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A controlled multi-centre study of herbal versus synthetic secretolytic drugs for acute bronchitis

E. Ernst[1], R. März[2], Ch. Sieder[2]

[1] Department of Complementary Medicine Postgraduate Medical School, UR
[2] Plantamed Arzneimittel, Preclinical Research, Germany

Summary

Herbal expectorants and secretolytic drugs hold a sizeable share of the European market. Therefore it is essential to test their clinical effectiveness and safety. The aim of the present study was to compare the herbal medication Bronchipret® with various other pharmacotherapeutical options for acute bronchitis. The study was designed as a matched-pair comparison of 7783 patients. Clinical outcomes of bronchitis and adverse reactions were documented. The data were evaluated by comparing the treatment success of the test medication and 3 control groups using ordinal regression. The results suggest that clinical effectiveness of Bronchipret® was not less than with synthetic drugs. There was a tendency for better results with Bronchipret®, particularly in the treatment of adults. Similar results were obtained with respect to adverse reactions. Particularly in the adult sub-group, these were markedly less with herbals as compared to synthetic drugs. These findings imply that a risk/benefit evaluation would favour Bronchipret® over synthetic drugs for acute bronchitis. Their interpretation is limited through the fact that this study could not be randomised nor blinded. The results therefore require confirmation through randomised, double-blind trials.

Key words: controlled multi-centre study. Herbal medicine (Bronchipret®), acute bronchitis.

Introduction

Acute bronchitis lists amongst the most frequent conditions in primary care (De Lozier et al., 1989). Viruses and bacteria are implicated in its etiology. When bacterial infections are suspected, antibiotics are commonly used (Verheij et al., 1989, Ellner, 1988). When viral infections are implicated, antiviral drugs can be considered (Am Acad Pediat Committee on Infectious Disease, 1993). In practice, the identification of a specific causative agent is, however, often difficult or impossible (Verheij, 1989, Gwaltney, 1990). For severely ill patients, steroids or beta-antagonists may be an option (Everard, 1996). In less serious cases with a productive cough, cough suppressants have been advocated (Gwaltney, 1990). Considerable controversy therefore persists over the treatment of choice (Everard, 1996, Dere 1992).

About 30% of all antibiotic prescriptions are for acute bronchitis (Col et al., 1987, Davey et al., 1992, Townsend et al., 1979). The resulting costs are impressive: in the US, an estimated 200–300 million dollars are incurred each year (Orr et al., 1993). In addition, the indirect expenditure, e.g. absenteeism, lost productivity etc., should be accounted fore. The socio-economic relevance of bronchitis and its treatment is therefore considerable.

Since treatment options are of debatable value, costly and burdened with adverse effects (e.g. Am Acad Pediat Committee on Infectious Disease, 1993, Dere 1992, Orr et al., 1993) a safe, effective and inexpensive therapy would be welcome. This study tests the hypothesis that herbal expectorants constitute a viable treatment option for acute bronchitis.

Material and Methods

TLC- and GC-Fingerprint analysis of Bronchipret®

Bronchipret film coated tablets
1 film coated tablet contains: 60 mg dried extract of Primulae radix (6,0–7,0:1; extractant ethanol 47,4% v/v); 160 mg dried extract of Thymi herba (5,9–10,0:1; extractant: ethanol 70% v/v)

The content of primula acids in the dragees was checked by a TLC-method:

Stationary phase:	silica gel 60 (Merck)
Mobile phase:	upper phase of the mixture: 1-Butanol:water:acetic acid = 100:80:20
Detection:	Anisaldehyd Reagent R
Rf of primula acid:	0,2–0,3
Reference compound:	Primula acid – Na salt, Roth, Art. No 1–7112
Concentration of Reference:	2 mg primula acid in 10 ml methanol

The content of terpenoids was checked by the following GC-method:

Apparatus:	HP 5890/FID
Column:	HP-Innowax (crosslinked PEG) 50 m × 02 µm × 0,2 mm
Split ratio:	1:80
Injector temperature:	220 °C
Detector temperature:	250 °C
Flow rate (N2):	ca. 1 ml/min
Temperature program:	80 °C–220 °C
Injection volume:	1 µl

Clinical Study

A controlled, multi-centre, post-marketing surveillance study was conducted with 771 German general physicians participating. All doctors were asked to match patients in "lots" of 5 each, one group receiving Bronchipret® tablets and another group receiving any other secretolytic drug which the practitioner felt was indicated (Table 1). These "lots" of patients were mateched as closely as possible according to age, gender and severity of disease. All patients

Table 1. Drugs prescribed.

Trade name	Constituents	Sample size	
		Children	Adults
• Bronchipret®	Extracts of thyme, extracts of primula	1490	3139
• Other herbals*			
Bronchoforton	Oil of eucalyptus, anis, peppermint	14	–
Hedelix	Ivy extract	32	8
Prospan	Ivy extract	73	16
Sinupret	Rad. Gentianae, Flos Primulae cum calycibus, Herba Rumicis, Flos Sambuci, Herba Verbenae	45	92
Soledum	Extract of thyme	–	21
• Synthetic drugs			
NAC		299	1044
Ambroxol		479	590

* all preparations listed under "other herbals" were pooled into 1 treatment group.

Table 2. Demographic data of children and adults and of sub-groups.

	Children treated with				
	Bronchipret® (n = 1490)	Ambroxol (n = 479)	NAC (n = 299)	Other herbals (n = 207)	Total
Average age	5.7 ± 2.9	5.7 ± 2.9	6.6 ± 2.5	5.5 ± 3.2	5.8 ± 2.9
% females	49.2	46.5	44.2	53.1	48.3
Body weight (kg)	23.6 ± 11.0	23.4 ± 10.0	26.2 ± 11.1	21.3 ± 10.4	23.7 ± 10.8
Body height (cm)	116.7 ± 20.1	116.4 ± 21.3	123.3 ± 20.2	111.2 ± 23.3	117.0 ± 21.3
% smokers (parents)	3.7	4.7	6.7	6.2	4.4
	Adults treated with				
	Bronchipret® (n = 3139)	Ambroxol (n = 590)	NAC (n = 1044)	Other herbals (n = 183)	Total
Average age	40.9 ± 18.6	41.4 ± 19.1	43.5 ± 18.7	39.1 ± 18.6	41.6 ± 18.7
% females	55.1	52.6	51.6	60.5	54.2
Body weight (kg)	69.7 ± 14.4	69.8 ± 13.6	71.0 ± 12.4	67.3 ± 13.1	70.0 ± 13.8
Body height (cm)	169.5 ± 9.3	169.6 ± 9.0	170.6 ± 8.9	168.3 ± 10.0	169.8 ± 9.2
% smokers	29.9	28.8	32.5	24.0	30.0

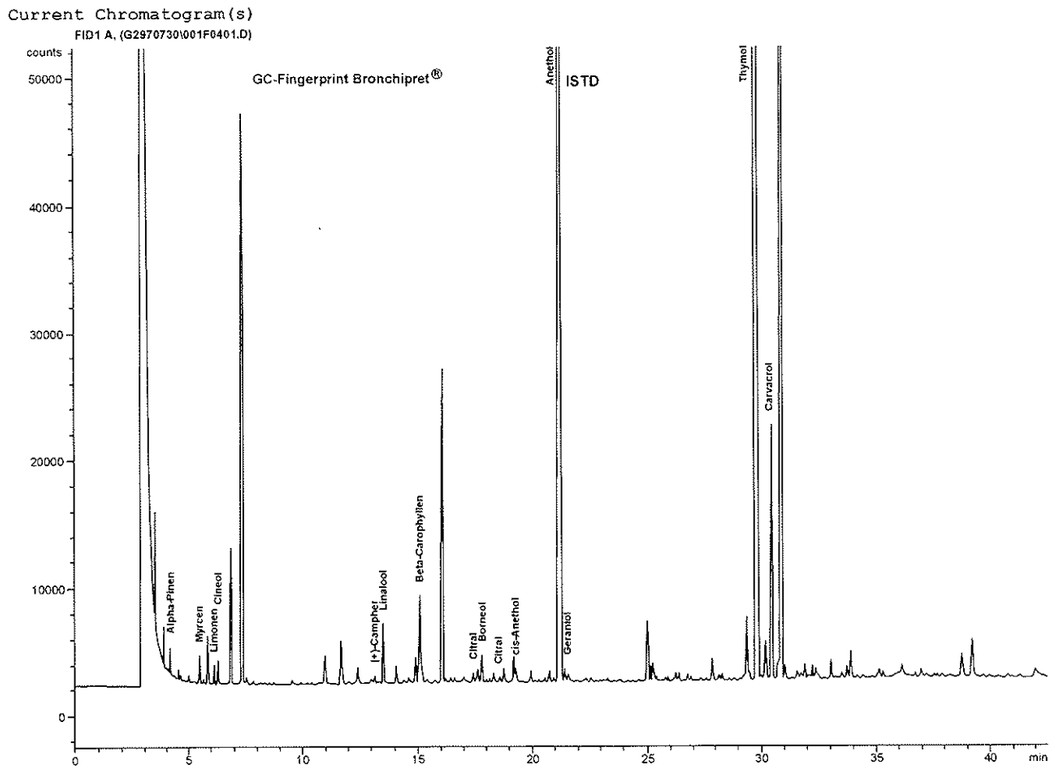

Fig. 1. Print of window 38: Current Chromatogram(s).

gave informed consent and had to suffer from acute bronchitis as diagnosed clinically. Patients on bronchodilators were excluded. Patients who were treated with a remedy not prescribed frequently enough to constitute a subgroup sizeable enough for a meaningful statistical analysis were exluded from the present analysis (see below).

Two major age groups had been pre-defined: patients younger than 12 years and patients twelve years or older. Within each age group, four further subgroups were formed according to treatments received. Three of these treatment groups were selected retrospectively for those drugs being administered in numbers large enough for a meaningful statistical evaluation: a) Ambroxol, b) N-Acetylcysteine (NAC), c) other herbals (= herbal preparations other than Bronchipret®). Figure 2 schematically outlines the study design. Table 2 summarises the demographic data for all subgroups. At their first visit, patients received a thorough physical examination and were prescribed either Bronchipret® (in 50% of the cases) or other secretolytic drugs chosen ad libitum (in the other 50% of the cases). All patients were seen again after 10 days and re-assessed by the same physician according to the same criteria. These

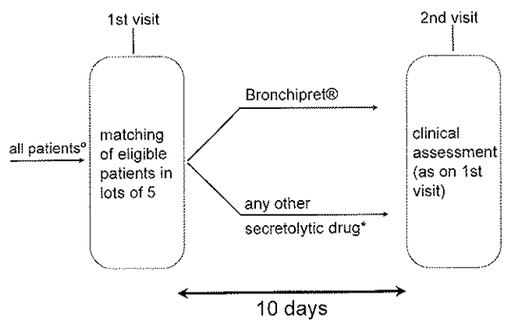

Fig. 2. Schematic outline of study design.
° according to the protocol of the trial, two age groups were differentiated.
* this group was later (post hoc) subdivided according to medications prescribed

Table 3. Clinical endpoints used for assessment.

Parameter	Method[x]
body temperature	sublingual thermometer, applied by patient
auscultation	by physician
auscultation during coughing	by physician
coughing during daytime	assessed by patient
coughing during the night	assessed by patient
pain during coughing	assessed by patient
quality of cough	assessed by patient
quantity of sputum	assessed by patient
viscosity of sputum	assessed by patient
patient judgement	assessed by patient

[x] except for body temperature, all parameters were assessed on a 3 point rating scale

pre-defined criteria for clinical evaluation are listed in Table 3. For each criterion, the treatment success was quantified on a 4-point-scale by comparing the pre- and the post-treatment ratings: 1) symptom free, 2) symptoms improved, 3) symptoms unchanged, 4) symptoms deteriorated. An overall score was calculated as an average of the success ratings of each symptom. This score and the patients' judgement can be interpreted as an (subjective and objective) indicator of the patients' condition.

Adverse drug reactions (ADRs) were monitored by specifically asking patients about side-effects and indicating the likelihood (as judged by the physician) of a causal relationship with the medication prescribed. Each participating physician entered these ADRs into the evaluation sheets ac-

Table 4. Results obtained in adults. Odds ratios of treatment success control: Bronchipret® and 95% confidence intervals.

parameter	control medication					
	Ambroxol		NAC		Herbals	
	OR	CI	OR	CI	OR	CI
body temperature	0.79	(0.62–1.02)	0.79	(0.65–0.97)	1.41	(0.82–2.4)
auscultation	0.53	(0.41–0.68)	0.58	(0.47–0.71)	0.79	(0.47–1.32)
auscultation during coughing	0.48	(0.38–0.61)	0.55	(0.45–0.66)	0.81	(0.51–1.3)
coughing during the day	0.51	(0.43–0.6)	0.56	(0.49–0.64)	0.63	(0.47–0.84)
coughing during the night	0.53	(0.45–0.63)	0.54	(0.47–0.62)	0.66	(0.49–0.89)
pain while coughing	0.55	(0.34–0.87)	0.51	(0.35–0.74)	2.04	(0.49–8.38)
quality of cough	0.79	(0.67–0.94)	0.74	(0.64–0.85)	0.97	(0.72–1.31)
quantity of sputum	0.69	(0.58–0.82)	0.79	(0.69–0.9)	0.77	(0.57–1.05)
viscosity of sputum	0.60	(0.49–0.74)	0.67	(0.57–0.8)	0.50	(0.34–0.73)
quality of sputum	0.68	(0.53–0.87)	0.71	(0.58–0.87)	0.57	(0.35–0.92)
overall score	0.49	(0.42–0.58)	0.52	(0.46–0.60)	0.81	(0.62–1.07)
patient's judgement	0.40	(0.34–0.48)	0.45	(0.39–0.52)	0.70	(0.52–0.95)

Sample size: Bronchipret®: n = 3094; Ambroxol: n = 585; NAC: n = 1029; herbals: n = 179
Legend: OR<1: Bronchipret® better OR=1: no difference OR>1: control better

Table 5. Results obtained in children. Odds ratio of treatment success control: Bronchipret® and 95% confidence intervals.

parameter	control medication					
	Ambroxol		NAC		Herbals	
	OR	CI	OR	CI	OR	CI
body temperature	0.94	(0.74–121)	0.92	(0.68–1.25)	0.80	(0.55–1.17)
auscultation	1.23	(0.87–1.75)	0.89	(0.61–1.31)	0.90	(0.56–1.46)
auscultation during coughing	1.26	(0.88–1.81)	0.62	(0.43–0.88)	0.80	(0.5–1.28)
coughing during the day	0.85	(0.7–1.04)	0.88	(0.7–1.12)	0.78	(0.59–1.04)
coughing during the night	1.04	(0.85–1.28)	0.91	(0.71–1.16)	0.83	(0.62–1.11)
pain while coughing	0.61	(0.29–1.28)	1.24	(0.42–3.67)	0.40	(0.15–1.03)
quality of cough	1.16	(0.95–1.42)	1.08	(0.84–1.38)	0.92	(0.68–1.25)
quantity of sputum	0.71	(0.55–0.91)	1.05	(0.78–1.4)	0.81	(0.56–1.16)
viscosity of sputum	0.70	(0.52–0.94)	1.04	(0.72–1.5)	0.84	(0.54–1.32)
quality of sputum	0.65	(0.43–0.98)	0.83	(0.52–1.31)	1.00	(0.54–1.86)
overall score	0.80	(0.67–0.97)	0.84	(0.67–1.06)	0.92	(0.70–1.20)
patient's judgement	0.75	(0.61–0.92)	0.68	(0.53–0.86)	0.52	(0.39–0.7)

Sample size: Bronchipret®: n = 1444; Ambroxol: n = 470; NAC: n = 297; herbals: n = 195
Legend: OR<1: Bronchipret® better OR=1: no difference OR>1: control better

cording to the WHO Adverse Reaction Dictionary (Version of 22. 2. 1994).

The statistical analyses were performed by ordinal regression of the success ratings with respect to the treatment group. Odds ratios and their confidence intervals were calculated according to the Proportional Odds Model (McCullagh 1980) to compare the success probabilities of the Bronchipret®-group to the respective reference groups. The results of the statistical analyses should be interpreted as exploratory.

Results

7,783 complete data sets were available and considered for analysis. A comparison of the sub-groups at baseline shows that few inter-group differences existed in any of the outcome variables. In the sub-group of children treated with NAC, symptoms were marginally less severe at entry. The other sub-groups were fully comparable.

Table 4 summarises the odds ratios relating to each variable for the adult groups and Table 5 for the children

Table 6. ADRs according to WHO System Organ Class Adults.

	n	Gastro-intestinal System		Skin and Appendages		Psychiatric		Centr.&Per. Nerv. System		Respiratory System		Total	
		ADRs	%	ADRs	%	ADRs	%	ADRs	%	ADRs	%	ADRs	%
Bronchipret													
monotherapy	1917	7	0.37	1	0.05	0	0.00	0	0.00	1	0.05	9	0.47
comb. therapy	1223	8	0.65	1	0.08	0	0.00	1	0.08	1	0.08	11	0.90
Total	3140	15	0.48	2	0.06	0	0.00	1	0.03	2	0.06	20	0.64
Ambroxol													
monotherapy	306	2	0.65	0	0.00	0	0.00	0	0.00	0	0.00	2	0.65
comb. therapy	284	7	2.46	0	0.00	1	035	0	0.00	0	0.00	8	2.82
Total	590	9	1.53	0	0.00	1	0.17	0	0.00	0	0.00	10	1.69
NAC													
monotherapy	582	16	2.75	0	0.00	0	0.00	0	0.00	0	0.00	16	2.75
comb. therapy	464	12	2.59	2	0.43	0	0.00	1	0.22	0	0.00	15	3.23
Total	1046	28	2.68	2	0.19	0	0.00	1	0.10	0	0.00	31	2.96
Herbals													
monotherapy	103	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
comb. therapy	80	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total	183	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Table 7. ADRs according to WHO System Organ Class Children under 12 Yrs.

	n	Gastrointestinal System		Dermatologic		Psychiatric		Total	
		ADRs	%	ADRs	%	ADRs	%	ADRs	%
Bronchipret									
monotherapy	939	2	0.21	3	0.32	0	0.00	5	0.53
comb. therapy	551	4	0.73	0	0.00	0	0.00	4	0.73
Total	1490	6	0.40	3	0.20	0	0.00	9	0.60
Ambroxol									
monotherapy	299	1	0.33	0	0.00	0	0.00	1	0.33
comb. therapy	180	1	0.56	0	0.00	0	0.00	1	0.56
Total	479	2	0.42	0	0.00	0	0.00	2	0.42
NAC									
monotherapy	181	3	1.66	1	0.55	0	0.00	4	2.21
comb. therapy	118	5	4.24	0	0.00	0	0.00	5	4.24
Total	299	8	2.68	1	0.33	0	0.00	9	3.01
Herbals									
monotherapy	134	0	0.00	0	0.00	1	0.75	1	0.75
comb. therapy	73	1	1.37	0	0.00	0	0.00	1	1.37
Total	207	1	0.48	0	0.00	1	0.48	2	0.97

groups. These odds ratios depict the likelihood of therapeutic success; the lower a given odds ratio, the lower the probability for a patient on control medication to profit from treatment compared to a patient on Bronchipret®. An odds ratio of 0.5, for instance, would indicate a 50% higher chance for someone on Bronchipret® to symptomatically improve compared to the reference medication.

The odds ratios in Table 4 imply that Bronchipret® is, on average, superior to the three control medications. In particular the two summary scores suggest a substantially greater therapeutic benefit from Bronchipret® compared to the reference medications. Table 5 shows a similar situation for children. Again, Bronchipret® is, on average, more effective than the control medications. The superiority of Bronchipret® is, however, less pronounced in children compared to adults.

Table 6 and 7 depict the ADRs in adults and children. Overall, ADRs are rare. Across all treatment groups, ADRs are more frequent when more than one drug was administered. In adults, no ADRs were observed for herbals other than Bronchipret®. For Bronchipret®, the ADR rate was well below 1% and superior to the two other treatment groups (Table 6). For children (Table 7), both herbal groups yield ADR rates well below 1%.

Discussion

Placebo-controlled trials have previously demonstrated the efficacy of NAC (Ventresca et al., 1989) and Ambroxol (Zavattini et al., 1989) in the treatment of acute bronchitis. For Bronchipret® no placebo-controlled studies are available. The present findings suggest that Bronchipret® is a safe and effective treatment of acute bronchitis in children and (even more so) in adults. The effectiveness of Bronchipret® is best borne out by the overall score summarising all the symptoms and signs evaluated as well as by the patients' judgement. The latter is regularly more favourable reflecting the subjective nature of this variable.

No accepted, validated instrument exists to objectively assess symptomatic improvement in bronchitis based on clinical signs. The score used for this study might therefore represent a pragmatic option for future investigation. It would, however, require formal validation. The fact that the score is as yet not validated represents a serious drawback of the present study.

The two constituents of Bronchipret® both have a positive monograph from the German "Kommission E" (Monograpie, 1984, Monographie, 1988). According to these documents, the indication for thymi herba is "symptoms of bronchitis" and for primulae radis "catarrh of the respiratory system". Primula contains triterpensaponines, phenylglycosides and salicylic acid derivates while thyme is characterised by flavonoids and essential oils (Hänsel et al., 1993). The pharmacological profile of this combination encompasses secretolytic activity (primula) and anti-inflammatory, anti-bacterial, anti-viral as well as bronchiospasmolytic properties (thyme) (Hänsel et al., 1993). Thus the usefulness of Bronchipret® as a remedy for acute bronchitis has a scientific rationale.

The rate of ADRs observed in this study is generally low. Our results confirm that herbal secretolytic drugs have advantages over synthetic drugs in terms of safety (Ernst et al., 1995). The most frequent ADRs relate to the gastrointestinal system and are seen with all drugs investigated. These symptoms are benign and rarely require discontinuation of therapy. These data also confirm the low toxicological risk as demonstrated in appropriate models (Hänsel et al., 1993).

The trial methodology used for this investigation is innovative. In terms of scientific rigor, it goes beyond a simple post-marketing surveillance study: it includes a control group. Thus the results relating to safety and effectiveness become more reliable. A further advantage is the fact that large patient numbers can be included lending more weight to the results. An obvious disadvantage is the lack of randomisation. Randomisation was not incorporated for legal and logistic reasons. To minimise attribution bias, a matched pair procedure was used instead. Even though not entirely free of potential for (sponsor) bias, this study design represents an improvement to post-marketing surveillance studies and might be considered for future, similar investigations.

In conclusion, this study suggests that Bronchipret® is a safe and effective form of symptomatic treatment for acute bronchitis. The findings, however, require confirmation in a randomised clinical trial.

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Address

E. Ernst, Department of Complementary Medicine Postgraduate Medical School, 25 Victoria Park Road, Exeter, EX2 4NT, UK

Tel.: 0044 1392 43080; Fax: 0044 1392 424989; e-mail: E.Ernst@exeter.ac.uk