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Association between the number of coadministered P-glycoprotein inhibitors and serum digoxin levels in patients on therapeutic drug monitoring

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Abstract

Background: The ABC transporter P-glycoprotein (P-gp) is recognized as a site for drug-drug interactions and provides a mechanistic explanation for clinically relevant pharmacokinetic interactions with digoxin. The question of whether several P-gp inhibitors may have additive effects has not yet been addressed.

Methods: We evaluated the effects on serum concentrations of digoxin (S-digoxin) in 618 patients undergoing therapeutic drug monitoring. P-gp inhibitors were classified as Class I, with a known effect on digoxin kinetics, or Class II, showing inhibition *in vitro* but no documented effect on digoxin kinetics in humans. Mean S-digoxin values were compared between groups of patients with different numbers of coadministered P-gp inhibitors by a univariate and a multivariate model, including the potential covariates age, sex, digoxin dose and total number of prescribed drugs.

Results: A large proportion (47%) of the digoxin patients undergoing therapeutic drug monitoring had one or more P-gp inhibitor prescribed. In both univariate and multivariate analysis, S-digoxin increased in a stepwise fashion according to the number of coadministered P-gp inhibitors (all *P* values < 0.01 compared with no P-gp inhibitor). In multivariate analysis, S-digoxin levels were 1.26 ± 0.04, 1.51 ± 0.05, 1.59 ± 0.08 and 2.00 ± 0.25 nmol/L for zero, one, two and three P-gp inhibitors, respectively. The results were even more pronounced when we analyzed only Class I P-gp inhibitors (1.65 ± 0.07 for one and 1.83 ± 0.07 nmol/L for two).

Conclusions: Polypharmacy may lead to multiple drug-drug interactions at the same site, in this case P-gp. The S-digoxin levels increased in a stepwise fashion with an increasing number of coadministered P-gp inhibitors in patients taking P-gp inhibitors and digoxin concomitantly. As coadministration of digoxin and P-gp inhibitors is common, it is important to increase awareness about P-gp interactions among prescribing clinicians.

Background

Knowledge about mechanisms of interactions makes it possible to predict and prevent pharmacokinetic drug interactions. The *MDR1* gene encodes the ABC transporter P-glycoprotein (P-gp), which functions as an efflux pump and is recognized as a site for drug-drug interactions [1-5]. Several commonly used drugs inhibit P-gp efflux, which can increase gastrointestinal absorption, decrease elimination in the bile and urine, and affect the distribution of drugs to certain compartments, such as the central nervous system (CNS) [2-5].

Digoxin has a narrow therapeutic range and is recognized as a high-affinity P-gp substrate [6]. Risk factors for digoxin toxicity are well known to clinicians and include advanced age, impaired renal function and low body weight. Despite this, statistics show that unintended digoxin intoxication remains a common problem [7]. Digoxin has again become a subject of discussion after recent publications demonstrated sex-based differences in mortality [8] and increased mortality among men with serum concentrations of digoxin (S-digoxin) > 1.5 nmol/L [9]. In this context, heightened attention to a patient's S-digoxin level is warranted.

Certain inhibitors of P-gp have been demonstrated to increase S-digoxin levels in healthy volunteers [2,10,11], sometimes in a dose-dependent manner [12]. As digoxin is frequently coadministered with P-gp inhibitors, we wanted to i) evaluate whether clinically relevant interactions are observed in a large group of ordinary digoxin patients and ii) investigate whether patients taking several P-gp inhibitors have additive elevations in S-digoxin levels compared with patients with one concomitantly prescribed P-gp inhibitor.

Methods

Study population and analysis of S-digoxin

All patients on digoxin therapeutic drug monitoring (TDM) at Uppsala University hospital (Sweden) over the past three years were considered for this study. Patients were included if they were on oral digoxin treatment; their S-digoxin values were above the detection limit; steady-state concentrations had been reached; the serum samples were measured at trough; and information about concomitant treatment was available.

The S-digoxin levels had been determined by a fluorescence polarization immunoassay (TDx®, Abbott Scandinavia AB, Sweden).

Substance classification

To classify the concomitantly administered drugs as P-gp inhibitors, PubMed was systematically searched for the INN substance name and English spelling combined with the terms 'P-gp', 'Pgp' and '*MDR1*'. Substances were classified as P-gp inhibitors when demonstrating a clear inhibitory effect on P-gp in cellular transport assays, in cellular uptake assays or in animal models using *mdr1*a(-/-)mice. A literature review was also performed combining the search terms 'digoxin' and the substance names. Any effect of each drug on digoxin pharmacokinetics *in vivo* was documented.

To evaluate whether only P-gp inhibitors with well-recognized digoxin interactions *in vivo* contribute to a change in S-digoxin, the P-gp inhibitors were further divided into two groups: Class I P-gp inhibitors, with well-documented effects on digoxin pharmacokinetics *in vivo*, and Class II P-gp inhibitors, with established P-gp inhibitory effect *in vitro* and putative effects on S-digoxin *in vivo*. Class I and II P-gp inhibitors were compared with drugs that had no or unknown effects on P-gp. Only substances administered orally were included in the classification.

Statistical analysis

Adjusted mean S-digoxin values for each category of P-gp were computed on the basis of the regression estimates calculated with the General Linear Model using Proc GLM in SAS 8.02 (SAS Institute Inc., NC, USA), with the confounding factors at their mean values. Data are presented as mean values ± SE. Two different models were used: one univariate and one multivariate, including the potential covariates age, sex, digoxin dose and total number of prescribed drugs for each individual (all continuous). In addition, subclass analysis including p-creatinine values was performed.

Results

Patient characteristics

Therapeutic drug monitoring charts from 618 patients (256 men and 362 women) fulfilled the inclusion criteria. The study population included patients with a diagnosis of heart failure and/or atrial fibrillation. See Table 1 for patient characteristics. Forty-seven percent of the study population were taking at least one P-gp inhibitor. Patients with S-digoxin levels above the recommended therapeutic range, > 2.5 nmol/L, (the upper limit of the therapeutic range at the time of the study) were more likely to have coadministered P-gp inhibitors compared with patients with S-digoxin = 2.5 nmol/L (68% *vs.* 47%, $P = 0.01$, using Chi-square test).

Substance classification

Our study population had a total of 228 different drug substances prescribed. Of these, 21 were documented P-gp inhibitors and eight were P-gp inhibitors with reported digoxin interactions (Table 2).

Table 1: Patient characteristics

Characteristic	TDM patients *N* = 618
Age (years)*	84 (24–99)
P-creatinine (mmol/L)*	100 (36–598)
Daily digoxin dose (mg)*	0.13 (0.04–0.5)
Concomitant drugs*	5 (1–21)
Patients below therapeutic range (< 1.2 nmol/L)	263
Patients within therapeutic range (1.2–2.5 nmol/L)	317
Patients above therapeutic range (> 2.5 nmol/L)	38

*Median (range). TDM = therapeutic drug monitoring.

Table 2: Drug classification

Class I substance	No. of patients using the drug	References
Amiodarone	12	[21], [22]
Atorvastatin	12	[11], [20]
Cyclosporine A	3	[23]
Dipyridamole	12	[24]
Quinidine	1	[1], [25]
Quinine	1	[26], [27]
Spironolactone	106	[25]
Verapamil	31	[25]
Class II substance	**No. of patients using the drug**	**References**
Bromocriptine	1	[28]
Flupentixol	1	[29]
Glibenclamide	46	[30]
Isradipine	2	[21], [31]
Lansoprazole	51	[32]
Loperamide	2	[33], [34]
Medroxyprogesterone	2	[35]
Omeprazole	35	[32]
Pantoprazole	6	[32]
Paroxetine	6	[36]
Sertraline	29	[36], [37]
Simvastatin	17	[20]
Terfenadine	1	[38]

The coadministered drugs were classified for their effects on P-gp and on digoxin pharmacokinetics. Class I P-gp inhibitors have well-documented effects on digoxin pharmacokinetics *in vivo*, while Class II P-gp inhibitors have established P-gp inhibitory effects *in vitro* and putative effects on S-digoxin *in vivo*.

Association between S-digoxin levels and number of coadministered P-gp inhibitors

Overall, patients with concomitant P-gp inhibitors had higher S-digoxin levels than patients without: 1.55 ± 0.04 compared with 1.26 ± 0.04 nmol/L, $P < 0.001$ (the results differed in the third decimal between the univariate and multivariate analyses [Figure 1A]). Subclass analysis of the 542 patients for whom p-creatinine was available did not alter these results. An increasing number of P-gp inhibitors was associated with stepwise elevations in S-digoxin levels (Figure 1B).

Analysis of classified P-gp inhibitors

The S-digoxin levels were 1.25 ± 0.04 nmol/L for patients with no P-gp inhibitors compared with 1.65 ± 0.07 and 1.83 ± 0.17 for patients with one and two Class I P-gp inhibitors, respectively (Figure 2). The differences in the calculations using the univariate compared with the multivariate model were minute. The effect on mean S-

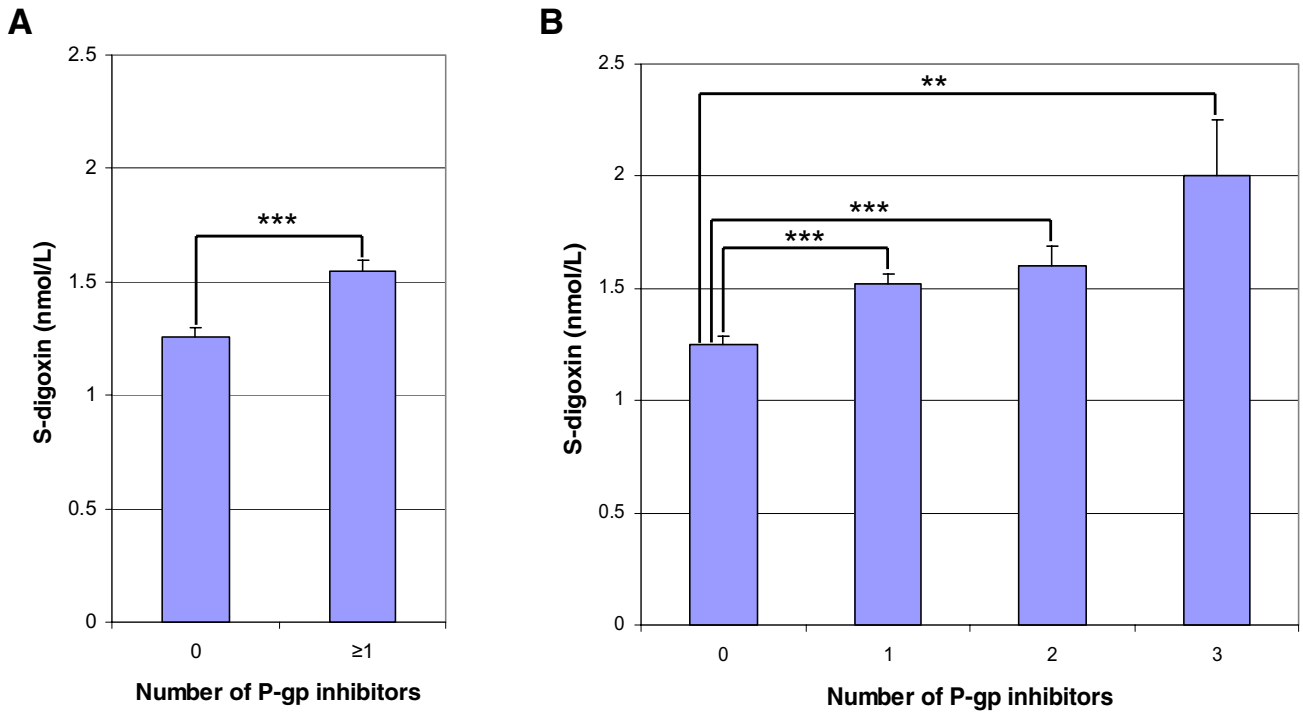

Figure 1

The association between S-digoxin levels and the number of prescribed P-gp inhibitors (A) Adjusted* S-digoxin means for the patients without ('0') (*N* = 328, S-digoxin mean ± SE 1.26 ± 0.04 nmol/L) or with ('≥ 1'), P-gp inhibitors (*N* = 290, S-digoxin mean ± SE 1.55 ± 0.04 nmol/L). **(B)** Adjusted* S-digoxin means for patients taking zero, one, two or three P-gp inhibitors. The number of patients were 328, 204, 78 and eight, respectively. The S-digoxin means ± SE (nmol/L) were 1.26 ± 0.04, 1.51 ± 0.05, 1.59 ± 0.08 and 2.00 ± 0.25. *Adjusted for age, sex, digoxin dose and total number of prescribed drugs.

digoxin levels among patients with Class I P-gp inhibitors was not solely attributed to the most frequently coadministered P-gp inhibitors, spironolactone and verapamil, because exclusion of patients with these drugs gave similar, although smaller, differences. Patients taking one or two Class II P-gp inhibitors also tended to have elevated S-digoxin levels compared with patients with no P-gp inhibitors, although these differences were not significant in the multivariate model.

Discussion

Rathore *et al.* (2003) [9] recently reported that the mortality rate was increased at S-digoxin levels above 1.5 nmol/L. Therefore, it is particularly important to be aware of factors that influence S-digoxin levels. We consider the magnitudes of the differences seen in S-digoxin in this study, 20–60% increases, to be of clinical importance. The patients taking one or more P-gp inhibitor had S-digoxin levels above 1.5 nmol/L, while patients without P-gp inhibitors were below this limit.

Pharmacokinetic interactions with digoxin can arise from mechanisms other than P-gp, for example, changes in renal function, changes in gut motility or pH, disturbances of digoxin-metabolizing intestinal bacteria or possibly from interactions with other transport proteins, such as members of the solute carrier family (SLC) [13]. P-gp seems, however, to be a major determinant for digoxin pharmacokinetics.

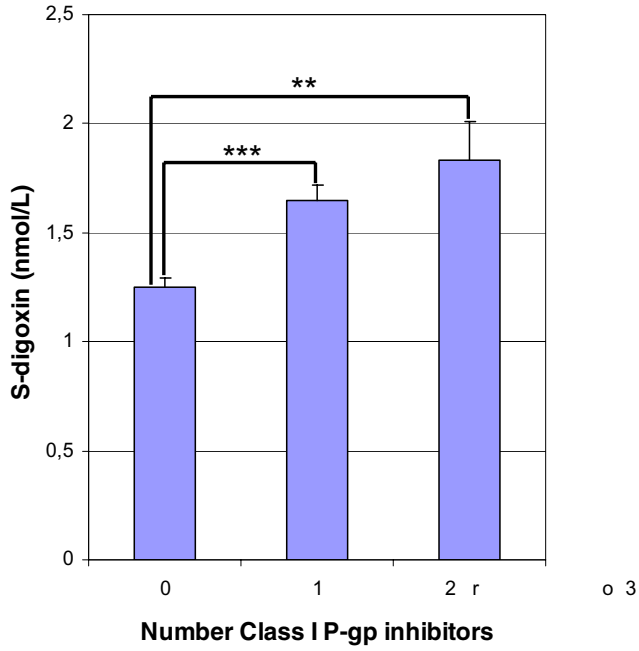

Figure 2
The association between S-digoxin levels and the number of prescribed Class I P-gp inhibitors Adjusted* S-digoxin means for patients taking zero, one or two Class I P-gp inhibitors. The numbers of patients were 328, 96 and 17, respectively. The S-digoxin means ± SE (nmol/L) were 1.25 ± 0.04, 1.65 ± 0.07 and 1.83 ± 0.17. *Adjusted for age, sex, digoxin dose and total number of prescribed drugs.

Drugs with structures similar to digoxin can interfere with digoxin immunoassays [14]. Of the concomitant drugs taken by the patients in this study, spironolactone and its metabolites have been reported to interfere with the digoxin readings [15]. That spironolactone can interfere with digoxin immunoassays has been known for 30 years [16], but until recently little information about this effect has been available for newer digoxin assays. In a 1999 report by Steimer *et al.* [17], a case of digoxin toxicity resulted from falsely low values using the MEIA II assay for digoxin (AxSYM®; Abbott). Canrenone and spironolactone were identified as the major interfering substances. In a subsequent study, Steimer *et al.* (2002) [15] examined nine digoxin assays including the TDx® used in our study. False-negative results were attributable to spironolactone, canrenone and other steroids in several newer digoxin assays. In contrast, falsely increased digoxin concentrations could be detected in the TDx assay®, although these were very small except in the absence of digoxin and at high concentrations of the interfering substance. In updated product information for the TDx assay® released by Abbott Scandinavia AB [18], the results of a careful study of the analytical interference from spironolactone, canrenone and other steroids confirmed the results of Steimer *et al.* [15]. Spironolactone and canrenone, at concentrations estimated to be the maximal blood concentrations found in patients treated with these drugs, were shown to increase the digoxin concentration by 4% and 15%, respectively. Spironolactone metabolites at concentrations corresponding to a daily intake of 100 mg falsely increased the digoxin concentration by 7%.

It is important to note that the doses recommended for patients with heart failure are considerably lower than this (12.5–50 mg). The average intake in our study was 34 mg/day. Furthermore, our results cannot be due to assay interference because the association between serum digoxin concentrations and P-gp inhibitors remains statistically significant even when all patients on spironolactone are excluded from the study (1.46 ± 0.05 compared with 1.26 ± 0.04 nmol/L, $P < 0.001$, for patients with and without concomitant P-gp inhibitors, respectively).

Likely explanations for the more pronounced effect of Class I P-gp inhibitors on S-digoxin levels compared with Class II P-gp inhibitors are the inhibitory concentrations for a certain drug in relation to the concentrations achieved in clinical use. As the drugs have been evaluated for P-gp inhibitory effect using several different *in vitro* methods, it was not proper to perform a comparison of the K_i or IC_{50} values from the literature. A majority of the Class I inhibitors are given at higher doses than Class II inhibitors (the range of the lowest recommended doses is 10–200 mg for Class I *vs.* 0.25–60 mg for Class II), and the Class I inhibitors are often more potent, inhibiting digoxin transport by P-gp *in vitro* at lower concentrations. Other factors, such as time-point for the administration and physiochemical properties of the drug, might also contribute to the effect seen *in vivo*. Today, the *in vitro* data used to select the Class II drugs is not sufficient for the prediction of clinically relevant P-gp interactions *in vivo*. Before such interactions are fully understood, the Class II drugs should be regarded as potential mediators of drug-drug interactions when coadministered with digoxin or other P-gp substrates.

P-gp has a broad substrate specificity and, unfortunately, it is not possible to state that a particular group of drugs, for example, calcium channel blockers or HMG-coenzyme

A inhibitors, are P-gp inhibitors with potential clinical consequences. For instance, verapamil is a P-gp inhibitor demonstrating clinical effects on digoxin kinetics, whereas diltiazem is not [19]. Similarly, the HMG-coenzyme A inhibitor pravastatin is not an *in vitro* P-gp inhibitor [20], in contrast to atorvastatin, which is an *in vitro* P-gp inhibitor that also demonstrates *in vivo* effects on P-gp [11]. Any investigation of P-gp inhibitory effects and possible clinical consequences should, therefore, be made for each single drug entity.

Conclusions

In this report we show that coadministration of P-gp inhibitors with digoxin is associated with significant elevations in S-digoxin levels in an ordinary group of digoxin patients. To avoid exposing patients to excessive digoxin levels, prescribing clinicians should consider potential P-gp interactions. Particular notice should be taken when more than one P-gp inhibitor is coadministered with digoxin, as administration of more than one P-gp inhibitor is associated with additive elevations in S-digoxin levels.

Competing interests

None declared.

Authors' contributions

GE participated in the collection of the patient material, the computer analysis of the data, the classification of P-gp-inhibitors and in the writing of the manuscript. PH participated in the collection of the patient material, the computer analysis of the data and in the writing of the manuscript. PA participated in the analysis of the data and in the writing of the manuscript. KM participated in the in the computer analysis of the data. HM conceived the study and participated in its design and in the writing of the manuscript.

All authors read and approved the final manuscript.

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