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ORIGINAL ARTICLE

Assessing the accuracy of a computerized decision support system for digoxin dosing in primary care: an observational study

W. L. G. Kroese* Drs, A. J. Avery† BMedSci DM FRCGP, B. S. P. Savelyich† BSc MRes, N. S. Brown‡ MA MSc FRCPath, H. Schers* MD PhD, R. Howard§ MPharmS DipClinPharm, J. Hippisley-Cox† MD MRCP MRCGP and P. Horsfield† BMedSci BM BS

**Department of Family Medicine, Catholic University of Nijmegen, UMC Nijmegen, The Netherlands, †Division of Primary Care, School of Community Health Science, University of Nottingham, the Medical School, Queen's Medical Centre, Nottingham, UK, ‡Department of Clinical Chemistry, Queen's Medical Centre, Nottingham, UK and §Nottingham Primary Care Research Partnership, Hucknall Health Centre, Hucknall, Nottingham, UK*

SUMMARY

Background: **This study was carried out as part of a European Union funded project (PharmDIS-e+), to develop and evaluate software aimed at assisting physicians with drug dosing. A drug that causes particular problems with drug dosing in primary care is digoxin because of its narrow therapeutic range and low therapeutic index.**

Objectives: **To determine (i) accuracy of the PharmDIS-e+ software for predicting serum digoxin levels in patients who are taking this drug regularly; (ii) whether there are statistically significant differences between predicted digoxin levels and those measured by a laboratory and (iii) whether there are differences between doses prescribed by general practitioners and those suggested by the program.**

Methods: **We needed 45 patients to have 95% Power to reject the null hypothesis that the mean serum digoxin concentration was within 10% of the mean predicted digoxin concentration. Patients were recruited from two general practices and had been taking digoxin for at least 4 months. Exclusion criteria were dementia, low adherence to digoxin and use of other medications known to interact to a clinically important extent with digoxin.**

Results: **Forty-five patients were recruited. There was a correlation of 0·65 between measured and predicted digoxin concentrations ($P < 0·001$). The mean difference was 0·12 μg/L (SD 0·26; 95% CI 0·04, 0·19, $P = 0·005$). Forty-seven per cent of the patients were prescribed the same dose as recommended by the software, 44% were prescribed a higher dose and 9% a lower dose than recommended.**

Conclusion: **PharmDIS-e+ software was able to predict serum digoxin levels with acceptable accuracy in most patients.**

***Keywords*: computerized decision support, digoxin, prescribing, primary care, validation**

INTRODUCTION

There are concerns about the safety of prescribing by general practitioners (1). Errors occur in up to 11% of prescriptions, and the use of incorrect doses is a particular problem (2). A survey has shown that GPs have difficulties with drug dosing for certain groups of patients (3), particularly children, the elderly and those with renal impairment.

When prescribing, GPs need to balance risks and benefits and it is important to have all necessary information available about the drug and the patient in order to make the best decision (4). Errors in the prescribing process often occur because the

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Correspondence: A. J. Avery, Division of Primary Care, School of Community Health Sciences, C Floor, The Medical School, University Hospital, Nottingham NG7 2UH, UK. Tel.: +44 (0)115 9709387; fax: ++44(0)115 9709389; e-mail: tony.avery@nottingham.ac.uk

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GPs do not have immediate access to this information (5). Computerized decision support systems provide one potential solution to this problem (6, 7).

Several studies have shown the usefulness of computerized programs in preventing prescribing errors and improving quality of care (6–8). Kaushal and Bates (9) showed that use of information technology decreased rates of medication errors in hospital. Walton *et al.* (10) showed that using computers to determine the correct dose of certain drugs was beneficial in an acute hospital setting, but suggested further research was needed to determine the risks and benefits of computer support, particularly in general practice. Further testing of computerized decision support in general practice has been recommended by Gurwitz *et al.* (11).

Although most GPs are familiar with computerized drug interaction alerts, prescribing could be made safer if computer systems linked information on renal and hepatic function to the prescription of potentially hazardous drugs (4). Schiff *et al.* (12) suggested that clinical decision support systems should draw on three databases: (i) patient drug history, (ii) scientific drug information and guideline references and (iii) patient-specific (weight, laboratory) data, and that developing computerized prescribing tools requires consortia of health professionals to create validated software and care guidelines.

The PharmDIS (Pharmacokinetic-Pharmacodynamic Drug Information and Dosage Adjustment System) consortium was funded by the European Union in 1998. It is a partnership of seven European countries, including the UK. The PharmDIS-e+ project began with the aim of developing and evaluating software to assist physicians with drug dosage adjustment. The version of the software used in this study was MWPharm Lite version 1.3.

The software uses patient parameters such as age, weight, height and serum creatinine levels and (using pharmacokinetic algorithms and data derived from international scientific literature) predicts drug levels (where a drug has been prescribed) or advises on the appropriate dosage of a drug for a particular patient (13).

We set out to determine whether the software was able to accurately predict serum digoxin levels in patients who are taking this drug regularly and whether there were statistically significant differences between predicted and actual drug levels. We chose digoxin because it is a drug that is commonly used in general practice, hazardous in overdose and requires knowledge of a patient's age, weight and renal function for making appropriate dosage decisions.

A further objective was to determine the extent to which the digoxin dose suggested by the software was similar to that prescribed by GPs. One reason for looking at this was because our earlier survey had indicated that GPs might prescribe inappropriately low doses of drugs such as digoxin in order to avoid overdosing patients (3).

METHODS

Ethical committee approval was obtained from the Nottingham Research Ethics Committee.

A Power calculation for equivalence demonstrated that we needed 45 patients for a maximum difference of 0·1 μg/L between the mean serum digoxin concentration and the mean predicted digoxin concentration assuming a standard deviation of 0·2 μg/L with 95% Power and a 0·05 one-sided significance level.

The setting was two general practices in Nottingham, UK. Participants were adult male and female patients from the above practices, who were taking digoxin at the time of the study and had been taking the drug for at least 4 months.

Given the need to have patients who were able to understand the study and to be taking their digoxin dose on a regular basis, exclusion criteria were: (i) dementia and (ii) low adherence to digoxin therapy according to the computerised medical records.

In addition we excluded patients who were taking medications known to interact to a clinically important extent with digoxin (see below) as the software was not programmed to take such interactions into account.

We sent a letter and copy of the protocol to the doctors in the two practices to inform them about the study and invite them to take part. GPs taking part in the study identified potential participants by selecting from their computer systems all those who were taking digoxin.

The GPs were asked to exclude patients with evidence of low adherence to their digoxin treatment or dementia. Following this, a GP in each

practice reviewed the selected patients' medical records to see whether any were taking other medications known to interact to a clinically important extent with digoxin (14, 15). We excluded patients if they were taking spironolactone, amiodarone, cyclosporine, quinidine, quinine or a regular intake of diclofenac.

For those patients remaining, the GPs sent a letter and information sheet about the study, asking them if they were willing to take part.

Patients expressing an interest in the study were invited for an assessment. During each assessment the details of the study were explained and the patient's consent was sought. For those who signed the consent form, we recorded study ID, date of birth, height, weight, gender, current digoxin dose, year digoxin treatment started, medical history and other drugs currently taken. Some patients were excluded at this stage because they were found to have exclusion criteria such as starting on an interacting drug.

We used the assessments to reinforce patients' adherence to digoxin therapy by explaining to them the importance of taking their drug therapy as prescribed. We asked them to record their digoxin intake in a specially designed diary for a period of 2 weeks. It was emphasized that any missed doses needed to be recorded. We also contacted the patients by telephone during the 2-week period, in order to further reinforce the need to take the medication regularly.

After the 2-week period we took a blood sample from each patient, after checking the diary for recorded irregularities or problems. The sample was taken either at the surgery or at the patient's home approximately 24 h after ingestion of the last digoxin tablet. The blood samples were all sent to the Department of Clinical Chemistry, Queen's Medical Centre Nottingham for analysis. Serum digoxin and creatinine measurements were performed on a Vitros 950 analyser (Ortho Clinical Diagnostics Ltd, Rochester, NY, USA).

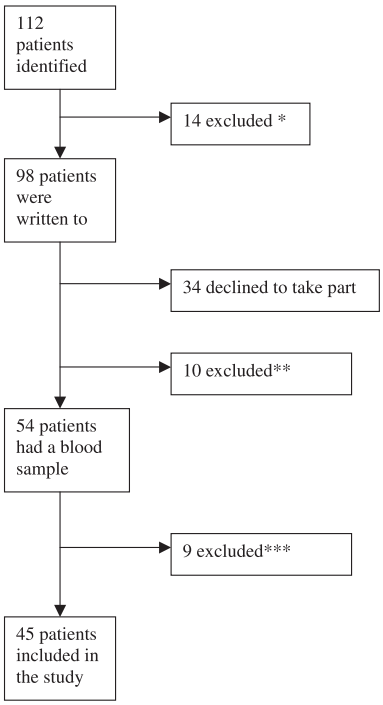
Statistical Analysis

We used SPSS version 11 to do the statistical analyses. Validation of data-input was performed by double entry of the data. Data were checked for possible errors by running frequencies and we checked for normality by plotting histograms. A scatter plot was carried out to look at the relationship between measured and predicted digoxin levels and Pearson's correlation was used to determine the correlation between these factors. We also used the Bland–Altman plot to compare the two measurement techniques graphically (16).

A parametric, paired *t*-test with a 0·05 two-sided significance level was used to assess whether there were statistically significant differences between measured and predicted digoxin levels.

RESULTS

Figure 1 is a flow diagram showing the number of patients identified for possible inclusion in the study, the number that declined to take part, the numbers excluded and reasons for exclusions. It should be noted that five of the patients having blood tests had to be excluded from the final analysis because they had serum digoxin levels below



*10 on interacting drugs (diclofenac, spironolactone or verapamil), 2 dementia, 2 not on digoxin anymore
**2 started taking interacting drugs after they had been initially identified as eligible, 5 dementia, 2 not on digoxin anymore, 1 had only just started digoxin treatment
***1 started taking an interacting drug, 1 had a change of drugs by consultant, 1 no regular intake, 1 amputation of both legs (Body Mass Index unreliable), 5 digoxin level was not measurable by clinical chemistry (< 0.3 μg/L).

Fig. 1. Flow of patients through the study.

the range reported by the laboratory (presumably because of low adherence).

Of the 45 patients included in the final analysis 21 (47%) were women and 24 (53%) men. The mean age was 78 years (SD 8·42; range 59–94). The mean height was 1·68 m (SD 0·11) and the mean weight 68·5 kg (SD 14·2). Most people had a creatinine level within the reference range (men: 60–120 μmol/L; women: 50–100 μmol/L). Two men had levels above the creatinine reference range. On average the patients had been taking digoxin for 7 years and all had been on the drug for at least 4 months. The digoxin doses prescribed for the patients were between 62·5 μg and 375 μg/day. Two patients (4·4%) were treated with a dosage higher than 250 μg/24 h and one patient (2·2%) was treated with a dose <125 μg (62·5 μg/24 h).

The measured serum digoxin level ranged from 0·30 to 1·70 μg/L (SD 0·34), with a mean of 0·84 μg/L. The levels predicted by the PharmDIS-e+ software were between 0·25 and 1·46 μg/L (SD 0·28), with a mean of 0·72 μg/L. The mean difference between the measured and predicted concentrations was 0·12 μg/L (SD 0·26; 95% CI 0·04, 0·19; $P = 0·005$).

Figure 2 shows a Bland–Altman plot of the differences between measured and predicted serum digoxin levels for each patient plotted against the average of these measures. Despite the statistically significant differences between measured and predicted serum digoxin levels it can be seen that there was an acceptable agreement between the levels for the vast majority of patients.

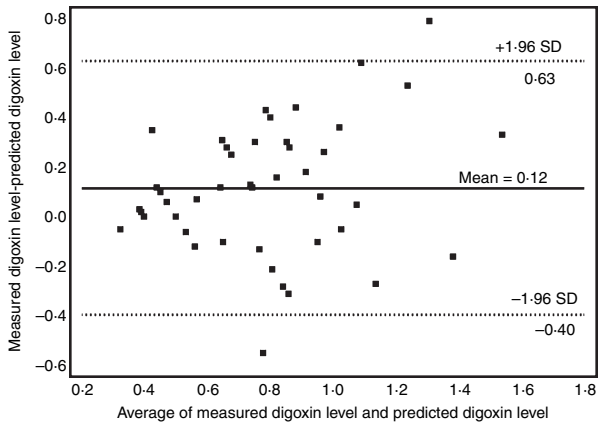


Fig. 2. Bland–Altman plot showing differences between measured and predicted serum digoxin levels.

We compared the actual digoxin doses prescribed by the GPs to the digoxin doses recommended by the computer program. For 21 patients (46·7%) the program suggested the same dose as the GPs. In 20 patients (44·4%) the GPs prescribed higher doses than the program recommended, and in four patients (8·9%) the GPs prescribed lower doses than the program recommended.

DISCUSSION

This study has shown that PharmDIS-e+ software is able to predict serum digoxin levels with acceptable accuracy for most patients, although differences between measured and predicted levels were statistically significant.

One of the strengths of this study is that we collected detailed data on patients in primary care and took steps to try to ensure that these patients were taking their medication as prescribed. In addition, we excluded patients where there were clear reasons why the program was not capable of accurately predicting the serum digoxin concentration.

Although the computer program did not manage to predict within a mean of 10% of the measured levels, there were relatively few patients with marked differences between predicted and measured serum levels. Our results may have been affected by excluding five patients whose levels fell below the range reported by the laboratory. In addition, it should be noted that serum digoxin results can vary depending on the assay used and the laboratory (17). Therefore, had the blood samples been analysed by another laboratory it is possible that the levels would have been closer to those predicted by the program.

A recent study has indicated dangers for heart failure patients taking digoxin if serum levels are above 0·8 μg/L (18) and it has been suggested that, irrespective of indication, low doses should be used (19). The PharmDIS-e+ software aims to suggest digoxin doses that produce serum concentrations within the range 0·58–0·80 μg/L. In our study, the software suggested that 44% of patients could have been managed on a lower dose of digoxin, thus potentially reducing the risk to some of these patients had the software been used.

We believe the PharmDIS-e+ software program would be useful for GPs when starting digoxin

treatment but, because of differences in pharmacokinetics between individuals, GPs may need to review their patients for signs of toxicity, or check digoxin serum levels, once they are at steady-state.

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