over 200 cases a year in England and Wales with a fatality rate of up to half in the earlier years. By the