Antihistamines

Jorge** A. **Quel*

In 1910 Dale and Laidlaw **first** identifíed histamine.
1937 Bobitt and Staut produced the first H 1 antagonist.
1942 The first antiHISTAMINE (phen-benzamine) **was** released for the treatment of allergic conditions.

Recently new antihistamines have been discovered with minimal sedating effects and antiallergic and antiinflammatory effects.

*Anühistamine FIRST GENERA **TION***
Ethanolamine
Benadryl diphenhydramine HCí, strength 25 or 50 mg are also used as sleeping pills.

Rondec-TR carbinoxamine maléate, 8mg.

Tavist clemastine fumarate, 2.68 mg.

Naldecon phenyltoloxamine, 15mg.

ACTION: Very potent Hl antagonist
CNS frequency of drowsiness varíes with antihistamine compounds.
Anticholinergic effects are weak.
Gastrointestinal: side effects are rare.

Ethylened iamines
PBZ tripelennamine 25 to 50 mg used in pregnancy
Histalet forte pyrilamine maléate
oldest ciass of Hl antagonists

CNS some sedation
Gastrointestinal can cause gastroinsteestinal upset
Anticholinergic effects weak

PHENOTHIAZINE
Phenergan promethazineHCL 12.5 5,25, 50 mg
USE frequent added to codeine for cough me dicine.
Tacaryl methdilazine HCL 8mg

CNS produces heavy sedation

PIPERAZINES
Atarax hydroxyzine
USE motionsickness and urticaria
CNS produces dull mental alertness

ALKYLAMINES
Actifed triprolidine HCL 2.5mg
Chlor-trimeton chlorpheniramine maléate, 4, 8, 12mg Polaramine
dexchlorpheniramione maléate, 2, 4, 6 mg
Dimetapp brompheniramine maléate, 4mg
Drixora dexbrompheniramine maléate, 6mg
USE are very effective with modérate drowsiness in adults; in childrens produce central nervous stimulation more so than others group

** Inmunólogo Pediatra. Director Ejecutivo Hispanic American Allergy and Inmunology Association. Marina del Rey, Ca. U.S.A.*

OTHERS

Trinaiíne azatadine maléate, Img
USE rhinitis

Periactin cyproheptadine HCI, 4mg
USE urticarias.

SECOND GENERATION

Seldane terfenadine
USE due to interaction with macrolites, can produce cardio toxicity

Hismanal astemizole
USE due to interaction with macrolites, can produce cardio toxicity and weighí gain

Claritine loratadine lOmg (syrup Img per mi)

METABOLITES

Allegra fexofenadine HCI 30, 60, 180mg and syrup metabolite of terfenadine (seldane)

Zyrtec cetirizine HCI tablets 5, 10 mg and syrup Img 4ml metabolite of atarax

TOPICALS

Azteline azelastine nasal spray

Livostin levocabastine eye drops

POORER SCHOOL PERFORMANCE (VUURMAN, 1992)

1. Study compared performance *oí* children with SAR and matched normáis on the use of a didactic computer simulation in a classroom setting.
2. Children who received diphenhydramine or placebo leamed signifícantly less than normal (non-allergy) controls.
3. Children who receved loratadine performe better than those who received eiíher placebo or diphenhydramine, but less well than children without allergies.

INCREASE RISK OF WORK-RELATED INJURIES (GILMORE, 1996).

1a. Síudy conducted with Group Health Cooperative of Puget Sound. 2b. Patients prescribed sedating antihistamines had elevated ri sk of i nj ury (1:1.5)
5 0% i ncrease ri sk of traum atic work-related injury

ANT1H1STAMINE DOS1NG COMBINING SEDATING AT N1GHT AND NON SEDATING IN THE DAYTIME.

1. Chlopheniramine pm dosing (in combination with terfenadine am dosing) demonstrated and adverse effect on daytime sleepiness and level of alertness. 2. Chlorpheniramine pm dosing (in combination with terfenadine am dosing) demonstrated an adverse effect on day time brain functioning.

BRONCHODIATION EFFECTS OF ANTI-HISTAMINE.

1. Produce increase forcé expiratory volume first second in pulmonar test.

Antihistamines exert many effects that have anti=allergic or anti-inflammatory consequences.

These effects are unrelated to their H1 receptor blockade activity
The precise mechanisums by which these effects are exerted have not been elucidated but appear to be related to the caíionic amphiphilic nature of the antihistamine molecule and the ability of the

antihistamine molecuíe to inserí itself in cell membranes.
The effects occur on many inflammatory cells-the model best studied is mast ceill/basophil histamine reléase
The ability of antihistamines to prevent mast cell and basophil degranulation extends to numerous stimuli of the degranulation process including allergen-induced degranulation

However, it should be clearly stated that clinical effects of this anti-allergic/anti-inflammatory activity are unclear.
The concentrations of antihistamines necessary to achieve these effects in vitro are oftentimes higher than those achied during the admilnistration of these drugs for therapy.

Anti-leukotrienes in the treatment of asthma

Jorge A. Quel

In 1938, Feldberg and Kellaway used the term slow-reacting substance of anaphylaxis (SRS-A) to describe a smooth muscie-contracting factor that appeared in the exúdate of the guinea-pig lung when treated with cobra venom. Two years later, Kellaway and Trethewie suggested that SRS-A may play a role in the treatment of asthma. However their role in asthma was not clarified until much íater in 1983 by Samuelsson who called them leukotrienes due to the possiblity of their leukocyte origin.

Of the three esential fatty acids (arachidonic, linolenic and alpha íinolenic), arachidonic acid is the one that synthesis leukotrienes.

When arachidonic acid coming from the perinuclear membranes is activated by phos-pholipase A2, the liberated substance follows two pathways: The fírst pathway is cyclolooxygenase which give origin to prostaglan-dines and thromboxanes.
The focus of our interest is the second pathway, the 5 Lipoxygenase, which gives origin to LTA4.

From LTA4

LT4 under the influence of LTA4 hydrolased becomes LTB4
Also, LT4 under the influence of the LTC4 synthase becomes
LTC4\---------- LTD4- ..... ------- LTE4

In normal individuáis, inhaled LTC4 and LTD4 are about lOOOx as active as histamine in causing bronchodilation. Bisguard has demonstrated that the airways of asthmatic subjects are 100 times to 1000 times more responsive to LTD 4 than those of nonasthmatic controls. The onset of action of inhaled LTD4 and LTE4 is four to six minutes compared with the ten to twenty minutes required for LTC4.

There is a receptor for LTD4 and this receptor could be inhibited by **antagonists.**

2aflrlukast(accolate) is a selective and

competitive antagonist of leukotriens LD4 and LTE4.
Montelukast(singulair)is also a selecíive and competitive antagonist of leukotriens LD4 and LTE4.
Zileuton (zyflo)is an **inhibitor** of the 5 lipoxynase

EXERCÍSE INDUCED ASTHMA When 20 mg of zafirlukast was given orally prior to exercise it caused a mean máximum percentage fall in FEV1 of 21.6% compared with 36.0% **following** placebo. When 400mg zafirlukast was inhaled 30 minutes before exercise, the percentage fall in FE VI was 14.5% after medication compared with 30.2% after placebo. It is imporíant to realise that patients using inhaled beta agonists as their regualr preventative therapy experience a loss of the bronchoprotective effect. **However,** recent studies revea! that the bronchoproíective effects of Zafirlukast and montelukast remain through many weeks of treatment.

COLD AIR ÍNDUCED ASTHMA
A study of zarfirlukast in cold-induced asthma showed a significant attenuation of bronco-constriction 30 minutes after a single dose of the receptor antagonist.
Another study shows the effect of zileuton after a single 800mg dose produced signifícant attenuation of the asthmatic patient's response to cold dry air.

ASPIRÍN INDUCE ASTMA
I. In Patients with aspirin-induced asthma Zileuton reduced the main máxima! urinary LTE4 levéis after aspirin challenge by 68%; Zileuton also blocked nasal, gastroinstesinal and dermal responses to aspirin.
Montelukast has demonstrated signifícant clinical improvement in aspirin sensitive patients.

ALLERGEN INDUCED ASTHMA

Inhalational challenge studies in sensitized sheep showed that zafírlukast suppressed the airway responses to antigens, this includes the early and late response. In humans, zafirlukast also attenuated inhalation of various antigens such as as grass, caí dander, and ragweed including the early and late response.
Singulair inhibited 75% of bronchoconstriction to antigens in the early phase and 57% in the late phase.

DRUG 1NTERACTIONS

Zafíriukast (accolate) metabolizes by CYP2C9 (tolbutamide, phenytoin,carbamazepine) or CYP3A4 (dihydropyridine calcium channel blockers, cyclosporine, astemizole, cisapride). Zarfirlukast plasma ievels are reduced by erythromycin and theophylline and Zafirlukast plasma levéis are increased by aspirin.

Montelukast (Singulair) is metabolized in the CYP450 3A4 and 2C9. After a single injection of theophilline, singulair did not cause changes in the blood level of theophilline.
Phenobarbital decreased the AUC of montelukast by 40 %
Clinical monitoring should be done with concominant administraron of phenobarbital and rifampin
Zileuton **(Zyfio)** metabolizes by the P450 3A.
Hepatic elevation of one or more Üver test may occur during ziflo treatment, contraindication liver disease.

ANTI-LEUKOTRINES ANTAGONISTS AND INHIBITOR IN ASTMA

Singulair in adults reduces *as needed* beta 2 angonist use by 26.1% from baseline compared with 4.6% for placebo. In patients with nocturnal awakening at least two nights per week, Singulair

reduces noctural awakening by 34% compared with 15% with placebo.

Accolate

In other studies accolate improved the FEVl by 11% as well as the daytime symptoms by 26%.

Zileuton showed improvement in FEVl of 33.4% to 14.6% verses placebo.

Concominant use of these medications also demonstrated a significant reduction in the use of corticoids and beta 2 agonists. The magnitude of improvement in airway function after four weeks of administration is an increase in FEVl along wth an increase in morning peak flow. These medications have become another tool in the effective management of asthma.