

Serum Levels of Digoxin in Sudden Cardiac Deaths

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Summary. Digoxin was determined in postmortem serum samples from 100 patients who died suddenly of cardiac disease. Twenty patients had digoxin levels below the therapeutic range. Twenty-one patients had normal values within the therapeutic range (1.2–2.5 nmol/l). In ten cases there was probably an overdose. Another 15 patients had markedly elevated levels. No digoxin concentration was found (below 0.5 nmol/l) in 34 patients. The importance of determination of digoxin levels both by the clinician and the pathologist is stressed as well as the necessity of using a correct sampling technique at autopsy.

Key words: Cardiac disease, serum levels of Digoxin – Digoxin, intoxication

Zusammenfassung. Digoxin wurde in postmortal aus der Schenkelvene entnommen Blutproben radioimmunologisch bestimmt. Das Untersuchungskollektiv bestand aus 100 über 60 Jahre alten plötzlich infolge von Herzerkrankungen Verstorbenen. Zwanzig Patienten hatten Serumspiegel unterhalb des therapeutischen Konzentrationsbereichs, bei 21 Patienten bestanden Konzentrationen im therapeutisch wirksamen Bereich (1,2–2,5 nmol/l). Bei 15 Patienten bestanden erhöhte Konzentrationen und bei zehn Patienten lag wahrscheinlich eine Überdosis vor. Vierunddreißig Patienten mit Konzentrationen unter 0,5 nmol/l waren als unbehandelt anzusehen. Auf die besondere Bedeutung von Digoxin-Bestimmungen bei der Bewertung unerwarteter Todesfälle mit Glykosidmedikation wird aufmerksam gemacht; die Blutentnahme sollte aus der Schenkelvene erfolgen.

Schlüsselwörter: Herztod, Digoxinnachweis im Serum – Digoxin, Vergiftung

Digoxin is a commonly used drug in medical practice. It is, however, potentially dangerous and overdose may be common since the symptoms are vague and may be overlooked easily. Investigations concerning the frequency of digoxin

intoxications have revealed strikingly different frequencies. Hillestad et al. [5] found 5% intoxications in hospitalized digoxin-treated patients, whereas Smith [13] reported 35% of the patients to be suffering from overdosage.

Research in digitalis poisonings has usually been limited to clinical materials. Therefore, we are presenting a report concerning serum levels of digoxin in a postmortem material. The aims of the present study were not only to investigate the level of digoxin in another type of material, i.e. in postmortem serum samples but also to relate the levels found to point out an easily overlooked cause of death in forensic practice.

Material and Methods

Serum levels of digoxin were determined in 100 consecutive cases of sudden unexpected death of cardiac origin in patients older than 60 years, autopsied at the Institute of Forensic Medicine, Uppsala University, Sweden. The patients were all suffering from acute and/or chronic heart disease. Patients who had been dead for 4 days or more or had hemolytic blood were excluded from the study. A microscopic investigation was performed when there was any doubt of the diagnosis at autopsy, using the hematoxylin and eosin (HE) and the Picro-Mallory methods [9]. The mean age was 74 ± 7.4 years (range: 61–93) and male/female ratio was about 4:1.

Blood samples were taken at autopsy from the right femoral vein, centrifugated at $3,000 \times g$ for 15 min at $+4^\circ\text{C}$, frozen to -20°C , and stored until analyzed. Analysis was performed by a RIA method, RIANEN assay system, New England Nuclear. The therapeutic range of digoxin in this assay is 1.2–2.5 nmol/l.

All patients with levels of less than 0.5 nmol/l were regarded as untreated. Since digoxin levels increase in postmortem serum we had to correct our results to estimate the antemortem level. Such corrections were performed by Vorpahl et al. [15] and Aderjan et al. [1] who found an elevation of digoxin levels in postmortem femoral vein blood in a ratio of 1.42 and 1.31, respectively. To achieve a safe border when interpreting our data all values *above the normal range* were divided by 1.5.

Results

Serum levels of digoxin in patients with recent myocardial infarction (RMI) or without recent myocardial infarction (non-RMI) after correction of digoxin values above the therapeutic range are seen in Table 1.

Thirty-four patients had serum concentrations of digoxin below 0.5 nmol/l. Twenty patients had levels below the therapeutic range. Another 25 patients had elevated levels. The range was 2.7–6.8 nmol/l (mean \pm SD 4.7 ± 1.40 nmol/l) after correction for the expected postmortem elevation. Ten of those patients had digoxin levels between 2.7 and 3.0 nmol/l and were therefore regarded as

Digoxin (nmol/l)	RMI	Non-RMI
<0.5	24	10
0.5–1.2	3	17
1.2–2.5	11	10
2.5–3	5	5
>3	10	5

Table 1. Concentration of digoxin in postmortem plasma samples in relation to recent myocardial infarction (RMI)

overdosage. Only 21 patients seemed to have been treated with a suitable amount of digoxin.

In 53 patients a recent myocardial infarction was seen at autopsy. Fifteen of these patients had elevated digoxin levels. Of the remaining 47 patients, ten had increased levels of digoxin. No statistical differences in digoxin were found between the levels of the RMI-group the non-RMI-group.

Discussion

The present investigation shows that the digoxin levels in postmortem serum are mainly outside of the therapeutic range. Of 66 patients who had detectable amounts of digoxin, 45 had digoxin concentrations considered to be outside of the therapeutic range. Similar findings in living patients have been noticed [5,13]. Previous investigations of cardiac glycosides in autopsy materials have usually been limited to case reports or series of patients with suspected overdosage of accidental origin or suicide [2, 7, 10–12, 14] and in one case of suspected murder [4].

Holt et al. [6] investigated postmortem digoxin levels and found the leg veins to be the most favorable collecting place. Comparisons between antemortem and postmortem digoxin levels [1, 15] have also shown that the femoral veins seem to be the most suitable place for sampling blood when digitalis levels are to be investigated. This problem is easily overlooked and extensively discussed by Arnold et al. [2].

From the present study it can be concluded that most patients were not correctly treated with digoxin which has previously been shown in clinical materials [5, 13].

The proportion of not properly treated patients in our material cannot be determined because of the fact that the total number of digoxin-treated patients was not known. Neither can it be stated to which extent the overdosages contributed to the deaths. However, it is known that high doses of cardiac glycosides are apt to cause myocardial necrosis and fibrosis [8]. Another cause of sudden death in our material, apart from myocardial damage, may be arrhythmias, since patients with an overdosage of cardiac glycosides seem to be more prone to suffer from such disturbances [3].

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