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

With great interest we read the article by Aarnoudse et al.,[1] who analysed all acute hospital admissions registered in a national computerised registry for which 'digoxin intoxication' had been coded as the primary or secondary diagnosis. Age- and gender-specific incidence of digoxin-related hospital admissions were calculated by using prescription data covering 90% of all community pharmacies. We appreciate this work, providing evidence for the safety of an almost 'ancient' drug, namely digitalis glycosides. As their data show, digoxin contributes significantly to adverse drug reactions (ADRs), especially in the elderly population.

In addition to the study limitations already discussed by the authors in their paper,[1] patients can experience clinically relevant digoxin-associated ADRs without having elevated digoxin levels. This can be the case when pharmacodynamic drug-drug interactions occur between digoxin and, for example, β-adrenergic receptor antagonists (β-blockers) or verapamil. In such instances, digoxin intoxication will not be coded. Thus, problems associated with the use of digoxin will only be partly detected by the approach used by Aarnoudse et al.[1] On the other hand, the inclusion of patients who have elevated digoxin serum levels but who are not experiencing clinically relevant symptoms might result in an overestimation of the incidence of ADRs with digoxin. This is possibly the case in patients with digoxin intoxication as secondary diagnosis.

We wish to supplement the important findings from Aarnoudse et al.[1] by highlighting some findings from the German national pharmacovigilance centers. In Germany, ADRs resulting in hospital admissions are analysed in a project funded by the BfArM (Federal Institute for Drugs and Medical Devices). As described previously,[2] all admissions to departments of internal medicine in the four pharmacovigilance centers are prospectively screened with regard to the existence of admission-related ADRs, and prescribing data are collected from pharmacy computing centers. Incidences are calculated for different drugs that have been assessed as at least 'probably' associated with an ADR according to the causality assessment of Bégaud et al.[3] Using data on digitalis glycosides collected using this methodology, we calculated the incidence for hospital admissions related to digitalis glycosides to be 1.9 (95% CI 1.0, 3.3) per 1000 patients exposed per quarter[4] compared with the relatively low figure of 0.49 (95% CI 0.46, 0.51) as estimated by Aarnoudse et al.[1] Our somewhat higher results are supported by the findings of Warren et al.[5] and Kernan et al.[6] These authors calculated the incidences over longer time periods; however, estimation for a 3-month period would result in incidences of 2.1 and 1.8, respectively, per 1000 exposed patients. Nevertheless, a comparison of the results of Aarnoudse et al.[1] with those of Warren et al.[5] and Kernan et al.[6] is limited by the fact that lower digoxin dosages are used in most regimens nowadays, contributing to a lower incidence of digoxin-related ADRs than in the past, as already stated by Aarnoudse et al.[1] In our study, about 28% of patients with a digitalis glycoside ADR-associated hospital admission actually had a normal digitalis glycoside serum level. These ADRs possibly remain undetected when ICD codes are used instead of prospective event assessment.

Furthermore, different prescription attitudes regarding digitalis glycosides might contribute to the observed differences. In Germany,[7] particularly in the Eastern regions, the most frequently prescribed digitalis glycoside is digitoxin, while digoxin is the most frequently prescribed in The Netherlands. Not surprisingly, 90% of digitalis glycoside ADR-related hospital admissions were related to digitoxin since, at present, case identification is performed in the Eastern part of Germany. Because of the extremely low use of digoxin, we were not able to calculate proper incidence rates for digoxin-related ADRs. However, a retrospective analysis by Roever et al.[8] found a three times higher toxicity rate

(defined as dose reduction or drug discontinuation) in hospitalised elderly patients taking digoxin compared with digitoxin.

Although both digitalis glycosides vary substantially with regard to their pharmacokinetic properties,[9] digitoxin does not seem to be safer in the elderly than the predominantly renally excreted digoxin. In our study, almost 60% of all patients experiencing an ADR and 90% of patients with a bodyweight <70 kg were overdosed, reflecting the essential need for, and more particularly, the lack of, correct bodyweight-adapted digitoxin dose calculation, especially in the group of over 80-year-olds (figure 1).

As figure 1 shows, in our data analysis, women (77.7%) were more likely than men to experience a digitalis glycoside ADR-associated hospital admission, which is in accordance with the findings by Aarnoudse et al.[1] and other gender specific analyses for digitalis glycosides.[10,11] Our female patients with ADRs had a significantly lower bodyweight and more frequently received a digitoxin dose that was too high in relation to their bodyweight than did the men (70.6% vs 29.3%; $p < 0.001$). Unfortunately, we are not able to calculate gender-specific ADR incidences from our database. However, using aggregated prescription data from Germany,[12] digitalis glycosides seem to be more frequently prescribed for men than for women, suggesting that the incidence of digitalis glycoside-associated ADRs is markedly higher in women when compared with men.

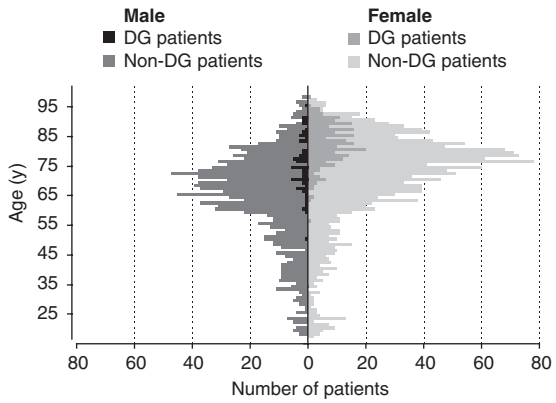


**Fig. 1.** Gender- and age-related analysis of adverse drug reactions leading to hospital admission in male (left) and female (right) patients associated with a digitalis glycoside (DG) or with other drugs (non-DG).

In conclusion, our findings support the results reported by Aarnoudse et al.[1] Despite the long-term experience, both analyses highlight the necessity of careful dosing of digitalis glycosides and even more careful monitoring of therapy with these foxglove derivatives, especially in frail, elderly women. A detailed analysis of frequent ADRs associated with well known and frequently used drugs might be more important in terms of overall patient safety than focusing on very rare ADRs of newer drugs. Therefore, the results of Aarnoudse et al.[1] contribute significantly to our knowledge about an old drug.

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