Verena Annemarie Bergk
Dr. sc. hum.

Drug-drug interactions: Risk determination and information requirements for appropriate management in ambulatory care

Geboren am: 13.03.1975 in Mainz
Staatsexamen der Fachrichtung Pharmazie am 01.12.1999 an der Universität Mainz

Promotionsfach: Klinische Pharmakologie
Doktorvater: Prof. Dr. med. W.E. Haefeli

With a growing life expectancy the number of people suffering from chronic conditions will increase and complex combination therapy therefore will become a major therapeutic strategy. While the concurrent use of several drugs often improves therapeutic effectiveness, combination therapy is also a risk factor for drug-drug interactions. However, in most cases the combination of interacting compounds does not result in a clinical manifestation if it is adequately managed. Studies so far may have overestimated the risk arising from drug-drug interactions because they only considered the severity of potential outcomes but not manageability. On the other hand, the number of different pharmacological agents is growing and physicians may need information support for providing optimum management.

To estimate the risk associated with drug-drug interactions in outpatients when also measures for their prevention are considered, all pairs of compounds concurrently prescribed to 9481 adults aged 50 to 75 years who participated in a health-screening examination were evaluated in a cross-sectional study according to a new algorithm with four decision layers (severity, manageability, risk/benefit assessment, and patient-related risk factors), and this risk evaluation was compared with the conventional evaluation solely on the basis of severity. 669 different compounds were prescribed in 13,672 individual combinations. 881 (6.4%) of these were identified as interacting according to DRUGDEX®. Of these 881 drug-drug interactions, 132 (15.0%) were of major severity but 101 of 132 (76.5%) were manageable. Only 31 major interactions offered no management option and of these, 11 were only relevant in predisposed patients. Consequently, earlier studies which did not consider management options have substantially overestimated the risk. The proportion of manageable drug-drug interactions may vary in outpatient populations with a different degree of morbidity. The new algorithm, however, is universally applicable to other populations to provide a subtly differentiated risk evaluation of drug-drug interactions.

The evaluation of actual dose adjustment of three pairs of compounds in the study population suggested that two (verapamil-simvastatin, digoxin-potassium-depleting diuretics) were well managed while in the combination of spironolactone with angiotensin-converting enzyme inhibitors, 79% of the patients were maintained on excessive spironolactone doses with the risk of hyperkalaemia. It remains, therefore, a continuing challenge to ensure that management is actually practiced in ambulatory care. However, explicit drug-drug interaction information was only available for 7.5% of prescribed pairs of compounds, and evidence of the absence of a drug-drug interaction, which is valuable for the choice of safe alternatives, was only provided for 1.1% of pairs of compounds.

Drug-drug interaction information requirements in general practice with respect to both content and way of its presentation were determined in a mail survey among 2,000 randomly selected general practitioners in Baden-Württemberg using a four-step intervention strategy to

achieve a good response rate. More than half of the 1,216 respondents were dissatisfied with the amount of information on severity and management currently available in their sources of information. Particularly information on non-interacting alternatives (85%) was considered to be lacking. Although general practitioners were asked to list clinically relevant pairs of interacting compounds, 85% of the combinations were mentioned at the drug class level. Of these class labels, 58% did not apply because of differences in metabolic pathways among the compounds indicating that explicit information at the level of compounds is required. Users of drug-drug interaction software more frequently retrieved drug-drug interaction information than non-users (Odds ratio 1.95; 95% Confidence intervals 1.50, 2.52) but only 28.6% of the general practitioners had access to such a system. There was a significant trend towards electronic sources among younger physicians, but at present still 41.7% of general practitioners favour printed sources. The identified requirements may help to develop management-oriented drug-drug interaction information sources which meet general practitioners' expectations at the point of care.

Because the survey revealed that 60% of general practitioners would consult the Summary of Product characteristics the quality of drug-drug information provided by the Summary of Product Characteristics was compared with the evidence from three standard sources according to five evaluation criteria. 579 pairs of interacting compounds were evaluated which consisted of the compounds most frequently mentioned as interacting in the survey and required active management. 16% of these clinically relevant drug-drug interactions were not characterised at all in the Summary of Product Characteristics and 51% were insufficiently characterised as compared with the standard sources because of unjustified class labelling or a lack of appropriate effect descriptions, management recommendations, or explicit advice for dose adjustment. Hence, if physicians relied solely on drug-drug interaction information provided by the Summary of Product Characteristics, adverse events due to lacking recommendations are likely to occur.

This work has provided evidence that the majority of drug-drug interactions represent a manageable risk in ambulatory care. However, general practitioners need access to management-oriented compound-specific information sources which reflect the current state of medical knowledge to implement optimum measures of risk reduction. For the choice of safe alternatives, more information on non-interacting combinations should be generated. Incorporation of patient-related risk factors will allow a further individualisation of drug-drug interaction management in the future. Providing adequate drug-drug interaction management will open up new possibilities of using the benefits of complex drug regimens in future therapy and prophylaxis.