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# Appropriateness of digoxin level monitoring

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## Summary

*Aim:* To evaluate the proportion of inappropriate digoxin level determinations.

*Methods:* We performed a retrospective analysis of 210 randomly selected digoxin plasma level determinations in inpatients. Appropriateness criteria were defined combining existing criteria from the literature. The main outcome measure was the proportion of digoxin levels assessed as inappropriate using *a priori* defined criteria.

*Results:* Of the 210 digoxin levels assessed, 125 (59%; 95% confidence interval [CI] 52–66%) were considered inappropriate, 81 (39%; 95% CI: 32–45%) were appropriate, and 4 (2%) determinations could not be evaluated. Of the 125 levels assessed as inappropriate, the majority (79%) was performed as routine monitoring. Extrapolating the results to all digoxin level determinations in inpatients at our institution resulted in estimated yearly costs of CHF 28,025 (approximately € 18,995) for inappropriate digoxin level determinations.

*Conclusions:* The majority of digoxin plasma levels determinations were assessed as inappropriate. This was mainly due to the lack of an adequate indication and due to incorrect timing of drawing the blood samples. With regard to indication, routine monitoring was the reason for the majority of levels assessed as inappropriate.

*Key words: digoxin; therapeutic drug monitoring; hospital; inpatients*

## Introduction

Pharmacodynamic effects are usually monitored by direct measurement of physiological indices of therapeutic responses, such as lipid concentrations, blood pressure or blood glucose. However, for many drugs a readily available effective measure is lacking or is insufficiently sensitive. Furthermore, a large interindividual variability with regard to dose or concentration and response can make individualising drug dosage difficult. This is especially the case for drugs with a narrow therapeutic index, large interindividual variability in pharmacokinetics, or a concentration-dependent pharmacokinetics. Drug level monitoring (therapeutic drug monitoring, TDM) combines the measurement of drug concentrations in body fluids (especially in plasma, serum, whole blood, saliva) with pharmacokinetics and pharmacodynamics. Hence, TDM can be a valuable and useful tool for some specific drugs to optimise and individualise pharmacotherapy. Furthermore, TDM may contribute to minimise the risk of concentration-dependent adverse drug reactions and therefore, may be an essential part of clinical management [1–4]. This also applies to digoxin which is still a widely used drug for congestive heart failure and atrial fibrillation, even though its effectiveness is debated controversially [5–9]. In addition to the above mentioned indications for TDM, assessment of digoxin levels may be clinically useful for evaluating compliance in specific populations such as the elderly with drug toxicity or for verifying drug toxicity [10–12]. Elderly patients are especially prone to enhanced susceptibility to digoxin toxicity. Patients over 70 years of age may show clinical signs of digoxin toxicity despite having digoxin concentrations within the recommended therapeutic range [13].

However, digoxin level monitoring without a proper indication, with a wrong sampling time or a wrong interpretation of the result, may not only significantly limit its benefits but additionally cause significant unnecessary costs [14–16]. A preliminary study at our institution suggested that the proportion of inappropriate digoxin level monitoring is relatively high [17].

The present retrospective study was performed to assess the proportion of digoxin level determinations in hospitalised patients not fulfilling criteria for appropriate digoxin level monitoring, and to identify the reasons for inappropriate digoxin level monitoring.

The present study was not founded.

# Methods

## Setting

The study was conducted at the University Hospital of Basel, a 855-bed teaching hospital providing primary and tertiary care to an urban population of approximately 200,000 inhabitants. It also serves as a tertiary care referral centre for Northwest Switzerland with a catchment area of approximately 450,000 people. Resident physicians are the primary orderers of tests. The Division of Clinical Pharmacology provides routine pharmacokinetic consultations only for aminoglycosides. However, a variety of drug level determinations, including those of digoxin, are interpreted and, if necessary, dosage recommendations are provided in writing by the clinical pharmacology team.

## Appropriateness criteria

Criteria for appropriate digoxin level monitoring were defined *a priori* and were derived from criteria previously described in the literature [14–16, 18–25]

Digoxin level monitoring was considered appropriate if each of the following three criteria were fulfilled (see Appendix 1 for explicit criteria for appropriateness): (1) there was an adequate indication for digoxin level monitoring; (2) the blood sample had been drawn at least 6 h after digoxin had been administered in order to ensure that the distribution phase of digoxin was terminated; additionally, steady state conditions of digoxin had to have been reached (defined as 4 half-lives after digoxin was initiated or after digoxin dose adjustment; i.e. 6 days in patients with normal renal function); (3) the laboratory result had to be rationally interpreted by the physician, i.e. the clinical consequences with regard to digoxin therapy had to be comprehensible in consideration of the patient's clinical state.

## Measurement of digoxin plasma levels

Digoxin plasma levels were measured by the clinical medicine laboratory using the AxSYM® Digoxin II assay (a polarisation fluorescence immunoassay, by Abbott Laboratories, Abbott Park, IL). The therapeutic range of digoxin was defined as 0.9 nmol/L through 2.6 nmol/L (0.7–2.0 ng/mL).

The laboratory results were interpreted by a member of the clinical pharmacology team. A written comment and, if necessary, information for dosage adjustment or other remarks were provided for each digoxin level determination requested.

The cost for one digoxin level measurement from a hospital perspective is approximately CHF 50 (€ 34).

**Table 1**

Characteristics of 210 inpatients for whom digoxin levels were determined.

| Characteristics | |
|---|---|
| Age [yrs], median (range) | 79 (52–97) |
| Female, n (%) | 109 (51.9) |
| Hospital speciality, n (%) | |
| Internal medicine | 112 (53.3) |
| Surgery | 60 (28.6) |
| Other | 38 (18.1) |
| Length of stay [days], median (range) | 17 (2–141) |
| Estimated creatinine clearance, n (%) | |
| >50 ml/ min | 92 (43.8) |
| 20–50 ml/min | 57 (27.1) |
| <20 ml/min | 1 (0.5) |
| N.A.* | 60 (28.6) |
| Renal function, n (%) | |
| Stable | 152 (72.4) |
| Unstable / worsening** | 55 (26.2) |
| N.A.*** | 3 (1.4) |

* N.A. = not applicable (creatinine clearance was not estimated if the renal function was unstable or worsening, or in highly obese patients [i.e. body mass index >35])

** change of serum creatinine of more than 30 mmol/L since the last measurement

*** data on weight and/or serum creatinine not available

## Patient sampling and data collection

From a total of 1288 digoxin plasma levels for adult in- and outpatients determined during one year (January to December 2000), 942 (73.1%) were ordered for inpatients. Of these, 210 (22.3%) digoxin level determinations were randomly selected for further analysis.

Charts of those patients for which a digoxin level determination was ordered and that was included in the analysis were reviewed to obtain the following information: age, sex, weight, patient status, digoxin dose and dosing interval, indication for digoxin level determination, previous digoxin level measurement during the same hospitalisation, use of concomitant drugs potentially interacting with digoxin (i.e. amiodarone, quinidine, propafenone, verapamil), and serum creatinine concentration. To estimate the creatinine clearance as a marker for renal function we used the equation by Dettli [26]: (150 – age) × body weight [kg] × 0.9 [women] or 1.1 [men] / serum creatinine [µmol/L]).

These data were used to categorise digoxin level monitoring as "appropriate" or "inappropriate" according to the criteria defined above.

## Statistical analysis

Data are presented as median with the corresponding range. Ninety-five percent confidence intervals (95% CI) were calculated for point estimates.

# Results

The characteristics of the 210 patients selected for which digoxin level monitoring was performed is displayed in table 1. The median age of patients was 79 years and the majority of patients were female. Fifty-three percent were medical, 29% surgical inpatients, and the remaining 18% from other in-hospital services. Most patients had a stable renal function and an estimated creatinine clearance above 50 ml/min. Information on performance characteristics (e.g. indication for digoxin therapy, dose, dosage interval) are displayed in table 2. The majority of digoxin plasma levels (81%) were ordered for patients with atrial fibrillation with or without heart failure, oral ad-

**Table 2**

Performance characteristics of 210 digoxin level measurements.

| Characteristics | |
|---|---|
| Indication for digoxin, n (%) | |
| heart failure | 23 (10.9) |
| atrial fibrillation with or without heart failure | 170 (81.0) |
| other | 17 (8.1) |
| Digoxin dose [mg/d], median (range) | 0.18 (0.05–0.5) |
| Dosage interval [hours], n (%) | |
| 24 hours | 192 (91.4) |
| 48 hours | 6 (2.9) |
| other | 12 (5.7) |
| Route of administration, n (%) | |
| oral | 189 (90.0) |
| intravenous | 19 (9.1) |
| not available | 2 (0.9) |
| Potentially relevant drug interactions, n (%) | |
| none | 187 (89.0) |
| amiodarone | 17 (8.1) |
| verapamil | 6 (2.9) |
| Previous digoxin level measurements in the same patient during the same hospitalisation, n (%) | |
| none | 133 (63.3) |
| 1 measurement | 47 (22.4) |
| 2 measurements | 24 (11.4) |
| >2 measurements | 6 (2.9) |
| Duration since last measurement [days], n (%) | |
| 1–3 days | 22 (28.6) |
| 4–7 days | 17 (22.1) |
| >7 days | 25 (32.5) |
| other | 13 (16.9) |
| Digoxin level [nmol/L], median (range) | 1.4 (<0.26–22.8) |
| Digoxin level, n (%) | |
| subtherapeutic (<0.9 nmol/L) | 41 (19.5) |
| therapeutic (0.9–2.6 nmol/L) | 139 (66.2) |
| supratherapeutic (>2.6 nmol/L) | 30 (14.3) |
| Through level*, n (%) | |
| yes | 177 (84.3) |
| no | 32 (15.2) |
| N.A. | 1 (0.5) |

* Lowest concentration during the dosing interval, usually just before the next dose

ministration was the predominant administration route. The digoxin concentration was in the therapeutic range in 66% of the patients. In 14% a potentially toxic concentration was measured, and 20% were below the therapeutic range. Concomitant use of potentially interacting drugs was seen in 11% of the patients. Almost 37% of the patients had more than one digoxin measurement ordered during their hospital stay.

Of the 210 digoxin levels measured, 68% (95% CI, 62%–75%) were assessed as having an appropriate indication, while 32% (95% CI, 25%–38%) had no appropriate indication (table 3). Of the 67 levels with the indication assessed as inappropriate, 78% were due to routine monitoring.

In 35% of the 210 determinations, digoxin level monitoring was performed while no steady state conditions were reached. Seventeen samples (8%) were taken during the distribution phase of digoxin, which may result in non interpretable and usually clinically irrelevant increased digoxin concentrations [11, 25]. Overall, the timing was assessed as inappropriate in 32% (95% CI, 26%–39%) of the 210 measurements.

On the whole, including the criteria for appropriate indication, appropriate timing and appropriate interpretation of the result, 39% (95% CI: 32%–45%) of the digoxin level determinations were assessed as appropriate, 59% (95% CI 52%–66%) as inappropriate, while 2% were not classifiable.

When extrapolating the proportion of 59% of inappropriate digoxin level determinations to the total of 942 digoxin plasma measurements for all hospitalised patients in the year 2000, we estimated the costs for these inappropriate determinations to be CHF 28,025 (approximately € 18,995). Applying the same proportion to the total of all digoxin level determinations of the same year (including those determined in outpatients; n = 1288) would result in estimated costs of CHF 38,320 (approximately € 25,973) for inappropriate digoxin level determinations.

## Discussion

Because it may be difficult to assess the therapeutic effect of digoxin and, furthermore, because there is a simple assay to determine digoxin plasma concentrations, digoxin level monitoring is often performed, even though its benefit may still be questioned [20, 27]. Therefore, it is essential that there be a clinically relevant question that may be addressed by measuring and interpreting a digoxin plasma concentration.

Using the criteria developed for this study, 59% of all analysed digoxin levels were considered inappropriate with regard to indication, timing of sampling and/or appropriateness of interpretation of the result and/or action taken following receipt of the result. Only 39% of the analysed digoxin level determinations fulfilled the criteria for all three requirements. In other studies, where the three criteria mentioned above had also to be fulfilled in order for the level determination to be classified as appropriate, this percentage varied between 15 and 72% [14, 15, 28, 29]. However, because in other studies some of the individual crite-

**Table 3**

Indications for digoxin *level monitoring* (for further explanations see Appendix 1).

| Indication appropriate, n (%; 95% confidence interval) | |
|---|---|
| yes | 143 (68; 62–75) |
| no | 67 (32; 25–38) |
| Indication for appropriate levels, n (%) | 143 |
| newly initiated therapy | 51 (36) |
| high risk patient | 30 (21) |
| combination of several criteria | 19 (13) |
| suspected toxicity | 16 (11) |
| inadequate effect | 10 (7) |
| decision for future therapy | 10 (7) |
| uncertain digoxin exposure | 5 (4) |
| dose adjustment in patient with unstable renal function | 2 (1) |
| Indication for inappropriate levels, n (%) | 67 |
| routine monitoring | 52 (78) |
| other | 15 (22) |

ria used to assess appropriate digoxin level monitoring were defined differently, a direct comparison is only of limited value.

One of the main reasons why a high proportion of digoxin levels were assessed as inappropriate was because digoxin concentrations were measured when steady state conditions were not yet reached. With the exception of suspected digoxin toxicity or for the control after stopping digoxin because of supratherapeutic concentrations, it is generally of no use to measure the concentration before reaching steady state conditions. Interpreting a concentration before reaching a steady state is quite difficult, unless the individual patient's digoxin pharmacokinetic data are known to the physician ordering the drug level determination, which is most probably rarely the case. In our study, 35% of the patients had not reached steady state conditions at the time of sampling. In other studies this proportion was around 20% [15, 16, 20], and in one study this was the case in 88% of the levels analysed [30]. However, definition of the time to reach steady state conditions differed between the various studies.

Digoxin level determination during the absorption and distribution phase is, in general, not meaningful. Digoxin has a relatively long initial distribution phase lasting 4–8 hours which reflects the distribution from the central compartment to peripheral tissues compartments [31]. Because of high interindividual variability and the lack of a correlation with the concentration at the site of action, rational interpretation of such a concentration is almost impossible. Moreover, elevated digoxin plasma concentrations during the distribution phase, which in most cases are clinically irrelevant, might prompt physicians to unnecessary actions such as adjusting the digoxin dose. Therefore, it is usually not recommended to take a digoxin sample less than 6 hours after digoxin intake [18, 25, 28]. The proportion of digoxin levels determined before 6 hours after intake was relatively low in our study (8%), while other studies reported proportions around 25% [15, 32] and up to 64% [33].

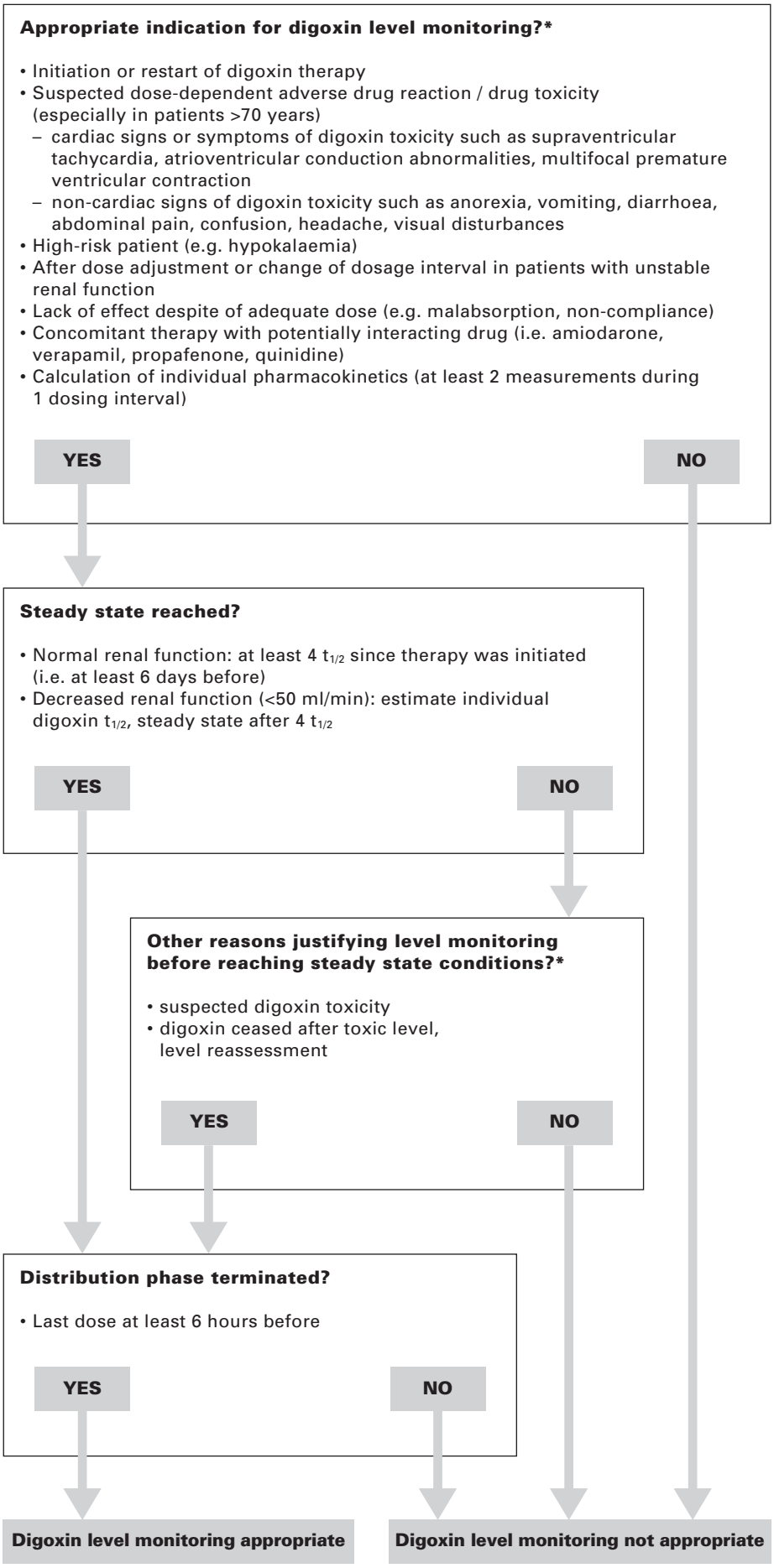
Digoxin level monitoring is most helpful when ordered in the context of a patient's symptoms and clinical condition. Levels should be performed to address a particular clinical question or to monitor a stable patient's condition at reasonable time points [11, 14, 20, 34]. However, in the present study almost every fourth measurement was ordered for routine monitoring in patients with long-term digoxin therapy, which in general does not justify digoxin level monitoring [20, 27].

This study has a number of limitations. The assessment of the indication for digoxin level monitoring was mainly based on information taken from the TDM request form; however, since this information was often not available, patients' charts were searched to find the relevant information. While comments about potential digoxin toxicity could sometimes easily be retrieved, other information such as suspected non-compliance, might not have been specifically written in the patients' charts and in consequence may have been overlooked. Therefore, assessment of some criteria based on chart review may not always have revealed the reason for ordering a digoxin level; this may have resulted in an underestimation of the proportion of appropriate levels. Additionally, information on the exact timing of blood sampling was often not possible to retrieve from the TDM request form; instead, we used the time when the sample arrived in the clinical chemistry laboratory as a surrogate marker assuming that blood sampling usually occurred within approximately one hour before arriving there. However, this might also be associated with some misclassification. Furthermore, the study only included certain laboratory parameters as markers for the patients' organ functions or clinical condition (e.g. creatinine as a marker to estimate the renal function), while other important parameters such as hypercalcaemia or hypokalaemia as risk factors for some toxic digoxin symptoms were not taken into consideration. Hypokalaemia is an important and common factor which increases the sensitivity of the tissues to digoxin. Reduction in plasma potassium concentration from 3.5 to 3.0 mmol/L is accompanied by an increase in sensitivity to digoxin of about 50%. If the potassium level is low, digoxin toxicity should be assumed without waiting for the plasma digoxin measurement [10]. Moreover, the appropriateness criteria defined in this study do not take into consideration other specific clinical situations (e.g. thyroid dysfunction) or specific populations (e.g. pregnant women, children).

While appropriate digoxin level monitoring may improve therapy and drug safety, inappropriate digoxin level monitoring is in most cases not associated with important clinical consequences [14]. However, it may result in considerable additional costs as estimated in our and in previous

**Figure 1**

Algorithm for digoxin level monitoring (for further explanations see Appendix 1).




* at least 1 criterion needs to be fulfilled

studies [14]. Using the information from our study we developed an algorithm which can guide clinicians in ordering digoxin drug levels (figure 1). Applying this algorithm might contribute to reduce the number of unnecessary digoxin level determinations, without loss of clinically useful information.

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# Appendix 1: Explicit criteria used to assess appropriateness of digoxin therapeutic drug monitoring (TDM) [14–16, 18–25]

**1. Adequate indication for digoxin level monitoring:**

1.1. Suspected digoxin toxicity / concentration dependent adverse drug reaction
- Appearance of arrhythmias (suspected to be associated with digoxin therapy; e.g. supraventricular tachycardia, atrioventricular conduction abnormalities, multifocal premature ventricular contractions)
- Non-cardiac symptoms of digoxin toxicity (i.e. loss of appetite, nausea, vomiting, diarrhoea, abdominal pain, visual disturbances, confusion, headache)

1.2. Newly initiated or reinitiated therapy with digoxin

1.3. Dosage adjustment or change of dosage interval in patients with unstable renal function

1.4. Subtherapeutic response despite adequate dose
- Suspected non-compliance
- Suspected absorption problem (i.e. malabsorption, antacids, antibiotics, diarrhoea)
- No improvement or worsening of congestive heart failure, or atrial fibrillation or flutter

1.5. High risk patient
- Unstable or declining renal function (change of serum creatinine of >30 μmol/l since last measurement)
- Surgical patient
- Hypothyroidism or hyperthyroidism
- Other (i.e. advanced age [i.e. >90 years], electrolyte abnormalities, patients in intensive care unit, low weight [BMI <15])

1.6. Digoxin therapy uncertain or unknown
- Emergency patient
- Admission level for inpatients if no digoxin level determined within the previous nine months is available

1.7. Potentially relevant drug interaction with digoxin (i.e. with amiodarone, verapamil, propafenone, quinidine)
- Start of potentially interacting concomitant drug
- Newly initiated digoxin therapy

1.8. Suspected digoxin abuse

1.9. Calculation of individual digoxin pharmacokinetics (with at least two drug level determinations during one dosing interval)

1.10. Decision for future therapy
- Validation of a previous abnormal or unusual digoxin concentration
- Withdrawn after toxic level
- Other (i.e. sufficient effectiveness despite a subtherapeutic concentration)

**Combinations of different indications are possible**

**The following indications do not fulfil appropriate criteria for digoxin level monitoring:**
- Routine monitoring after long-term digoxin therapy without any of the above mentioned indications
- Change of the dose, the dosage interval or the administration route in patients with stable renal function
- Drug level at admission if a digoxin level has been measured within the previous nine months and if there is none of the above mentioned indications
- Drug level after stopping digoxin (except after toxic levels)
- No effect but inadequate dose

**2. Appropriate timing for digoxin TDM:**
The timing of digoxin TDM was considered appropriate if the blood sample was taken at least 6 hours after the last digoxin dose (after termination of the digoxin distribution phase) and if digoxin therapy was started or the digoxin dose changed at least 6 days (in patients with normal renal function) before the digoxin measurement (i.e. after four half-lives; steady state)
Exception: if a dose-dependent adverse drug reaction or toxicity is suspected, digoxin TDM can be performed before a steady state is reached, but the sampling should be carried out at least 6 hours after the last dose

**3. Rational interpretation of the result (only applicable for determinations with correct timing) – consequence for continuation of digoxin therapy must be reasonable:**
Subtherapeutic concentration → dose increase (except: toxic symptoms, hypothyroidism, sufficient or good therapeutic response, high dose)
Therapeutic concentrations → no dose adjustment required (except: toxic symptoms, insufficient therapeutic response)
Potentially toxic concentrations → dose decrease (except: no apparent toxic symptoms)

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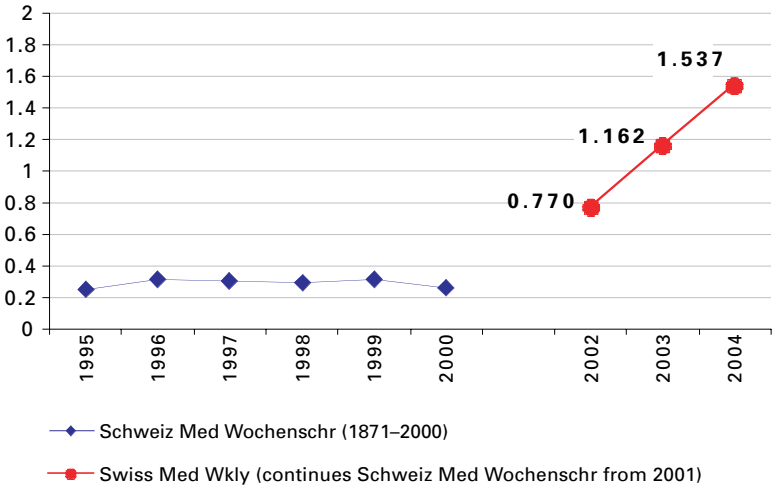


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