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Evaluation of Clinical Pharmacy Service Impact on Therapeutic Drug Monitoring of Digoxin At A Teaching Hospital

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Abstract ❑ **A retrospective study was run to review serum digoxin concentration (SDC) orders during a two year period. A total of 1110 SDC determinations were used to identify hospital wards of highest request of SDC order and to report the number of digoxin over- and underdose requests per ward. Also studied were the outcomes of clinical pharmacy intervention on the number of serum digoxin orders, appropriateness of ordering SDC level and the clinical pharmacist's influence on appropriate handling and interpretation of the reported levels. Out of the total 1110 SDC orders, 8.5% were toxic while about 20% were sub-therapeutic. Cardiology wards were found to request the highest number of SDC determinations. A much lower incidence of SDC overdose was found during clinical pharmacist intervention compared to that obtained without implementing such service (1.49% and 5.81%), respectively). In 98.01% of the total orders, digoxin doses were adjusted based on the reported SDC level and the clinical pharmacist recommendations. Therefore, SDC determination, when performed appropriately in presence of clinical pharmacist involvement and intervention, will improve therapeutic drug monitoring (TDM) utilization and outcomes. Our results stressed the need for ongoing corrective in-service programs for the medical team and red-flagging the wards within the hospital that need such services most.**

Keyphrases ❑ **Digoxin, therapeutic drug monitoring, clinical pharmacy service, drug-level.**

A poor correlation has been reported to exist between drug dosing and ability to attain desirable drug concentration level as well as clinical response (1). A better correlation is usually observed between serum drug concentration (SDC) and clinical response. Therefore, therapeutic drug monitoring (TDM) has become a valuable, rapidly growing laboratory tool to measure and monitor both the pharmacological and toxicological effect of many drugs (2). This is of particular importance for drugs with narrow therapeutic index or those which follow zero order kinetics such as digoxin and phenytoin. In practice, clinicians use TDM technique to dose drugs accurately, promote optimum treatment and prevent harmful toxicity to patients.

The availability of rapid and reproducible drug assay methods for drugs with a narrow therapeutic index has made TDM a popular tool. However, a large literature body has shown that the frequency and percentage of SDC determinations for many drugs are both hazardly requested and inappropriately used in hospitals (2-7, 9).

The present study was conducted to retrospectively identify hospital wards within a teaching hospital with the highest frequency of SDC requests. In addition, the study aimed at prospectively assess the impact of clinical pharmacist intervention on the frequency, appropriateness and utilization of serum digoxin level orders.

Methods :

This study was conducted at a 650-bed teaching hospital, King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia. This pharmacokinetic laboratory routinely analyzes serum concentration of eight drugs namely digoxin, theophylline, gentamicin, amikacin, phenobarbitone, phenytoin, carbamazepine, and valproic acid. Data were obtained from pharmacokinetic laboratory computer data base, Clinical Pharmacy Department, College of Pharmacy, King Saud University.

All SDC samples were processed in the University Hospital Pharmacokinetic Laboratory using an Abbot TDX Analyzer. The technique utilizes Fluorescence Polarization Immunoassay Technology (FPIA) and competitive binding immunoassay methodology for monitoring therapeutic drug levels. For each SDC order, information such as patient's name, sex, hospital identification number (I.D.), date of digoxin order, name of the ward and the name of consultant or treating physician, and SDC readings are routinely collected. For the purpose of this study, these data were then entered into a computer program (dbase-IV) for further processing and analysis. All patients with complete information from the pharmacokinetic laboratory were included in this part of the study. Unidentified ward, unreported digoxin level either because of inappropriate sample size or unavailability of digoxin reagent at the time of assay, were excluded from the study.

The study consisted of two parts. The first was a retrospective study which consisted of reviewing patient's digoxin orders during the period of April 1990 until May 1992. Digoxin level orders were analyzed for patients who were admitted to either male or female cardiology wards (MCW and FCW respectively) from the retrospective part of the study (Group A). Serum digoxin level readings which showed either overdose (SDC level of > 2.0 ng/mL) or underdose (SDC level < 0.5 ng/mL) were separately analyzed.

A subgroup analysis of Group A consisted of the three months (October, November, and December) of the cardiology wards (MCW and FCW) for the year 1991. Matching the three months of the prospective period of the study was selected to take into account the possibility of seasonal variation.

The other part of study represented a prospective analysis of clinical pharmacist intervention, including in-service education and consultation to the medical team. The clinical pharmacist conducted informal education sessions for house-staff physicians and nurses on the criteria for appropriate SDC order and its importance. This information was re-emphasized during daily ward rounds. Our intervention was limited to the two cardiology wards for a period of three months (Group C).

The clinical pharmacist in-charge followed up SDC results with the ordering physician, resident or intern after the results were reported rather than at the time of ordering, and discussed appropriateness of the order and therapeutic consequences.

A patient's data collection form was designed to collect pertinent information. The collected information consisted of biodata, disease state, indication for ordering SDC, results of digoxin assay, important laboratory values (specially potassium, BUN, and serum creatinine) and criteria for inappropriate SDC determination, if any. The measures taken by the clinician in response to digoxin level were also noted for each patient. Special considerations were given as to label requests as inappropriate when sample time was not mentioned, or wrong sample time was written, or if no reason for requesting SDC was ticked. Finally, a documentation was recorded if a dose adjustment according to SDC level was performed.

RESULTS

The total number of serum digoxin concentration (SDC) orders during the retrospective period was 1236. The total number of patients' admissions per month was 2594, 2274, and 2248 during years 1990, 1991 and 1992, respectively. The average monthly digoxin level orders were 72.3, 57.5. and 61.3 for the same period. One hundred and twenty six of these SDC were excluded because of lack of digoxin reagent at the time of assay request, insufficient sample specimen required to perform the assay, or when no ward was assigned to the SDC request.

Serum digoxin levels of the retrospective study period (total of 1110 orders) were sorted and ranked by ward in terms of the highest number of SDC orders requested. Number and percent of digoxin overdosing was noted in 95 orders (8.56%) while underdosing was noted in 221 orders (19.91%). However, digoxin level was within the therapeutic range in 794 requests (71.53%), ***(Fig.1)***.

Hospital wards with the highest digoxin level orders were ranked in descending order in terms of the percentage of digoxin orders of the entire 1110 orders ***(Fig. 2)***. It was found that female and male cardiology wards (FCW and MCW) represented the top wards in terms of the percentage of digoxin orders, 17.2% and 13.8%, respectively. Medical outpatient department (MOPD) came second followed by surgical intensive care unit (SICU) then

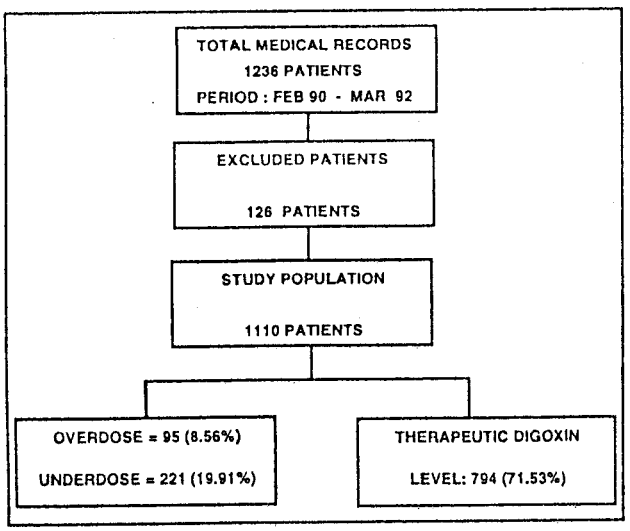

Fig. 1: Retrospective Part: Study Design and Outcomes.

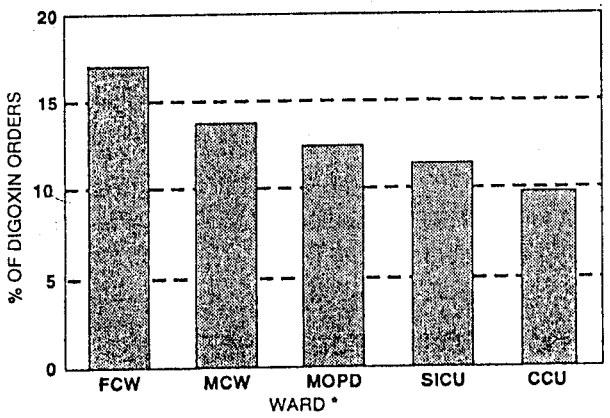

Fig. 2: Digoxin Utilization Per Ward. *See text for abbreviations.

coronary care unit (CCU). Digoxin overdose and underdose orders per hospital ward were ranked in a descending order in terms of the number of orders per ward. The top five wards in terms of the number of digoxin overdose per ward were found to be the surgical intensive care unit (SICU), the female cardiology ward (FCW), medical intensive care unit (MICU), coronary care unit (CCU) and lastly the male medical ward (MMW). On the other hand, the top five wards in terms of the number of digoxin underdose per ward were MCW, MOPD, FCW, cardiac surgery (CS), and the male medical ward (MMW), ***(Figs. 3*** and ***4)***.

When frequencies of SDC order of the two cardiology wards for Groups A and C were compared, overdose levels were found to be 20 (5.81%) and

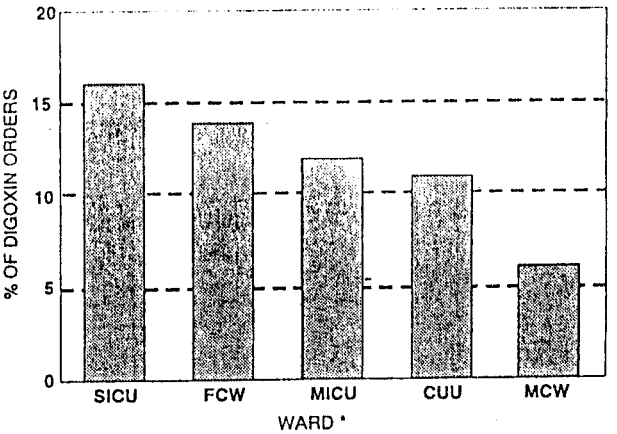

Fig. 3: Digoxin Overdose Per Ward * See text for abbreviations.

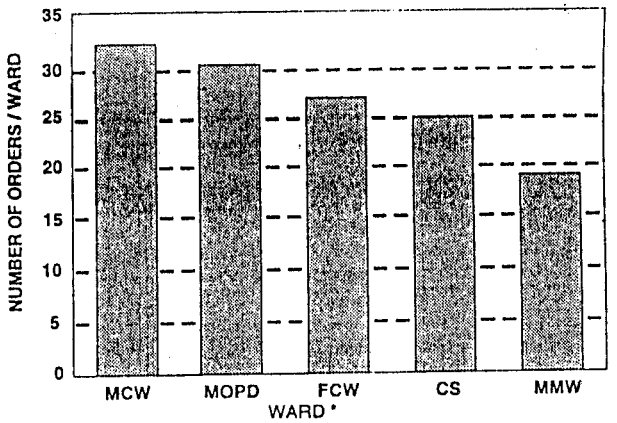

Fig. 4: Digoxin Underdose Per Ward. *See text for abbrevations.

one (1.49%), respectively. However, underdose requests were found to be 59 (17.15%) for Group A and 11 (16.42%) for Group C ***(Fig. 5)***.

A subgroup analysis of an equivalent three months (Group B), from the retrospective part of the study for the year 1991, showed an overdose level of four (5.88%) out of 68 orders compared to one level (1.49%) in Group C. Calculated underdose level for the two Groups B and C were six (8.82%) and eleven (16.42), respectively ***(Fig. 5)***.

Careful analysis of the prospective part of the study (Group C) showed some interesting results. Digoxin sampling time for 25 out of 67 requests was not written at all (37.31%). The reason for ordering serum digoxin level was not stated in 23 requests (34.33%). Inappropriate sampling time was noted in requests (20.58%). To follow up on actions taken to adjust digoxin dose according to the

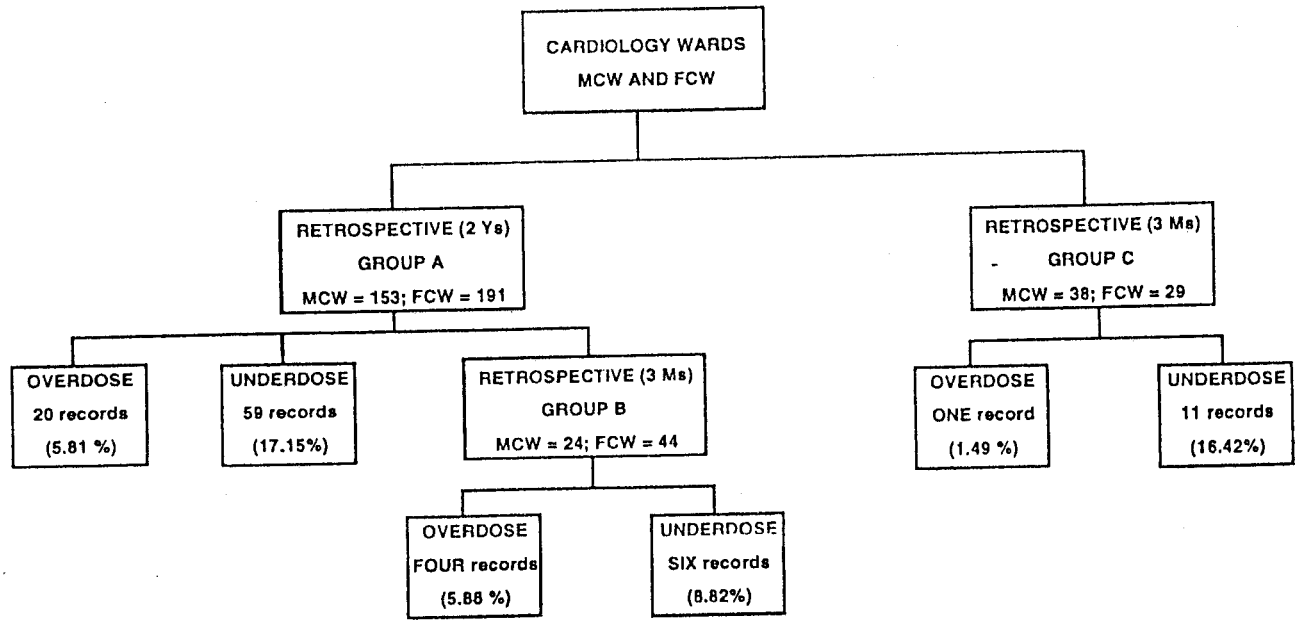

Fig. 5: **Cardiology Wards Outcomes.**

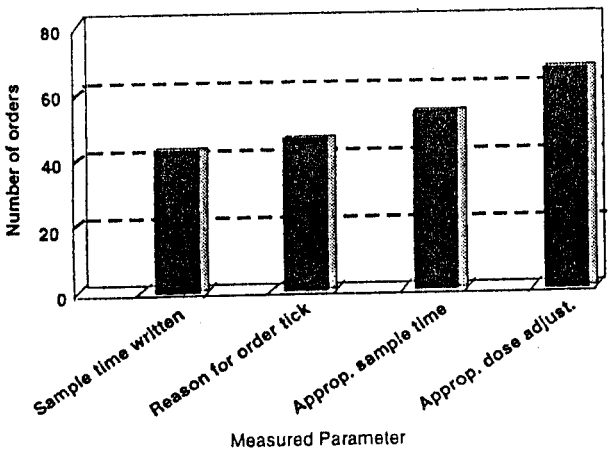

Fig. 6: **Outcomes of the Prospective Study.**

patient's underlying disease state and his reported serum digoxin level, it was found out that appropriate dose adjustments was noted in 65 (97.01%) of the cases ***(Fig. 6)***.

Digoxin dose was increased based upon reported low levels in only three cases (4.48%), whereas it was decreased to prevent toxicity in four cases (5.97%).

The mean and the range of number of SDC levels ordered per patient for the retrospective part (Group A) totalled to 344 digoxin levels, which was performed for 214 patients, (range 1-7 levels) with a mean of 1.60 levels per patient. For Group B, a total of 68 levels was performed for 44 patients (range 1-7 levels) with a mean of 1.55 level per patient. On the other hand, a total of 67 digoxin levels was ordered for 34 patients (range 1-6 levels) of Group C patients with a mean of 1.86 level per patient.

DISCUSSION

Failure to treat cardiac patients who were on digoxin as well as exposing them to harmful or toxic states may be attributed to several factors. Among these factors, the most important are over- or under-dosing, inappropriate sampling time, inappropriate interpretation and utilization of SDC results as a guide for treatment modification. In a recent study (2), among 275 serum digoxin level determinations, a low (33.5%) overall appropriate utilization of therapeutic drug monitoring (TDM) has been reported. Inappropriate sampling collection time for digoxin level determination was as high as 39.7 % along with high incidence of inappropriate dose adjustment of 46.8 based on reported levels. Similarly; it was stated (3) that the percentage of inappropriate serum digoxin concentration determinations, was as high as 56%. These two studies have declared that digoxin level determination is probably not utilized appropriately as a guide for treatment modification and hence

nullifies the value of TDM. Fortunately, several solutions have been suggested in clinical studies to restore the usefulness of TDM in daily practice. Clinical pharmacy and pharmacockinetic services were crucial elements involved in surveillance, and interventions to assure the quality of TDM and appropriate implementation of the reported request results. It was proposed that pharmacist intervention through in-service continuing educational programs, elimination of unnecessary repeated assays and participation in ward rounds would have a great impact on cost and appropriateness of serum digoxin level monitoring (2, 3).

Several indices have been used to predict positive outcomes when dealing with TDM and the overall patient care including cost of treatment. Maintaining high quality of care, a lower monthly serum digoxin levels orders, a fewer number of SDC level per patient, fewer over- and underdose levels and appropriate sample collection time for SDC determinations are reasonable objectives to assure positive outcomes. Our study showed a lower average monthly SDC utilization of 22.3 compared to 36.8 and 68.7 level in the previously published studies (2, 3).

The average number of SDC levels per patient in our study is 1.86 compared to 3.64 levels per patient as reported by klamerus and Munger (3). However, the authors reported a reduction in the average number of SDC determinations per patient from 5.1, when no clinical pharmacy services were provided, to an average of 2.9 during implementation of such service. Our data did not show similar results, since the average number of SDC per patient during clinical service intervention **(Group C)** was 1.86 compared to 1.60 and 1.54 for **Group A** and **Group B,** respectively.

Interestingly, the number of patients who had an overdose level (SDC > 2.0 ng/ml) was found to be much lower (1.49%) in **Group C** than in **Group A** (5.81) or in **Group B** (4.11%); while the figures of underdose level were 16.42, 17.15%, and 8.82% for **Groups C, A,** and **B,** respectively.

It appears reasonable to improve the quality of serum digoxin level determination and utilization, and, whenever possible, to decrease the quantity and frequency of its order. In our prospective study, we had only one overdose level in a 70 year patient who was treated initially at the CCU for refractory congestive heart failure (CHF). The patient initial baseline digoxin level was < 0.2 ng/ml which was raised to 0.4 ng/ml after appropriate digitalization. Digoxin dose was increased from 0.125 mg to 0.25 mg per day to control his CHF symptoms. Eight days later, when it was noted that the patient had an impaired renal function, SDC level was ordered and found to be 2.3 ng/ml. A dose of 0.0625 mg daily was calculated and administered to the patient with successful control of his CHF and achieving therapeutic SDC of 0.7 ng/ml.

Appropriate utilization of SDC results was found in 65 (97.15%) out of the 67 patients. Serum digoxin concentration was found to be within therapeutic range in 82.1% of the cases, and patients were asymptomatic or apparently so. On the other hand, digoxin dose was increased in three patients only (4.48%), two because the levels were subtherapeutic while the third patient had a good level (1.2 ng/ml) but the patient's atrial fibrillation was not well controlled. Lowering digoxin dose was necessary in four cases (5.97%). In the first case, digoxin dose was temporarily reduced since the patient was scheduled for stress ECG, and was put back on the second day on his normal dose. The second and third cases had atrial fibrillation which has been controlled. Digoxin dose was subsequently reduced in the second case with a stable level of 1.1 ng/ml. In the third patient, quinidine was added with subsequent pharmacological conversion to sinus rhythm. In the fourth case, which was mentioned earlier, the patient was a known case of CHF and chronic renal failure who had a SDC of 2.3 ng/ml. Digoxin dose was calculated and administered and a follow-up level was 0.7 ng/ml.

It has been noted from these figures that SDC levels were mostly within the normal therapeutic range, and dose adjustment with concurrent auditing by clinical pharmacists were appropriately handled. This was in accord with the report of Makela, ***et al.*** (10), who documented a significantly more DCs meeting the standard criteria when clinical pharmacists, who were concurrently monitoring

drug therapy and participitating with the treatment team, interfered compared to those obtained under retrospective audit.

The outcomes of the clinical pharmacist intervention, as shown in ***Fig. 6,*** emphasizes the need of a more frequent in-service programs for nursing staff on accurate documentation of digoxin sampling time. In addition, the medical team needs to be aware of justifying and documenting SDC orders.

Starting January 1995, we have implemented formal clinical pharmacokinetic service for the entire hospital. We are planning to conduct a prospective study on a larger number of patients for a longer period. We are aiming at rationalizing drug serum level order and its utilization for the sake of patient safety, sparing nursing and clinical laboratory time, and hospital costs. A revised in-service education program for physicians, nurses and technicians dealing with potential problems encountered with therapeutic drug monitoring, will be considered.

In conclusion, the prospective part of this study has clearly demonstrated the positive impact of the clinical pharmacist participation in ward round and his input in appropriate utilization of TDM, patient's safety and, indirectly, cost saving. Few patients were exposed to digoxin overdose, with a higher percentage of patients maintained within the therapeutic range for digoxin. However, in-service education program needs to be reinforced to improve appropriateness of digoxin sampling time and clarifying the rational reasons for ordering such levels for SDC analysis. A more reliable assessment of TDM service in our hospital will be based on the currently on-going prospective study, aiming at perfecting and fine-tuning practical guidelines and necessary mechanisms for ordering serum digoxin assays.

References:

1) M.E. Burton, M.R. Vasko and B.D. Craig, **Clin. Pharmacokinet.**, 10, 1 (1985).
2) M.S. Al-Ghamdi, A. Eferakeya and S. Al-Sowayan, **Annal. Saudi Med.**, 12, 178 (1992).
3) K.J. Kalmerus and M.A. Munger, **Am. J. Hosp. Pharm.**, 45, 1887 (1988).
4) S. Vozeh. **Clin. Pharmacokinet.**, 13, 131 (1987).
5) C.B. Crisp, J.R. Lane and M. Murray, **Crit. Care Med.**, 18, 734 (1990).
6) M.S. Winter, E.T. Herfindal and L.R. Bernstein, **Am. J. Hosp. Pharm.**, 43, 2178 (1986).
7) H.W. Clague, Y. Twum-Barima and S.G. Carruthers, **Ther. Drug Monit.**, 5, 249 (1983).
8) R.L. Salughter, P.J. Schneider, J.A. Vasconti, **Am. J. Hosp. Pharm.**, 35, 1376 (1978).
9) J.R. Horn, D.B. Christensen and P.A. Deblaquiere, **Drug Intell. Clin. Pharm.**, 19, 45 (1985).
10) E.H. Makela, S.K. Davis, K. Piverak, W.A. Miller, R.A. Pleasants, R.H. Gadsden and R.B. Leman, **Am. J. Hosp. Pharm.**, 45, 126 (1988).

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