Effect of an oral gold compound, auranofin, on non-specific bronchial hyperresponsiveness in mild asthma

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Abstract

Background **– A recent double blind clinical trial in Japan has shown that auranofin (6 mg/day) is a useful treatment for patients with moderate to severe asthma. To investigate the mechanism of action of auranofin the bronchial responsiveness to inhaled methacholine has been studied in well controlled asthmatic subjects.**

Methods **– Nineteen adult asymptomatic asthmatic subjects received auranofin (3 mg orally twice a day) or inactive placebo in random order for 12 weeks in a double blind fashion. Bronchial responsiveness to inhaled methacholine and pulmonary function tests were measured at the same time on different days before, and six and 12 weeks after, each treatment.**

Results **– Non-specific bronchial hyperresponsiveness 12 weeks after treatment with auranofin was decreased compared with that before treatment with auranofin and 12 weeks after treatment with inactive placebo, although the treatment did not improve pulmonary function tests.**

Conclusions **– Non-specific bronchial hyperresponsiveness 12 weeks after treatment with auranofin is decreased in a group of mild asymptomatic asthmatic patients with normal lung function.**

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At present few gold compounds are approved for treatment of bronchial asthma because they can have severe adverse effects and, moreover, other effective drugs are available. However, gold compounds have been used for the treatment of patients with severe asthma since the 1950s and can improve non-specific bronchial hyperresponsiveness in patients with steroid-dependent asthma after long term therapy.[1]

Auranofin is an oral gold compound used for the treatment of rheumatoid arthritis[2] and has fewer adverse effects than other gold compounds.[3] It has recently been reported in an open trial that auranofin was of benefit in the treatment of patients with steroid-dependent asthma.[4] In addition a double blind, multicentre study in Japan showed that treatment with auranofin for more than 12 weeks was beneficial for moderate to severe asthmatics. In the present study we have investigated the effect of auranofin on non-specific bronchial hyperresponsiveness in asymptomatic asthmatic patients in a double blind, placebo controlled fashion.

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Methods

PATIENTS

Twenty five asymptomatic outpatients with bronchial asthma were recruited from our asthma clinic. Patients who had received systemic steroid treatment were excluded from the study. All other routinely used agents were continued for 12 weeks before and during the period of the study. Of 15 patients receiving beclomethasone dipropionate 13 had taken it for more than one year and two for more than six months. None had experienced an exacerbation of asthma or respiratory tract infection for 12 weeks before the study. The study was approved by the ethics committee of the Tohoku University School of Medicine and all patients gave written informed consent.

STUDY DESIGN

Auranofin or placebo, in 3 mg tablet form, was administered orally twice a day for 12 weeks in a double blind fashion. Blood sampling and measurements of bronchial responsiveness to methacholine and pulmonary function tests were carried out at the same time on different days before, and six and 12 weeks after, each treatment. All subjects were required to record clinical symptoms and concomitant medication during the study period.

METHACHOLINE CHALLENGE AND PULMONARY FUNCTION TESTS

Bronchial responsiveness to inhaled methacholine was measured by the astograph method.[5] To evaluate response curves of total respiratory resistance (Rrs) three indices were defined as follows: (1) Rrs-cont: mean values of respiratory resistance during inhalation of saline; (2) Dmin: cumulative units of methacholine from the start of the study to the beginning of an increase in respiratory resistance; and (3) PD_{35}-Grs: cumulative units of methacholine from the start of the study to the point at which total respiratory conductance decreased 35% from its baseline value. One unit represents one minute of inhalation of 1 mg/ml methacholine.

FEV_1 and FVC were measured with a spirometer (OST-80A; CHEST, Tokyo) and the best of three satisfactory measurements was recorded.

MEASUREMENT OF SERUM GOLD CONCENTRATION

Five ml of blood was collected in a heparinised container before, and six and 12 weeks after, the start of treatment. Gold concentrations in the blood were measured by atomic absorption analysis spectrophotometry after the study had been completed.

STATISTICAL ANALYSIS

Twenty four patients, excluding one who was found to be suffering from a duodenal ulcer one week after the treatment, completed the study. Before unblinding the data all subjects were reviewed and five were excluded because of respiratory tract infection (two), a more than 25% change in Rrs-cont (two), and poor compliance (one).

Logarithmic transformation of Dmin and PD_{35}-Grs was used for statistical analysis. Results were expressed as mean (SD). Results from the auranofin and placebo groups were compared by the unpaired Student's *t* test and those within each group were compared by the paired Student's *t* test.

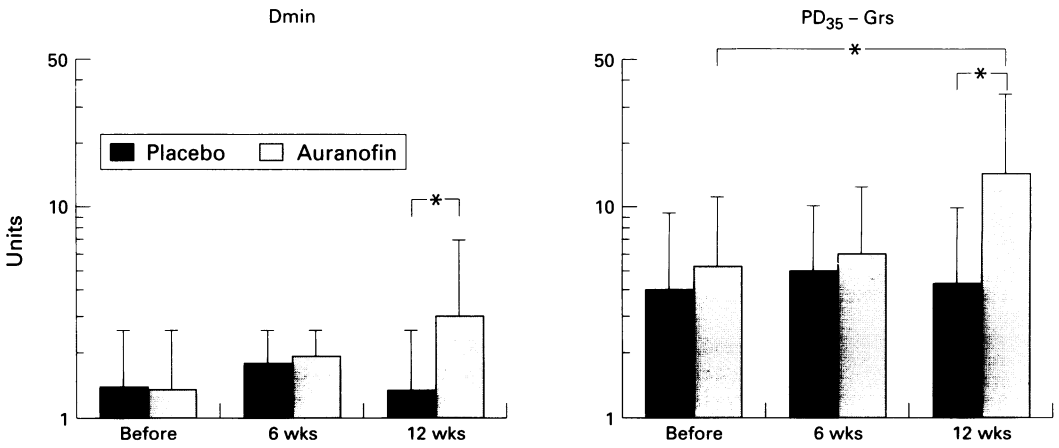
Results

Efficacy data were analysed for the 19 subjects who completed the study. Nine patients received auranofin and 10 received an inactive placebo. Mean (SD) age in the auranofin group was 46·2 (12·7) years and mean (SD) baseline FEV_1 was 104·3% (20·4%) of predicted. In the placebo group the mean age was 40·0 (13·9) years and mean baseline FEV_1 was 101·7% (17·5%) of predicted. Eleven patients (five in the auranofin group and six in the placebo group) were receiving an inhaled steroid. Thus, there were no significant differences in age, baseline FEV_1, or concomitant medications between the two groups.

As shown in the figure there was a significant improvement in Dmin ($p<0·05$) and PD_{35}-Grs ($p<0·05$) 12 weeks after auranofin treatment compared with 12 weeks after placebo treatment, although no significant differences in Dmin or PD_{35}-Grs were found 0 and six weeks after treatments between the groups. In the auranofin group there was an improvement in Dmin ($p<0·05$) and PD_{35}-Grs ($p<0·05$) 12 weeks after the treatment compared with baseline. Treatment with auranofin for 12 weeks therefore significantly decreased non-specific bronchial responsiveness. In addition, after 12 weeks of treatment with auranofin the mean (SD) values of PD_{35}-Grs increased from 0·652 (0·474) to 0·921 (0·668) units in five steroid-dependent asthmatic subjects and increased from 0·285 (0·381) to 0·695 (0·401) units in the remaining four patients. In contrast, the corresponding values in the placebo group were from 0·542 (0·439) to 0·362 (0·445) units in six steroid-dependent subjects and from 0·253 (0·264) to 0·399 (0·543) units in the remaining four subjects.

The mean (SD) values of baseline FEV_1, FVC, and Rrs-cont are summarised in the table. There was a small decrease in FEV_1 after treatment, and a statistically significant ($p<0·05$) decrease between 0 and 12 weeks. There was no significant difference in the placebo group. Thus, no improvement was seen in FEV_1, FVC, or Rrs-cont after either treatment.

The mean (SD) blood concentrations of gold were 0·003 (0·001), 0·460 (0·114), and 0·483 (0·100) µg/ml 0, six, and 12 weeks after the treatment, respectively. The concentrations after six and 12 weeks of treatment were therefore significantly higher than those after 0 weeks, although there was no significant difference in the concentration between six and 12 weeks. In the placebo group no increase in the blood concentration of gold was found in any of the subjects.



*Changes in Dmin and PD_{35}-Grs 0, 6, and 12 weeks after treatment with auranofin or placebo. Compared with the placebo group patients in the auranofin group showed significant improvement in Dmin and PD_{35}-Grs after 12 weeks of treatment. Significant improvement in PD_{35}-Grs occurred after 12 weeks of treatment with auranofin compared with the baseline value; *$p<0·05$. Dmin = cumulative units of methacholine from the start of the study to the beginning of an increase in total respiratory resistance; PD_{35}-Grs = cumulative units of methacholine from the start of the study to the point at which total respiratory conductance decreased 35% from its baseline values.*

Mean (SD) values of FEV_1, FVC, and $\%FEV_1$ to predicted values, and of respiratory resistance during inhalation of saline (Rrs-cont)

	Placebo group				*Auranofin group*			
	FEV_1 (l)	*FEV_1 (%)*	*FVC (l)*	*Rrs-cont (cm H_2O/l/s)*	*FEV_1 (l)*	*FEV_1 (%)*	*FVC (l)*	*Rrs-cont (cm H_2O/l/s)*
0 weeks	2·84 (0·81)	101·7 (17·5)	4·00 (0·81)	5·3 (1·3)	2·65 (0·57)	104·3 (20·4)	3·75 (0·67)	5·4 (1·3)
6 weeks	2·84 (0·74)	102·0 (15·2)	3·96 (0·82)	5·2 (1·2)	2·56 (0·73)	99·6 (24·2)	3·64 (0·95)	5·4 (1·6)
12 weeks	2·78 (0·73)	99·8 (17·2)	3·98 (0·81)	5·3 (1·4)	2·55 (0·65)*	99·6 (22·2)*	3·64 (0·80)	5·2 (1·2)

* $p < 0·05$ compared with 0 weeks.

Four of the 11 patients treated with auranofin experienced gastrointestinal symptoms. Two patients suffered mild diarrhoea several days after starting auranofin, but the symptoms cleared within one week. The remaining two patients had loose stools throughout the study period but required no treatment. In one patient on placebo, diarrhoea was also observed. None of the patients exhibited any biochemical or haematological changes at 12 weeks after either treatment.

Discussion

Bronchial hyperresponsiveness has been reported to be increased by various stimuli and also by exacerbations of asthma.[6,7] On the other hand, long term treatment with gold compounds decreased hyperresponsiveness in an open trial.[1] To avoid other factors which might influence the responsiveness only asymptomatic asthmatic subjects were selected for the present study. Some of the subjects were therefore taking inhaled steroids which may have improved their bronchial hyperresponsiveness and baseline pulmonary function tests.[8,9] The 12 weeks of treatment with auranofin significantly improved non-specific bronchial hyperresponsiveness without any bronchodilator effect, suggesting that bronchial hyperresponsiveness after treatment with auranofin was significantly decreased in a group of mild asymptomatic asthmatic patients with normal lung function.

Bronchial hyperresponsiveness has been reported to be increased by various substances such as antigen,[10] sulphur dioxide,[11] ozone,[12] leukotriene E_4,[13] platelet activating factor,[14] toluene diisocyanate,[15] and C5a.[16] Auranofin has been reported to inhibit the release of histamine[17] and leukotriene C_4[18] from human basophils and mast cells stimulated by IgE, to inhibit release of leukotriene C_4 and B_4 from human peripheral leucocytes stimulated by fMLP,[19] to inhibit generation of superoxide radicals from human peripheral leucocytes,[20] and to inhibit the chemotactic activity of human mononuclear leucocytes.[21] The anti-allergic effects of auranofin may therefore be responsible for the decrease in bronchial hyperresponsiveness, although the precise mechanism of its action requires further investigation.

Serious adverse effects have been reported following parenteral therapy with gold compounds. However, in this study only gastrointestinal symptoms were observed and no treatment was required. Thus, no serious adverse effects were found, as is consistent with previous reports on the action of auranofin.

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