Drug Saf 2010; 33 (8): 705-707
0114-5916/10/0008-0705/$49.95/0

Adverse Drug Reactions of Remedies Containing Asteraceae Extracts

Herewithin, we would like to refer to the article ''Remedies Containing Asteraceae Extracts: A Prospective Observational Study of Prescribing Patterns and Adverse Drug Reactions in German Primary Care'' published in *Drug Safety*.[1]

As a company manufacturing homeopathic and anthroposophic medicinal products we were very pleased to see an article dealing with homeopathic, anthroposophic and phytotherapeutic therapy systems in your esteemed journal. However, while reading through the paper, we came across some important inconsistencies that we would like to share with your readership.

In our opinion, the most crucial issue is that within the article the authors conclude that homeopathically diluted medicinal products cause more adverse drug reactions (ADRs) than phytotherapeutic preparations. This conclusion is incomprehensible from a medical-allergological point of view, because homeopathic diluted medicinal products are usually less concentrated than phytotherapeutic remedies. However, in some cases homeopathic medicinal products are highly concentrated, such as in undiluted 'mother tinctures', which are comparable to phytotherapeutic preparations in their concentration level. Without a differentiated discussion of this issue, however, the conclusion as such is misleading and remains fragmentary. Similarly, the medicinal products are not assigned correctly to the corresponding groups (homeopathically diluted medicinal product or phytotherapeutic [i.e. not homeopathically diluted] medicinal product), which are defined in the Methods section. Five of the 11 reported ADRs (see table IV) are incorrectly assigned to the group of homeopathically diluted medicinal products; they contain undiluted dried extracts or mother tinctures of Asteraceae ingredients, which are comparable to phytotherapeutic extracts with regard to the concentration of their active compounds. For example, Contramutan N syrup contains the composite ingredients *Echinacea angustifolia* and *Eupatorium perfoliatum* undiluted as the mother tincture, and *Carduus marianus* capsules contain the highly concentrated composite ingredient undiluted as a dried extract from fruit (drug : extract ratio [DER] = 36–44 : 1 with ethyl acetate as solvent). To be conclusive and accurate, the medicinal products should be assigned to the class of the undiluted herbal preparations. The analysis would then come to the following conclusion: five ADRs are assigned to the phytotherapeutic preparations, five ADRs are assigned to the group homeopathically diluted <D4 preparations and one ADR is assigned to the group homeopathically diluted ≥D4 preparations. This correct analysis also seems to be more comprehensible from a medical-allergological point of view.

A second discrepancy within the article is the incorrect use of the terms 'monopreparation' and 'combined preparation'. These terms are clearly defined in the pharmaceutical and medical terminology and address preparations with a single ingredient or several ingredients, respectively. Beginning in the Methods section of the article, the expressions 'monopreparation' and 'combined preparation' are repeatedly mistakenly used for the term 'mono-composite-preparation' and 'preparation containing different composite ingredients'. In relation to the article, the terms 'monopreparation' and 'combined preparation' are used for preparations with one or more than one Asteraceae ingredients, respectively. This is misleading because several of these so-called 'monopreparations' (one Asteraceae component) are 'combined preparations' (Asteraceae and non-Asteraceae ingredients) in the proper meaning of the word. For example, for the *C. marianus* capsules, which are a 'mono-composite-preparation' and a 'monopreparation' containing only one composite ingredient, the term 'monopreparation' is correctly used in the article. On the contrary, for the *Argentum nitricum* comp. ampoules, which are also a 'mono-composite-preparation' but adhering to the correct pharmaceutical nomenclature, a 'combined preparation' with one composite (*Echinacea pallida*) and several noncomposite ingredients (*Argentum nitricum*, *Chlorophyceae*,

Eucalytus globulus and *Thuja occidentalis*), the term 'monopreparation' is mistakenly used in the article.

These misleading terms subsequently result in incorrect conclusions regarding the assessment and discussion of the ADRs, which directly leads to the third discrepancy: in the article, the authors only focus on the Asteraceae (composite) ingredients, but in 7 of 11 cases the ADRs are very likely related to the noncomposite components, which is already stated in some of the package information leaflets, e.g. preparations containing *Chelidonium* alkaloids very rarely increase liver function values (see below). A detailed discussion and comprehensible explanation is lacking in the article and, therefore, the final conclusion appears too one-sided. For example, apart from the composite ingredients (*Solidago virgaurea* and *Taraxacum officinale*), the Aquilinium comp.® Globuli velati mentioned in the Discussion section contains *Chelidonium majus* and *Dryopteris filix-mas*, which are hepatic-, bile- and gastrointestinal-effective substances. These noncomposite ingredients are more likely responsible for the reported ADR 'abdominal pain' than the Asteraceae ingredients. The package information leaflet states: ''During treatment with preparations containing *Chelidonium* (celandine) alkaloids, increases in liver function values (transaminases) and bilirubin, including drug-induced jaundice (medicinal-toxic hepatitis), have very rarely been observed when using this medicinal product. In such cases, use of this medicinal product should be discontinued and a doctor consulted.'' Furthermore, in the case of *A. nitricum* comp. ampoules, the 'off-label' application technique (subcutaneous injection instead of the authorized intramuscular injection application) and not the ingredients themselves might have caused the ADRs (redness, pruritus). As a consequence of this missing discussion, the article gives incorrect group effects of Asteraceae without comment.

Summarizing the discrepancies, it is clear that the condensed conclusion of the article, stating that homeopathically diluted medicinal products cause more ADRs than phytotherapeutic preparations, does not draw a correct picture regarding the safety assessment of homeopathic and phytotherapeutic medicinal products containing Asteraceae preparations. In our view, it is far from being plausible that diluted Asteraceae-containing homeopathic medicinal products should cause more allergic-mediated ADRs than undiluted, concentrated phytotherapeutic remedies. A more differentiated data evaluation would imply a correct assignment of the drugs and an adequate discussion of the corresponding effects including a sound causality assessment of the ADRs, both with regard to the noncomposite ingredients and their off-label use.

We hope to encourage scientists to deal carefully with pharmacovigilance data, in particular in the very special research area of homeopathic and phytotherapeutic therapy.

Ulrike Sobeck, Florian C. Stintzing
and *Peter Vögele*
WALA Heilmittel GmbH, Bad Boll, Germany

Acknowledgements

All authors are employees of WALA Heilmittel GmbH, Bad Boll, Germany, the manufacturer of some of the products discussed in this letter.

Reference

1. Jeschke E, Ostermann T, Lüke C, et al. Remedies containing Asteraceae extracts: a prospective observational study of prescribing patterns and adverse drug reactions in German primary care. Drug Saf 2009; 32 (8): 691-706

The Author's Reply

We appreciate the opportunity to reply briefly to the critique from Sobeck, Stintzing and Vögele, who have pointed out a weakness in our classification of homoeopathic remedies.

We are grateful for their assistance in this regard but must rebut their claim that we conclude that ''homoeopathically diluted medicinal products cause more adverse drug reactions (ADRs) than

phytotherapeutic preparations.'' We stand by our assertion that a ''subgroup analysis comparing phytotherapeutic and homoeopathic preparations does not reveal any relevant differences.''[1]

Because we were unable to identify clearly which ingredients caused the ADRs, we put forward a conservative estimate of potential risk and discussed this topic in great detail. Moreover, our main focus was not to discuss the various aspects of risk posed by single remedies, but to characterize the risk of remedies containing Asteraceae extracts. We have no doubt that the conclusion of our study is valid as it stands: ''Our results indicate that treatment with Asteraceae-containing remedies is not associated with a high risk of ADRs.''

Elke Jeschke
Havelhoehe Research Institute, Berlin, Germany

Acknowledgements

E. Jeschke has received restricted grants from Wala Heilmittel GmbH and Weleda AG within the past 5 years.

Reference

1. Jeschke E, Ostermann T, Lüke C, et al. Remedies containing Asteraceae extracts: a prospective observational study of prescribing patterns and adverse drug reactions in German primary care. Drug Saf 2009; 32 (8): 691-706