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Measurement of digitalis-glycoside levels in ocular tissues:

A way to improve postmortem diagnosis of lethal digitalis-glycoside poisoning? I. Digoxin*

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Summary. Prompted by animal studies reporting the accumulation of digitalis-glycosides in ocular tissues, we investigated whether measurement of digoxin levels in human ocular tissues can improve the postmortem diagnosis of lethal digoxin intoxication. Digoxin was measured in the vitreous humor and choroid-retina of patients who had received in-patient treatment with digoxin prior to death (therapeutic group) and in a single case of suicidal intoxication. The results were compared with the digoxin levels in the femoral vein blood, myocardium, kidney and liver, and evaluated in light of the medical history of each patient. In the therapeutic group the mean digoxin level was higher in the choroid-retina than in other tissues and body fluids. The range of variation in levels in the choroid-retina following therapeutic doses was comparable to that in the other tissues. An extremely high level of digoxin was present in the choroid-retina in the case of suicidal intoxication. In all cases, levels in the vitreous humor were very low compared to those in the choroid-retina. Hence, it is unlikely that significant distortion of choroid-retinal levels occurs due to postmortem diffusion of digoxin into the vitreous body. Our results indicate that measurement of digoxin levels in the choroid-retina can aid the postmortem diagnosis of lethal digoxin intoxication.

Key words: Digoxin poisoning – Postmortem diagnosis – Ocular tissues

Zusammenfassung. Nachdem von anderen Autoren tierexperimentell hohe Digitalisglykosidkonzentrationen in okulären Geweben nachgewiesen werden konnten, sollte die Frage geklärt werden, ob durch Bestimmung der Digoxinspiegel in Augengeweben ein Beitrag zur Verbesserung der postmortalen Diagnostik von tödlichen Digoxinintoxikationen geleistet werden kann. Bei mit Digoxin behandelten, in Kliniken verstorbenen Patienten (therapeutisches Kollektiv) sowie in einem Fall einer suicidalen Vergiftung wurden Digoxinkonzentrationen in Glaskörperflüssigkeit und Choroidretina bestimmt. Die in den okulären Geweben bestimmten Werte wurden den Digoxinspiegeln in Femoralvenenblut, Myocard, Niere und Leber gegenübergestellt und unter Berücksichtigung anamnestischer Daten interpretiert. In der Choroidretina wurden im therapeutischen Kollektiv Digoxinkonzentrationen gefunden, die im Mittel deutlich über den in den übrigen Organen bestimmten Werten lagen. Die Streuung der Choroidretinakonzentrationen nach therapeutischer Dosierung war mit der Streuung der übrigen Gewebespiegel vergleichbar. In dem Intoxikationsfall wurde eine ausgesprochen hohe Choroidretinakonzentration festgestellt. Im Vergleich zu den Choroidretinawerten waren die Glaskörperflüssigkeitsspiegel in allen Fällen sehr niedrig; mit einer wesentlichen Verfälschung der Choroidretinakonzentrationen durch eine mögliche Diffusion des Digoxins in den Glaskörper ist danach nicht zu rechnen. Nach unseren Untersuchungsergebnissen ist die Bestimmung des Digoxinspiegels in der Choroidretina in fraglichen Vergiftungsfällen sinnvoll.

Schlüsselwörter: Digoxinintoxikation – Postmortale Diagnostik – Okuläre Gewebe

Introduction

Most instances of lethal digitalis-glycoside intoxication encountered in forensic medical autopsy material involve suicidal or accidental poisonings [1, 9, 17, 18, 29, 37, 40, 45]. However, the extremely narrow therapeutic range of digitalis-glycosides often leads to iatrogenic poisoning. According to Habermann and Löffler [23], digitalis-glycoside intoxication is the most common type of iatrogenic poisoning. Even in hospitalized patients, who can be supervised continually, the incidence of digitalis-glycoside poisoning is reported to be 8%–20% (!); in 3%–21% of cardiac glycoside poisoning cases death was

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found to occur "in direct connection with glycoside intoxication" [32].

When lethal iatrogenic poisoning by digitalis-glycosides occurs, charges [of malpractice] may be brought against the attending physician. If legal proceedings are held, it is of utmost importance to determine whether digitalis-glycoside intoxication was in fact the cause of death.

Definitive *postmortem* diagnosis of lethal digitalis-glycoside poisoning is difficult for the following reasons:

- Reliable anamnestic data are often unavailable to the forensic practitioner.
- There are no characteristic morphological findings in cases of lethal digitalis-glycoside poisoning.
- The interpretation of postmortem blood levels is difficult. The following factors in particular must be considered: a) a relatively large overlap exists between therapeutic and toxic digitalis-glycoside levels [8, 32, 39]; b) misleadingly high blood levels can be found before completion of the distribution phase [8, 31, 44]; c) serum digoxin levels can rise before and after death [1, 3–6, 21, 31, 35, 37, 41, 46, 47]; and d) postmortem digoxin blood levels vary according to the site from which the blood is taken [4, 28].
- Tissue levels of digitalis-glycosides, especially digoxin, have been shown to vary widely following therapeutic doses [1–3, 11, 13, 15, 25, 29, 30, 36, 38, 47].

Because of the uncertainty in interpreting postmortem blood levels, digitalis-glycoside concentrations should also be determined in other body fluids and tissues in cases of suspected cardiac glycoside poisoning [3, 5, 6, 9, 24].

However, the wide variation in digitalis-glycoside tissue levels makes it necessary to set very high threshold values for individual organs to enable reliable differentiation between therapeutic cases and cases of intoxication. Accordingly, Aderjan and Rietbrock [5] set threshold values of 400 ng/g for cardiac tissue, 500 ng/g for kidney tissue, and 250 ng/g for liver tissue. These threshold values are reported to be valid for both digoxin and digitoxin [2]. However, the literature reports cases of lethal intoxication in which tissue concentrations clearly fall below these threshold values [9, 29, 40]. According to Härdle and Aderjan [24], such cases can be correctly classified by applying discriminant analysis, which evaluates several parameters simultaneously. It follows that the greater the number of appropriate tissues and body fluids (heart, kidney, liver, femoral vein blood) in which digitalis-glycoside levels can be measured, the more accurately a distinction can be made between therapeutic and toxic cases [24].

Since the reliability of the differentiation between "intoxication" and "non-intoxication" increases with the number of parameters considered, we investigated whether the measurement of digitalis-glycoside levels in ocular tissues could contribute to postmortem diagnosis of lethal poisoning.

Many of the ocular symptoms associated with digitalis-glycoside intoxication (described as early as 1785 by Withering [48]) are apparently not due to an attack by digitalis-glycoside on the central nervous system, but rather to impairment of *retinal* function [10, 16, 19, 20, 22, 26, 33, 34, 43]. The effects of digitalis-glycosides on the eye have even been observed following subtoxic or therapeutic doses [19, 26]. Like the effects of digitalis-glycosides on the heart, they appear to be caused by an inhibition of the Na-K-ATPase [19, 43], which is present in high levels in the retina [12, 19, 43]. Animal experiments have shown that large concentrations of digoxin and digitoxin can be found in the retina and other ocular tissues following administration [10, 19, 20, 27, 33, 34]. Duncker and Herzig [20] found rapid accumulation of digoxin and digitoxin in the retina of guinea pigs to levels at or even above those in the myocardium. The same authors also detected high levels of digoxin and digitoxin in other ocular tissues well supplied with blood, such as the choroid and the iris, whereas low levels were found in ocular tissues poorly supplied with blood, such as the cornea, lens, vitreous body and sclera.

We determined digitalis-glycoside levels in ocular tissues of hospitalized patients who had received therapeutic doses and in cases of suicidal digoxin and digitoxin poisoning. The levels in ocular tissues were compared with those in femoral vein blood, myocardium, kidney and liver, and evaluated in light of the medical history of each patient. The results of our measurements of digoxin levels are reported in this paper; a second study describes our findings for digitoxin [42].

Patients and methods

Postmortem digoxin levels in vitreous humor, choroid-retina[1], serum, myocardium, kidney and liver were measured in 12 patients who had received digoxin therapy (therapeutic group) and in a single case of suicide by β-acetyldigoxin poisoning.

All patients in the *therapeutic group* died in the University Hospital of Christian-Albrechts-University in Kiel; autopsies were performed in the University Institute of Pathology. The postmortem interval (the time between death and autopsy) ranged from 20.5 to 80 h.

Medical records and autopsy protocols were evaluated, and according to the data, all patients had died of natural causes; in no case was a lethal digitalis-glycoside intoxication suspected. Six of the patients were women and 6 men; their ages ranged between 60 and 90 years. In 5 patients, impaired kidney function was present for an extended period prior to death.

At least 7 patients in the therapeutic collective had received *long-term therapy* with digoxin or β-acetyldigoxin (0.25 mg/day digoxin peroral in one case; 0.2 mg/day β-acetyl-digoxin peroral in 5 cases, 0.1 mg/day β-acetyl-digoxin peroral in one case) up to the time of death. In one patient therapy (0.3 mg/day β-acetyldigoxin peroral) had been terminated 10 days prior to death; in 2 other patients it was impossible to determine up to what time the documented therapy (0.25 mg/day digoxin intravenously, 0.2 mg/day β-methyldigoxin peroral) had been carried out. Two further patients died at the onset of therapy, before intravenous β-acetyldigoxin or digoxin saturation could be completed. The interval between the last administration of digoxin and death (therapy-free interval) ranged from 3.5 to 240 h in the therapeutic group.

The *case of suicidal poisoning* involved a 78-year-old woman found dead in her apartment. Three empty 100 tablet containers of "Novodigal" (β-acetyldigoxin, 0.2 mg) and a suicide note were

[1] Choroid and retina were investigated together as "choroid-retina"

found near the body. No signs of violence were noted at autopsy. Neither macroscopical nor histological findings could explain the cause of death. A substance that could have been the remnants of tablets was found in the intestinal tract extending as far as the ileum.

The specimens we investigated were all obtained at autopsy. The *choroid-retina* and *vitreous humor* were obtained by opening the orbital roof and exposing the bulbus oculi. The wall of the bulbus was opened and the vitreous humor was carefully (to avoid contamination) extracted. The entire posterior wall of the bulbus oculi, including the choroid and retina, was dissected. Since postmortem preparation of choroid and retina is difficult, both tissues were carefully separated from the sclera and investigated jointly as "choroid-retina". Approximately 100 mg of tissue (wet weight) were thus obtained in each case.

The *myocardium* specimens were taken from the posterior wall of the left ventricle; macroscopically visible subepicardial fat and fibrotic tissues were removed. The *renal* tissue samples included approximately equal portions of cortex and pulp. *Liver* specimens were taken from the center of the right liver lobe. *Blood* was extracted from the femoral vein. Blood samples were centrifuged in order to obtain serum. All samples were stored deep frozen.

Tissue samples were lyophilized, pulverized and homogenized in 0.1 *M* phosphate buffer (pH 7.6). Digoxin was extracted in 2 steps using dichloromethane. All further steps and measurements of serum and vitreous humoral levels were done according to the manufacturer's instructions for the measuring system.

Digoxin levels were measured by fluorescence polarization immunoassay (FPIA; TDx Measuring System for Therapeutica, TDx Digoxin II, Abbott Laboratories).

Table 1. Range of variation, mean values and standard deviations (Mv ± s) for digoxin levels in tissues and body fluids of the entire therapeutic group ($n = 12$) and of the subgroup of seven patients who received long-term therapy

Tissues and body fluids	Digoxin levels (ng/g wet weight or ng/ml)	
	Entire therapeutic group ($n = 12$)	Long-term therapy subgroup ($n = 7$)
Myocardium	45.7–276.1 ng/g ($n = 12$)	103.3–275.1 ng/g ($n = 7$)
	Mv ± s: 151.1 ± 51.2 ng/g	Mv ± s: 160.3 ± 60.0 ng/g
Kidney	50.0–393.1 ng/g ($n = 12$)	71.0–243.4 ng/g ($n = 7$)
	Mv ± s: 129.0 ± 62.3 ng/g	Mv ± s: 140.9 ± 65.2 ng/g
Liver	24.5–175.4 ng/g ($n = 12$)	33.6–98.5 ng/g ($n = 7$)
	Mv ± s: 70.9 ± 19.7 ng/g	Mv ± s: 73.0 ± 22.6 ng/g
Serum	1.2–38.9 ng/ml ($n = 6$)	1.2–5.0 ng/ml ($n = 3$)
	Mv ± s: 3.0 ± 1.6 ng/ml	Mv ± s: 2.6 ± 2.1 ng/ml
Choroid retina	63.9–485.0 ng/g ($n = 12$)	140.0–369.9 ng/g ($n = 7$)
	Mv ± s: 184.3 ± 95.6 ng/g	Mv ± s: 233.1 ± 75.4 ng/g
Vitreous humor	2.2–7.1 ng/ml ($n = 12$)	2.2–6.1 ng/ml ($n = 7$)
	Mv ± s: 3.4 ± 1.3 ng/ml	Mv ± s: 3.8 ± 1.4 ng/ml

Results

1. Therapeutic Group

Table 1 gives an overview of the range of variation in digoxin levels in tissues and body fluids in the therapeutic group as a whole and in the subgroup of 7 patients who had undergone *long-term* digoxin therapy. Digoxin levels in all tissues showed a considerable variation and 4 of the 6 serum digoxin levels exceeded the (clinical) therapeutic range of 0.7–2.2 ng/ml.

Figure 1 is a graphic depiction of the mean digoxin levels and standard deviations in the 7 cases receiving long-term therapy. By far the highest mean value was found in the choroid-retina, followed in descending order by the myocardium, kidney, liver, vitreous humor and serum.

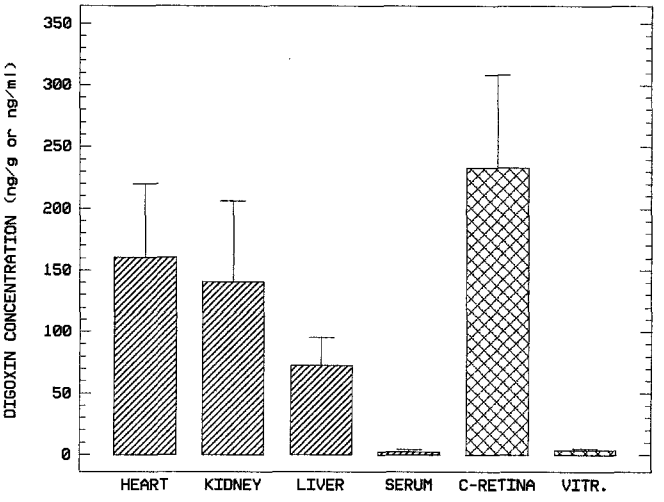

Fig. 1. Mean digoxin levels (columns) in tissues and body fluids of the group of 7 hospital patients who underwent long-term therapy; the respective standard deviations are indicated by the lines on the columns ("C-retina" = Choroid-retina, "Vitr." = vitreous humor)

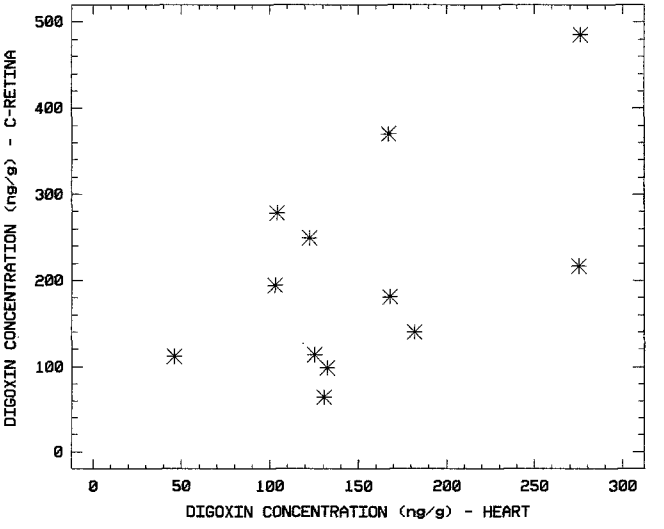

Fig. 2. Digoxin levels in the choroid-retina ("C-retina") of the therapeutic group ($n = 12$) in relation to levels in the myocardium

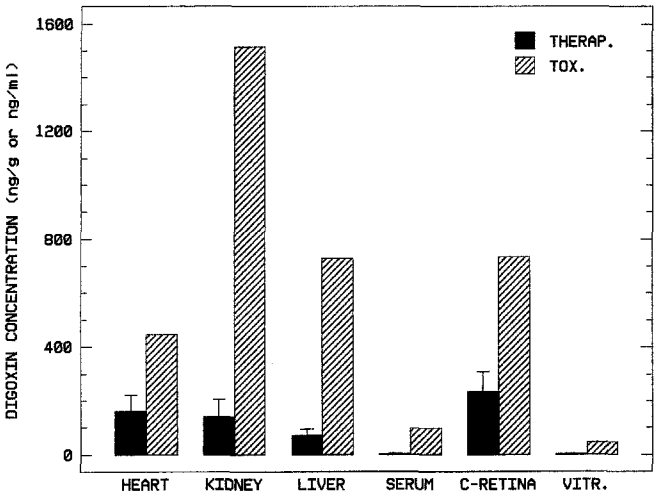

Fig. 3. Comparison of digoxin levels in the case of lethal intoxication (hatched columns) with the mean values for the 7 hospital patients who underwent long-term therapy (dark columns; the lines on the columns indicate standard deviations): "C-retina" = choroid-retina, "Vitr." = vitreous humor

In Figure 2 the digoxin levels in the choroid-retina are compared with those in the "target tissue", the myocardium. To the extent that one can generalize from such a small number of cases, a loose correlation at most exists between digoxin levels in the choroid-retina and those in the myocardium following therapeutic doses. A similar correlation was seen between digoxin levels in other tissues and body fluids, especially between levels in the choroid-retina and vitreous humor.

Digoxin levels in vitreous humor were in some cases greater, in other cases less than the corresponding levels in serum. The ratio of vitreous humoral levels to serum digoxin levels showed no discernable correlation with the length of the therapy-free or postmortem intervals.

In the 5 patients with impaired renal function mean digoxin levels in tissues were higher than in the other patients. One patient in particular had the following high digoxin levels:

- serum: 28.9 ng/ml,
- myocardium: 276.1 ng/g,
- kidney: 293.1 ng/g,
- liver: 175.4 ng/g,
- choroid-retina: 485.0 ng/g,
- vitreous humor: 7.1 ng/ml.

This patient, who was 90 years old and weighed only 42 kg, had received peroral treatment with 0.25 mg/day digoxin. The therapy-free interval could not be determined. Approximately 4 weeks before death a nephrectomy was carried out because of a kidney cell carcinoma. Postoperatively, the patient showed initial improvement but then the condition deteriorated. Death occurred under signs of cardiovascular failure. A lengthy antemortem period of high serum creatinine levels had been observed; the daily digoxin dose was not reduced. Autopsy revealed pre-existing ischemic damage to the heart and signs of cardiovascular failure.

2. Suicidal Intoxication

Extremely high digoxin levels were found in the case of suicidal β-acetyldigoxin poisoning:

- serum: 98.4 ng/ml,
- myocardium: 446.9 ng/g,
- kidney: 1514.4 ng/g,
- liver: 727.2 ng/g,
- choroid-retina: 734.2 ng/g,
- vitreous humor: 47.8 ng/ml.

In Fig. 3 these values are compared with the mean digoxin levels in the subgroup of the 7 patients who had undergone long-term therapy. Digoxin levels in the case of suicidal poisoning were many times higher for all tissues investigated, including choroid-retina and vitreous humor, than the mean values in the 7 long-term therapy patients.

Discussion

The diagnosis of lethal digoxin intoxication should be based on the medical history, if available, and on postmortem digoxin levels in tissues and body fluids. In the individual case, digoxin levels should be evaluated in light of published data on patients who had received therapeutic doses and confirmed cases of digoxin poisoning.

It is difficult to compare the results in the extensive literature on digoxin levels in tissues and body fluids following therapeutic and toxic doses, chiefly because of the variety of methods used for measurements. The most commonly employed method has been radio immunoassay, which – like the FPIA we used – also detects variable quantities of digoxin metabolites. Plum and Daldrup [37] suggested that the results of such measurements are difficult to compare since they are affected by the detected metabolites, which in turn depend on the extraction method used.

Furthermore, the site from which the samples are taken as well as the type of patient population can influence findings on postmortem digoxin levels [1, 4, 7, 28, 30, 47] and thus reduce the validity of comparisons between different studies.

The digoxin levels we measured in myocardium, kidney, liver, and femoral vein blood agree well with levels reported by many authors [1, 3, 5, 7, 29, 30]. They differ, however, from the results of others, for example Ottoson et al. [36] and Weinmann et al. [47]. Ultimately, the widely divergent findings on digoxin levels following therapeutic doses and in cases of digoxin poisoning are "only relatively and not directly comparable with each other" [5].

Distinguishing between "intoxication" and "non-intoxication" is complicated even more by the fact that therapeutic doses of digoxin produce widely varied concentrations in body fluids and tissues [1, 11, 13, 15, 25, 29, 30, 36, 38, 47], which makes determination of the therapeutic range difficult.

In our therapeutic group also large variations in the digoxin levels in body fluids and tissues were found (Table 1). Even the myocardium, the "target organ" of digitalis-glycosides, showed widely divergent digoxin levels following therapeutic doses. This has been explained by fluctuations in the digitalis-glycoside levels due to pathological, structural and metabolic changes [15, 47] in the tissue. Moreover, a variable, nonspecific, receptor-independent binding of digitalis-glycosides could also play a role [3, 5, 11, 13].

Some authors have recommended measuring digoxin levels in *vitreous humor* in cases of suspected poisoning [14, 18, 35, 46].

Di Maio et al. [18] suggested that lower levels in vitreous humor than in blood indicate a time of death prior to completion of the distribution phase. Our findings could not confirm this; the ratio of vitreous humoral levels to serum levels showed no discernable relationship to the length of time between the last digoxin intake and death.

Margot et al. [35] regarded digoxin levels exceeding 6 ng/ml in vitreous humor to be an indication of lethal intoxication. In several patients in our therapeutic group vitreous humoral levels of approximately 6 ng/ml were found. A postmortem diffusion of digoxin from the retina into the vitreous body may explain these high values. Binnion and Frazer [10] reported such a postmortem diffusion in animals. However, no reliable correlation was found between the vitreous humoral levels, the choroid-retinal levels and the length of the postmortem interval. It appears that the extent of postmortem diffusion of digoxin into the vitreous body can vary widely.

In the *choroid-retina* we found high postmortem digoxin levels after therapeutic doses; the mean value was clearly above those in other tissues (Fig. 1). This agrees with animal studies showing that the blood-retina barrier (in contrast to the blood-brain barrier) appears to be extremely porous to digoxin, and that an enhancement of the digoxin concentration is especially evident in the retina [10, 19, 20, 27, 33, 34].

In the therapeutic group, the variation in digoxin levels in the choroid-retina was comparable to that in the other tissues examined.

It appears that at best a loose correlation exists between digoxin levels in the choroid-retina and those in the myocardium (Fig. 2) and in other tissues. This may be due to alterations in digoxin levels caused by pathological changes in structure and function of the tissues [15, 19, 47] and to a variably high rate of nonspecific binding of digoxin in tissues, as has been described for the myocardium [11, 13, 32, 47].

Compared to choroid-retinal levels, digoxin levels in the vitreous humor were low. Hence, significant distortion of choroid-retinal levels due to postmortem diffusion of digoxin into the vitreous body is unlikely.

In the single case of suicidal intoxication, the diagnosis of lethal digoxin intoxication was easily made on the basis of the massive digoxin levels in all body fluids and tissues.

An example of a diagnostically difficult case is the one patient in the therapeutic group where digoxin levels far exceeded the mean levels in all tissues (myocardium: 276.1 ng/g; kidney: 293.1 ng/g; liver 175.4 ng/g; choroid-retina: 485.0 ng/g). The serum level in particular was remarkably high (28,9 ng/ml) even in the light of a possible rise in serum levels before or after death. The levels in the myocardium, kidney, and liver were below the threshold values suggested by Aderjan and Rietbrock [5]. On the other hand, the concentrations in these tissues exceeded those reported by some authors in cases of lethal intoxication [9, 29, 40]. In such critical cases the clinical data – if available – must be considered. In our patient (a 90-year-old male weighing only 42 kg) impairment of renal function – the most frequent contributing cause of digoxin intoxication [32] – began long before death; the daily digoxin dose was not reduced. The high postmortem digoxin levels found in body fluids and tissues support the hypothesis that impaired renal function resulted in an accumulation of digoxin from therapeutically administered doses that were too high under the circumstances. The patient's general condition before death was poor. "Typical" symptoms of digitalis-glycoside intoxication, in particular cardiac arrythmia, were not mentioned in the medical records; however, electrocardiogram tests were not made in the last days antemortem. Hence, the clincial data could neither confirm nor exclude (lethal) digoxin intoxication.

In this and in similar cases in which digoxin has not been ingested in excessive amounts and where suspicion of lethal digoxin intoxication is neither supported nor ruled out by anamnestic data, it is imperative that levels are measured in as many appropriate tissues and body fluids as possible [5, 24, 40].

Our results indicate that measurement of digoxin levels in the choroid-retina could contribute to improving postmortem diagnosis of digoxin intoxication. However, before choroid-retinal levels can be employed in cases of suspected poisoning, studies of sufficiently large series of therapeutic and toxic cases must provide reliable data for comparison.

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