EDITORIAL

INHALED IBUPROFEN CASE REPORTS IN CHRONIC RESPIRATORY PATHOLOGIES

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SUMMARY

A large number of respiratory pathologies have a single factor in common: inflammation. The limitation they provoke in patients´ quality of life is indisputable, as well as the enormous economic cost that they cause in productive and health systems.

Inhaled hypertonic Na-ibuprofenate solution (NIH), has very important characteristics to deal with a high percentage of these disabling pathologies.

KEY WORDS: Inhaled Ibuprofen Inflammation Respiratory Pathologies

INTRODUCTION

Inflammation 1,2,is the common factor in many chronic lung diseases (Fig. 1)3.

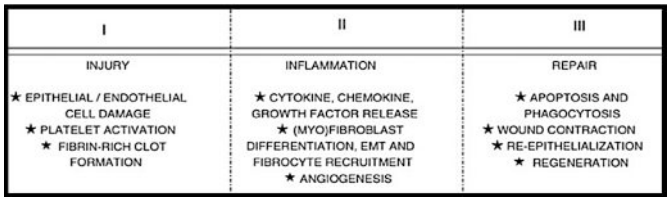

Fig. 1: Stages In Lung Repair And Damage

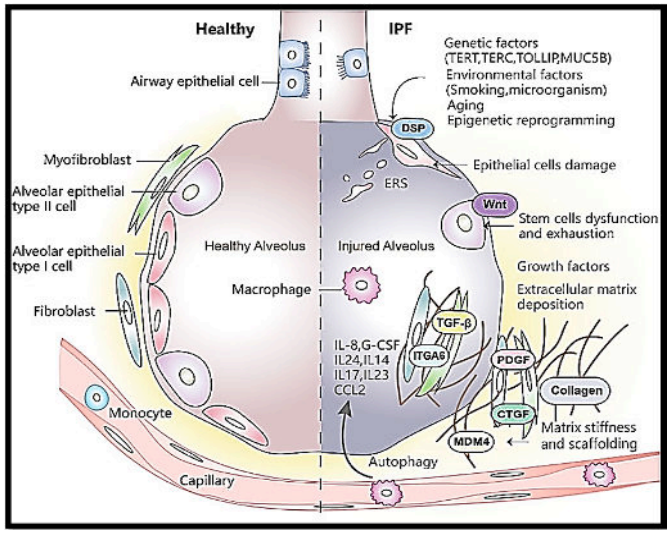

Fig. 2: Pathogenesis Of Idiopathic Pulmonary Fibrosis

INTERSTITIAL LUNG DISEASES

Diffuse interstitial lung diseases (DILD) constitute a heterogeneous group of entities affecting alveolar-interstitial spaces and pulmonary vasculature (Fig. 2)4-6.

PNEUMOCONIOSIS

Pneumoconiosis comprises a broad group of diseases caused by chronic inhalation of high concentrations of inorganic dust (Fig. 3) 7-10.

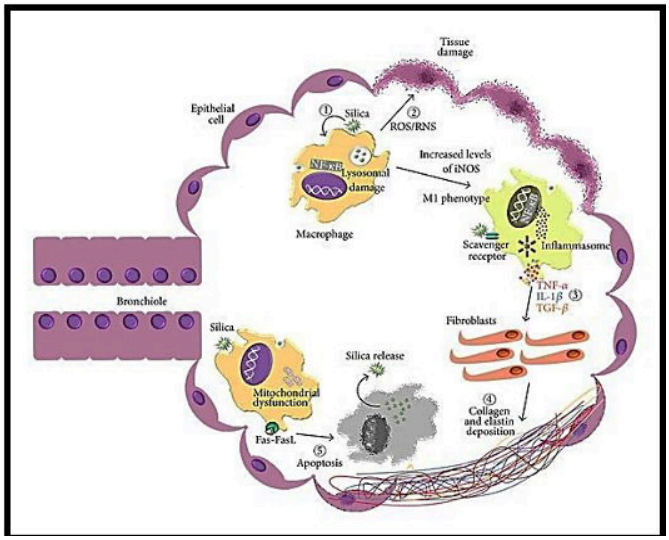

Fig. 3: Pathogenesis Of Pneumoconiosis (Based On Silicosis)

PULMONARY EOSINOPHILIA

Pulmonary eosinophilia (PE) groups diseases that share the presence of pulmonary infiltrates and blood or pulmonary eosinophilia (Fig. 4) 11,12.

Eosinophilic dysregulation
- Simple eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Acute eosinophilic pneumonia
- Churg-Strauss granulomatosis
- Idiopathic eosinophilic syndrome

Infectious Causes
- Allergic Bronchopulmonary Aspergilosis
- Parasite related pulmonary eosinophilia
  - Strongyloides
  - Ancylostoma
  - Toxacara
  - Ascaris
  - Paragonimus westermani
- Fungus related pulmonary eosinophilia
  - Coccidiosis
  - Aspergillus

Miscellaneous
- Drug-induced pulmonary eosinophilia

Fig. 4: Pulmonary Eosinophilia Causes

DRUG-INDUCED PULMONARY EOSINOPHILIA

Drugs as a cause of interstitial lung disease (ILD) correspond to 3% of all ILD (Fig. 5) 13.

ALLERGIC ALVEOLITIS

Extrinsic allergic alveolitis (EAA), or hypersensitivity pneumonitis (HP), is a diffuse interstitial disease caused by the inhalation of organic products (Fig. 6) 11,12.

Disease	Source	Antigens
Farmer's lung	Mouldy hay/vegetable material	Micropolyspora faeni, thermophilic actinomycetes
Mushroom picker's lung	Mushroom dust	Thermophilic actinomycetes
Bird fancier's lung	Avian excreta and feathers	Various proteins
Malt worker's lung	Germinating barley	Aspergillus clavatus
Humidifier fever	Contaminated humidifiers	Various bacteria and/or amoebae

Fig. 6: Most Frequent Antigens In Extrinsic Allergic Alveolitis

COPD

Chronic obstructive pulmonary disease is airflow limitation caused by an inflammatory response to inhaled toxins, often cigarette smoke 14-19.

Chronic obstructive pulmonary disease (COPD) is characterized by poorly-reversible airflow obstruction and abnormal inflammatory lung response (Fig. 7).

Medication name	Pharmacological group
Daptomycin	Antibiotics
Minocycline	
Nitrofurantoin	
Azithromycin	
Dapsone	
Sulfonamide	
Ceftaroline	
Ethambutol	
Ampicillin	
Imipenem	
Isoniazid	
Piperacillin-tazobactam	
Cefaclor	
Clarithromycin	
Roxithromycin	
Tosufloxacin	
Tetracycline	
Dapsone-pyrimethamine	Antimalarial
Fansidar	
Mefloquine	
Atovaquone/proguanil	
Methotrexate	Chemotherapy
Gemcitabine	
Tegafur uracil UFT	
Fludarabine	
Aminoglutethimide	
Cisplatin	
Amitriptyline/Maprotiline	Antipsychotic
Venlafaxine	
Risperidone	
Clozapine	
Trazodone	
Paroxetine	
Duloxetine	
Sertraline	
Levetiracetam	Antiepileptic
Valproic acid	
Idantoin/Phenytoin	
Carbamazepine	
Captopril	Antihypertensive
Ifenprodil	
Mesalamine	Antiinflammatory
Sulfasalazine	
Ibuprofen	
Piroxicam	
Diclofenac	
Balsalazide	
Benzbromarone	
Nimesulide	
Bucillamine	
Naproxen	
Ustekinumab	Immunotherapy
Interferon alpha	
Infliximab	
Abatacept	
FK-506	
Amiodarone	Cardiac
Mexiletine	
Diltiazem	
Simvastatin	Lipid-reducing
Acetaminophen	Others
Progesterone	

Fig. 5: Drugs Related To Eosinohilic Pneumonitis

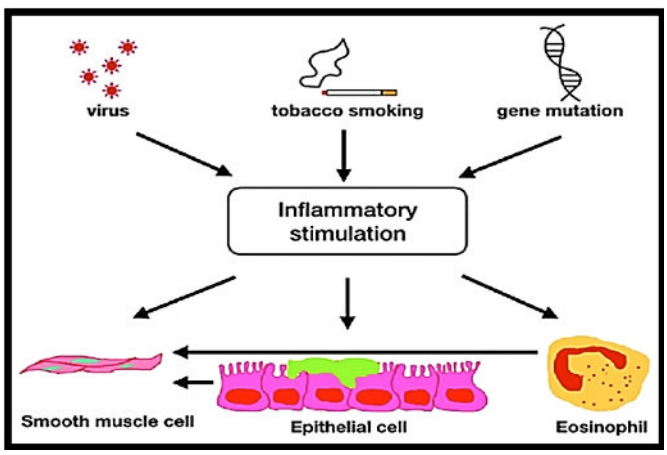

Fig. 7: Pathophysiology Of Copd

SLEEP APNEA

Disorder in which pauses in breathing during sleep occur more often than normal.

Sleep apnea may be obstructive (OSA, in which breathing is interrupted by a blockage of air flow), central (CSA, in which regular unconscious breath stops), or a combination of the two (Fig. 8).

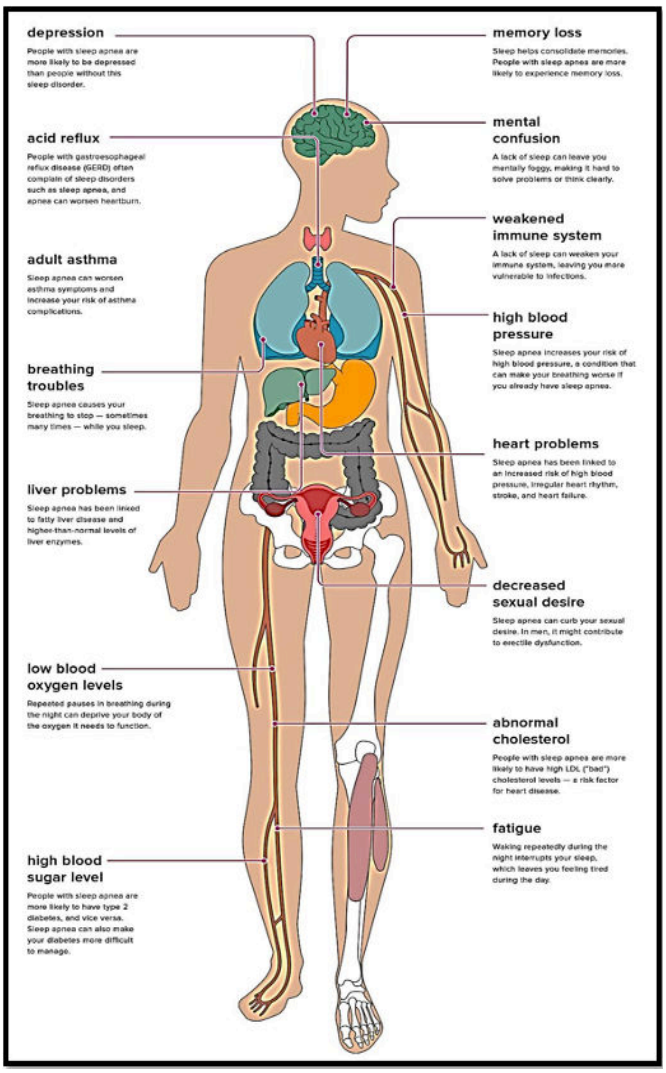

Fig. 8: Consequences Of Sleep Apnea

PULMONARY FIBROSIS

Pulmonary fibrosis seems to be the end of the road for most of the above-mentioned pathologies (fig. 9) 14-19.

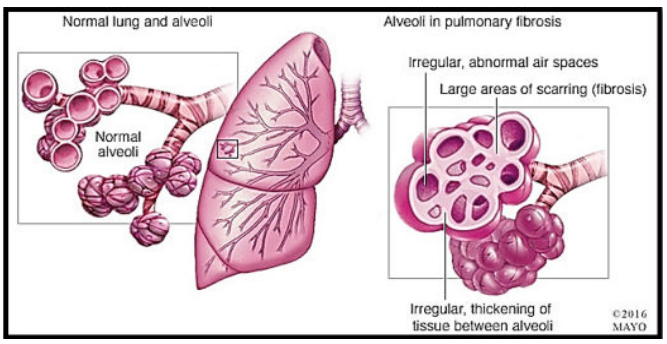

Fig. 9: Structural Tissue Damage Related To Pulmonary Fibrosis

INHALED IBUPROFEN

IBU is a NSAID compound.

NSAIDs are widely used in therapy due to their analgesic, antipyretic, and anti-inflammatory effects (Fig. 10) 20-23.

IBU inhibits the migration, adhesion, and aggregation of the leukocytes, and decreases the release of lysosomal enzymes.

It maintains optimal body weight and improves FEV1.

Local therapy administers drugs directly to the lungs, with limited absorption into the systemic circulation, minimizing the possible side effects.

A large surface area is available for administration with a dense vasculature, which provides for rapid onset of action.

Degradation of drug by gastrointestinal enzymes and first-pass metabolism in the liver does not occur.

It is bactericidal, virucidal, mucolytic and has a known anti-inflammatory property 24,25.

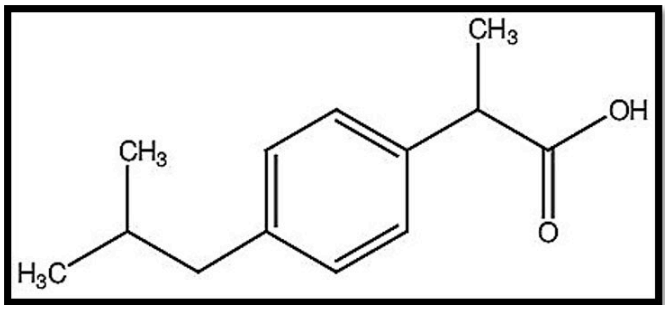

Fig. 10: Chemical Structure Of Ibuprofen

ANTI-INFLAMMATORY PROPERTIES

Mediated through cyclooxygenase inhibition, NIH is also seen to produce a marked decrease in reactive oxygen species (ROS).

This ROS reduction was only observed when Na-Ibuprofenate was administered by inhalation.

BACTERICIDAL PROPERTIES

They are based on the fact that NIH penetrates and destabilizes lipid membranes.

This interaction is strongly stabilized by the presence of a high ionic strength of the hypertonic solution.

VIRUCIDAL PROPERTIES

In vitro studies demonstrated NIH virucidal activity against enveloped or lipid-coated viruses.

MUCOLYTIC PROPERTIES

These are due to three different mechanisms that are observed acting together:

1- the alkaline formulation neutralizes the acidic pH present in the Goblet cells, which would allow the structure of the mucins that are supercoiled at acidic pH to fluidize

and thus be exposed to the medium more easily, 2- Ibuprofen can bind and remove the Ca++ found in the amino terminus of the mucins and that keeps them together forming a large stable complex, thus allowing them to fluidize for easier secretion, and
3 - the presence of high ionic strength in the formulation facilitates the dissociation of the mucins that are attached to the lung tissue by breaking the electrostatic interaction of the mucins with the cells to which they are adhered, thus achieving the release of lung secretions that allow better ventilation.

SAFETY OF IBUPROFEN

In a protocol designed to expose rats at a very high dose from NIH, the rats were nebulized for one hour for three months, after which they were sacrificed for histopathological evaluation of the lungs.
No significant NIH-induced injury was found.
The final concentration of this preparation is 50 mg of sodium ibuprofenate / ml of isotonic solution.
Ibuprofen, (2,4-isobutylphenyl propanoic acid), is a weak acid. Therefore, by subjecting it to a mol-by-mol reaction with sodium bicarbonate (weak base), in a suitably preserved isotonic solution of sodium chloride, the salt of this acid (sodium ibuprofenate) is obtained.
This resulting molecule has amphiphilic characteristics, the polar part is hydrophilic (the carboxyl group) and the nonpolar is lipophilic (hydrocarbon tail), thus acquiring surfactant properties (Fig. 11).

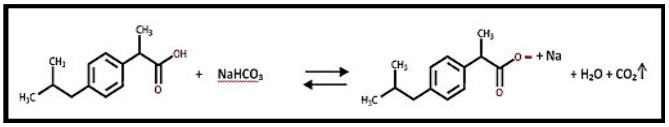

Fig. 11: Chemical Reaction From Ibuprofen To Sodium Ibuprofenate

CORRECT CHOICE / USE OF THE NEBULIZER DEVICE

Sodium ibuprofenate is a saponified solution.
So, the greater the turbulence generated by the nebulizer device, the more foam it will produced.
Foam can remain adhered to the walls of the nebulizer ducts, reducing the amount of active principle that reaches the lung.
Classic nebulizers with pistons are preferred.
Ultrasonic nebulizers must be programmed at the lowest possible power.

CASE REPORTS:

Between May 2022 and April 2023, we assisted eight patients with different lung restrictive conditions.

Case # 1
Male, 44 years.
32 years´smoking.
COPD GOLD 4.
Dyspnea score: 5
O2 permanent requirement.
Poor response to inhaled corticosteroids.
Received INH twice a day for two months, without suspending previous medication.
O2 requirement reduced to very sporadic use.
Dyspnea reduced to score 3.

Case # 2
Male, 68 years.
52 years´smoking.
Pulmonary Fibrosis.
IPF Score very severe (<24.3 % vital capacity)
Dyspnea score: 5
O2 intermitent requirement.
Poor response to inhaled corticosteroids.
Received INH twice a day for two months, without suspending previous medication.
No O2 requirement.
Dyspnea reduced to score 3.

Case # 3
Female, 51 years.
Post COVID Pulmonary Fibrosis.
IPF Score severe (<45 % vital capacity)
Dyspnea score: 4
O2 intermitent requirement.
Poor response to inhaled corticosteroids.
Received INH twice a day for one month, without suspending previous medication.
No O2 requirement.
Dyspnea reduced to score 2.

Case # 4
Female, 56 years.
41 years´smoking.
COPD GOLD 4.
Dyspnea score: 4
O2 intermitent requirement.
No response to inhaled corticosteroids.
Received INH twice a day for 1,5 months, without suspending previous medication.
No O2 requirement.
Dyspnea reduced to score 2.

Case #5
Male, 56 years.
43 years´smoking.
COPD GOLD 4.
Dyspnea score: 5
O2 permanent requirement.
No response to inhaled corticosteroids.
Received INH twice a day for 2 months, without suspending previous medication.
O2 intermitent requirement.
Dyspnea reduced to score 3.

Case # 6
Male, 60 years.
Post COVID Pulmonary Fibrosis.
IPF Score severe (<45 % vital capacity)
Dyspnea score: 4
O2 intermitent requirement.
Poor response to inhaled corticosteroids.
Received INH twice a day for 2 months, without suspending previous medication.
O2 sporadic requirement.
Dyspnea reduced to score 2.

Case # 7
Male, 60 years.
46 years´smoking.
COPD GOLD 4.
Dyspnea score: 5
O2 permanent requirement.
Poor response to inhaled corticosteroids.
Received INH twice a day for two months, without suspending previous medication.
O2 requirement reduced to intermitent use.
Dyspnea reduced to score 3.

Case # 8
Female, 60 years.
39 years´smoking.
COPD GOLD 3.
Dyspnea score: 4
Poor response to inhaled corticosteroids.
Received INH twice a day for two months, without suspending previous medication.
Dyspnea reduced to score 2.

STATISTICS ON CASES:

We studied 8 (eight) subjects.
Three female (37.5 %) and 5 male (62.5 %) (Fig. 12)
Ages ranged from 44 to 68, with a median of 51.9 years (Fig. 13).
COPD was the most frequent diagnosis, found in five subjects (62.5 %) (Fig. 14).
Post COVID fibrosis was second found diagnosis in our series.
O2 requirement was present in 7 subjects (87.5 %)
Previous response to inhaled corticosteroids had been poor (75 %) to nule (12.5 %).
Dyspnea after INH was reduced around 50 %, if compared with previous status.
O2 requirement was reduced 80 %, and suspended in one subject.

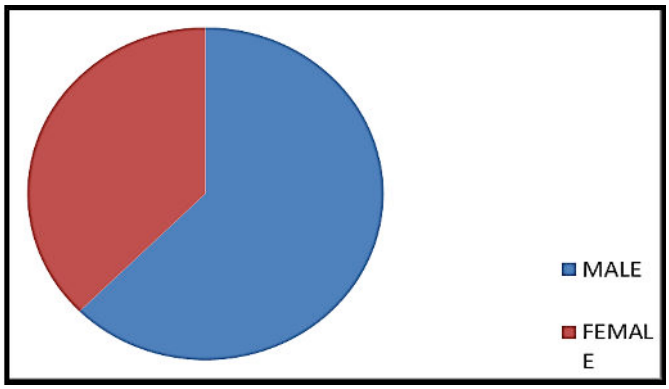

Fig. 12: Gender Of Subjects

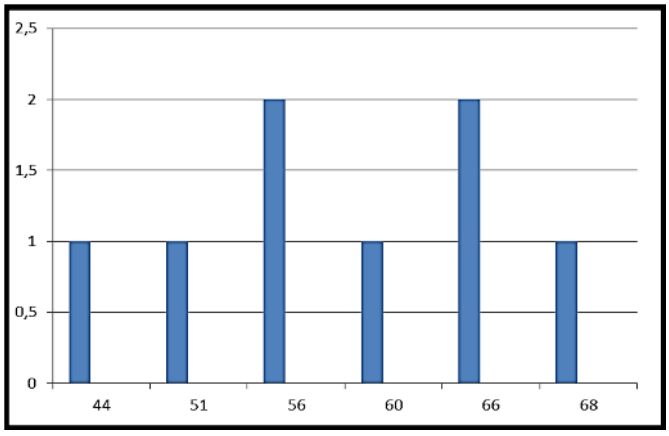

Fig. 13: Ages Of Subjects

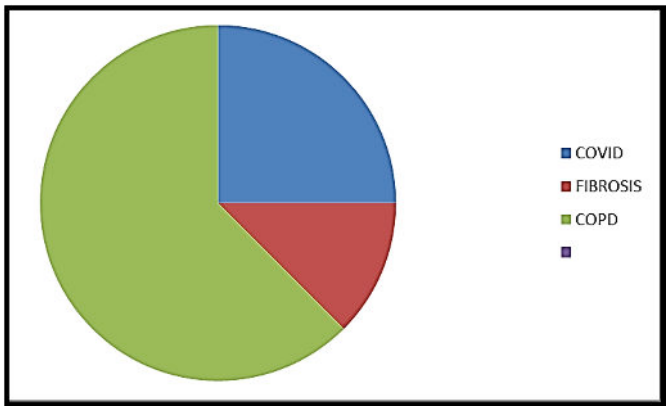

Fig. 14: Diagnoses Of Subjects

CONCLUSIONS

The inexorable handicap that these chronic pathologies produce in the quality of life of the affected patients is indisputable, as well as the enormous economic cost that they originate in the productive and health systems.
Inhaled Ibuprofen could give a simple, unexpensive, very effective response to the following conditions: COPD, sleep apnea, and other chronic, restrictive lung diseases, because of its multiple therapeutic effects (Fig. 15) 26-28. Limitations of this work are based on the necessary evaluation in larger cohorts.

EFECTO MUCOLÍTICO	EFECTO BACTERICIDA	EFECTO ANTIALÉRGICO	EFECTO ANTIINFLAMATORIO	ACCIÓN INTERSTICIAL	ACCIÓN EN EL PARÉNQUIMA	ACCIÓN SOBRE LOS BRONQUIOS
X	X	X	X	X	X	X

Fig. 15: Benefits Of Inhaled Ibuprofen In Reference To Its Effects And Action Levels

CONFLICT OF INTERESTS

None.

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