

ORIGINAL ARTICLE

EFFECT OF MONTELUKAST SODIUM ADMINISTRATION ON AIRWAY HYPERSENSITIVITY OF TANNERY WORKERS

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Background: Tannery workers are prone to develop Bronchial Hypersensitivity. Objective of this study was to see the role of leukotriene receptor antagonist Montelukast Sodium (MKS) on airway hypersensitivity in tannery workers. **Methods:** One-hundred and fifty asymptomatic tannery workers were divided into 3 groups based on their duration of exposure to tannery chemicals, i.e., 6 months to one year Group I, 1–2 years Group II, and 2–5 years Group III, with 50 subjects in each group. After baseline Pulmonary Function Tests (PFTs), subjects were categorized into those with Forced Expiratory Volume in First Second (FEV₁) <80%, and those who had FEV₁ >80%. Histamine inhalation challenge was given to all subjects with FEV₁ >80% via provocative cumulative dose of methacholine causing a 20% fall in FEV (PD₂₀). Later, MKS was given to subjects for six weeks and PFTs were repeated again.

Results: Out of 150 subjects, 34 had FEV₁ <80% and 116 had FEV₁ >80%. Hyper-responsiveness of airways was affected in 6% subjects in Group-I, 24% in Group-II, and 38% subjects in Group-III. PD₂₀ within subjects of all groups before giving MKS at day 0 and 42 was non-significantly different. After giving MKS, the PD₂₀ at day 42 was significantly improved in all experimental groups as compared to day 0 ($p=0.05$, $p=0.05$, and $p=0.05$ respectively). **Conclusion:** Tannery workers have high histamine sensitivity and reduced pulmonary efficacy which improves with administration of MKS.

Keywords: Bronchial hyper-responsiveness, Histamine diphosphate, Histamine Inhalation Challenge, HIC, Montelukast Sodium, MKS, Occupational Hazards, Pulmonary function tests

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INTRODUCTION

Exposure to tannery pollutants such as chromium, oxides of nitrogen (NOX), oxides of sulphur (SOX), particulate matter (PM₁₀), volatile organic compounds (VOCs), and hydrogen disulfide (H₂S) has been linked to an increased prevalence of allergic diseases, bronchial asthma, and enhanced airway responsiveness to inhaled allergens.¹ This finding has highlighted the role of these pollutants in triggering inflammatory and immune responses in exposed individuals. Chromium salts, specifically, bound with epidermal proteins to form complex antigens that stimulate elevated IgE antibody levels, ultimately contributing to the development of bronchial asthma.²

The initiation of occupational asthma (OA) among tannery workers is believed to result from histamine surges experienced in response to inhalation of tannery-related chemicals.³ Experimental studies have demonstrated that histamine exposure in otherwise healthy individuals leads to non-significant reduction in Forced Expiratory Volume in 1st second (FEV₁), an effect that is exacerbated in individuals with prior exposure to asthma-inducing pollutants.⁴ In workers with co-existence of asthmatic tendencies, histamine surges are often associated with further declines in Forced Vital Capacity (FVC) in addition to reduction in FEV₁, indicating progressive increase in airway obstruction.⁵

Among various drug classes available for managing asthma, leukotriene receptor antagonists like

montelukast sodium (MKS) have gained increasing attention. Recent work confirms that montelukast effectively antagonizes leukotriene D₄ (LTD₄) at the cysteinyl leukotriene receptor in human airways, thereby preventing airway oedema, smooth muscle contraction, and excessive mucus secretion.⁶ Despite its established efficacy in managing asthma and allergic rhinitis⁷, limited data exist regarding its comparative superiority over corticosteroids or antihistamines, particularly within occupational asthma cases.⁸

Since limited data is available regarding airway hypersensitivity and/or asthma within tannery workers, and since the amount of data regarding the efficacy, supremacy and toxicity of Montelukast within this population is limited, this study was conducted with the aim to explore these facts in depth. This data, in turn was aimed to be utilized to create awareness regarding the occupational asthma within the society and for effective prophylactic use of MKS.

MATERIAL AND METHODS

A cohort study was conducted through the collaboration of the Departments of Physiology of Multan Medical and Dental College, Multan, and Nishtar Medical University, Multan. Approval from the Institution Review Board and Ethical Committee vide letter No. C-92-1046 dated 1-1-2024 was obtained. The sample size of 150 for study was approached by convenient random selection and calculated utilizing WHO Sample Size Calculator⁹.

The protocol of histamine inhalation was standardized according to American Academy of Allergy and Immunology.¹⁰ Histamine inhalation test, now called bronchial provocation test (BPT) and PD₂₀ is defined as the dose of histamine diphosphate in µmoles, which produces a 20% decrease in baseline FEV₁.⁹⁻¹¹

The tannery workers were divided into 3 groups of 50 each depending upon their duration of exposure: Group I= 6 months to 1 year, Group II= 2–5 year, Group III= 6–20 year. Within each exposure group, subjects were further divided based on FEV₁ <80 or >80%. Histamine inhalation challenge (HIC) was performed on FEV₁ >80% group.¹² The test was performed to find the state of airways whether they are hypersensitive to inhale histamine diphosphate or not. The test was performed as standardized by Yan *et al*¹¹ by a standardized protocol.

Half of the subjects in each subgroup received MKS, while the other half served as controls. The dose protocol started from 0.5 µmol up to maximum of 8.0 µmol, the inhalation protocol was as standardized as Yan *et al*¹¹. Spirometry and HIC were performed accordingly to evaluate lung function and airway responsiveness. The uniform design allowed comparisons across time and within subgroups to minimize the cofounders.

Kruskal-Wallis Test was applied to compare the means and standard deviations of group at a confidence interval 95%. Mann Whitney U-Test was applied to compare the means in subgroups as their ultimate size was smaller, and $p < 0.05$ was considered statistically significant.

RESULTS

Table-1 shows frequency distribution of the study population, categorizing subjects into three groups based on the duration of exposure to environmental factors, airway sensitivity (HIC+ or HIC-), and MKS administration (MKS+ or MKS-). The table includes groups with varying exposure periods ranging from 0.5 to 5 years, distinguishing between subjects who are hyperresponsive to inhaled histamine (HIC+) and those who are not (HIC-). It also highlights whether the subjects received MKS treatment or not.

Table-2 presents the comparison of PD₂₀ values in HIC+ subjects after 42 days of MKS administration among three different duration groups. The data indicate a significant improvement in airway sensitivity, even when PD₂₀ values increased to the maximum level of 8 µmole for all groups ($p < 0.05$).

Table-3 shows comparison of PD₂₀ values of HIC positive subjects who did not receive MKS treatment. In these groups, no significant changes in airway sensitivity were observed after 42 days. The PD₂₀ values remained relatively unchanged or slightly altered, ($p > 0.05$).

Table-1: Frequency distribution of study population

Group	Baseline Airway Sensitivity		MKS Administration	
	FEV ₁ Status	N (%)	-	+
Group-1 n=50	<80%	3 (6)	1	2
	>80%	47 (94)	-	-
Group-2 n=50	<80%	12 (24)	7	5
	>80%	38 (76)	-	-
Group-3 n=50	<80%	19 (38)	9	10
	>80%	31 (62)	-	-
Group	Airway sensitivity after HIC		MKS Administration	
	HIC Status	N (%)	-	+
Group-1 n=50	HIC +	15 (30)	8	7
	HIC -	32 (64)	17	15
Group-2 n=50	HIC +	16 (32)	9	7
	HIC -	22 (44)	10	12
Group-3 n=50	HIC +	16 (32)	7	9
	HIC -	15 (30)	7	8

KEY: MKS(-) Montelukast Sodium not given; MKS(+) Montelukast Sodium given. HIC(+) Hyper responsive to inhaled histamine (PD₂₀<8 µmole); HIC(-) Non-responsive to inhaled histamine (PD₂₀>8 µmole)

Table-2: Comparison of PD₂₀ of HIC+ subjects after 42 days of MKS administration

Groups	(Duration of exposure)	N	PD ₂₀ (µmole) At 0 Day	PD ₂₀ (µmole) After 42 Days	p
Groups 1	0.5–1 Year	7	3.11±0.90	8±0	0.01**
Groups 2	1–2 Year	7	4.88±0.30	8±0	0.01**
Groups 3	2–5 Year	9	4.91±0.31	8±0	0.01**

*Statistically significant

Table-3: Comparison of PD₂₀ of HIC+ subjects after 42 Days without MKS administration

Groups	(Duration of exposure)	N	PD ₂₀ (µmole) At 0 day	PD ₂₀ (µmole) After 42 Days	p
Groups 1	(0.5–1 Year)	8	3.80±0.19	4.11±0.19	0.92
Groups 2	(1–2 Year)	9	5.15±0.27	3.71±0.10	0.81
Groups 3	(2–5 Year)	7	3.81±0.12	4.99±0.10	0.70

DISCUSSION

The study investigated the impact of montelukast sodium (MKS) on histamine hypersensitivity and airway responsiveness among tannery workers exposed to occupational irritants. Subjects receiving MKS demonstrated significant improvements in PD₂₀ values, as evidenced by the increase from baseline levels across all exposure durations. This finding has also been reported elsewhere.¹³

It could be explained on the basis of logical reasoning provided by contemporary research which suggests that leukotriene antagonists reduce airway hyperresponsiveness by blocking leukotriene D₄ receptors, thereby justifying bronchoconstriction and inflammation.¹⁴

In Group 1, PD₂₀ increased from 3.11±0.90 µmol to 8.00 µmol in MKS-treated subjects ($p < 0.001$). Subjects in Group 2 exhibited an improvement from 4.88±0.30 µmol to 8.00 µmol, and group 3 exhibited an increase from 4.91±0.31 µmol to 8.00 µmol. These outcomes suggest that montelukast sodium effectively alleviates histamine-induced airway constriction regardless of the duration of exposure. This is in agreement with Chen *et al*¹⁵.

This finding has been reported in literature and can be attributed to montelukast's capacity to decrease leukotriene-mediated inflammation, as suggested by research on airway re-modelling mechanisms.¹⁶

Subjects who did not receive MKS showed no significant improvement in PD₂₀ values after 42 days, with baseline levels remaining relatively unchanged. For instance, in the 0.5–1 year group, the PD₂₀ improved only marginally from 3.80±0.19 µmol to 4.11±0.19 µmol, and *p* across all groups exceeded 0.05. This finding has been observed in similar studies and could be explained by evidence indicating that natural resolution of histamine sensitivity without pharmacological intervention is minimal¹⁷, as histamine-mediated airway inflammation tends to persist without targeted treatment.¹⁸

Notably, the consistency of montelukast's efficacy across exposure durations underscores its value as a preventive treatment in occupational settings. Workers exposed for up to 5 years showed comparable improvements in PD₂₀ to those with shorter exposure durations, suggesting the drug's potential to address both acute and chronic airway hypersensitivity. This observation aligns with Gauvreau *et al*¹⁹ and could be explained by the sustained effect of leukotriene receptor antagonists in reducing chronic airway inflammation and hyperresponsiveness, as indicated in recent mechanistic studies.²⁰ Another study has also reported this and could be explained on the basis of logical reasoning given by contemporary research.²¹

Our findings suggest that leukotriene antagonists prevent bronchoconstriction and inflammation, the key mechanisms in occupational asthma and airway hyperresponsiveness²².

CONCLUSION

This study reinforces the role of montelukast sodium in managing histamine hypersensitivity and preventing airway hyperresponsiveness. By improving PD₂₀ significantly, MKS can be an effective intervention for tannery workers exposed to chemical irritants. Further studies could explore its long-term benefits and applicability to other occupational environments.

OUTCOME AND UTILIZATION

This study advocates to the medical practitioners to consider administration of montelukast sodium to all those who are exposed to the tannery environment so that if they get afflicted by an exacerbating factor like COVID-19 or smog, the emergence of acute or chronic asthmatic attacks could be prevented. This in turn will considerably reduce burden of respiratory emergencies as well as chronic morbidities.

LIMITATION & RECOMMENDATIONS

This was a single-centre study, hence the results cannot be generalized. Further work is recommended to generalize our findings.

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