Drug Safety 2007; 30 (12): 1173-1174
0114-5916/07/0012-1173/$44.95/0

The Authors' Reply

We would like to thank Dr Schmiedl and colleagues for their thoughtful comments and valuable additions to our article on the age- and gender-specific incidence of hospitalisation for digoxin intoxication.[1] According to their letter, their prospective method of case identification allowed for further analyses of factors contributing to digitalis glycoside toxicity risk such as high dose regimens relative to bodyweight. It is interesting to see that their data confirm our findings that the safety of digitalis glycoside use has much improved over the last two to three decades and that women are at higher risk of digitalis glycoside toxicity than men.

In their first comment, Dr Schmiedl and colleagues point out that using ICD coding without further clinical information may result in misclassification of the diagnosis. We are very much aware, as we already mentioned in our discussion, that we might indeed miss cases of digoxin toxicity where the clinician did not note toxicity in cases of 'normal' serum digoxin concentration or where more severe co-morbidity was coded as the main discharge diagnosis. On the other hand, we might include non-toxicity cases with elevated serum digoxin concentrations.[1] However, since ICD coding is based on information in discharge letters rather than on laboratory information, this does not automatically mean that toxicity cases with normal serum levels will not get an ICD code for digoxin toxicity. Misclassification can indeed be reduced by a prospective approach as performed by Dr Schmiedl and colleagues and by Schneeweiss et al.,[2] where more accurate information on toxicity can be gathered.

There are several possible explanations for the notably higher incidence of digitalis glycoside toxicity as presented by Dr Schmiedl and colleagues in their comment. As they already mentioned, there could be small differences in toxicity of the glycosides preferentially prescribed in Germany (digitoxin) versus those in The Netherlands (digoxin). However, other phenomena might (temporarily) cause a substantial difference in toxicity between products, as demonstrated in the article by Schneeweiss et al.[2] They showed that an increase in digitalis glycoside toxicity, restricted to digitoxin, during the study period, was most likely caused by a problem with one manufacturer. Also, there might be differences in dose regimen used in the two countries. Unfortunately, our data did not allow us to explore this, but it might be interesting to further investigate this.

However, we believe the main problem resides in the fact that the nominators in the study of Dr Schmiedl and colleagues are difficult to compare with those in our study.[1] We used the number of dispensed prescriptions, whereas they used the number of exposed persons per quarter. We extrapolated the number of person years assuming prescriptions for a 3-month period. However, since patients starting a digitalis glycoside will get a first prescription for a 2-week period instead of a 3-month one, the real number of person years may be lower. This means that our extrapolation slightly underestimated the incidence rate per person year. Also, we used dispensing data. Not everybody will use all dispensed drugs, resulting in a further underestimation of the incidence per person year of actual use.

The two studies by Warren et al.[3] and Kernan et al.[4] referred to in the letter are older, as already discussed by the authors and therefore are likely to reflect toxicity rates from a higher dose regimen.

In conclusion, the results from Dr Schmiedl and colleagues, together with previous studies,[3,5] further confirm our finding that women are at increased risk of digitalis glycoside toxicity. Also, both the findings by Dr Schmiedl and colleagues and our study[1] strongly suggest that the safety of digitalis glycoside use has improved over the past two to three decades. Nevertheless, since the drug is rather widely used and toxicity can probably still be further reduced by an even more careful dose adjustment, we agree that attention needs to be continuously paid to digitalis toxicity risk factors.

Adrianus L.H.J. Aarnoudse,[1,2] *Jeanne P. Dieleman*[3] and *Bruno H.Ch. Stricker*[1,2]

1 Department of Epidemiology & Biostatistics, Erasmus Medical Center, Rotterdam, The Netherlands

2 Inspectorate of Health Care, The Hague, The Netherlands

3 Department of Medical Informatics, Erasmus Medical Center, Rotterdam, The Netherlands

Acknowledgements

The authors have no conflicts of interested directly relevant to the content of this letter.

References

1. Aarnoudse AL, Dieleman JP, Stricker BHC. Age- and gender-specific incidence of hospitalisation for digoxin intoxication. Drug Saf 2007; 30 (5): 431-6
2. Schneeweiss S, Hasford J, Gottler M, et al. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. Eur J Clin Pharmacol 2002 Jul; 58 (4): 285-91
3. Warren JL, McBean AM, Hass SL, et al. Hospitalizations with adverse events caused by digitalis therapy among elderly Medicare beneficiaries. Arch Intern Med 1994 Jul 11; 154 (13): 1482-7
4. Kernan WN, Castellsague J, Perlman GD, et al. Incidence of hospitalization for digitalis toxicity among elderly Americans. Am J Med 1994 May; 96 (5): 426-31
5. 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