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ORIGINAL ARTICLE

Clinical Studies of Linkus Syrup for Efficacy and Safety for the Treatment of Cough, Respiratory Infection in Children

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ABSTRACT

Background: Linkus syrup has been used to maintain healthy respiratory system and soothes throat, exert potent anti-tussive, expectorant and decongestant actions. Different clinical trials on Linkus have been conducted in hospitals to assess the efficacy and safety among adult and children.

Material and Methods: The size of the patients administered Linkus, in these studies are 80 in number. In some clinical trials conducted Linkus was naïve as the drug evaluated where as in others Linkus as test herbal drug was compared with allopathic drugs. Physical Examination: stethoscope observation for wheezing (a whistling or squeaky sound when breathe) or other abnormal sounds.

Diagnostic Tests: exam of the mucus of nose or throat for bacterial infection.

Results: In all children Linkus was given as a test and the (Mucaltin) control group, there was a significant improvement from the day before treatment to the day of treatment. However, the improvement was greater in the test (Linkus) groups for all the main outcome measures. Over all biochemical parameters of blood test dynamics in test and control groups on the background of Linkus syrup 90 ml administrations.

Conclusion: The participating physicians rated the Linkus products higher than the control drug for symptomatic relief of their children cough and overcome the difficulty due to upper respiratory tract infection (URI). Linkus may be a preferable treatment for cough and sleep difficulty associated with childhood URI.

INTRODUCTION

Viral infection is the most common among respiratory infections and antibacterial drugs are ineffective and their excessive administration only worsens the course of infection and lowers natural immunity [1]. Due to this major attention should be paid to symptomatic therapy in treating in viral infections. Cough relief should be considered for the anti-inflammatory expectorant and sputum liquefying, sedative and anti-allergic effects [2]. Therefore, the drug administration is also an important link in general therapy complex in bacterial infection treatment, without it condition's course lengthens up to becoming chronic. The herbal therapy for cough should be effective and safe as well as tolerable and has pleasant organoleptic qualities. Diseases of

respiratory organs are the most important leading to acute respiratory infections. The fever and respiratory tracts catarrh are the leading clinical syndromes of acute respiratory infections. Cough is a frequent and in overwhelming majority of cases an obligatory symptom of the disease. Cough is the protective reflex promoting respiratory tract purification from pathologically changed trachea bronchial secret [3]. The cough leading physiological mechanism of respiratory tracts sanitation is a mucociliar clearance. Respiratory inflammation is accompanied by compensatory increase of mucous formation, at the same time, simultaneously with mucous hyper production there are changes in trachea bronchial secret structure resulting to cough occurrence. However anti-cough administration arises only when cough affects healthy state, but more often it is observed as unproductive, dry, obtrusive cough which is not accompanied by respiratory tracts clearing from accumulated trachea bronchial secrete [4]. Anticough therapy in principle addresses phlegm attenuation, decrease of its sticking to bronchial tubes surface, and thereby, cough and its efficiency strengthening. Hence, anticough therapy efficiency is a cough strengthening under condition of its conversion from dry unproductive cough to damp and productive one. Natural expectorative product is based on the ciliary epithelium activity increase, bronchiole peristalsis strengthening and bronchial glands secretion stimulation [5].

Pharmacological Properties of Linkus Ingredients

Adhatoda vasica: It acts as expectorant, broncholytic, mucolytic and antipyretic. It contains essential oils, vitamins and alkaloids, including Vasicin, Vasicinol and Vasicinon. These highly effective combinations possess mucolytic (reduce density and viscosity of secret), anti-inflammatory, broncholytic (remove spasms of bronchial tubes, facilitate breath) and expectorating (raise cilia mobility and accelerate phlegm emission) action. Besides it possesses anti-asthmatic action and prevents bronchospasm caused by gistamin. Glycyrrhiza glabra: liquefies sputum and facilitates its expulsion, having antiallergic and anaphylactic effects. It contains glycyrrhizin, glycyrrhizin acid salts and other components. They have strong immune potentiating, antioxidant, anti-inflammatory and antiallergic activities. Glycyrrhiza glabra inhibits virus's growth, inactivates virus's particles and stimulates interferon activity. Glycyrrhizin renders powerful inhibiting action on prostaglandin E2, produced by macrophages. Last researches showed, that glycyrrhizic acid derivative also inhibits enzymes which participate in allergic reaction. Hyssopus officinalis: provides antiseptic, anti-inflammatory, anesthetic, antitussive effects, reduces excessive perspiration. It is translated as a sacred grass. It contains diosmine and has strong expectorant, diaphoretic, antiallergic, spasmolytic and diuretic actions. Piper longum exhibited expectorant effect and its active ingredients are piperin and piplartine. It is antibacterial and anti-allergic and tonic. Alpinia galangal (WILD). It is characterized by potent bactericidal effect, anti-inflammatory and expectorant properties. It is used in folk medicine as analgesic, expectorant, stringent in respiratory tract disorders as well as in GIT and mouth cavity inflammations and skin diseases. Alpina galanga is expectorant preparation. It contains essential oils, camphoric, galangin and alpinin Althea officinalis: having expectorant, coating, emollient, anti-inflammatory effects. Zizyphus vulgaris: provides emollient and expectorant effect in throat pains, having sedative and antibacterial effect. Viola odorata is a natural antigistamin preparation. It has antipyretic, sedative and anti-inflammatory actions. It softens cough, removes irritation and promotes fast phlegm emission. Viola odorata: anti-inflammatory, analgesic, expectorant, sedative, antimicrobial, spasmodic effects. Cordia latifolia acts as antiseptic, analgesic and spasmolytic agent.

METHODOLOGY

Linkus Dosage Form Preparation

Linkus manufactured by Herbion Pakistan (Pvt.) Limited and the syrup contains extract of Adhatoda vasica, Glycyrrhiza glabra, Piper longum, Cordia latifolia, Althea officinalis, Zizyphus vulgaris, Onosma bracteatum, Alpinia galangal, Hyssopus officinalis, Viola odorata. Every bottle contains 90 ml of syrup. Syrup is brown with taste and odor of peppermint. Pharmacotherapeutical group of the drug is herbal expectorant. It contains following as accompanying components: Sugar (70%); Glycerin (1%); Sodium Methyl Paraben (0.1%); Propylene glycol (0.01%); Peppermint oil (0.00375 ml); Olive oil (0.00125 ml); Deionized water (10.0 ml). The dosage form design is presented in Table **1**.

Table 1. Linkus dosage regimen for different categories of patients.

Dosages	
Children	1 teaspoon (5 ml), (3-4 times/day), (2 folds less than adults)
Infant (6 months to 1 year)	½ teaspoon (2.5 ml), (3-4 times/day), (2 folds less than children)
Duration of Treatment: The duration of treatment depends upon the severity of upper and lower acute infectious respiratory diseases such as; acute respiratory viral infection, ARVI=7 days, Bronchitis=14 days and Pneumonia = 21 days	

Indications

Linkus indications are anti-inflammatory, antipyretic, expectorant and mucolytic cough syndrome in acute inflammatory diseases of upper and lower respiratory tracts (rhinitis, laryngitis, phyringitis tracheitis, acute and chronic bronchitis, pneumonia), bronchial asthma. Cough syndrome at acute inflammatory diseases of respiratory ways (bronchitis, bronchopneumonia) and bronchial asthma.

Study Design

Open Comparative study.

Clinical Studies on Linkus

Different clinical studies have been conducted by different groups in settings of hospitals in CIS states are delineated herewith.

Studies are approved by Ethics and Pharmacological committees of Children's Health Scientific Centre (RAMS) Moscow, Russia, according to requirement of Qualitative clinical practice children's parents were informed of the studies' objects and tasks as well as signed informed consent developed for the studies. For data systematization and clinical signs observation a questionnaire was developed filled by doctor in charge, the information was also entered in medical file in current order. Obtained data was statistically processed. Eighty children participated in the study aged from 6 months to 3 years; out of them 46 boys and 34 girls. Main diagnosis of all the children was ARVI. All children's condition was estimated as medium severe. Duration of the drug administration was 6 (±2) days. Standard concomitant therapy was administered: intranasal sprays and drops, antihistamine therapy, counter-attracting therapy, percussion drainage and physiotherapy. In a number of cases antibiotics were administered (amoxiclav, amoxicillin, rovamicin).

Linkus used in a complex acute respiratory virus infection (ARVI) treatment scheme has mild expectorant and spasmolytic actions, relieves clinical course of disorder reducing medicinal burden. No allergic reactions were observed during the trials. Thus, the preparation can be recommended for ARVI treatment in young children. Report Pathology characteristics: Infectious and inflammatory disorders of respiratory tract accompanied by cough with hard expelling sputum (on the background of acute respiratory conditions, flu, tracheitis, bronchitis, tracheo-bronchitis, pneumonia and other inflammatory conditions of respiratory tract).

Dosage regimen: Main group – 40 patients. Linkus syrup 90 ml. Control group – 40 patients. Mucaltin tablets 0.05 g. Dissolve a tablet in 1/3 of a glass of warm water, take 3 times a day before meals. In case of insufficient efficacy of the main or control preparation according to doctor in charge opinion they were administered additional drugs including antibiotics (usually if no effect was seen in the 3rd day of the treatment). Prescribed drugs were noted on the back of patient's medical file.

RESULTS

Eighty children, 40 each in test and control with URIs were enrolled and all completed the 7 days study. Forty children received Linkus, where as 40 Mucaltin. The dropout was nil. The median age of the patients completing the study was 21 months (range 06–36 months), with no significant difference in age among the treatment groups (Table **2**, Figure **1**). Efficacy evaluation is conducted on the basis of subjective and objective data during dynamic clinical observation (Table **3**).

Figure 1. Patient's distribution.

Table 2. Age wise distribution among the patients.

6 Months		1 Year		1.5 Year		2 Years		2.5 Years		3 Years	
Test	Control	Test	Control	Test	Control	Test	Control	Test	Control	Test	Control
3	4	2	3	5	6	10	8	9	12	11	7

Table 3. Dynamics of cough syndrome duration and intensity.

	1 Day		2 Day		3 Day		4 Day		5 Day		6 Day		7 Day		After the Course	
Cough intensity	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C
Slight	10	17	10	17	13	19	13	20	20	21	22	27	6	22	5	14
Moderate	21	14	21	14	18	12	16	11	12	11	7	8	1	6	0	5
Severe	9	9	9	9	7	9	6	8	3	7	1	2	0	0	0	0
Absence	0	0	0	0	2	0	5	1	5	1	10	3	33	12	35	21

In addition, there were no significant differences between measures of symptom severity at base line. When symptom scores were compared for reach treatment group from the day one to 7 days of treatment, 87.5% (35 out of 40) of the patients. There was a significant feeling of well being and absence of low grade fever such as 90% in case of Linkus and 82.5% in Mucaltin. The recurrence of cough was also minimized quite significantly with the use of Linkus and this maintenance of quality of life in chronic cough.

Efficacy evaluation is conducted on the basis of subjective and objective data during dynamic clinical observation. Therapy duration is 7 days. Clinical symptoms evaluated in the study were: complaints to intoxication syndrome (fever, weakness, and hyperhidrosis), sore throat (scratchy throat, painful swallowing), rhinorrhea (exudates characteristics, duration), cough syndrome (duration, intensity, productiveness) (Table **4-7**) (Figure **2-3**).

Table 4. Cough productiveness dynamics.

	1 Day		**2 Day**		**3 Day**		**4 Day**		**5 Day**		**6 Day**		**7 Day**		**After the Course**	
Cough	T	C	T	C	T	C	T	C	T	C	T	C	T	C	T	C
Dry	15	17	12	19	9	17	33	5	33	8	17	8	1	9	5	9
With sputum	20	11	27	11	31	14	7	22	7	19	2	13	0	9	0	5
Absence	5	12	1	10	0	9	0	13	0	13	21	19	39	22	35	26

Table 5. Fever syndrome, intoxication duration and intensity dynamics.

Syndrome Intensity	**1 Day**		**2 Day**		**3 Day**		**4 Day**		**5 Day**		**6 Day**		**7 Day**		**After Course**	
Slight	T11	C13	T15	C1	T21	C16	T16	17	T12	C15	T7	C12	T5	8	T4	C7
Moderate	18	14	14	13	5	10	4	7	3	3	1	2	0	1	0	0
Severe	9	8	5	6	2	5	2	3	0	2	0	1	0	0	0	0
Absence	2	5	6	6	12	9	18	13	25	20	32	25	35	31	36	33

Slight – 36,6 to 36,9-37,1 °C; Moderate – up to 37,2-37,4 °C; Severe – up to 37,9 °C; Absence – up to 36,6 °C.

Table 6. Laboratory parameters of blood test dynamics in test and control groups on the background of Linkus syrup 90 ml administration.

Lab Tests	Test Group		Control Group	
	1 Day	7 Day	1 Day	7 Day
Hb	122	139	126	135
WBC	12.3	8.2	11.7	9.3
Neutrophils	42	39	43	30
Lymphocytes	37	40	34	45
Monocytes	9	6	10	9
Eosinophils	10	15	12	15
Basophils	2	0	1	1
RBC	4.19	3.89	4.02	3.93
Platelets	358	262	342	298
Erythrocyte sedimentation rate	21	17	19	16

Table 7. Laboratory parameters of urine test dynamics in test and control groups on the background of Linkus syrup 90 ml administration.

Lab Tests	Test Group		Control Group	
	1 Day	7 Day	1 Day	7 Day
Relative density	1010	1012	1009	1013
Quantity	50.0	90.0	60.0	80.0
Sugar	Negative	Negative	Negative	Negative
Protein	Traces	Negative	Traces	Traces
WBC	5-8	3-5	8-9	3-4
RBC	2-3	0-2	2-3	1-3
Bacteria	Single	Single	Single	Single

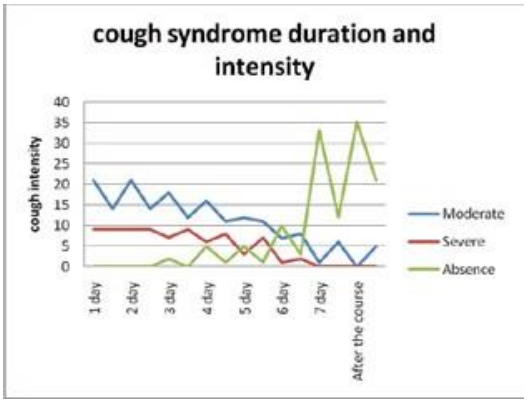

Figure 2. Cough syndrome duration and intensity.

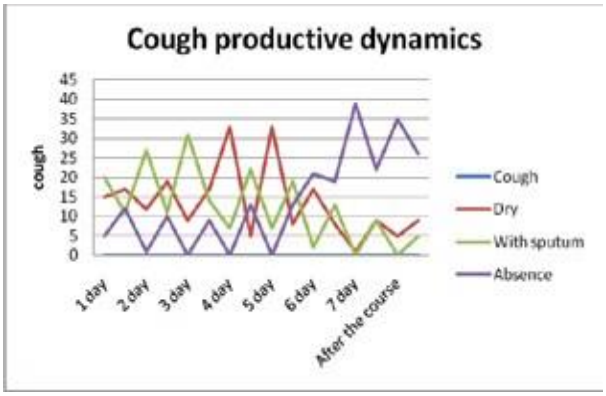

Figure 3. Cough productive dynamic.

DISCUSSION

In the study conducted to assess chronic cough in the patients as well as cough respiratory infection and to assess antitussive, expectorant and decongestant actions of Linkus, clinical trials have shown positive results. In pediatric patients prolonged duration of cough can affect the pulmonary functions and the risks of developing opportunistic infections are also higher. Linkus have better bronchodilator Activity demonstrated in clinical trials. The studies on Linkus syrup substantiate the beneficial effects in the treatment of respiratory disorders claimed in the Indian medicinal literature [6]. We have already described evaluation of acute and repeated dose toxicity of the polyherbal formulation Linkus syrup in experimental animals [7]. In addition, communication the design, development and phytochemical evaluation of a polyherbal formulation Linkus syrup [8].

CONCLUSION

The results of the study presented suggest that there is a good potential of using Linkus syrup to prevent the cough in children

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