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Immunomodulatory effect of a glycoprotein from *Klebsiella* versus levamisole in asthmatic patients with phagocytic deficiency

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ABSTRACT

Background: Levamisole and *Klebsiella* glycoprotein (KGP) are immunomodulators used to increase phagocytosis in cases of moderate immunodeficiency, as those observed in patients with bronchial asthma and chronic bronchitis. Frequently such patients develop phagocytic dysfunctions with recurrent respiratory infections. Although levamisole has been extensively studied, comparative studies regarding effectiveness, and side and adverse effects of KGP are lacking.

Objective: To compare the effectiveness of levamisole and KGP regarding phagocytic index, frequency and severity of infectious processes, and side and adverse effects in patients with respiratory infections and bronchial hyperresponsiveness.

Methods: Thirty-six patients with bronchial asthma, rhinosinusitis or chronic bronchitis with bronchial hyperresponsiveness secondary to respiratory infections, and phagocytic deficiency were enrolled in a randomized, double-blind trial comparing oral levamisole with oral KGP. Efficacy of the two treatments was compared based upon changes in rest and activated phagocytic index, recurrent infectious processes, and side and adverse effects.

Results: No statistically significant differences were detected between the two treatment groups, except for side effects which occurred with significantly lower frequency after KGP ingestion.

Conclusion: KGP treatment is recommended over levamisole for patients with phagocytic deficiency due to the lower occurrence and severity of side effects produced.

Key words: Levamisole, *Klebsiella* glycoprotein, immunomodulation, phagocytic deficiency, asthma, bronchitis, bronchial hyperresponsiveness, respiratory infections.

RESUMEN

Antecedentes: Las glicoproteínas de levamisol y de *Klebsiella* (KGP) son inmunomoduladores, usados para aumentar la fagocitosis en casos de inmunodeficiencia moderada, tal como se observa en pacientes con asma y bronquitis crónica. Frecuentemente estos pacientes desarrollan disfunciones de fagocitosis con infecciones respiratorias recurrentes. Aunque se ha estudiado extensivamente a levamisol, no existen estudios comparativos con KGP, acerca de la eficacia y los eventos adversos.

Objetivo: Comparar la eficacia de levamisol y de KGP en cuanto al índice fagocítico, la frecuencia y gravedad de los procesos infecciosos y los eventos adversos en pacientes con infecciones respiratorias e hiperreactividad bronquial.

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Método: Se reclutaron 36 pacientes con asma, rinosinusitis o bronquitis crónica con hiperreactividad bronquial secundaria a las infecciones respiratorias, y deficiencia fagocitaria, en un ensayo aleatorio, a doble ciego, comparando levamisol oral con KGP oral. Se comparó la eficacia de los dos tratamientos basándose en los cambios en índice fagocítico en estado activado y no activado, en los procesos infecciosos recurrentes y los eventos colaterales y adversos.

Resultados: No se detectó ninguna diferencia estadísticamente significativa entre los dos tratamientos, con la excepción de los eventos adversos, que ocurrieron con una frecuencia significativamente menor después de la ingesta de KGP.

Conclusión: Se recomienda el tratamiento con KGP sobre levamisol para pacientes con deficiencia fagocítica por la menor ocurrencia y gravedad de los eventos colaterales que este tratamiento produce.

Palabras clave: Levamisol, glicoproteína de *Klebsiella*, inmunomodulación, deficiencia fagocítica, asma, bronquitis, hiperrespuesta bronquial, infecciones respiratorias.

INTRODUCTION

Infections of the tracheobronchial tree are the most common antecedents of relapse and acute respiratory failure in patients with bronchial asthma, as well as in patients with chronic bronchitis with bronchial hyperreactivity (BHR).¹ Such patients frequently develop phagocytic dysfunctions which present with recurrent bacterial or viral infections.²

In such cases stimulation of immune defense mechanisms is desirable, and immune modulators are indicated. Levamisole and a glycoprotein from *Klebsiella* are two immune modulators widely used in clinical studies.³

Levamisole initially was synthesized as an anti-helminthic agent. Subsequent studies in human beings demonstrated that levamisole can increase delayed hypersensitivity and/or T-cell mediated immunity.⁴ It augments macrophage chemotaxis and phagocytosis⁵ in cases of moderate immunodeficiency. Its mechanism of action is unknown, but it seems to help in maintaining microtubule integrity which is essential for macrophage and lymphocyte adequate functioning.⁶ According to several studies, the recommended dose of levamisole to stimulate the immune system is 300-400 mg in weekly pulses during, at least, four weeks.⁷

Klebsiella glycoprotein (KGP) is known as RU 41740 and obtained from *Klebsiella pneumoniae*. KGP has been shown to activate B and T lymphocytes with a consequent increase of IgG. This might explain its effect on experimental infections induced by *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*.⁸ KGP also activates phagocytosis in PMN, monocytes and macrophages *in vitro* and *in vivo*, and it induces interleukin 1 (IL-1) secretion.⁸

Studies performed to compare the effect of KGP versus placebo in patients with chronic bronchitis and secondary BHR as well as recurrent infections have shown an increased phagocytic activity only in KGP-treated patients.⁹ Similar studies in children showed a significant reduction in the frequency of infections and of

antimicrobial ingestion. KGP has been found to induce an early increase of the antibody titer.¹⁰

Effectiveness of levamisole as an immunomodulator is largely known, as well as the side and adverse effects occurring after its administration, such as nausea, vomiting, sickness, hepatic deterioration, and agranulocytosis. Conversely, KGP effectiveness has been proved only compared to placebo, and there are no studies on side and adverse effects due to its administration. Therefore, the aim of this study was to compare the effectiveness of both drugs by evaluating the phagocytic index, infectious processes, and side and adverse effects.

SUBJECTS AND METHODS

Patients

Thirty-six patients (11 males, 25 females; mean age (SEM) = 38 (\pm 13) with diagnosis of either bronchial asthma, mixed rhinosinusitis with BHR or chronic bronchitis with BHR participated in this study. All patients manifested phagocytic deficiency and had received antimicrobial treatment at least twice during the last two months. Patients signed an informed consent for the study which was approved by the ethical committee of the «Hospital de Especialidades, Centro Médico Nacional Siglo XXI». All patients filled in a questionnaire stating their name and age. In the same questionnaire the investigators stated the diagnosis, phagocytic index prior to treatment, complete blood count, results of hepatic function tests, number and severity of infections and total levels of immunoglobulin and complement.

Study design

Patients were assigned to receive oral treatment with either KGP or levamisole in a double-blind and randomized trial. The treatment schedules were as follows: for KGP 2 mg daily for seven days, three weeks rest, 1 mg daily for seven days, three weeks rest, 1 mg daily for seven days. For levamisole: 300 mg in weekly pulses for four weeks.



Patients were clinically evaluated during 36 weeks, and every four weeks a clinical evaluation was performed including number, duration and severity of infections, as well as side and adverse effects. At the end of 10, 23 and 36 weeks, phagocytic index, hepatic function tests and a complete blood count were performed again.

Phagocytic index

This was assessed with the nitro blue tetrazolium reduction technique, previously validated in 20 healthy subjects and according to the following parameters: rest = 0.046 - 0.089; activated = 0.149 - 0.240; R-A = 0.084 - 0.182; R/A = 2-4.

Evaluation of infectious processes

Infectious processes were evaluated according to the following scale:

Number: 0 = no, 1 = yes. Frequency: x = n times. Duration: y = m days.

Severity: 1 = mild; 2 = moderate; 3 = severe,

Data analysis

Squared chi was applied to assess differences between both treatments regarding infectious processes and secondary effects. Mann-Whitney U test was used to evaluate differences in the phagocytic index before

and after treatment with either KGP or levamisole. A p value < 0.05 was considered as statistically significant.

RESULTS

The phagocytic index at rest was significantly increased only after 10 week-KGP treatment ($p < 0.001$) (Table 1), whereas the activated phagocytic index was significantly increased after both KGP and levamisole treatments ($p < 0.001$) (Table 2).

A - R and A / R were significantly increased after 10, 23 and 36 week- KGP and levamisole treatments ($p < 0.001$) (Tables 3 and 4). No difference was observed between treatments in any case.

Table 5 shows the number of recurrent infections in 11 patients (30%) during the first 10 weeks. No differences between KGP and levamisole treatments were found in either number of relapses or severity of infections.

A greater number of side effects was found with levamisole. Sickness developed significantly more frequent during this treatment ($p = 0.005$), whereas the frequency of nausea reached a borderline significance ($p = 0.06$) (Table 6).

No difference between treatments was found when the hepatic function and agranulocytosis were evaluated.

Table 1. Rest phagocytic index.

Treatment	Before treatment	Rest phagocytic index		
		After 10 weeks	After 23 weeks	After 36 weeks
KGP	0.064	0.072*	0.070	0.068
Levamisole	0.064	0.063	0.068	0.068

Values represent mean. * $p < 0.0001$ before vs. after treatment; Mann-Whitney U test.

Table 2. Activated phagocytic index.

Treatment	Before treatment	Activated phagocytic index		
		After 10 weeks	After 23 weeks	After 36 weeks
KGP	0.125	0.185*	0.185*	0.182*
Levamisole	0.119	0.179*	0.180*	0.180*

Values represent mean. * $p < 0.0001$ before vs. after treatment; Mann-Whitney U test.

Table 3. A-R phagocytic index.

Treatment	Before treatment	A - R		
		After 10 weeks	After 23 weeks	After 36 weeks
KGP	0.085	0.130*	0.130*	0.130*
Levamisole	0.070	0.123*	0.123*	0.123*

Values represent mean. * $p < 0.0001$ before vs. after treatment; Mann-Whitney U test.



Table 4. A/R phagocytic index.

Treatment	Before treatment	A/R phagocytic index		
		After 10 weeks	After 23 weeks	After 36 weeks
KGP	1.36	2.44*	2.44*	2.42*
Levamisole	1.49	2.41*	2.41*	2.41*

Values represent mean * $p < 0.0001$ before vs. after treatment; Mann-Whitney U test.

Table 5. Recurrent infectious processes.

Treatment	During first 10 weeks		After 23 weeks		After 36 weeks	
	KGP	Lev	KGP	Lev	KGP	Lev
Num. of relapses	6	5	0	0	0	0
Severity						
Mild	4	1	0	0	0	0
Moderate	2	4	0	0	0	0
Severe	0	0	0	0	0	0

Table 6. Side and adverse effects induced by KGP and levamisole during the first 10 weeks of treatment.

	Side and adverse effects	
	KGP	Levamisole
Nausea	2	8
Vomit	1	2
Sickness	0	7*
Altered hepatic function	0	0
Agranulocytosis	0	0

* $p = 0.005$ Fisher exact test.

DISCUSSION

According to our results, the two treatments assayed to immunomodulate and to increase the phagocytosis were completely efficacious with no significant difference between them. We found an effectiveness higher than the 75% reported for levamisole to restore phagocytic function in macrophages.¹² KGP displayed an effectiveness of 100% in our study as previously reported in other clinical studies.^{10,13-15}

Side effects due to levamisole treatment were, in decreasing order, nausea, sickness and vomiting, that occurred only immediately after ingestion of levamisole, and lasted for approximately 24 h. These findings are in agreement with those reported elsewhere.¹⁶⁻¹⁸

After ingestion of KGP, nausea and vomiting also occurred, but with significantly lower frequency than they did after levamisole treatment. To our knowledge, in

previous publications side effects caused by KGP have not been mentioned.

With regard to the occurrence of infectious processes, we found that both treatments diminished frequency and severity in a similar way, which agrees with previous reports.^{10,19}

Although some physicians might choose levamisole as the indicated therapy because of its price—it is cheaper than KGP—, according to our findings, KGP treatment is recommended over levamisole to be used for patients with phagocytic deficiency, as the lower occurrence and severity of side effects might guarantee patients will finish the treatment.

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