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REPORT

ON LIMITED CLINICAL TRIALS OF

KOFOL COUGH SYRUP

Manufactured by Charak Pharmaceutical, India

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ABSTRACT

Kofol cough syrup, chronic obstructive bronchitis

This is a report on clinical trials of Kofol cough syrup manufactured by Charak Pharmaceutical, India.

The expectorant, mucolytic and anti-inflammatory actions of Kofol make it useful for treatment of chronic obstructive bronchitis.

Limited clinical trials in an open parallel study were conducted on 30 patients with chronic obstructive bronchitis.

The results of these trials show that Kofol has an expectorant and anti-inflammatory effect, is well tolerated by patients and does not induce pathological changes in the laboratory and biochemical parameters of the patients with chronic obstructive bronchitis.

This report consists of 17 pages, 5 tables

Bibliography: 18 references.

INTRODUCTION

According to WHO data, 1-1.5 million new cases of chronic non-specific diseases of the lungs (CNDL) are diagnosed every year throughout the world and in about 35000 of these cases the patient becomes a total invalid [1, 2]. In the current Worsening ecological conditions, not only in the Ukraine, but also in other Countries, there is a trend of growing incidence of diseases of the broncho-Pulmonary system. Chronic bronchitis affects about 20% of men and 5% of women. Aggravation of bronchitis occurs 2-4 times every year.

The current epidemiological situation in Ukraine is characterized by a significant increase in the incidence of non-specific diseases of the lungs (NDL). These diseases are already among the main causes and are gradually becoming the primary causes of disability and death [3,4].

Chronic obstructive diseases of the lungs (CODL) are the most common type of NDL and the most typical example is chronic obstructive bronchitis (COB) [5].

The main feature of these diseases is inflammation of the bronchial tree which occurs because of complex disorders in systemic and local immunity, in non-immune regulation of cellular metabolism, in the oxidant-antioxidant system, in mucociliary clearance and in the quantitative and physico-chemical properties of surfactants [6, 7, 8]

One of the main steps in the pathogenesis of chronic obstructive diseases of the lungs is disorder of bronchial permeability. There are six main mechanisms causing bronchial obstruction: bronchospasm, inflammatory changes in the bronchi, disorders of mucociliary transport, tracheobronchial dyskinesia and expiratory collapse of the bronchi because of reduction in the elastic properties of the lungs [9].

An important and largely reversible pathogenetic mechanism of obstructive syndrome is disorder of mucociliary transport (MCT) induced by ciliary insufficiency, hyper secretion and changes in the rheological properties of mucus. This disorder can be effectively treated [10, 11, 12].

Expectorant and mucolytic therapy used in obstructive syndromes is particularly useful in cases of marked disorders of mucociliary transport where it is necessary to restore effective bronchial drainage. The formulations used for this purpose can be divided into two main groups: expectorants and mucolytics.

Expectorants stimulate the physiological activity of the ciliated epithelium and peristaltic movements of the bronchi and bronchioles. This facilitates movement of the secretions from the lower parts to the upper parts of the respiratory tract. Formulations of this group can be nominally alb-divided into two categories: reflex action (formulations of thermopsis, marshmallow (Althea officinalis), liquorice (Glycyrrhiza), sodium benzoate, terpine hydrate, etc.); resorbtive action (sodium and potassium iodides, ammonium chloride, sodium hydrocaibonate, etc.).

Mucolytic (or secretolytic) formulations act mainly by reducing the viscosity of secretions through changes in their physicochemical properties. This group of formulations indudes some enzymes (trypsin, chemotrypsin, ribonuclease, deoxyribonuclease) and some synthetic formulations (acetylcysteine, bromhexine, lasolvan, bisolvon, etc.). Different mucolytic formulations are distinguished by their mechanism of action and effectiveness. The collection of viscous secretions in the respiratory tract not only affects the ventilation function of the lungs, but also increases the danger of infection and formation of complexes between the mucoproteins and DNA which can block the bronchi. Proteolytic enzymes and detergents have the ability to destroy these complexes by disrupting the peptide bonds of the protein molecules [13, 14, 15, 16, 17].

Various medicines recently introduced in the market for treating CODL include different active substances which can simultaneously act on several mechanisms involved in the pathogenesis of CODL. This is very convenient for treating aggravations of chronic obstructive diseases (18]. One such medicine is the herbal-mineral formulation - Kofol cough syrup manufactured by Charak Pharmaceutical, India. This formulation is made from herbal extracts.

The ingredients include Vasika adhatoda (200 mg), Solanum xanthocarpum (120 mg), Clerodendros serratum (40 mg) and Piper longum (30 mg) which facilitate expectoration of secretions and act as spasmolytics; Glycerrhiza glabra(150 mg) has a softening action and reduces irritation; Viola odorata (50 mg). Curcuma longa (20 mg), Cubeba officinalis (10 mg), Zingiber officinale (10 mg). Piper nidrum (10 mg) also reduce irritation and moreover have a sudorific, anti-inflammatory action (the last substance also improves digestion); Terminalia belerica (100 mg) facilitates expectoration; Ocimum sanctum (60 mg) is an anticatarrhal and anti-infective; Juniperis communis (50 mg) facilitates expectoration and has an antiseptic action; Ammoni chloridi (15 mg) helps to liquefy the mucus; Purethrum indicum has a sedative action. This composition of the formulation ensures a broad spectrum of action: mucolytic action - faciftates liquefaction and easier excretion of secretions); prevention of oedema - reduces hyperemia and oedema of the mucous membranes in the respiratory tract; spasmolytic action - reduces bronchospasm; antitussive action; anti-inflammatory action - reduces local inflammatory processes

in the bronchial mucous membranes; sedative action - normalises psycho-physiological reactions, reduces anxiety and discomfort during bronchospasms); antihistaminic, hypothermic and local antiseptic actions.

The antitussive, expectorant, antibacterial, spasmolytic and anti-inflammatory actions of Kofol syrup make it suitable for treating all types of productive and unproductive coughs caused by infections of the upper respiratory tract, bronchitis, acute pneumonia, bronchiectasis, asthma, tuberculosis and coughs after colds; coughs caused by professional and ecological factors or conditions of work; smoker's cough; in local eosinophilia, during treatment of tracheobronchitis, chronic obstructive bronchitis (including bronchitis of infectious origin), mucoviscidosis, chronic bronchiectatic disease, disorders of formation of bronchial secretions and pathological increase in viscosity of the secretions. Kofol syrup is also recommended for symptomatic relief and faster recovery from colds, angina; rhinitis, laryngitis, pharyngitis, tonsillitis and sinusitis.

As Kofol does not contain alcohol, soporific and narcotic substances; it can be used by patients of any age.

The formulation rapidly relieves and eliminates all types of cough. It can be used as a safe, alcohol-free treatment for children with cough caused by infections of the upper respiratory tract, bronchitis, asthma, allergic bronchitis, whooping cough or cough after measles.

Kofol did not cause any side effects during clinical trials in India.

MATERIALS AND METHODS

Limited clinical trials ofKofol syrup were conducted in the clinic of the Department of Diagnosis, Therapy and Clinical Pharmacology of Pulmonary Diseases, F. G. Yanovsky Institute of Phthisiology and Pulmonology, Academy of Sciences of Ukraine (Kiev).

A group of patients was subjected to complex treatment including Kofol syrup (100 ml bottle) manufactured by Charak Pharmaceutical, India.

The group consisted of 30 in-patients (age 40-60 years) with chronic obstructive diseases.

All the patients include in the clinical trials had symptoms of chronic obstructive diseases confirmed by clinical, functional and laboratory tests: breathlessness under physical stress, cough with excretion of mucous or mucopurulent secretions, sub- febrile temperature, rapid fatigue.

Type of examination	Before treatment	On 4th day	On 8th day	On 12th day	On 14th day
Medical history	*				
Objective examination	*	*	*	*	*
Complex evaluation of External respiration	*				
Laboratory tests : Blood analysis Urine analysis	*				*
Evaluation of patient's Subjective complaints	*	*	*	*	*
Registration of side effects		*	*	*	*

The evaluation of the patient's subjective complaints was carried out on the following point-scale:

Cough:

0-absent
1 - insignificant
2 - moderate
3 - severe
4-exhausting

Quantity of secretions expectorated:
0-absent
1 - insignificant
2 - moderate
3 - significant

Nature of secretions expectorated:
-mucous
-mucopurulent
- purulent

Administration of the formulation

The complex therapy included 2 teaspoons ofKofol syrup thrice daily.

The other elements of complex therapy included traditional treatment with broncholytics - Atrovent, Berodual. In cases of infectious bonchitis the treatment included antibiotics (Amoxyclav, Rovamycin).

The duration of treatment was 14 days.

Evaluation of effectiveness

The effectiveness of the test formulation was evaluated as per the following scale:

Very high effectiveness	**Significant positive changes in the data from clinical and instrumental examinations, reduction in cough during the first few days of treatment; significant relief in expectoration.**
High effectiveness	**Absence of cough by the end of the treatment period; significant relief in expectoration; significant positive changes in the data from clinical and functional examinations.**
Satisfactory effectiveness	**Significant reduction in cough by the end of the treatment period; moderate relief in expectoration; insignificant changes in the data from clinical and functional examinations.**
Low effectiveness	**Inagnaficant changes in the parameters studied.**
Absence of effectiveness	**Absence of changes or negative changes in the parameters studied.**

Evaluation of tolerance

The tolerance to the drug was evaluated on the basis of subjective symptoms and opinions expressed by the patients, as well as objective data collected during treatment. The changes in the laboratory parameters of blood and urine and the frequency and nature of side effects were also considered.

The tolerance of the drug was evaluated in points on the following scale:

I point	Very good (no side effects)
2 points	Good (insignificant side effects which do not cause serious problems to the Patient)
3 points	Satisfactory (side effects which affect the patient's condition, but do not necessitate discontinuation of the formulation)
4 points	Unsatisfactory (adverse side effect which significantly affects the patient's condition and necessitates discontinuation of the formulation)
5 points	Highly unsatisfactory (adverse side effect which necessitates Discontinuation of the formulation and use of additional clinical measures)

The external respiratory function (ERF) was tested on the Master Lab apparatus (Erich Jaeger, Germany) and the "Flow-volume" curve was analyzed. The following ERF parameters were studied: vital capacity of the lungs (VC), forced vital capacity of the lungs (FVC), forced expiratory volume at one second (FEVI), maximum expiratory flow at 25, 50 and 75% of vital capacity of the lungs (MEF 25%, MEF 50%, MEF 75%), peak expiratory flow (PEF).

The data was subjected to statistical variance analysis using Student t-test.

RESULTS AND DISCUSSION

The dynamics of some clinical and objective examination parameters during treatment with Kofol syrup of patients with chronic obstructive diseases are given in Table I.

Table I - Dynamics of some clinical parameters before and after complex treatment.

Symptoms	Before treatment		After treatment	
	Abs	%	Abs	%
Breathlessness under severe physical stress	18	60	25	83.3
Breathlessness under severe physical stress	12	40	5	16.7
Cough:				
Absent	-	-	10	33.3
Insignificant	3	10	18	60.0
Moderate	15	50	2	6.7
Severe	20	40	-	-
Qty. of secretion expectorated				
Absent	-	-	19	63.3
Upto 50 ml	21	70	11	36.7
>50 ml	9	30	-	-
Nature of Secretion :				
Mucous	13	43.3	28	93.3
Mucopurulent	15	50	2	6.7
Purulent	2	6.7	-	-
Nature of respiration :				
Vesicular	2	6.7	12	40.0
Weak	8	26.6	8	26.6
Harsh	20	66.7	10	33.4
Rales:				
Absent	-	-	21	70.0
Individual dry	14	46.7	9	30.0
Dispersed dry	11	36.7	-	-
Moist	5	16.6	-	-

Analysis of the results showed that the patients who took Kofol syrup had positive changes in the clinical symptoms. Thus, there was a reduction in breathlessness under normal physical stress, while there was an increase in the number of patients who became breathless under severe stress. There was a significant reduction in

the number of patients with severe cough, while there was a significant increase in the number of patients with insignificant cough. All the patients experienced improved expectoration within 4 days after the start of treatment (cough was milder, expectoration was easier) and significant improvement after using the test formulation for 12 days. There was also a change in the nature and quantity of secretions: not a single patient had purulent secretions after the course of treatment and the number of patients with mucous-purulent secretions reduced by 50%. The quantity of secretion expectorated became less by 60%. The results of objective examinations also flowed positive changes in patients using Kofol syrup. Thus, there was a reduction in the number of patients with harsh respiration (by 33.3%), while the number of patients with vesicular respiration increased by 33.3%.

Dispersed dry rales were found in 26.7% of the patients, while 16.6% had moist rales before treatment. None of the patients had such rales after the course of treatment. The number of patients who had individual dry rales became less.

The parameters of external respiratory function (ERF) did not change significantly during treatment, but there was a trend towards normalization of most of the parameters (see table 2).

Table 2 - Dynamics of parameters of external respiratory function (M ± m), (n = 30)

Parameters (% of normal)	Before treatment	After treatment
R tot	125.3±13.8	130.9±16.3
TLC	103.8±4.2	103.9±4.4
RV/TLC	119.3±4.2	112.9±9.0
VC MAX	89.6±4.2	93.2±3.5
FVC	91.7±5.0	89.5±4.2
FEV 1	78.1±5.6	84.5±6.0
FEV 1 % VC MAX	81.5±3.5	83.2±4.5
FEF 75	50.3±6.7	47.8±8.8
FEF 50	51.4±6.8	54.4±9.1
FEF 25	58.3±5.7	63.1±8.2
PEF	63.5±4.9	72.4±6.5
FEF 75/85	54.9±5.3	60.0±11.1

Analysis of the changes in the clinical symptoms and functional tests show that Kofol syrup causes favorable shift in these parameters.

Sixteen patients -were subjected to bronchoscopy before and after the course of treatment. The results were as under (Table 3).

Table 3 - Results of bronchoscopy

Level of inflammation	Before treatment		After treatment	
	Abs	%	Abs	%
I	2	12.5	1	6.3
I-II	3	18.8	4	25.0
II	8	50	-	-
II-III	3	18.8	-	-

By the end of the course of treatment none of the patients had bronchial inflammation of levels H or III; inflammation of level H-III in 4 patients before treatment reduced to level 1-11; only one patient remained with inflammation of level 1.

The data from blood analysis is shown in Table 4.

Table 4 - Dynamics of parameters of blood analysis (M ± m), (n = 30)

Parameters (% of normal)	Before treatment	After treatment
Hb, g/1	115.8±4.3	118.7±4.3
Leukocytes*$10^{9/1}$	7.7±2.5	5.4±1.2
Eosinophils, %	5.2±1.5	3.6±1.1
Band neutrophils, %	6.5±1.8	5.9±2.7
Segmented neutophils, %	43.5±3.3	45.5±2.6
Lymphocytes, %	35.2±3.3	33.4±4.7
Monocytes, %	6.5±2.1	4.3±1.5
ESR, mm/hr	18.4±4.4	9.0±3.2

Analysis of this data shows that all the parameters of blood analysis became normal after treatment.

We also studied some biochemical parameters of blood during the course of treatment.

The data is shown in Table 5.

Table 5 - Dynamics of biochemical parameters of blood (M ± m), (n = 30)

Parameters (% of normal)	Before treatment	After treatment
Total proteins	75.0±0.17	77.2±0.2
Total bilirubin, mcmole/1	15.2±0.12	13.1±0.6
ALT, mmole/1	0.50±0.05	0.46±0.03
AST, mmole/1	0.47±0.02	0.43±0.04
Residual nitrogen, mmole/1	21.2±0.3	20.5±0.17
Urea, mmole/1	4.5±0.13	4.3±0.01

Analysis of this data shows that the test formulation, Kofol syrup, did not have an adverse effect on the kidneys and liver.

The results in terms of effectiveness of treatment were as follows:

Very high effectiveness in 7 (23.3%) patients

High effectiveness in 21 (70.0%) patients

Satisfactory effectiveness in 2 (6.7%) patients who had purulent-obstructive bronchitis for more than 10 years. Clinical symptoms of bronchitis remained after the course of treatment. These patients were advised to continue the complex treatment.

The test formulation was well tolerated by the patients and gave a positive clinics effect. Complications and side effects were absent. It is worth noting that there were no reports of individual intolerance during the clinical trials. This indicates that the formulation has low toxicity.

Thus, the clinical trials show that the Kofol cough syrup is a highly effective, non-toxic therapeutic formulation.

CONCLUSIONS

A study of the effectiveness and tolerance of Kofol cough syrup, manufactured by Charak Pharmaceuticals, India, was conducted in the clinic of the Department of Diagnosis, Therapy and Clinical Pharmacology of Pulmonary Diseases, F.G.Yanovsky Institute of Phthisiology and Pulmonology, Academy of Sciences of Ukraine (Kiev). The patients were given a dose of two teaspoons of syrup thrice daily for 14 days. The results of the study make it possible to draw the following conclusions:

1. **Kofol cough syrup, manufactured by Charak Pharmaceuticals, India, is an effective mucolytic and expectorant for treatment of patients with chronic obstructive bronchitis.**

2. **Kofol cough syrup, manufactured by Charak Pharmaceuticals, India, is well tolerated by patients and does not induce pathological changes in the clinical analytical parameters. The formulation did not have any toxic effects on the patients. The absence of side effects during use of the syrup indicates that the formulation is safe.**

3. **Kofol cough syrup, manufactured by Charak Pharmaceuticals, India, can be used in complex therapy of patients with chronic obstructive bronchitis along with other anti-inflammatory drugs, antibiotics and broncholytics.**

4. **Kofol cough syrup, manufactured by Charak Pharmaceuticals, India, can be recommended for use in medical practice.**

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