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Age- and Gender-Specific Incidence of Hospitalisation for Digoxin Intoxication

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Abstract

Background: The safety of digoxin (digitalis) therapy has greatly improved over the past three decades, but recent incidence rates for digoxin intoxication-related hospitalisation are not available. Recent literature suggests that women are at higher risk of digoxin toxicity.

Objective: To provide age- and gender-specific incidence rates for digoxin intoxication-related hospitalisation and mortality during digoxin intoxication-related hospitalisation in The Netherlands in the period 2001–4.

Study design and methods: We conducted a nationwide population-based cohort-study of all hospital admissions in the years 2001–4 using a national computerised hospital admission registry. All patients with acute admissions were included in the study (n = 2 987 580). From these admissions, we selected all hospitalisations that had digoxin intoxication coded as either a primary or secondary diagnosis. We obtained data on digoxin prescriptions from the Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen) pharmacy database, which extrapolates drug figures for The Netherlands from prescriptions dispensed by 90% of all community pharmacies. We computed age- and gender-specific incidence rates of digoxin intoxication.

Results: Digoxin intoxication was identified in 0.04% (n = 1286) of acute admissions. The incidence rate for digoxin intoxication-related admission was 48.5 (95% CI 45.9, 51.2) per 100 000 prescriptions, which corresponds to 1.94 admissions for intoxication per 1000 treatment-years. Women had a 1.4-fold higher risk of intoxication than men (95% CI 1.3, 1.6). The age- and gender-adjusted relative risk of mortality in patients with digoxin intoxication compared with those admitted for other reasons was 0.7 (95% CI 0.5, 0.8).

Conclusion: This study shows that digoxin intoxication in patients receiving current therapy is presently infrequent and that women are at higher risk of digoxin intoxication than men.

Background

The cardiac glycoside digoxin (digitalis) has been successfully used in the treatment of heart disease for over 200 years. Recently, digoxin was formally approved for ventricular response rate control in patients with atrial fibrillation and congestive heart failure, based on three clinical trials.[1-3] However, digoxin has been associated with toxicity problems since its introduction. In the past, it was associated with a high frequency of intoxication and high mortality. Studies on digoxin toxicity for the period from 1969 to 1983 showed a frequency of intoxication in users that was as high as 11–30%.[4-6] One prospective study performed in 1971 reported mortality of 41% in patients with definite digoxin intoxication,[6] and in another study 47% of patients with digoxin intoxication experienced life-threatening arrhythmias.[7]

Currently, there is widespread knowledge and awareness of the pharmacokinetics and drug interactions of digoxin, as well as a tendency towards the use of regimens incorporating lower dosages and more strict therapeutic drug monitoring than had been used in the past. These developments in therapy management have resulted in a major reduction in the incidence of digoxin intoxication and an improved prognosis over the last three to four decades. Recent studies have shown digoxin intoxication in 4.8% of inpatients admitted for heart failure who were using digoxin (0.8% definite),[8] 1.1% of randomly selected outpatients who were using digoxin[9] and 2% and 1.2% of closely monitored outpatients who were receiving digoxin in trials.[1,9] Furthermore, recent literature suggests that women are at an increased risk of digoxin toxicity.[10]

Current population estimates of the incidence rate for digoxin intoxication are lacking. In the present study, we investigated the incidence rate of digoxin intoxication in the general population and the mortality rate during admission. Specifically, we assessed whether women were at higher risk of digoxin intoxication than men.

Methods

Population

Data on hospital admissions were retrieved from a nationwide computer database for hospital discharge records (National Hospital Registration) in The Netherlands. This database contains basic patient characteristics, the dates of admission and discharge, the discharge diagnosis, additional diagnoses during or preceding admission, surgical procedures, the treating medical specialty and special codes indicating drug-related hospitalisations (E-codes), based on the International Classification of Diseases (9th Edition), Clinical Modification coding system. All general and university hospitals in The Netherlands participate in this system. Characteristics of all hospitalisations are registered by medical doctors in hospital discharge letters and coded by professional code clerks. Reimbursement of hospital and specialist fees does not depend on the way an admission or disease is coded. For every admission, one discharge/main diagnosis (mandatory) and up to nine secondary diagnoses (optional) are registered. All diagnoses are submitted in the same format, mostly electronically.

All patients with an acute (non-planned) admission to a Dutch academic or general hospital in the period January 2001–December 2004 were included in the study (n = 2 987 580). A digoxin-related admission was defined as a hospitalisation with the ICD code 972.1 as the main or one of the secondary diagnoses or the code E942.1 as a secondary diagnosis (usually the diagnosis of the cause of the main diagnosis).

Digoxin Use

Data on the use of digoxin were obtained from the Stichting Farmaceutische Kengetallen (SFK) [Foundation for Pharmaceutical Statistics] database, which extrapolates drug figures for The Netherlands based on filled prescriptions from 90% of all community pharmacies. As community pharmacies deliver 90% of all outpatient prescriptions, this database covers >80% of such prescriptions in The

Netherlands. Due to different anonymisation procedures in the hospitals as well as in the SFK database, it was not possible to link individual prescription data to admission data. Prescription data were only available as the number of prescriptions per age group (eight fixed age groups) stratified by gender and by year. The range of the age categories was chosen on the basis of the distribution of overall drug use over age and on the relevance of specific age groups (less drug use in age groups 20–55 years results in wide age ranges, special interest in children results in smaller age ranges). This resulted in age groups with different age ranges instead of more conventional age groups with equal age range. Since there were no data on drug regimens and digoxin dosages can vary greatly among patients, the data did not allow for the calculation of the incidence rate in terms of person-years of use.

Analyses

We calculated the proportion of acute admissions that were attributable to digoxin intoxication according to the coded discharge diagnoses. Since digoxin prescription rates vary across different patient groups, the proportion of admissions may not reflect the actual risk of digoxin intoxication. Therefore, we also calculated incidence rates of digoxin intoxication by dividing the number of admissions for digoxin intoxication by the number of filled digoxin prescriptions. Using similar methods, we calculated age- and gender-specific incidence rates.

Descriptive statistical methods were used for subgroup comparisons and consisted of Student's t-tests (unpaired) and Chi-squared tests. The relative mortality risk during admission for digoxin intoxication versus other reasons for admission was estimated using age- and gender-adjusted logistic regression analysis. The association between the length of hospital stay and admission for digoxin intoxication was studied using age- and gender-adjusted linear regression analysis. All analyses were carried out in SPSS 11.0 for Windows. The age-adjusted relative risk (RR) of admission for digoxin intoxication per 100 000 prescriptions in females versus males was computed using Mantel-Haenzel methods across the eight age strata.

Results

Of all 9 729 819 admissions over the years 2001–2004, 30.7% (n = 2 987 580) were acute admissions. The baseline characteristics of the study population are shown in table I. The mean age of acutely admitted patients was 49.1 years and 53.5% were female. The most frequent main diagnoses were of a cardiovascular nature including chest pain, myocardial infarction, heart failure and stroke (13.5% of all acute admissions). The mean duration of admission was 8.8 days and 4.9% of all acute admissions ended in death.

Digoxin intoxication was reported in 0.04% (n = 1286) of acute admissions. Patients with digoxin

Table I. Characteristics of all acute admissions (n = 2 987 580)

Characteristic	
Mean age (y)	49.1
Age in years (no. of patients)	
0–10	380 827
11–20	128 653
21–40	641 910
41–54	383 175
55–64	349 304
65–69	203 664
70–74	242 968
≥75	657 079
Female sex (%)	53.5
Top 10 most frequent main diagnoses (% admissions)	
chest pain	5.8
myocardial infarction	3.0
heart failure	2.7
stroke	2.0
pneumonia	1.9
atrial fibrillation	1.9
abdominal pain	1.7
chronic obstructive pulmonary disease	1.4
fetal distress	1.3
acute appendicitis	1.3
Digoxin intoxication (% admissions)	0.04[a]
Mean duration of admission (days)	8.8
Died during admission; % (no.) admissions	4.9 (147 379)

a n = 1286, mean age 77.4 years.

intoxication were significantly older (77.4 vs 49.1 years, $p < 0.001$) and more often female (68.0% vs 53.5%, $p < 0.001$) than other acutely admitted patients. The mean duration of admissions for digoxin intoxication was 14.2 days. The age- and gender-adjusted difference in duration compared with other acute admissions was 2.1 days (95% CI 1.3, 2.8). Admissions for digoxin intoxication ended in death more often than other acute admissions (7.7% [n = 99] of admissions for digoxin intoxication vs 4.9% of other acute admissions); however, patients who were admitted for digoxin intoxication were older than patients admitted for other causes. After adjustment for age and gender, the risk of death during admission appeared to be lower for patients admitted with digoxin intoxication than for those admitted for other reasons (RR 0.7, 95% CI 0.5, 0.8).

There were 2.6 million digoxin prescriptions during the study period, 1.6 million of which (61.5%) were prescribed to women. The number of digoxin prescriptions and intoxications was stable over the study period. The overall incidence rate of digoxin intoxication was 48.5 (95% CI 45.9, 51.2) per 100 000 digoxin prescriptions. Assuming an average prescription length of 3 months (maximum period dispensed per prescription for chronic use in The Netherlands), this corresponds to 1.94 intoxications per 1000 person years of digoxin use. The highest rates of intoxication were found in very young (0–10 years of age) users. After the age of 40 years, there was a slow increase in risk of intoxication with increasing age (table II). Women were at a higher risk of digoxin intoxication than men, with 55.2 (95% CI 51.6, 59.0) versus 38.6 (95% CI 35.0, 42.5) intoxications per 100 000 prescriptions, resulting in an age-adjusted RR of 1.4 (95% CI 1.3, 1.6) for women versus men.

Table II. Gender-specific incidence rates for digoxin intoxication per 100 000 prescriptions, by age category (n = 1286)

Age (y)	Males		Females	
	cases	incidence rate (95% CI)	cases	incidence rate (95% CI)
0–10	10	229.8 (123.6, 427.1)	9	251.3 (114.9, 477.0)
11–20	1	65.0 (1.7, 362.3)	1	76.8 (1.9, 427.6)
21–40	7	110.5 (44.4, 227.7)	6	122.7 (45.0, 267.1)
41–54	7	17.8 (7.2, 36.7)	11	52.8 (29.3, 95.4)
55–64	28	23.0 (15.9, 33.3)	34	55.2 (39.4, 77.2)
65–69	34	30.3 (21.7, 42.4)	43	63.0 (46.7, 85.0)
70–74	68	40.0 (31.6, 50.8)	86	64.8 (52.5, 80.0)
≥75	256	42.1 (37.2, 47.6)	685	53.0 (49.2, 57.1)
Total	411	38.6 (35.0, 42.5)	875	55.2 (51.6, 59.0)

Discussion

In this study, we show that the absolute number of cases of digoxin intoxication requiring hospitalisation in The Netherlands between 2001 and 2004 was rather low (1286 in 4 years, around 2 per 1000 person-years of use). This confirms the observation that current management of digoxin treatment has reduced the risk of digoxin toxicity dramatically. At the current time, digoxin treatment appears to be rather safe, probably due to regimens that employ lower dosages than were used in the past and to increasing awareness of the risk factors for intoxication. This improved prognosis is confirmed by the fact that we found a lower risk of in-hospital death for patients admitted for digoxin intoxication compared with other acutely admitted patients. In the past, mortality from digoxin intoxications has been as high as 41%.[6] By the 1980s, all-cause mortality for patients with a discharge diagnosis of digoxin intoxication had already been reduced to 5%, and only 1.1% of intoxicated patients died as a direct result of the intoxication.[8] There have been several changes in the therapy of heart disease that explain this dramatic reduction in mortality. First, the dosage administered in most digoxin regimens is much lower than in the past, leading to less severe intoxication with fewer lethal arrhythmias. Second, the patient population receiving digoxin has changed. In the past, many patients received digoxin for the treatment of coronary heart disease, but currently the main indications for treatment are congestive heart failure and atrial fibrillation. Of the patients with digoxin intoxication in 1971, 74% also experienced coronary artery disease. In the 1980s, this was reduced to 35%. Old or recent myocardial infarction in intoxicated patients decreased from 60% to 20%.[6,8] Third, the diagnosis of digoxin intoxication has changed over time, resulting in the recognition of less severe cases. In the past, the diagnosis

was based on the patient history and ECGs. Therefore, only more severe cases of intoxication were identified. Presently, serum digoxin levels may support the diagnosis in patients with a less severe presentation.[11] Fourth, changes in the treatment of heart disease, especially the introduction of potassium-sparing diuretics and ACE-inhibitors, has drastically reduced the incidence of hypokalaemia in patients treated with diuretics. In previous studies, hypokalaemia often complicated digoxin intoxication, giving rise to more serious arrhythmias.[7] Finally, patients with severe intoxication resulting in lethal arrhythmias might not reach the hospital alive. This might have resulted in the selection of cases of intoxication that had relatively good prognoses in this study.

In addition, we found that women were at increased risk of digoxin intoxication. This observation supports the concerns that were raised earlier in the gender-stratified analysis of the Digitalis Investigation Group (DIG) data about a higher risk of digoxin therapy complications in women. In a post hoc analysis of the DIG trial, the group of women treated for heart failure with digoxin had a higher mortality rate than the placebo group and than men treated with digoxin. Women had slightly higher serum digoxin levels than men after 1 month of use, despite lower doses of digoxin per body mass index unit.[10] The only other study on the effect of gender on the outcome of digoxin treatment (the SOLVD trial) showed no difference in survival between men and women.[12] However, the SOLVD trial included a much lower number of women than the DIG study, resulting in lower power to detect a difference. Furthermore, the outcome in both studies was death, and as we have shown that the current mortality from digoxin intoxication is low, this would make it more difficult to detect a difference in rates between men and women in those studies. However, studies on the subject of gender differences in digoxin intoxication remain scarce since gender-stratified results are not available for most digoxin trials and women are traditionally under-represented in trials. One hypothesis about the cause of the increased risk of digoxin intoxication in women is the inhibition of P-glycoprotein by hormone replacement therapy (HRT), which reduces the excretion of digoxin in the renal tubes.[10,13] However, HRT use in The Netherlands is relatively low, making this an unlikely explanation for our findings. An alternative hypothesis, that seems more likely and also involves P-glycoprotein, is the suggestion that women have lower P-glycoprotein expression,[14] resulting in higher uptake and lower excretion of digoxin. It is unlikely that the difference in the incidence of digoxin intoxication is explained by a difference in renal clearance, since renal function tends to deteriorate more with increasing age in men than in women.[15] Adjustment for renal function might therefore even further increase the RR of digoxin intoxication in women compared with men. On the other hand, it remains possible that there were differences in co-medication or co-morbidity between men and women that might account for at least part of the difference in incidence that was found. In the *post hoc* analysis of the DIG trial, for instance, women used diuretics more often than men, which might lead to lower potassium levels and hence, higher susceptibility to digoxin toxicity.[10] However, we were not able to investigate the influence of these factors in the current study.

Although we used a nationwide registry with complete coverage of all hospital admissions in The Netherlands, there may be some misclassification in our estimates. In patients with severe comorbidities in addition to digoxin intoxication, the comorbidity rather than digoxin intoxication may have been coded as the main diagnosis. Also, symptoms may not have been recognised as digoxin toxicity and instead have been coded as nausea or arrhythmia. In addition, digoxin intoxications causing death before reaching the hospital, and patients with only mild symptoms of toxicity who were not hospitalised but instead treated by a simple dose reduction, will have been missed. These inaccuracies may have led to a slight underestimation of the incidence rate. Furthermore, individual data on the dose and duration of digoxin use were not available, and we were unable to adjust for comorbidity or multiple hospitalisations per patient.

Conclusion

Despite its limitations we believe that this study provides an accurate quantification of digoxin intoxication-related admissions relative to digoxin prescriptions, showing that current digoxin treatment is rather safe. Added to the fact that digoxin therapy has been proven to be effective[1] and its use has been recommended in heart failure treatment guidelines, digoxin might be used more often in heart failure treatment than it currently is. Furthermore, this study supports the previous finding that women are at higher risk of the negative consequences of digoxin treatment.

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References

1. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. N Engl J Med 1997 Feb 20; 336 (8): 525-33
2. Uretsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure: results of the PROVED trial. PROVED Investigative Group. J Am Coll Cardiol 1993 Oct; 22 (4): 955-62
3. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. N Engl J Med 1993 Jul 1; 329 (1): 1-7
4. Boman K. Digitalis intoxication in geriatric in-patients: a prospective clinical study of the value of serum digitalis concentration measurement. Acta Med Scand 1983; 214 (5): 345-51
5. Hurwitz N, Wade OL. Intensive hospital monitoring of adverse reactions to drugs. BMJ 1969 Mar 1; 1 (643): 531-6
6. Beller GA, Smith TW, Abelmann WH, et al. Digitalis intoxication. A prospective clinical study with serum level correlations. N Engl J Med 1971 May 6; 284 (18): 989-97
7. Lehmann HU, Witt E, Temmen L, et al. [Life-threatening digitalis intoxication with and without additional diuretic treatment (author's transl)] Lebensbedrohliche Digitalisintoxikationen mit und ohne saluretische Zusatztherapie. Dtsch Med Wochenschr 1978 Oct 6; 103 (40): 1566-71
8. Mahdyoon H, Battilana G, Rosman H, et al. The evolving pattern of digoxin intoxication: observations at a large urban hospital from 1980 to 1988. Am Heart J 1990 Nov; 120 (5): 1189-94
9. Steiner JF, Robbins LJ, Hammermeister KE, et al. Incidence of digoxin toxicity in outpatients. West J Med 1994 Nov; 161 (5): 474-8
10. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med 2002 Oct 31; 347 (18): 1403-11
11. Williamson KM, Thrasher KA, Fulton KB, et al. Digoxin toxicity: an evaluation in current clinical practice. Arch Intern Med 1998 Dec 7-21;158 (22): 2444-9
12. Domanski M, Fleg J, Bristow M, et al. The effect of gender on outcome in digitalis-treated heart failure patients. J Card Fail 2005 Mar; 11 (2): 83-6
13. Ichikawa-Haraguchi M, Sumizawa T, Yoshimura A, et al. Progesterone and its metabolites: the potent inhibitors of the transporting activity of P-glycoprotein in the adrenal gland. Biochim Biophys Acta 1993 Nov 28; 1158 (3): 201-8
14. Schuetz EG, Furuya KN, Schuetz JD. Interindividual variation in expression of P-glycoprotein in normal human liver and secondary hepatic neoplasms. J Pharmacol Exp Ther 1995; 275 (2): 1011-8
15. Baylis C. Changes in renal hemodynamics and structure in the aging kidney; sexual dimorphism and the nitric oxide system. Exp Gerontol 2005 Apr; 40 (4): 271-8

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