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Digoxin Levels and It's Stability in Different Blood Collection Tubes

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ABSTRACT

Objective: Digoxin is monitored because of its narrow range of therapeutic doses and risk of toxicity. Thus, we aimed to evaluate the effect of different blood collection tubes on digoxin levels and its stability.

Methods: Samples from 30 volunteers who received digoxin therapy were collected in 5 different tubes: no additive and gel-free glass tube (Z-tube) (reference tube), clot-activator tubes containing gel (Vacusera), clot-activator tubes containing gel (serum separator tube), barrier-free lithium heparinized tube (LiH), and new lithium heparinized tube with a barrier (Barricor). Digoxin levels in tubes were analyzed at 0 and 48 hours (h).

Results: No statistical difference was found between 0 and 48 h results in other tubes, except for LiH, and the difference in LiH was also not clinically significant. Digoxin levels in other tubes were not statistically different according to the reference tube, except for Barricor. The digoxin level in Barricor was clinically significantly higher than that in the reference tube. Although a strong correlation was found in the digoxin level between Barricor and Z-tubes, a proportional increase in digoxin level in Barricor was determined.

Conclusion: The digoxin levels in the tubes may be used interchangeably, except for Barricor. The reliability and accuracy of digoxin levels may be increased by the identification of a new therapeutic range for Barricor.

Keywords: Therapeutic drug monitoring, digoxin, specimen collection tube, serum, plasma

INTRODUCTION

Digoxin is a well-known prescribed medicine due to its positive inotropic effect in heart failure and reduction of ventricular rate in atrial fibrillation (1). In recent years, the recommended therapeutic range of digoxin in heart failure has been reduced from 0.8-2.0 to 0.5-0.9 ng/mL (2). The blood levels of digoxin need to be monitored because of its narrow range of therapeutic doses and the risk of toxicity.

Serum or plasma samples have been used in the monitoring of therapeutic drug levels as recommended by most manufacturers. To obtain these specimens, the manufacturers produce blood collection tubes with or without barrier and with or without additive. Because of its various advantages, plastic tubes with gel barriers, which are made from acrylic, polyester, or silicone, are preferred. In particular, blood tubes with gel barriers have more advantages, such as reducing the need for transfer to a secondary tube, minimizing cell-supernatant contact during storage,

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decreasing the risk of hemolysis and thrombolysis, increasing the stability of an analyte, and obtaining higher volumes of serum or plasma.

A gel separator has been reported to show absorption or adsorption effect, and therefore, this phenomenon may interfere with the analysis of certain therapeutic drugs. The effect changes depending on the hydrophobic structure of the drug, sample storage time, and sample volume (3-8). In addition, it is also stated that the elution of the gel material to sample may affect the analysis results (9). Therefore, the producers have developed new blood collection tubes with different structural barriers that can reduce the effect of gel and have better separation advantages. Although manufacturers aimed to produce blood collection tubes that can provide the most accurate and reliable results in the preanalytical process and are the best fit for clinical laboratories, laboratory specialists verify whether these blood collection tubes can meet their own needs in their clinical laboratory practice.

A number of studies have evaluated the effect of gel on drug levels and drug stability in tubes with gel due to the hydrophobic structure of digoxin. Most of these studies have been conducted *in vitro* in blood samples obtained by spiking an exogenous drug that cannot mimic protein binding and drug distribution in the circulation, and hence, it cannot directly reflect the *in vivo* status (3-5,10-12). Some studies were designed as *in vivo* and conducted in blood samples obtained from a small number of patients on digoxin treatment (7-8,13,14). However, no study was conducted on tubes consisting of a new-generation barrier on drug levels and drug stability. Therefore, the digoxin levels in four plastic tubes containing lithium heparinized with new-generation barrier, lithium heparinized without barrier, and gel with clot activator (two different brands) were compared with no additive and barrier-free glass tube (reference tube), and the stability of digoxin in each tube was also evaluated.

METHODS

Subjects

The study included 30 outpatients on digoxin treatment in the cardiology clinic and randomly selected volunteers. Blood samples were collected from volunteers between 08:00 and 10:00 AM after they fasted overnight [8-10 hours (h)]. Blood was collected from the antecubital vein into blood collection tubes. Detailed information about the study was provided to all participants before their participation, and their signed consents were obtained. This comparative analytical study was conducted in accordance with the Helsinki Declaration and approved by the Dokuz Eylül University Local Ethics Committee (approval number: 2016/26-32).

Methods

Blood samples from each individual were collected in five different types of tubes: a) No additive and gel-free glass tube [Becton Dickinson and Company (BD) Vacutainer ®Z-tube, 7 mL, 13×100 mm, catalog number 367615, NJ, USA] (Z-tube); b) a clot-activator tube containing gel (BD Vacutainer® SST II Advance tube, 5 mL, 13×100 mm, catalog number 367955, NJ, USA) serum separator tube (SST); c) a barrier-free lithium heparinized tube (BD Vacutainer ®BD Lithium Heparin, 4 mL, 13×75 mm, catalog number 368884, NJ, USA) (LiH); d) a newly produced lithium heparinized tube with a barrier (BD Vacutainer ®Barricor LH Plasma tube, 3 mL, 13×75 mm, catalog number 365031, NJ, USA) (Barricor); and e) a clot-activator tube containing gel (Vacusera Z-serum tube, 3.5 mL, 13×100 mm, catalog number 234303, İzmir, Turkey) (Vacusera).

A new-generation blood collection tube (Barricor) consists of two components: an elastomer top, which stretches during centrifugation and creates a seal on the inside wall of the tube at the end of centrifugation, and a high-density base, which uses the differential buoyancy between plasma and cells to ensure the separator orientates correctly during centrifugation.

Serum and plasma samples were separated according to manufacturers' centrifugation recommendations. Although the Z-tube, SST, LiH, and Vacusera tubes were centrifuged for 10 min at 1500 g, the Barricor tube was centrifuged for 10 minimum at 2700 g. After centrifugation, serum and plasma digoxin levels were immediately analyzed in the primer tubes. Serum (Z-tube) and plasma (LiH) in the primer tubes without a separator were transferred to the secondary tube to discontinue the cell-supernatant contact. To assess the stability of digoxin in different tubes, serum and plasma in the primer and secondary tubes were re-analyzed after being stored for 48 h at +4 °C. No visible hemolysis, lipemia, and icterus were detected in any serum and plasma samples. Care was taken to ensure that the tube sequences were random during the analysis period.

The digoxin levels were analyzed with a chemiluminescent method (ADVIA Centaur®DIG Lite Reagent, catalog number 110772, revised November 2011, Tarrytown, NY, USA) using the autoanalyzer (ADVIA Centaur XP, Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA). Daily internal quality control (IQC) for digoxin was performed using commercial IQC (Bio-Rad Lyphochek Immunoassay Plus Control, LOT number 40332, Bio-Rad Laboratories, CA, USA) at two different levels per day as part of routine laboratory practice. The within-run and between-run coefficient of variation values for the reagent were 4.0% and 3.9% for 0.83 ng/mL and 3.2% and 1.6% for 2.04 ng/mL, respectively.

The Z-tube was identified as the reference tube because it has no additive and is a gel-free glass tube, and the other plastic blood tubes might lead to an interference with the test results. This modality was also adopted from a study published by Dasgupta et al. (15,16).

Statistical Analysis

The SPSS 20.0 program (SPSS Inc., Chicago, USA) was used for all statistical analyses. The normality of the variables was tested with the Shapiro-Wilk test. Because all data show a

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normal distribution, statistical analyses were performed using parametric tests. Continuous variables were presented as mean and standard deviation (SD). The statistical difference between the sample results was evaluated using the paired t-test. While comparing digoxin results between 0 and 48 h, $p<0.05$ was considered statistically significant. While comparing digoxin levels of the 4 blood tubes with the reference tube, the Bonferroni method was used to adjust the value of the significance level, and $p<0.0125$ was considered statistically significant.

Clinically significant differences between digoxin concentrations based on the storage times (0 and 48 h) of each tube were assessed using the significant change method (17). In brief, the usual SD (USD) of 7 months' IQC data for digoxin was collected. The IQC with target mean that closely matched the mean of the 0-h digoxin levels was used to determine the USD. The significant change limit (SCL) was calculated as the mean of the 0-h digoxin levels in each tube ±2.8 USD. It was accepted as a clinically significant difference if the mean of the 48 h digoxin levels in each tube exceeded the SCL limit. Furthermore, the bias between the 0 and 48 h results was calculated with the formula as follows: [(mean of the 48 h results-mean of the 0-h results)/mean of the 0-h results] *100.

The clinical significance of digoxin concentrations between the compared and reference tubes at both 0 and 48 h was evaluated. The bias between the compared and reference tube results was calculated with the following formula: [(mean of the compared tube results-mean of the reference tube results)/ mean of the reference tube results] *100. The total allowable error was determined with the root mean square of the deviation according to RiliBAK of 14.00% (18). The total error was defined as bias (%) + 2CV (%) by the Clinical Laboratory Improvement Amendments (19). If 50% and 25% of the total error budget comes from systematic and random errors, respectively, the desirable quality specification for bias ($Bias_d$) (7.00%) was calculated with 50% of the total allowable error (14.00%). If the bias was higher than $Bias_d$, it was considered a clinically significant difference.

The digoxin levels in the compared and reference tubes were also compared using Passing and Bablok regression analyses, and subsequently, these results were visually demonstrated on Bland and Altman plots.

RESULTS

The mean and SD of digoxin levels determined in different tubes, SCLs, $Bias_d$, bias values, and statistical significance are shown in Table 1. The mean of the digoxin levels in each tube depending on the time is shown in Figure 1.

Although no statistical difference was found between the 0 and 48 h results in the Z-tube, Vacusera, SST, and Barricor tubes, the digoxin levels in LiH at 48 h increased statistically compared with 0 h. When SCLs were evaluated with regard to the stability of digoxin, the drug level in any tube did not exceed the limit. The bias between the 0 and 48 h results in all tubes was lower than $Bias_d$.

The digoxin levels in the LiH, Vacusera, and SST tubes at both 0 and 48 h were not statistically different according to the reference tube, but a statistically significant difference was found in the Barricor tube. The drug levels in the Barricor tube at both 0 and 48 h were higher than those in the reference tube. When assessed according to the $Bias_d$, the bias of digoxin results in LiH, Vacusera, and SST tubes were acceptable compared with the reference tube, except the Barricor tube at 0 h.

The digoxin levels obtained from the different tubes are shown using Passing and Bablok regression graphs and Bland and Altman plots in Figure 2. In the regression analyses, the digoxin levels between the LiH, Vacusera, and SST tubes with the Z-tube were strongly correlated, and any proportional or constant errors between tubes were not detected. Although the drug levels between the Barricor and Z-tubes were strongly correlated, a proportional error was found between the results of the Barricor and Z-tubes. According to the Bland-Altman plots, all paired data were within the confidence interval of agreement limits in comparison of all tubes with the Z-tube.

Table 1. Evaluation of digoxin stability according to different tubes and storage times

Tubes	0 h Mean ± SD (ng/mL)	48 h Mean ± SD (ng/mL)	Bias% and p-value between h		-SCL	+SCL	Bias% and p-value between reference and compared tubes at 0 h		Bias% and p-value between reference and compared tubes at 48 h		$Bias_d$%
											7.00
Z-tube	1.04±0.65	1.08±0.66	3.29	0.207	0.82	1.27					
LiH	1.04±0.62	1.10±0.66	5.96	0.020*	0.82	1.26	-0.29	0.874	2.29	0.036	
Vacusera	1.06±0.65	1.10±0.68	3.51	0.107	0.84	1.29	1.88	0.278	2.10	0.121	
SST	1.09±0.67	1.10±0.67	1.47	0.475	0.86	1.31	4.12	0.027	2.29	0.031	
Barricor	1.16±0.70	1.14±0.69	-1.62	0.357	0.93	1.38	10.70‡	<0.001†	5.44	<0.001†	

Z-tube: Glass tube without additive (reference tube), SST: clot-activator tube with gel, LiH: lithium heparin tube without gel, Barricor: lithium heparin tube with barrier, Vacusera: clot-activator tube with gel, SCL: significant change limit, $Bias_d$: desirable quality specifications for bias, Bias%: difference between the compared tube and reference tube results, p-value: significance value, *p<0.05 was considered statistically significant, †The level of significance was adjusted with Bonferroni's correction, and p<0.0125 was considered statistically significant, ‡Desirable quality specification for bias exceeded, SD: standard deviation

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DISCUSSION

Digoxin is one of the drugs that are frequently requested in therapeutic drug monitoring (TDM). In the current literature, there are different recommendations regarding the use of tubes with gel for TDM. The ADVIA Centaur systems, which produce the digoxin kit used in our laboratory, recommend that each laboratory should apply for TDM tests to its own specific tube manufacturer, but the recommended sample type is the serum. The manufacturer also stated that the samples should be stored at room temperature up to 8 h and at +4 °C after 8 h, and should be frozen at ≤-20 °C unless analyzed within 48 h.

The World Health Organization reports that plasma reflects the pathological condition of the patient better than serum (20). In the study published by the manufacturer of blood collection tube (BD) used in our laboratory, the digoxin levels in BD Barricor and BD plasma separator tubes were clinically acceptable compared with the BD SST; the digoxin levels in all tubes were stable for 48 h at room temperature and 7 days in the refrigerator (21). Therefore, we aimed to verify the statistical and clinical acceptability of differences in the LiH, Barricor, SST, and Vacusera tubes versus the Z-tube (reference tube) to evaluate the digoxin levels and stability in serum and plasma in our laboratory condition.

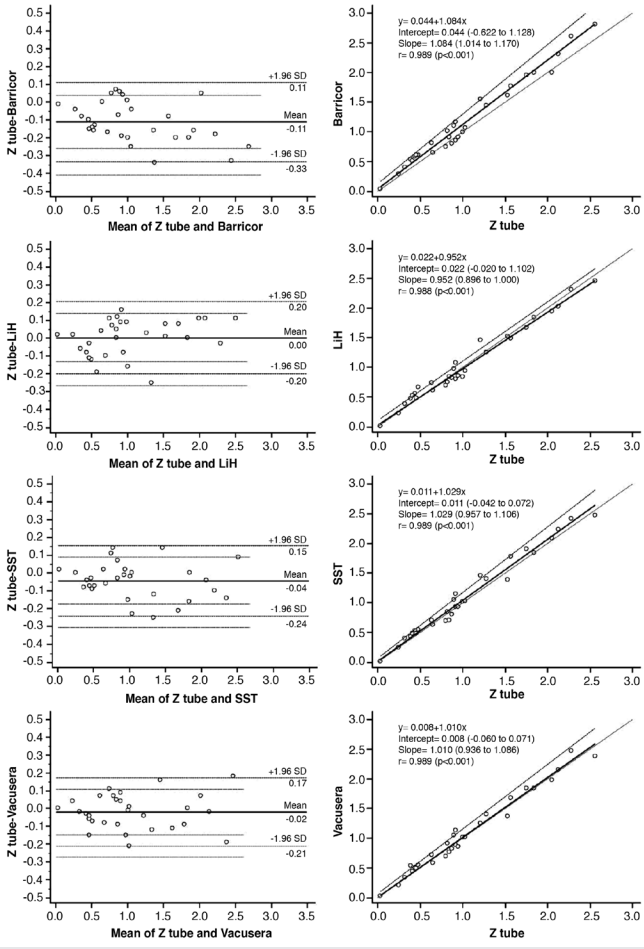

Figure 1. Bland-Altman plots and Passing-Bablok graphs for digoxin analyzed in five different types of blood collection tubes [Z-tube, glass tube without additive (reference tube)] at 0 h, SST: clot-activator tube with gel, LİH: lithium heparin tube without gel, Barricor: lithium heparin tube with barrier), Vacusera: clot-activator tube with gel. The solid, dashed, and identity lines in the Passing-Bablok regression graphs represent the regression line, its confidence intervals, and identity line (x=y), respectively. The thick solid, dashed, and thin solid in the Bland-Altman plots represent the mean difference, limits of agreement, and confidence intervals of limits of agreement, respectively

When the digoxin levels of LiH, Vacusera, and SST tubes were compared with those of the Z-tube at 0 h, the bias values were -0.29%, 1.88%, and 4.12%, respectively. The highest bias (10.70%) was in the Barricor tube and exceeded the $Bias_d$ limit (7.00%). The digoxin levels proportionally increased in the Barricor tube compared with the Z-tube. The digoxin level in a Barricor tube might possibly reflect real-time plasma digoxin level in relation with other tubes. Indeed, the digoxin metabolite in other tubes may be more trapped between cells and fibrin particles during blood clotting as seen in Z, Vacusera, or SST tubes. In the case of LiH tube, the digoxin levels were still lower than those in the Barricor tube despite both tubes using the same anticoagulant (Li heparin). The difference might be explained by the barrier effect in the Barricor tube, in which the drug metabolite was sprayed into the supernatant resulting to its effective separation. The drug levels in serum or plasma are preserved due to effective separation even in the presence of the barrier (a gel or not). The new barrier may also not absorb any significant amount of digoxin in the plasma because its structure is different from a gel structure.

At 48 h, only the bias between the Barricor and Z-tubes was statistically significant, but it did not exceed the $Bias_d$ limit. The

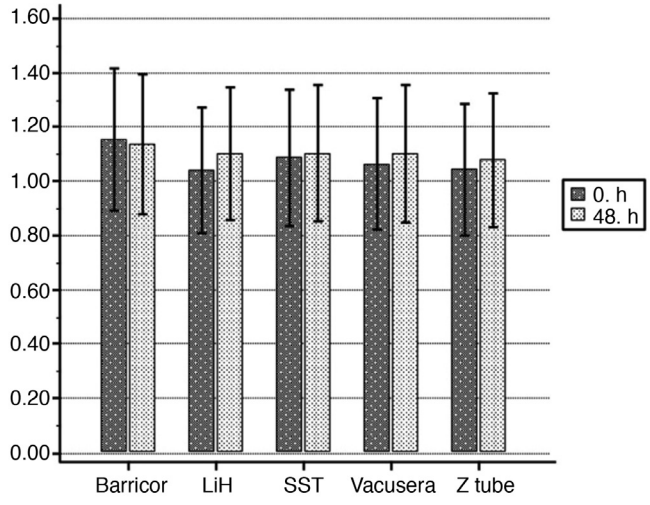

Figure 2. The comparison of digoxin level at 0 and 48 h obtained in different tubes. Z-tube, glass tube without additive (reference tube), SST: clot-activator tube with gel, LİH: lithium heparin tube without gel, Barricor: lithium heparin tube with barrier). Vacusera, clot-activator tube with gel. Data are shown as mean and 95% confidence interval for mean

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digoxin levels of the Z, LiH, Vacusera, and SST tubes showed a time-dependent increase, but those of the Barricor tube decreased at 48 h. Although the clinical significance of bias disappeared due to the increase in digoxin level of the reference tube and the decrease in digoxin level of the Barricor tube, statistical significance was preserved. The changes in other tubes except the LiH tube at 48 h were not statistically and clinically significant.

Boeynaems et al. (10) obtained comparable results between heparinized and non-heparinized plastic tubes with a glass tube. The digoxin levels of all three tubes were stable for 24 h. They considered that the plasma was interchangeable with serum in digoxin measurement (10). Chan et al. (22) detected a 5%-10% bias between the BD heparinized tube with gel (PST) and heparinized gel-free tube. In the study of Dukić et al. (13), the digoxin levels were compared in two plastic tubes with a gel barrier containing clot activator and lithium heparin. Similar to Boeynaems et al. (10), they showed that plasma or serum can be used interchangeably to measure the digoxin levels (13).

In this study, higher digoxin levels were found in the Barricor tubes compared with others, and no significant difference in any digoxin levels over time were accepted as evidence of the minimum effect of the new-generation barrier. Even if a glass tube was selected as a reference tube, it was estimated that the tubes with barrier better reflects digoxin levels in the matrix because of the barrier separating the cell-supernatant.

Dasgupta et al. (8) found that the increase in digoxin level at 24 h was not statistically significant in both tubes with gel separator and plane tube. Koch and Platoff (12) found a statistically significant increase in digoxin levels, depending on the time, in tubes with gel, but they could not explain its reason. Boeynaems et al. (10) showed that the digoxin levels in the glass tube without additive, heparinized, and heparin-free plastic tubes decreased in 24 h, but it was not statistically significant. Bailey et al. (11) reported that digoxin levels were stable up to 1 week in tubes with gel and plain tubes, and Landt et al. (4) reported that digoxin levels were stable up to 24 h in the tubes containing 3 different polymeric separators.

Study Limitations

Our study has also some limitations. Although our number of volunteers were compatible with local clinical validation of the blood collection tubes (23), it would be more convenient to include more volunteers. Another limitation was that the stability was evaluated only at 48 h due to both reagent and tube manufacturer specifying the stability for 48 h. Further studies involving different time periods can be chosen in case of different reagent/tube preferences.

CONCLUSION

The gel separator has been considered to have an absorption or adsorption effect, especially for hydrophobic therapeutic drugs. However, in studies to date, except for Koch and Platoff (12), the stability of serum and plasma digoxin in the different tubes has no significant time-dependent changes. Most likely, these differences can be attributed to differences in experimental procedures or conditions. In our study, because the most stable tube for digoxin was presumed to be SST containing gel, digoxin was not easily affected by the gel separator, similar to other hydrophobic drugs. Digoxin was the most stable in the SST tube, followed by the Barricor tube. The new-generation barrier makes a difference because the digoxin levels in the Barricor tube were higher than those in other tubes. This might be due to the Barricor tube being more efficient in separating between cells and supernatants. As a result, while the digoxin levels in the other tubes may be used interchangeably by existing therapeutic range, the reliability and accuracy of digoxin results may presumably increase by defining a new therapeutic range for the Barricor tube.

Ethics Committee Approval: Retrospective study.

Informed Consent: Detailed information about the study was provided to all participants before their participation, and their signed consents were obtained.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.D.A., İ.K., H.S., C.D., Design - H.S., C.D.; Data Collection and/or Processing - S.D., M.Z.A., A.B.; Analysis and/or Interpretation - S.D., B.İ.B., M.Z.A., A.B.; Literature Search - F.D.A., İ.K., B.İ.B.; Writing Manuscript - F.D.A., İ.K., B.İ.B.

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