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Therapeutic Use, Efficiency and Safety of the Proteolytic Pineapple Enzyme Bromelain-POS® in Children with Acute Sinusitis in Germany

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Abstract. *The therapeutic efficiency and safety of the proteolytic enzyme bromelaine obtained from pineapple (Bromelain-POS®, Ursapharm GmbH, Saarbrücken, Germany) was evaluated in children under the age of 11 years diagnosed with acute sinusitis. Data from 116 patients from 19 centres located across Germany were analysed in a pharmacoepidemiological cohort study. Patient cohorts were either treated with Bromelain-POS® (N=62), in combination with Bromelain-POS® and standard therapies (N=34), or with standard therapies (N=20). The primary parameter measuring effectiveness of the different treatment groups was the duration of symptoms. The shortest mean period of symptoms was observed in patients treated with Bromelain-POS® alone (6.66 days), followed by the standard therapy (7.95 days) and those treated with a combination of Bromelain-POS® and the standard therapy (9.06 days). Patients of the Bromelain-POS® monotherapy group showed a statistically significant faster recovery from symptoms ($p=0.005$) compared to the other treatment groups. One 10-year-old male patient, with a known pineapple allergy, showed a self-limiting mild allergic reaction. No other unwanted side-effects were reported. This trial documents that the proteolytic pineapple enzyme Bromelain-POS® is widely used in the treatment of young children diagnosed with acute sinusitis in Germany and that the use of proteolytic enzymes can benefit such patients.*

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Infections of the nose involve the sinuses because the mucosal lining of the nose and the paranasal sinuses are continuous. Acute sinusitis usually follows a cold and presents with nasal obstruction, facial pain, dental pain, purulent rhinorrhea, sinus tenderness and, in some cases, fever and malaise (1-3). The diagnosis is made on the history, the patient's lack of response to topical decongestants, and on finding pus in the nose with associated sinus tenderness. Treatment consists of combining topical or systemic decongestants with saline irrigations and an antibiotic, usually amoxycillin. Referral to a specialist should be considered if patients fail to respond to second-line antibiotic therapy and for those who get recurrent episodes of sinusitis (4).

Plant bromelaine is obtained from the stem of the pineapple (*Ananas commosum* L.). Sequencing of the plant cysteine endoproteinases bromelaine and papain demonstrated that both are members of the papain family (5). Raw stem bromelaine consists of at least 3 immunologically distinct proteases: stem bromelaine, fruit bromelaine and ananin (6). High performance liquid cation exchange chromatography characterized as many as 9 proteolytic active components in raw stem bromelaine (7). Scientific evaluations are currently being performed to demonstrate the medical/clinical relevance of those bromelaine components.

The objectives of this clinical trial were: i) to detect differences in the duration of symptoms between children treated with the proteolytic enzyme Bromelain-POS®, with a combination therapy of Bromelain-POS® and allopathica, or with allopathica alone; ii) to assess the influence of pain medication on the duration of symptoms; iii) to evaluate the influence of additional respiratory tract infections on the duration of symptoms; iv) and to document side-effects of Bromelain-POS® therapy.

Table I. *Demographic data of children with acute sinusitis treated with Bromelain-POS® (monotherapy verum group), with Bromelain-POS® in addition to allopathica (combination therapy group), and with allopathica (control group).*

		Treatment groups						Total	
		Monotherapy verum group		Combination therapy group		Control group			
		n	(%)	n	(%)	n	(%)	n	(%)
Age group	0 – 2 years	3	(4.8)	2	(5.9)	3	(15.0)	8	(3.9)
	3 – 5 years	11	(17.7)	12	(35.3)	4	(20.0)	27	(23.3)
	6 – 11 years	48	(77.4)	20	(58.8)	13	(65.0)	81	(69.8)
	total	62	(100)	34	(100)	20	(100)	116	(100)
Sex	male	28	(42.2)	18	(52.9)	12	(60.0)	58	(50.0)
	female	34	(54.8)	16	(47.1)	8	(40.0)	58	(50.0)
	total	62	(100)	34	(100)	20	(100)	116	(100)
Ethnic origin	Caucasian	62	(100)	31	(91.2)	19	(95.0)	112	(96.6)
	other			3	(8.8)	1	(5.0)	4	(3.4)
	total	62	(100)	34	(100)	20	(100)	116	(100)
Health insurance	private	12	(19.4)	6	(17.6)	2	(10.0)	20	(17.2)
	public	50	(80.6)	28	(82.4)	18	(90.0)	96	(82.8)
	total	62	(100)	34	(100)	20	(100)	116	(100)

n, number of patients; %, percentage distribution

Table II. *Respiratory tract infections of children with acute sinusitis treated with Bromelain-POS® (monotherapy verum group), with Bromelain-POS® in addition to allopathica (combination therapy group), and with allopathica (control group).*

		Treatment groups						Total	
		Monotherapy verum group		Combination therapy group		Control group			
		n	(%)	n	(%)	n	(%)	n	(%)
Acute sinusitis		60	(96.8)	15	(44.1)	13	(65.0)	88	(75.9)
Acute sinusitis +	other infections	2	(3.2)	19	(55.9)	7	(35.0)	28	(24.1)
	total	62	(100)	34	(100)	20	(100)	116	(100)
Acute sinusitis +	Tonsillitis	0		6	(17.6)	1	(5.0)	7	(6.0)
Acute sinusitis +	Bronchitis	0		9	(26.5)	5	(25.0)	14	(12.1)
Acute sinusitis +	Otitis	0		10	(29.4)	2	(10.0)	12	(10.3)
Acute sinusitis +	viral infections	2	(3.2)	0		1	(5.0)	3	(2.6)

n, number of patients; %, percentage distribution

Materials and Methods

Trial design. A GEP (good-epidemiological practice) study based on the design of a multicentric, epidemiological cohort analysis was used to assess the use, safety and efficiency of Bromelain-POS® (a standardized proteolytic enzyme preparation from the pineapple, *Ananas comosum* L. containing 500 FIP units enzymatic activity per tablet; Ursapharm GmbH, Saarbrücken, Germany) in children with acute sinusitis. Nineteen general practitioners located across Germany took part in the trial. All centres were comparable in relation to age of the medical practitioners, professional qualification, use of diagnostic methods and experience.

Patient cohort. Clinical data from children under 11 years of age, diagnosed with acute sinusitis between January 1998 and March 2003, were identified by the participating practitioners at random and were transferred by them to an anonymous standard case report form (CRF). The CRFs were analysed for completeness, plausability, and 25% of forms were randomly selected and monitored. The documentred demographic data (age, gender, ethnic origin and health insurance provider), symptoms and diagnosis, symptom onset and end, follow-up, therapeutic intervention and duration of therapy were coded and transferred into a database. In addition to the clinical data, the practitioners were asked to report observed side-effects of treatments and

Table III. *Therapeutic regimes of children with acute sinusitis treated with Bromelain-POS® (monotherapy verum group), with Bromelain-POS® in addition to allopathica (combination therapy group), and with allopathica (control group).*

	Treatment groups						Total	
	Monotherapy verum group		Combination therapy group		Control group			
	n	(%)	n	(%)	n	(%)	n	(%)
Antiphlogistica			8	(23.5)	3	(15.0)	11	(9.5)
Antihistaminica			1	(2.9)			1	(0.9)
Topica			7	(20.6)	2	(10.0)	9	(7.8)
Antibiotics			13	(38.2)	6	(30.0)	19	(16.4)
Bromelain-POS®	62	(100)	34	(100)			96	(82.8)
Other proteolytic enzymes					2	(10.0)	2	(1.7)
Analgesica			13	(38.2)	8	(40.0)	21	(18.1)
Physical therapies			15	(44.1)	8	(40.0)	23	(19.8)
Phytotherapy			5	(14.7)	3	(15.0)	8	(6.9)
Homeopathy					1	(5.0)	1	(0.9)
Other therapies			4	(11.8)	7	(35.0)	11	(9.5)

n, number of patients; %, percentage distribution

were able to state the degree of improvement of individual therapy schedules.

Statistical analysis. The anonymous coded clinical data were analysed using SPSS statistical software. The duration of symptoms in days was used to compare differences between treatment groups. Good clinical practice was followed in all parts of the trial.

Results

A multicentric, epidemiological cohort study was used to investigate the safety and efficiency in children with acute sinusitis treated with the proteolytic enzyme Bromelain-POS®, with a combination therapy of Bromelain-POS® and allopathica, or with allopathica alone. The duration of symptoms in days was used as the primary parameter to assess differences between the treatment groups. Overall clinical data from 116 children up to the age of 11 years were used in this trial. All children fulfilled the inclusion criteria. Sixty-two children were treated with Bromelain-POS® (monotherapy verum group), 34 with Bromelain-POS® in addition to allopathica (combination therapy group), and 20 with allopathica (control group).

Demographic data. The demographic data of the therapy groups are shown in Table I. The median ages of patients treated with Bromelain-POS® monotherapy (7.34 years), treated with Bromelain-POS® and allopathica (6.21 years), and patients treated with allopathica alone (7.15 years) ($p=0.147$), or the sex distribution ($p=0.473$) were statistically not different between the therapy groups.

Table IV. *Duration of symptoms (in days) of patients with acute sinusitis treated with Bromelain-POS® (monotherapy verum group), with Bromelain-POS® in addition to allopathica (combination therapy group), and with allopathica (control group).*

	Treatment groups			Total
	Monotherapy verum group	Combination therapy group	Control group	
mean	6.66	9.06	7.95	7.59
standard deviation	1.92	4.97	5.39	3.87
median	6	8	7	7
25. percentile	6	6	5	5
75. percentile	8	10	10	9
minimum	2	2	3	2
maximum	12	24	28	28
number of patients	62	34	20	116

n, number of patients; %, percentage distribution

Respiratory tract infections in combination with acute sinusitis. Statistically significantly fewer patients in the monotherapy verum group (3.2%) suffered from other infections in addition to acute sinusitis ($p<0.001$) (Table II) compared to patients from the combination therapy group (55.9%) or the control group (35.0%).

Therapeutic regime used to treat acute sinusitis. The use of naturopathic or allopathic agents was similar in the combination therapy and control group (Table III). Patients

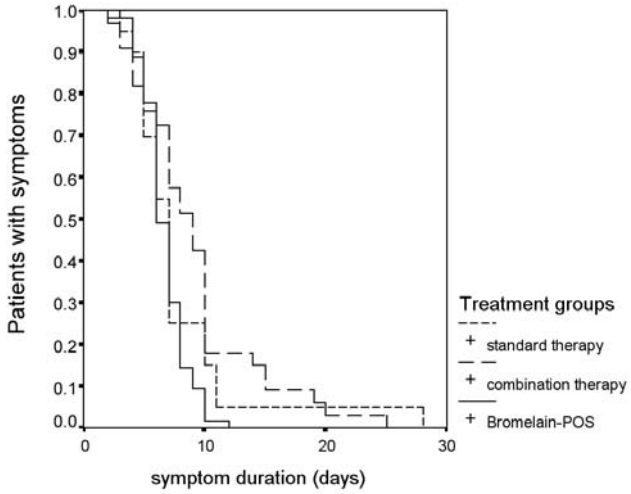

Figure 1. *Duration of symptoms (in days) of patients with acute sinusitis treated with Bromelain-POS® (monotherapy verum group), with Bromelain-POS® in addition to standard therapy (combination therapy group), and with standard therapy (control group).*

of the combination therapy group received, in addition to Bromelain-POS®, mainly physical therapies, analgesica and antibiotics, while patients of the control group were treated with a combination of physical therapies, analgesica, antibiotics and other therapeutic agents (*i.e.* nasal sprays, secretolytica).

Duration of symptoms. The mean duration of symptoms of all patients was 7.59 days (Table IV). There were statistically significant differences between the treatment groups ($p=0.012$). The shortest mean period of symptoms was observed within the monotherapy (verum) group (6.66 days), followed by the control (7.95 days) and the combination therapy groups (9.06 days). Patients of the monotherapy (verum) group showed a statistically significant faster recovery from symptoms ($p=0.005$) compared to the other treatment groups (Figure 1). Other infections, in addition to acute sinusitis or the use of analgesica did not have a statistically significant influence on the duration of symptoms.

Adverse side-effects of Bromelain-POS® therapy. One 10-year-old male patient showed a self-limiting mild allergic reaction and the Bromelain-POS® treatment was continued. An investigation by the physician showed that this patient suffered from a pineapple allergy. No other unwanted side-effects were reported, particularly no cases were reported where Bromelain-POS® therapy altered thrombocyte aggregation or had a negative effect on the pharmacodynamics or pharmacokinetics of other therapies used.

Discussion

Acute sinusitis is a common disease, usually diagnosed by clinical examination. Symptoms comprise nasal obstruction, purulent rhinorrhea, facial pressure and pain, sinus tenderness, and poor response to topical decongestants (8-10).

There are no convincing data on the treatment of acute sinusitis. Common practice includes decongestants that shrink the nasal mucosal oedema and help open the natural ostia of the sinuses and allow re-aeration and muco-ciliary drainage. For example, oxymetazoline 0.5% in the form of a nasal spray gives good mucosal decongestion with symptomatic relief. In addition, irrigation of the nose with normal saline nasal spray has also been found to improve symptomatology and outcome (1). Antihistamines and topical and systemic steroids have not been shown to give any additional benefit. The use of antibiotics to treat suspected cases of acute sinusitis is controversial. Many of the studies have had conflicting results. In general practice it can be difficult to be certain that the patient's symptoms are caused by sinusitis. If the diagnostic criteria are strict, acute bacterial sinusitis should be treated with antibiotics as they are significantly more effective than placebo (11). Most cases of acute sinusitis can be managed by the general practitioner. However, referral should occur if complications develop or if the patient fails to respond to second-line therapy. Referral should also be made for patients with recurrent acute sinusitis.

Plant extracts with a high content of proteolytic enzymes have been abundantly used in traditional medicine in South and Central America (12). Systemic enzyme therapy is currently being studied for defined indications, *e.g.* in infectiology (13). Its therapeutic use is partly based on scientific studies in agreement with evidence-based medicine (EBM), however, it is mostly empirical (12). Currently available enzyme preparations for oral therapy consist of combinations of the animal serine endopeptidases trypsin and chymotrypsin and the plant cysteine endopeptidases bromelaine and papain. Furthermore, bromelaine monotherapy is well established in traumatology and infectiology (14-16).

Evidence-based treatment protocols are rare in paediatrics since randomized controlled trials (RCTs) may raise ethical problems. Accordingly, this pharmacoepidemiological study was designed to evaluate the safety and efficacy of the proteolytic enzyme bromelaine (Bromelain-POS®) in children suffering from acute sinusitis. This type of study is classified as level II EBM and evaluates the treatment results of available and established medications that lack RCT testing.

In this study, children below the age off 11 years and diagnosed with acute sinusitis were enrolled into a study group (bromelaine monotherapy) and control groups (standard therapy; standard therapy plus bromelaine). The

primary aim of this study was to evaluate the duration of symptoms. Children of the study group (bromelaine monotherapy) presented the shortest mean period of symptoms (6.66 days) as compared to those of the control groups (7.95 and 9.06 days for standard therapy and standard therapy plus bromelaine). Furthermore, patients of the bromelaine monotherapy (study) group showed a statistically significant faster recovery time from symptoms ($p<0.005$) compared to the control groups. Thus, bromelaine treatment may be considered to be effective in acute sinusitis to reduce the mean time of symptomatic disease. Besides one mild self-limiting allergic reaction in one child with a known pineapple allergy, no adverse reactions of the bromelaine treatment were documented.

This epidemiological study has shown that bromelaine treatment of children suffering from acute sinusitis may be regarded as safe and beneficial. Further clinical studies on other indications are currently being performed so as to elucidate the clinical/therapeutical efficacy of the plant cysteine endopeptidase bromelaine.

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