Use and Safety of Anthroposophic Medications for Acute Respiratory and Ear Infections: A Prospective Cohort Study

Harald J. Hamre[1], Anja Glockmann[1], Michael Fischer[2], David S. Riley[3], Erik Baars[4] and Helmut Kiene[1]

[1]Institute for Applied Epistemology and Medical Methodology, Freiburg, Germany.
[2]ClinResearch GmbH, Cologne, Germany.
[3]University of New Mexico School of Medicine, Santa Fe, New Mexico, U.S.A.
[4]Louis Bolk Instituut, Driebergen, The Netherlands.

Abstract

Objective: Anthroposophic medications (AMED) are widely used, but safety data on AMED from large prospective studies are sparse. The objective of this analysis was to determine the frequency of adverse drug reactions (ADR) to AMED in outpatients using AMED for acute respiratory and ear infections.

Methods: A prospective four-week observational cohort study was conducted in 21 primary care practices in Europe and the U.S.A. The cohort comprised 715 consecutive outpatients aged ≥1 month, treated by anthroposophic physicians for acute otitis and respiratory infections. Physicians' prescription data and patient reports of adverse events were analyzed. Main outcome measures were use of AMED and ADR to AMED.

Results: Two patients had confirmed ADR to AMED: 1) swelling and redness at the injection site after subcutaneous injections of Prunus spinosa 5%, 2) sleeplessness after intake of Pneumodoron® 2 liquid. These ADR lasted one and two days respectively; both subsided after dose reduction; none were unexpected; none were serious. The frequency of confirmed ADR to AMED was 0.61% (2/327) of all different AMED used, 0.28% (2/715) of patients, and 0.004% (3/73,443) of applications.

Conclusion: In this prospective study, anthroposophic medications used by primary care patients with acute respiratory or ear infections were well tolerated.

Abbreviations: A-: anthroposophy; ADR: adverse drug reactions; AE: adverse events; AM: anthroposophic medicine; AMED: AM medication; C-: conventional; ENE-patients: eligible, not enrolled patients; IIPCOS: International Primary Care Outcomes Study

Keywords: Adverse effects, complementary therapies, drug monitoring, otitis media, respiratory tract infections

Introduction

Anthroposophic medicine (AM) is a system of medicine founded by Rudolf Steiner and Ita Wegman (Steiner and Wegman, 2000). AM is provided by physicians in 56 countries worldwide. A cornerstone of AM therapy is AM medication (AMED). AMED includes more than 2,000 different products of mineral, botanical or zoological origin as well as chemically defined substances. AMED are prepared in concentrated form or in homeopathic potencies (IAAP 2005). All AMED are manufactured according to Good Manufacturing Practice and national drug regulations; quality standards of raw materials and manufacturing methods are described in the Anthroposophic Pharmaceutical Codex (IAAP 2005).

Almost all AMED in current use have been on the market since the 1970s, some AMED even since the 1920s. Pre-clinical testing, pharmacovigilance reports, surveys, and 190 clinical studies suggest that adverse drug reactions (ADR) to AMED are infrequent and mostly mild to moderate (Kienle et al. 2006). However, safety data from the clinical trials are often sparse, and in two-thirds of the trials, the number of patients using AMED was less than 100.

The study IIPCOS-Anthroposophy (International Integrative Primary Care Outcomes Study (Hamre et al. 2005)) provided an opportunity to investigate the use and safety of AMED in a large patient sample.

Correspondence: Dr. med. Harald J. Hamre, IFAEMM e. V., Böcklerstr. 5, D-79110 Freiburg, Germany,
Tel. +49 761 15 60 307, Fax +49 761 15 60 306.
Email: harald.hamre@ifaemm.de

IIPCOS-Anthroposophy was a prospective, observational comparative study of patients with acute respiratory or ear infections seeing AM (n = 715 A-patients) or conventional physicians (n = 301 C-patients). Compared to C-patients, A-patients had more favorable clinical outcomes: adjusted odds ratios were 1.54 (95% confidence interval 1.03–2.31) for first improvement within 24 hours, 1.61 (1.16–2.22) for first improvement within 3 days, 1.50 (1.07–2.11) for response (major improvement or complete recovery) within 7 days, and 1.29 (0.82–2.00) for response within 14 days. A-patients were also more satisfied with therapy (odds ratio for "very satisfied": 1.39 (0.98–1.95)). Nineteen (2.7%) A-patients and 18 (6.0%) C-patients reported adverse events (AEs) with a possible or probable relationship to medication taken during the study. In the primary analysis (Hamre et al. 2005), these AEs were not further investigated but were all classified as ADR. Here we present a more detailed analysis of AMED use and safety in A-patients from the IIPCOS-Anthroposophy study.

Material and Methods

Objective and design

The primary objective was to investigate the use and safety of AMED. In this study, AMED was defined as any medication produced by the pharmaceutical companies Weleda AG, Arlesheim, Switzerland or Wala-Heilmittel GmbH, Eckwälden, Germany. The secondary objective was to investigate the safety of all (AMED + non-AM) medications used in AM settings. For this purpose we analyzed physicians' prescription data and patient reports of AEs in the AM arm of a prospective observational comparative study of AM vs. conventional treatment of respiratory and ear infections.

Setting, physicians, patients, and therapy

The study was conducted 1999–2000 in primary care practices in Austria, Germany, The Netherlands, U.K., and U.S.A. Participating AM physicians were recruited through national AM physicians' associations. All participating physicians had at least 5 years' clinical experience and were regularly prescribing at least 75% AMED in acute respiratory and ear infections. Physicians were also required to have computers with internet access available, in order to collect data by remote data entry. The physicians enrolled consecutive outpatients fulfilling the eligibility criteria. Inclusion criteria were (1) age ≥1 month, (2) chief complaint of sore throat, ear pain, sinus pain, runny nose or cough, (3) onset of chief complaint within seven days. Exclusion criteria were dementia, schizophrenia, psychosis, spinal cord injury, stroke, renal failure, severe hepatic disease, ongoing immunosuppressive treatment, chemotherapy or radiotherapy, alcohol or drug abuse. Patients were treated according to the physician's discretion.

Outcomes

Medication use

Medication use was assessed (for AMED and for non-AM medications, respectively) by the number of different medications used, the number of users and the number of applications. Patient self-reporting of compliance with medication prescription was also recorded.

Medication safety

For each AE the causal relationship of AE to all medication used by the patient between study entry and end of the AE was assessed (probable, possible, improbable, no relationship, unable to evaluate). In addition, the most probable cause of the AE (AMED, non-AM medication, primary illness, intercurrent illness, other) was noted. AEs with probable or possible causal relationship to any medication, confirmed by this analysis, were classified as confirmed ADR and described as follows:

- Name and duration of the ADR, intensity: mild/moderate/severe = no/some/complete impairment of normal daily activities.
- Necessary actions taken against the ADR: none, dose reduction/withdrawal/change of medication, admit to hospital, therapeutic counter actions, others.
- Outcome of the ADR: subsided, still being treated, uncertain—still under observation, patient lost to follow-up, permanent health damage, patient died.
- ADR serious: yes/no (Yes: necessary action: "admit to hospital" or outcome: "permanent health damage" or "patient died").
- ADR expected: yes/no (Yes: ADR previously

reported or may be expected because of a known mechanism of action of ingredients).

The frequency of ADR (to AMED and to any medication) was assessed in relation to the number of different medications, the number of users, and the number of applications.

Data collection

On Day 0, the physicians documented primary and concomitant diseases, ongoing medication, and all medication or non-medication therapy prescribed: name, dose, medication form, dosing frequency, number of days prescribed.

On Days 7, 14, and 28, patients (for children: legal guardians) were interviewed by telephone. The interviews included the degree of compliance with medication prescription, change in medication, and AEs. AEs were defined as any disorders of health, subjective and objective symptoms of illness including changes in laboratory findings, intercurrent medical problems, and accidents observed during the study, regardless of a possible causal relationship to any medication. For patients with complete recovery on Days 7 or 14, study participation was terminated and no further follow-up interviews were performed. Data collection, follow-up interviews, and queries were performed by the Institute for Numerical Statistics (now: Omnicare Clinical Research), Cologne, Germany. Except for patients' Day 0 questionnaire, all items were documented by remote data entry.

For patients with AEs with a probable or possible causal relationship to any medication, according to patient response, the study physicians were contacted by telephone and the following items were checked: diagnosis of chief complaint; complaint-related symptoms and concomitant disease present at study entry; prescribed therapy (name, duration); any consultation between study entry and end of the AE; beginning, end, outcome, and necessary actions against the AE. Information about previously reported or expected ADR was obtained from the manufacturers. AEs were coded according to the World Health Organization Adverse Reaction Terminology.

Quality assurance, adherence to regulations

The study was approved by local ethics committees and conducted according to the Helsinki Declaration, the International Conference on Harmonisation Good Clinical Practice guidelines, and legal requirements. Written informed consent was obtained from all patients before enrolment.

Data analysis

Medication use

Patients fulfilling all eligibility criteria with at least one follow-up interview were included in the prescription analysis. The statistical analysis (SPSS® 13.0.1) was descriptive. For the prescription analysis, AMED with identical ingredients and dosage form but different concentrations were grouped together.

Medication safety

The safety analysis comprised all AEs reported by the patient (or legal guardian) as having a possible or probable causal relationship to any medication. For each medication used between study entry and end of the AE, the causal relationship to the reported AE was classified by the first author (HJH) according to criteria formulated in the study protocol (Table 1) as probable, possible, improbable, no relationship or "unable to evaluate".

Results

Patient recruitment

26 AM physicians (19 general practitioners, three internists and four pediatricians) from 21 different practices in 20 different municipalities participated. The physicians had an average of 18.0 (SD 8.8) years in practice.

853 patients were enrolled: 715 patients were evaluable for prescription analysis; 138 were not evaluable (protocol violations: n = 98, no follow-up interview: n = 40). The last follow-up interview was performed an average of 16.2 (SD 8.5) days after inclusion.

A total of 878 patients were screened but not enrolled: 111 patients refused to participate; 306 did not fulfill all eligibility criteria; 461 (100%) screened patients fulfilled all eligibility criteria ("eligible, not enrolled patients" = ENE-patients). Reasons for non-enrolment of ENE-patients were: physician too busy (68.1%, 314/481 patients),

Table 1. Criteria for classification of causal relationship between adverse events and medication.

Probable

- Rational temporal relationship to the time of intake of the medication.
- AE is already known to be a side effect of the medication or may be expected.
- Regression or disappearance of the AE after discontinuation of medication or dose reduction.
- Reappearance of the AE after repeated exposure.
- AE cannot be explained in a reasonable manner by the clinical state of the patient.

Possible

- Rational temporal relationship to the time of intake of the medication.
- AE is already known as a side effect of the medication or may be expected.
- AE could be explained by numerous other factors.

Improbable

- Rational temporal relationship to the time of intake of the medication.
- AE has not been reported so far as a side effect of the medication or cannot be expected.
- AE persists after discontinuation of the medication or dose reduction.
- Repeated exposure does not lead to reappearance of the AE.
- AE could be explained by numerous other factors.

No relationship

- No rational temporal relationship to the time of intake of the medication.
- AE is evidently caused by other factors, e.g. symptom of a concomitant disease.

Unable to evaluate

- Amount and content of data do not permit a judgment of the relationship to the medication.

practical/technical (12.1%), ongoing therapy for chief complaint (2.0%), special diagnoses, e.g. mental handicap or scarlet fever (5.6%), other or not specified (12.1%). ENE-patients (n = 461) did not differ from evaluable patients (n = 715) regarding gender or chief complaint severity; ENE-patients were median 1.13 years younger (95% confidence interval: 0.38–1.95, p = 0.0036) and more ENE-patients were prescribed antibiotics on Day 0 (2.8% vs. 0.8%, p = 0.0153). A total of 83.1% (383/461) of screened, not enrolled patients were prescribed AMED.

Patient characteristics

The patients were recruited from Germany (50.6%, 362/715 patients), The Netherlands (21.3%), Austria (14.1%), U.K. (7.3%), and the U.S.A. (6.7%). Fifty-three percent (382/715 patients) were females; age groups were 0–17 years (68.1%, 487/715 patients), 18–64 years (30.2%), and ≥ 65 years (1.5%). Patients' chief complaint was cough (39.9%, 285/715 patients), sore throat (26.3%), ear pain (20.0%), sinus pain (7.0%), and runny nose (6.9%). Physicians' diagnosis of chief complaint was pharyngitis/tonsillitis (25.9%, 185/715 patients), bronchitis (19.3%), otitis media (17.2%), laryngitis/tracheitis (15.1%), rhinitis/common cold/upper respiratory infection unspecified (14.4%), sinusitis (7.4%), and other (0.7%).

Medication use

At study entry, 10.5% (75/715) of patients were using AMED for concomitant diseases, and all patients were prescribed AMED for their chief complaint. During follow-up (Day 1–28), 18.2% (130/715) of patients had at least one further AMED prescription. Altogether 73,443 applications of 327 different AMED were documented, thereof 265 different AMED prescribed on Day 0–28 (Table 2). Eight AMED were prescribed to at least 50 patients each (Table 3), 53 AMED were prescribed to at least ten patients each. The most frequent administration forms were liquids (35.4%, n = 830 of 2,346 prescriptions Day 0–28), pillules (11.2%), powders (11.0%), ointments (8.7%), ampoules (5.8%), tablets (4.7%), and eardrops (3.8%). The most common indications for AMED were acute otitis (18.9%, 467 of 2,468 prescriptions Day 0–28 + ongoing medication), bronchitis (15.7%), laryngotracheitis (14.4%), pharyngitis (9.6%), tonsillitis (9.2%), sinusitis (7.0%), and the common cold (5.4%).

In addition to AMED, patients used 12,130 applications of 218 different non-AM medications

Table 2. Overview of medication use.

	Patients with medication			Different medications			Applications		
Medication	**AMED**	**Non-AM**	**All**	**AMED**	**Non-AM**	**All**	**AMED**	**Non-AM**	**All**
A) Ongoing at study entry, used Day 0–28	75	78	125	94	59	153	8,656	3,576	12,232
B) Prescribed at Day 0	715	255	715	223	76	299	59,090	3,842	62,932
C) Prescribed at Day 1–28	131	179	211	130	119	249	5,697	4,712	10,409
B+C) Prescribed at Day 0–28	715	377	715	265	171	436	64,787	8,554	73,341
A+B+C) Ongoing + prescribed Day 0–28	715	429	715	327	218	545	73,443	12,130	85,573

during the study, altogether 85,573 applications of 545 different (AMED + non-AM) medications.

89.7% (641/715) of patients reported taking their medication as prescribed at all evaluable follow-ups.

Safety of anthroposophic medications

Reported AEs

AEs were reported by 136 patients. The relationship between the medication used and these AEs was, according to patient responses: probable (n = 9 patients), possible (n = 10), improbable (n = 7), no relationship (n = 97), unable to evaluate (n =13).

AEs with *possible or probable causal relationship* to any medication, according to patient responses, (n = 19 patients aged 0–53 years, male/female = 11/8, Table 4) were included in the safety analysis. The intensity of these AEs was mild (n = 17 patients), moderate (n = 1), and severe (n = 1). Median AE duration was 4 days (interquartile range 1–7 days). No AE was serious. Between study enrolment and end of the AE the 19 patients had used altogether 62 AMED (thereof 57 different AMED), 32 non-AM medications, and 13 non-medication therapies, with a median of 4 (range 0–8) medications/therapies per patient. For the 62 AMED in question, the causal relationship to the AE was classified as probable (n = 0), possible (n = 2, Table 5), improbable (n = 28), and no relationship (n = 32). The most probable cause of the AE was primary or intercurrent illness (n = 13 patients), non-AM medication (n = 3), AMED (n = 2), other (n = 1).

Seven patients reported a total of 11 AE with *improbable causal relationship* to medication used, according to patient responses: asthma, coughing, diarrhea, dry skin, erythema, hay fever, mesenterial adenitis, rash, rhinorrhea, upper respiratory tract infection, and whooping cough.

Ninety-seven patients reported a total of 151 AE with *no relationship* to medication used*;* the most common of these AE were: coughing (n = 22 patients), rhinitis (n = 22), diarrhea (n = 11), gastroenteritis (n = 8), fever (n = 7), and viral infection (n = 7). Patients reporting AEs with no relationship to medication were asked about the suspected cause of their AEs; in 93% (97/104) of interviews, the reported cause was a concomitant illness.

Frequency of confirmed ADR to AMED

Throughout the study, the patients used 327 different AMED, of which two (0.61%) AMED were associated with confirmed ADR. A total of 715 patients used AMED; in two (0.28%) patients, ADR to AMED occurred. Overall, 73,443 AMED applications were documented; three applications (0.004% or one in 24,481 applications) were associated with an ADR. Two (0.003%) applications were associated with an ADR of severe intensity.

Safety of all medication

Description of confirmed ADR to any medication

Five ADR were confirmed (Table 4). Median ADR duration was 2 (range 1–8) days; the five ADR were observed in conjunction with altogether 25 medication applications. The ADR intensity was mild in four patients and severe in one patient. All five ADR subsided after dose reduction (n = 2) or withdrawal (n = 3) of the causative medication. None of the ADR were serious, none were unexpected. No adverse reactions to non-medication therapies were found.

Table 3. Most frequently prescribed anthroposophic medications on Day 0–28.

Medication	Ingredients	Manufacturer	Patients with prescription*		Applications	
			N	%	N	%
Plantago Bronchial Balm	100 g contains: Camphora 2 g, *Cera flava* 15 g, *Drosera rotundifolia/ intermedia/anglica* e planta tota ferm. D3 1.0 g, *Eucalypti* aetheroleum 0.5 g, *Petasites hybridus* e radice ferm. D1 1.0 g, *Plantago lanceolata* e foliis ferm. D1 1.0 g, *Terebinthina laricina* 5.0 g, *Thymi aetheroleum* 0.5 g	Wala	117	16.4%	1945	3.0%
Erysidoron® 1 Liquid	10 g contains: Apis mellifica D2 1 g, *Belladonna* D2 1 g	Weleda	98	13.7%	3605	5.6%
Cinnabar comp. Powder	10 g contains: Apisinum D5 3.3 g, *Belladonna* D3 3.3 g, Cinnabar D5, 3.3 g	Weleda	96	13.4%	3037	4.7%
Pneumodoron® 1 Liquid	10 g (= 10.5 ml) contains: *Aconitum napellus*. D2 0.5 g, *Bryonia* D2 1 g	Weleda	70	9.8%	1789	2.8%
Cinnabar/Pyrit Tablets	1 tablet contains: Cinnabar D20 176 mg, Pyrit D2 20 mg	Weleda	69	9.7%	2075	3.2%
Bolus Eucalypti comp. Powder	10 g contains: Apis mellifica ∅ (= D1) 0.1 g, *Belladonna* ∅ 0.002 g, *Eucalyptus* ∅ (= D1) 0.1 g, White clay 9.97–10 g	Weleda	59	8.3%	2223	3.4%
Pine Reviving Bath Milk	Contains: Water (Aqua), Potassium olivate, *Abies alba* leaf oil, *Abies Sibirica* oil, Limonene	Weleda	53	7.4%	459	0.7%
Berdonia Nose Spray	1 g contains: *Berberis vulgaris* e fructibus ferm D2 0.1 g, *Citrus limon* e fructibus ferm D1 0.1 g, *Cydonia oblonga* e fructibus ferm D1 0.1 g, Quarz (Silicea) D19 0.1 g	Wala	50	7.0%	1599	2.5%
Echinacea comp. Mouthspray	100 g contains: Argentum nitricum D13 1.0 g, *Calendula officinalis*, flos rec. 10.0 g, *Echinacea pallida*, herba rec. 10.0 g, *Eucalyptus globulus* e foliis ferm. D1 1.0 g, Gingiva bovis Gl D4 1.0 g, Gingiva bovis Gl Dil. D8 1.0 g, *Salvia officinalis*, folium rec. 10.0 g, Tonsillae palatinae bovis Gl D4 1.0 g, Tonsillae palatinae bovis Gl D8 1.0 g	Wala	49	6.9%	1062	1.6%
Sticta Liquid	*Sticta* D3/D6	Weleda	48	6.7%	2144	3.3%
Hepar Sulfuris Powder	Hepar sulfuris D3/D4/D6/D12/D30	Weleda	47	6.6%	1970	3.0%
Chamomilla comp. Suppository	1 suppository (1 g) contains: *Belladonna* D3 20 mg, *Chamomilla recutita*, radix, ethanol. decoctum D2 20 mg, *Echinacea purpurea*, planta tota ∅ 135mg, *Papaver somniferum*, fructus immat. D3 20 mg, Argentum metallicum praeparatum D19 20 mg	Weleda	43	6.0%	555	0.9%
Aconitum comp. Eardrops	10g contains: *Aconitum napellus* e tubere ferm. D9 1.0 g, *Camphora* 0.1 g, *Lavandulae* aetheroleum 0.1 g, Quarz (Silicea) D9 1.0 g	Wala	42	5.9%	1680	2.6%

Infludo® Liquid	10 g (= 11.1ml) contains: *Aconitum napellus* D3 1 g, *Bryonia* D2 0.6 g, *Eucalyptus* D2 0,5g, *Eupatorium perfoliatum* D2 0.4 g, Phosphorus D4 1 g, *Sabadilla* D3 1 g	Weleda	40	5.6%	1130	1.7%
Levisticum Rh Liquid	Levisticum D2/D3/D4/D6/D10	Weleda	40	5.6%	1269	2.0%
Cough Elixir	100g (= 76ml) contains: 5g aqueous extract from 0.6 g *Althaeae radix*, 30 g aqueous decoctum from (0.15 g *Solanum dulcamara*, stipites sicc.; 0.35 g *Marrubium vulgare*, herba sicc.; 0.5 g *Anisi* fructus; 0.35 g *Serpylli* herba; 2.85g *Thymi* herba), *Drosera* D2 0.1g, Extractum Malti 5 g, *Ipecacuanha*, ethanol. decoctum ∅ (= D1) 0.1 g, *Pulsatilla vulgaris* D3 0.01 g	Weleda	34	4.8%	916	1.4%
Kalium carbonicum Liquid	Kalium carbonicum D3/D4/D6/D10/D12/D20/D30	Weleda	34	4.8%	1541	2.4%
Silicea (Quarz) 1% Eardrops	10 g (= 10.9 ml) contains: Quarz (Silicea) 0.1 g	Weleda	34	4.8%	676	1.0%
Nose Balm for Children	10 g contains: Balsamum peruvianum 0.05 g, *Berberis vulgaris* e fructibus ferm. ∅ 1.00 g, *Prunus spinosa*, fructus rec. 0.50 g, Silicea colloidalis 0.05 g	Wala	32	4.5%	611	0.9%
Capsicum annuum Liquid	*Capsicum annuum* D3/D4/D6/D10	Weleda	32	4.5%	418	0.6%
Other medications (n = 245)					34083	52.6%
Total			715	100.0%	64787	100.0%

*Multiple responses possible, sum of percentages <100%. D: Decimal potencies (1:10 dilution; e.g. D3 = 1:1000). ∅: mother tincture. GL: Mother tincture prepared using glycerol./: Medication exists in different concentrations grouped together.

Frequency of confirmed ADR to any medication

Throughout the study, the patients used 545 different (AMED + non-AM) medications, of which five (0.92%) medications were associated with confirmed ADR. A total of 715 patients used medication; in five (0.70%) patients ADR occurred. ADR of severe intensity occurred in one (0.14%) patient. Overall, 85,573 medication applications were documented; 25 applications (0.03% or one in 3,423 applications) were associated with an ADR. Two (0.002%) applications were associated with an ADR of severe intensity.

Discussion

Overall study findings

This is one of the first detailed analyses (Hamre et al. 2006) of use and safety of AMED within a large prospective cohort study. In outpatients with acute respiratory and ear infections we found a low frequency of confirmed ADR to AMED (0.28% of AMED users and 0.004% of AMED applications).

Strengths and limitations

This study has several strengths: Data collection was prospective with extensive quality assurance guaranteeing high data quality (100% source data verification performed for all baseline prescription data, i.e. for 88% of AMED applications). Patients were recruited by experienced physicians (average 18 years in practice) in a range of healthcare settings (20 different municipalities in five countries). Follow-up rates were high (only 5% of otherwise evaluable patients were lost to follow-up). AEs were documented in all patients at all follow-ups (instead of relying on spontaneous reporting). In the safety analysis, AEs were investigated with respect to a causal relationship to all ongoing medication according to predefined criteria, checking each case with physicians and patients.

Selection bias is unlikely for this study: Screening data suggest that enrolled patients are representative for eligible patients. Moreover, the percentage of eligible but not enrolled patients prescribed AMED (83%) was lower—and not higher—than the percentage of evaluable patients prescribed AMED (100%). Therefore, if any significant "selection-out" of patients from the

Table 4. Adverse events (AE) reported with possible or probable causal relationship to any medication, according to patient follow-up response.

Patient no.	Age Years	Sex	Diagnosis	Concomitant disease	N therapies	Adverse event			
						Name	Intensity	Duration Days	Most probable cause*
1	7	f	Acute tonsillitis	Purulent rhinitis	4	Nasal congestion	Mild	<1	Intercurrent illness
2	0	m	Acute otitis media	No	7	Condition aggravated, fever	Mild	1	Primary illness
3	23	f	Acute pharyngitis	No	2	Self-criticism	Mild	2	Other
4	45	f	Acute URI unspecified	Dust mite allergy	6	Nausea	Mild	4	Primary or intercurrent illness
5	8	m	Acute tonsillitis	No	4	Cramp abdominal, vomiting	Mild	<1	Primary Illness (mesenterial adenitis)
						Abdominal pain	Mild	<26	
6	**2**	**m**	**Acute pharyngitis**	**No**	**4**	**Diarrhea**	**Mild**	**1**	**Concomitant medication (ivy leaf extract)**
7	**6**	**m**	**Bronchitis**	**Atopic dermatitis**	**8**	**Eyelid edema**	**Mild**	**3**	**Concomitant medication (sodium cromoglycate and/or salbutamol)**
8	1	f	Acute laryngitis and tracheitis	No	3	Restlessness at night	Mild	8	Primary illness
9	1	m	Acute otitis media	No	6	Facial rash	Mild	<7	Intercurrent illness
10	**40**	**f**	**Acute sinusitis**	**No**	**3**	**Gastro-intestinal disorder NOS**	**Mild**	**8**	**Concomitant medication (myrtol)**
11	8	m	Bronchitis	Atopic dermatitis	2	Restlessness	Mild	8	Primary illness
12	39	f	Acute tonsillitis	No	3	Rash	Mild	7	Primary illness
13	53	f	Acute laryngitis and tracheitis	No	2	Mouth dry	Mild	4	Primary or intercurrent illness
14	32	f	Acute tonsillitis	No	0	Abdominal pain	Mild	<1	Primary or intercurrent illness
15	**39**	**f**	**Broncho-pneumonia**	**No**	**3**	**Sleep difficult**	**Severe**	**2**	**Pneumodoron® 2 Liquid, Weleda****
16	**14**	**m**	**Acute tonsillitis**	**No**	**6**	**Injection site swelling and redness**	**Mild**	**1**	**Prunus Spinosa 5% Injection, Weleda****

(Continued)

17	35	f	Acute naso-pharyngitis (common cold)	No	5	Dry lips	Mild	4	Primary illness
18	29	m	Acute tonsillitis	No	3	Concentration impaired, feeling bad, urine abnormal	Mode-rate	5	Primary illness
19	5	f	Bronchitis	Asthma	5	Increased bowel movements	Mild	11	Primary or intercurrent illness

N therapies: Number of different medications or non-medication therapies used between study entry and end of the AE (all patients except no. 14 used anthroposophic medications between study entry and end of AE). Confirmed adverse drug reactions in bold types. *Most probable cause was classified by the authors; other items were documented by physicians and patients.
**See Table 5.

study took place, these would have been patients not prescribed AMED, which would not affect the present analysis.

A limitation of our safety analysis is its restriction to AEs reported by patients as having a possible or probable causal relationship to any medication. Unidentified ADR could be present among the other AEs. However, inspection of these AEs suggests that in the overwhelming majority of cases they were symptoms of primary disease or intercurrent illness.

In the safety analysis, AEs were classified as "confirmed ADR" (probable/possible relationship to a medication) or "not confirmed ADR" (improbable/no relationship/unable to evaluate). False-negative classifications (true ADR is not confirmed) are unlikely, since for all medication for which an ADR was not confirmed, there was either no rational temporal relationship to the AE, or another cause (primary or intercurrent illness or another medication) was much more likely. However, false-positive classifications cannot be ruled out; the three "confirmed ADR" to non-AM medication might instead be symptoms of primary or intercurrent illness.

Implication for research

Classification of causal relationship between medication and AEs

In this study most AEs were disease symptoms and other subjective symptoms of 1–7 days' duration. Thus a major challenge of the safety analysis was to distinguish between true ADR and symptoms of primary or intercurrent illness. For example, in 13 analyzed patients the AE started the same day as the medication was first taken or within the following 1–2 days, suggesting a "rational temporal relationship to the time of intake of the medication" (Table 1). However, if the AE is a symptom of the primary disease for which treatment is sought, a temporal relationship between beginning of treatment and beginning of the AE does not in itself indicate a causal relationship between the treatment and the AE. The same applies to cases where the end of the AE coincided with end of treatment, since AM treatment of respiratory and ear infections is usually applied as long as symptoms persist. These problems will have to be addressed in future safety research into AMED.

Table 5. Confirmed adverse reactions to anthroposophic medications.

Patient No. 15: A woman aged 39 with bronchopneumonia (including severe cough, very severe hemoptysis, moderate shortness of breath, moderate expiratory wheezing, severe sputum expectoration, moderate pain with coughing or breathing, severe discomfort, and fever < 39.5 °C) was treated with three AMED (Pneumodoron® 1 Liquid 10 drops hourly, Pneumodoron® 2 Liquid 10 drops hourly, Tabulettae calcarea cum ferro three times daily) and quark compresses twice daily. The first two subsequent nights she experienced severe sleeplessness which subsided after she stopped taking Pneumodoron® 2 at night. Another possible explanation for this AE is severe illness present at study entry. She has however taken Pneumodoron® 2 once after the study upon which she experienced sleeplessness which again subsided after stopping taking Pneumodoron® 2 at night. Pneumodoron® 2 (10 g = 11.1 ml contains: Phosphorus D4 1 g, Tartarus stibiatus D2 1g) was classified as the most probable cause of the AE but her bronchopneumonia may have contributed to the intensity of the AE. According to the manufacturer's information, this AE can be expected from Pneumodoron® 2 in sensitive individuals, but has not been previously reported.
Patient No. 16: A 14-year old boy with acute tonsillitis was treated with daily subcutaneous injections of Prunus spinosa, Summitates 5% and three further AMED and developed mild swelling and redness at the injection site. The reaction was observed after the first injection and subsided after subsequent dose reduction of Prunus (the dose of the other three AMED was not reduced). This ADR has not been reported to the manufacturer previously, but has been observed repeatedly in other patients by the boy's physician.

Prescription profile of AMED—implications for safety research

A striking finding of this study is the broad prescription profile of AMED: 715 patients were prescribed altogether 265 different AMED; 53 AMED were prescribed to at least 10 patients each. Safety analysis assessed AMED as a single package: 2.7% (19/715) of patients reported AEs suspected to be ADR and 0.3% (2/715) of patients had confirmed ADR to AMED.

A conventional approach, assessing safety of individual AMED would not have been possible: To detect ADR from a single medication in a hypothetical frequency of 1% with sufficient power, at least 500 patients per medication are needed. To detect ADR from the 53 most common AMED with a frequency of 0.3% (as in this analysis), a sample size of approximately 90,000 patients would be required. If 2.7% of patients report AEs suspected to be ADR (as here), a study of this size would necessitate examining more than 2,000 AEs. This task would, if performed as in the present analysis, hardly be feasible. Therefore, safety studies of AMED for indications with broad prescription profiles will generally have to assess AMED as a package rather than as single medications.

Implications for risk-benefit assessment

For most individual AMED, scientific evidence of effectiveness is limited. This study evaluated the effectiveness and safety of AM treatment (265 individual AMED, adjunctive non-AM medication, and adjunctive non-medication therapies) of respiratory and ear infections (Hamre et al. 2005).

Using a conventional approach, focusing on each of the 265 individual AMED, a benefit-risk assessment would not have been possible: Effectiveness was not proven for any individual AMED (the study was not designed for this purpose) and ADR from two AMED were found, leading to a negative benefit-risk profile for two AMED and inconclusive data for the remaining 263 AMED. Instead, all AM treatment was analyzed as one therapy package, thus a benefit-risk assessment in comparison to conventional treatment was possible.

A broad AMED prescription profile is typical not only for respiratory and ear infections but for many other indications (Husemann and Wolff 1987; Ritchie et al. 2001). Therefore, therapy package evaluation will probably have an important role in future benefit-risk assessments of AMED.

Implications for practice

Safety of AM

This study of acute respiratory and ear infections demonstrated an excellent safety profile, both for comprehensive AM treatment (ADR in 0.7% of patients and 0.03% of applications with a median duration two days; severe intensity ADR in 0.1% of patients and 0.003% of applications) and for AMED (ADR in 0.3% of patients and 0.004% of

applications; severe intensity ADR in 0.1% of patients and 0.003% of applications).

Comparative risk-benefit assessment

In the primary analysis of this study (Hamre et al. 2005), AM treatment had a significantly lower frequency of reported ADR (2.7%, n = 19/715 patients) than conventional (C-) treatment (6.0%, n = 18/301) (Fisher's exact test, 2-tailed, $p = 0.0157$). For practical reasons, the present more precise secondary safety analysis was restricted to A-patients, confirming ADR in 0.7% (5/715) of A-patients. In C-patients the frequency of confirmable ADR may be between 0/301 and 18/301. At both ends of this range, this frequency will not be lower but will either be comparable to ($p = 0.3295$) or significantly higher ($p < 0.00005$) than the frequency in A-patients. In other words: AM had comparable or lower risk than conventional treatment. Since AM had more favorable clinical outcomes, AM had a more favorable benefit-risk profile than conventional treatment.

Conclusion

In this prospective study of 715 outpatients with acute respiratory and ear infections, we found a low frequency of ADR and no serious ADR to AMED. Study results suggest that short-term AMED therapy for acute respiratory and ear infections is well tolerated.

Acknowledgments

This analysis was funded by grants from Weleda and Wala. The sponsors had no influence on study design or planning; on the collection, analysis, or interpretation of data; on the writing of the manuscript; or on the decision to submit the manuscript for publication. We thank Peter Vögele, Wala and Jasmin Peschke, Weleda for providing safety data on AMED, and Gunver S. Kienle and Wilfried Tröger for valuable help and advice. Our special thanks go to the study physicians and their patients for participating. *Conflict of interest:* All authors declare that they have no conflicts of interest.

References

Hamre, H.J., Fischer, M., Heger, M. et al. 2005. Anthroposophic vs. conventional therapy of acute respiratory and ear infections: a prospective outcomes study. *Wien Klin Wochenschr.*, 117:256–68.

Hamre, H.J., Witt, C.M., Glockmann, A. et al. 2006. Use and safety of anthroposophic medications in chronic disease: a 2-year prospective analysis. *Drug Saf.*, 29:1173–89.

Husemann, F. and Wolff, O. 1987. The anthroposophical approach to medicine. Volume 2. London: Rudolf Steiner Press.

IAAP. 2005. Anthroposophic Pharmaceutical Codex APC. Dornach: The International Association of Anthroposophic Pharmacists.

Kienle, G.S., Kiene, H. and Albonico, H.U. 2006. Anthroposophic medicine: effectiveness, utility, costs, safety. Stuttgart, New York: Schattauer Verlag.

Ritchie, J., Wilkinson, J., Gantley, M. et al. 2001. A model of integrated primary care: anthroposophic medicine. London: Department of General Practice and Primary Care, St Bartholomew's and the Royal London School of Medicine and Dentistry, Queen Mary University of London.

Steiner, R. and Wegman, I. 2000. Extending practical medicine. Fundamental principles based on the science of the spirit. GA 27. Bristol: Rudolf Steiner Press.