150 KETOTIFEN IN THE MANAGEMENT OF PRE-SCHOOL ASTHMA:

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A double-blind placebo controlled cross-over trial was carried out to assess the efficacy of ketotifen in pre-school asthmatics. The trial period consisted of a 1 month run-in and two 6 month treatment periods, with ketotifen 1 mg b.d. or placebo, separated by a 1 month wash-out. 47 children with moderate to severe asthma completed the study. There were 29 boys and 18 girls age ranged from 1 yr 10 months to 5 yrs 11 months (mean 4 yr + 1 yr 3 months). In addition to the study treatment, patients were managed conventionally with beta agonists, theophylline, cromoglycate, inhaled oral steroids. Throughout the study attempts were made to reduce medications to the minimum level compatible with good symptom control. Patients were seen monthly (by BGL) and parents completed a diary card between visits. Benefit was assessed by comparing symptoms of asthma and rhinitis, concomitant medication, and parental and physician preference for the two treatment phases. A preliminary analysis of the data suggests that there was an order effect with symptom control improving and concomitant medication increasing throughout the study period. When active and placebo treatments were compared there was little difference with respect to symptom control, or level of concomitant medication. There was no clear preference expressed for active or placebo therapy. Ketotifen was well tolerated and was associated with increased weight gain.

151 EFFECT OF NIFEDIPINE ON THE HISTAMINE (H) OR ACETYLCHOLINE (A) INDUCED BRONCHOCONSTRICTION CONTROLLED BY PHARMACOCAPNOGRAPHY.

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Before and after administration of the Ca^{++} channel blocker nifedipine (Corinfar, GDR), bronchial provocation tests were performed in asthmatic children displaying an enhanced respiratory sensitivity to H and A aerosols. Continuous challenges with 0.05% H resp. with 0.1% A solution were administered for max. 15 minutes. Computerised on-line CO_2 analysis of exhaled air (Jaeger CO_2 Test) was used to detect subclinical bronchoconstriction. The results revealed full protection against the effect of H from a single oral dose of Corinfar in 4 out of 17 cases, and partial protection in 10 out of 17 cases. The corresponding data for A were 5 and 7 out of 17 cases, respectively. Thus, Corinfar exerts a sifnificant protective effect against both types of provocation. The lower sensitivity of spirometry than that of capnography meant that, although moderate protective effects could be demonstrated, these were not mathematically significant. The Ca^{++} channel blockers may be useful ancillary agents in the complex treatment of patients with bronchial hyperreactivity, partly because they decrease the bronchial smooth muscle spasm, partly because they inhibit the release of active mediators.

Ref.: Barnes: Calcium-channel blockers and asthma. Thorax 38, 481, 1983.

152 NEBULISED BECLOMETHASONE DIPROPIONATE SUSPENSION FOR ASTHMA IN CHILDREN UNDER SIX YEARS

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The role of beclomethasone in childhood asthma is established, but the efficacy of the suspension form in clinical practice is unconfirmed. In a double blind cross-over trial, we compared beclomethasone dipropionate with placebo in 16 children less than 6 years old (mean age 40.9 months). Each child received nebulised solutions containing 150 mcg of beclomethasone or 3 mls of water three times per day, each for two months, as the sole form of prophylaxis. Three children abandoned the trial prematurely due to marked worsening of symptoms, one during the first treatment period and two during the second treatment period - each was receiving placebo at the time. Parental preference indicated beclomethasone superior to placebo in 11 children. Of the 13 children who completed the trial, eight were improved on beclomethasone and five on placebo. There were no significant differences in daily symptom scores, bronchodilator and oral corticosteroid use or number of symptom free days. No side effects of active treatment were noted. These results show that beclomethasone dipropionate suspension may be an effective treatment in young children, though the figure of five who were better on placebo is disappointingly high. Further clinical studies are urgently needed.

153 ANTIASTHMATIC EFFECTS OF ONIONS - THIN LAYER CHROMATOGRAPHY FOR IDENTIFICATION OF THE ACTIVE COMPONENTS?

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Recently we reported on asthmaprotective effects of onions (Agents & Actions 14:262,1984, Eur. J. Pharmacol. 107:17,1985). Now we are trying to identify their active component(s).

Groups of 8-10 guinea pigs were sensitized to ovalbumin (OA) and challenged by OA inhalations as described. Their asthmatic reactions were quantificated as ml compressed air by whole body plethysmography. / Onion juice was obtained by sqeezing onions and lyophilized. Thin layer chromatography (Silica gel Woelm 63 200, chloroform/methanol 70/30, 65/35, 60/40, 50/50, 100/0 (v/v)) of fresh onion juice gave 6 subfractions. / 30 min.prior to the OA challenges the animals were fed with 1 ml lyophilized onion juice (1 - 100 mg/kg), its subfractions or saline (= solvent of both).

The whole extract prevented the asthmatic reactions in a dose dependent fashion: 100 mg/kg :91%, 50 mg/kg: 86% ($p < 0.005$), 20 mg/kg: 68% ($p < 0.05$), 1 mg/kg: 46% ($p > 0.05$, t-test for unpaired data)). Most active was subfraction 6 a dosage of 20 mg/kg being equipotent to 100 mg/kg of the whole extract. It contains at least 8 different substances. Their biological activity will be tested in future experiments.

154 SODIUM CROMOGLYCATE INDUCED CHANGES IN THE DOSE-RESPONSE CURVE OF INHALED METHACHOLINE IN CYSTIC FIBROSIS

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Patients with Cystic Fibrosis (CF) have an increased incidence of bronchial hyper-reactivity to inhaled methacholine (MCh). There is also an increased skin reactivity to inhaled allergens and an increased incidence of allergic rhinitis. Thus, CF shares some clinical features with asthma and drugs used in asthma may be useful in CF.

Sodium cromoglycate (SCG) is efficacious in asthma, blocking some patients against MCh challenge and decreasing bronchial hyper-reactivity. We studied the potential role of SCG in CF by determining if it could block acute bronchoconstriction induced by MCh, and predict CF patients whose bronchial hyper-reactivity and symptoms would lessen with longterm use.

Fifteen CF patients known to respond to an MCh challenge were studied. None had clinical asthma, nor had intercurrent infections at the time of the study. Three standard MCh challenges were performed on consecutive days at the same time; two after placebo (distilled water) and one after 2ml 1% SCG, which were given in random order in a double-blind manner. As well as providing a baseline, the two placebo studies provided a measure of the reproducibility of the MCh challenges (variation less than 10%). There were only small changes in FEV1 after placebo and SCG (less than 6%). The mean FEV1 was 65% (range 32-90) and PD20 was calculated from the dose-response curves of cumulative MCh inhaled versus drop in FEV1. Four patients (27%) were completely protected by SCG. We conclude that longterm trials of SCG in CF are indicated to assess predictive ability of MCh challenge blocking for improved symptom scores and decreased MCh sensitivity. SCG may benefit selected CF patients.

(Introduced by Melvin M. Grumbach, M.D.)

155 EFFECT OF INHALED AZLOCILLIN, MISTABRON AND COMBINATION THERAPY IN CHILDREN WITH CYSTIC FIBROSIS.

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Previous clinical trials have shown a beneficial effect of inhaled antibiotics and mucolytics in cystic fibrosis. In vitro studies have suggested significant enhancement of azlocillin inhibition of Pseudomonas aeruginosa by the addition of the mucolytic, mistabron (sodium 2 mercaptoethane sulphonate). We compared the clinical effect of inhaled azlocillin, mistabron and azlocillin combined with mistabron in 21 children with cystic fibrosis aged 6 to 15 years, chronically infected with Ps. aeruginosa, using a double blind cross over design with random order of 4 month treatment periods separated by 2 month treatment-free periods. 18 patients completed the study. The number of respiratory infections during combination therapy was significantly less compared with azlocillin ($p < 0.01$) and mistabron ($p < 0.01$). The number of hospital admissions was also less during combination therapy, compared with mistabron ($p < 0.02$). Percentage weight gain was significantly more during combination therapy compared with mistabron ($p < 0.05$). Lung function, chest X-ray scores and ventilation/perfusion lung scan scores were not significantly different during any treatment period. No apparent allergic, bronchospastic or other adverse reactions to treatment were noted. Although resistance of Ps. aeruginosa to azlocillin did develop during all 3 treatment periods, in no case did it persist. Combination therapy with inhaled azlocillin and mistabron is superior to either treatment used alone. These results support previous in vitro findings that inhibition of Ps. aeruginosa by azlocillin is enhanced by mistabron.