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Safety and compliance of a complex homeopathic drug (Contramutan N Saft) in the treatment of acute respiratory tract infections: A large observational (non-interventional) study in children and adults focussing on homeopathy specific adverse reactions versus adverse drug reactions

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ABSTRACT

Background: This non-interventional study was performed to generate data on safety and treatment effects of a complex homeopathic drug (Contramutan N Saft).
Patients and methods: 1050 outpatients suffering from common cold were treated with the medication for 8 days. The study was conducted in 64 outpatient practices of medical doctors trained in CAM. Tolerability, compliance and the treatment effects were assessed by the physicians and by patient diaries. Adverse events were collected and assessed with specific attention to homeopathic aggravation and proving symptoms. Each adverse effect was additionally evaluated by an advisory board of experts.
Results: The physicians detected 60 adverse events from 46 patients (4.4%). Adverse drug reactions occurred in 14 patients (1.3%). Six patients showed proving symptoms (0.57%) and only one homeopathic aggravation (0.1%) appeared. The rate of compliance was 84% in average for all groups and the global assessment of the treatment effects attributed to "good" and "very good" in 84.9% of all patients.
Conclusions: The homeopathic complex drug was shown to be safe and effective for children and adults likewise.

Adverse reactions specifically related to homeopathic principles are very rare. All observed events recovered quickly and were of mild to moderate intensity.

1. Introduction

Viral infections of the respiratory tract usually have a strong impact on the individual well-being. Symptoms such as coughing, running and/or obstructed nose, sore throat and hoarseness, head- and muscle ache and elevated temperature prompt patients for seeking symptomatic treatment.

Germany has a long standing tradition of plant-derived medicinal products including homeopathic drugs. Classical homeopathy uses high dilutions ("potencies") of single substances, whereas complex homeopathy usually uses combinations of different preparations, mostly in the form of low dilutions or even the homeopathic mother tinctures. Complex homeopathic remedies are usually in a concentration range where the single constituents can still be measured by analytical methods. From the regulatory point of view such products must undergo an assessment of safety similar to that applied to any other medicinal product. Regulatory authorities specifically call for data on safety and applicability in children. The method of choice for preparations with a long-standing use is the systematic documentation of safety issues in an observational or non-interventional trial.

The aim of this trial was the assessment of safety, of the compliance and the possible influence on symptoms in patients suffering from acute infections of the upper airways (flu-like infection and inflammatory disorders of the nose and throat). Specific attention was given to the inclusion of infants and children. Furthermore, an enigma of homeopathy was addressed by the assessment of the so-called "homeopathic aggravation" and the "proving symptoms", both important pillars in the special theory of homeopathy. The existence of homeopathic initial aggravation is still under debate: in a systematic review of double-blind trials on homeopathic drugs 24 studies were analysed for their documentations of homeopathic aggravations. 50 such effects were identified in

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patients treated with placebo, 63 in patients treated with homeopathic preparations, thus resulting in unclear evidence for the existence of the phenomenon, or for the adequacy of examining such effects within clinical studies (Grabia and Ernst, 2003).

The homeopathic theory considers initial aggravations as a signal for the starting action of a homeopathic treatment. They are defined as initial aggravations of the patient's symptoms, followed by an improvement, and must be differentiated from disease-related aggravations (Endrizzi et al., 2005). Another phenomenon discussed is the observation of proving symptoms related to the "homeopathic drug picture" – symptoms occurring during testing of the homeopathic drug in healthy subjects. Homeopathy relates such symptoms to the properties of the "materia medica", and uses these symptoms in the context of "the like cures the like" when similar symptoms are also observed with a given disease. However, homeopathic theory may therefore ascribe symptoms recorded during the treatment of a given ailment to the "homeopathic drug picture", in analogy to toxicity caused by a medication.

The study presented herein was therefore designed to assess adverse events also in the context of the phenomena of "homeopathic initial aggravation" and "homeopathic proving symptoms", next to the assessment of practical applicability of the study medication in the regular medicinal context and disease development. Finally, we aimed to assess additionally the global effectiveness of the preparation as assessed by physicians rating at the end of the treatment period.

2. Materials and methods

2.1. Study design

The study was designed as a non-interventional, prospective multicentre trial according to the recommendations of the German drug regulatory authority (Anon, 2010) and the "Guidance for the format and content of non-interventional post-authorization safety studies" (EMA/623947/2012). A positive vote of all concerned ethics committees and Institutional Reviewing Boards was obtained. All patients, respectively the caretakers of children, signed an informed consent.

The study was set up in 64 practices headed by general practitioners and paediatricians with practical experience in treatments with complementary remedies and homeopathy. More than 60% of the participating practitioners held a special qualification and board certification in homeopathy and/or naturopathy. Monitoring visits at the start and the end of the study and additional phone contacts during the study assured the quality of the data assessment and documentation with specific attention to adverse events and their potential relation to homeopathic aggravations and proving symptoms.

The first patient was included on 22 November 2012, the date of the final examination of the last patient was 20 March 2013.

In accordance with the experience in general practice/family medicine a treatment duration of 6–8 days was expected and an interim visit on day 2–4 planned. For patients not yet recovered on day 6–8, a further telephone contact after 12–16 days was foreseen in order to check on late adverse events.

Patients older than 1 year with no upper limitation of age could be included when diagnosed with symptoms of an acute catarrhal disease/common cold of the respiratory tract such as flu-like infections and inflammation of the nose and throat.

Exclusion criteria were all contraindications defined by the summary of product characteristics of the homeopathic drug, i.e., an allergy against any of the constituents of the study preparation, a diagnosis of tuberculosis, leucosis, collagenosis, multiple sclerosis, HIV and autoimmune diseases. Children at an age below 1 year and pregnant or lactating women were excluded from study participation.

2.2. Medication

The medication used was Contramutan N Saft (Cassella-med, Cologne, Germany), a complex homeopathic preparation (juice) with a German marketing authorization as a medicinal drug for the treatment of colds. 100 g of the liquid preparation contain 4.5 g mother tincture of the aerial parts of *Echinacea angustifolia*, 4.5 mg mother tincture of the aerial parts of *Eupatorium perfoliatum*, 9 mg *Aconitum napellus* D4 and 9 mg Belladonna D4.

Patients received 10 single doses in intervals of at least 1 h on the first day, and three single doses (one dose every 6–8 h) on all consecutive days. The single dose was adapted to the age group:

- Group 1: children in the age of <1–6 years: 3.5 ml.
- Group II: children in the age of 7–12 years: 5 ml.
- Group III: adolescents (>12 years) and adults: 10 ml.

2.3. Outcome measures

The patients were primarily assessed for the occurrence of adverse events by physicians interview and rating. In addition, compliance and the global development of symptoms were documented. All included subjects were given a diary for the documentation of dosing, a self-assessment of symptoms and well-being as well as a global assessment of effects.

Adverse events were systematically collected, assessed and evaluated by the treating physicians. In addition, an advisory board for pharmacovigilance with specific experience in safety issues related to the principles of homeopathy and herbal therapy evaluated all events at the end of the study. Thus there was an independent duplicate assessment of adverse events, one by the physician and one by the advisory board.

The severity of clinical symptoms (cough, rhinitis, sore throat, head- and muscle ache and fever) was assessed by the physician upon study entry and at both visits on a 4-step verbal rating scale (0 = not present, 1 = mild, 2 = moderate, 3 = severe).

A global assessment of effects and tolerability was made at the end of the study by the physicians and the patients on a four-step verbal rating scale (very good, good, satisfactory, unsatisfactory). The patient's rating of the effect was derived from the corresponding entries in the diaries.

Compliance was calculated from the individual doses documented in the diaries, with 100% set to the recommended dose. The time to recovery and the average duration of exposure was also derived from the diaries.

Concomitant diseases and co-medication had to be documented.

2.4. Sample size

The sample size was calculated with the aim of detecting a minimum incidence rate of adverse effects of 0.003 with a 90% probability, assuming a Poisson distribution throughout the study population. An inclusion of 900 patients was expected to lead to at least 750 complete data sets, sufficient for the exclusion or confirmation of any adverse effect occurring in 1 out of 1000 exposed patients (corresponding to the rating as "occasional"). A number of at least 250 patients per subgroup had to be reached.

2.5. Statistical methods

The study results were descriptively analysed by subgroups according to age. The applied statistical software was SAS v9.3.