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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Re: Expediente N° 06-113.683

Solicitud de Patente de Invención Titulada: "COMBINACION DE GLICOPIRROLATO Y (R)-5-[2-(5,6-DIETIL-INDAN-2-ILAMINO)-1-HIDROXI-ETIL]- 8-HIDROXI-1H-QUINOLIN-2-ONA MALEATO (INDACATEROL MALEATO)"

Solicitante: NOVARTIS AG

N. Ref.: P2006/000216

RESPUESTA AL OFICIO No. 8817 NOTIFICADO POR FIJACIÓN EN LISTA

No. 242, DE FECHA 9 DE JULIO DE 2010.

(REQUERIMIENTO ARTÍCULO 46)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 46 de la Decisión 486:

1. Presento copia completa de los siguientes documentos requeridos por el Examinador en el examen de búsqueda de anterioridades, según lo previsto en el Artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina:

106
183

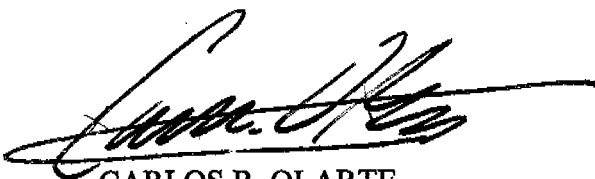
1)

CYDULKA R K ET AL: "EFFECTS OF COMBINED
TREATMENT WITH GLYCOPYRROLATE AND
ALBUTEROL IN ACUTE EXACERBATION OF CHRONIC
OBSTRUCTIVE PULMONARY DISEASE"
ANNALS OF EMERGENCY MEDICINE, LANSING, MI,
US,
vol. 25, April 1995 (1995-04), pages
470-473, XP000979833
ISSN: 0196-0644

2)

TZELEPIS G ET AL: "COMPARISON OF
NEBULIZED GLYCOPYRROLATE AND
METAPROTERENOL IN CHRONIC OBSTRUCTIVE
PULMONARY DISEASE"
EUROPEAN RESPIRATORY JOURNAL, MUNKSGAARD
INTERNATIONAL PUBLISHERS, COPENHAGEN, DK,
vol. 9, no. 8, 1996, pages 100-103,
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Atentamente,



CARLOS R. OLARTE
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Anexo: Artículos mencionados.

XP-000979833

P.D. 4-1995
P. 470-73 (4)

Effects of Combined Treatment With Glycopyrrolate and Albuterol in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Medicine, MetroHealth Medical
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Study objective: To investigate whether the addition of a single aerosolized dose of glycopyrrolate leads to a greater improvement in pulmonary function than treatment with albuterol alone for patients with acute exacerbation of chronic obstructive pulmonary disease (COPD).

Design: Prospective, randomized, blinded, controlled study. Fifty-seven patients with acute exacerbation of COPD were entered into the study. All patients received three aerosol treatments. Patients were randomized to receive 2 mg aerosolized glycopyrrolate (combination therapy group) or aerosolized placebo in addition to their first 2.5-mg albuterol aerosol treatment. All patients received 2.5 mg of aerosolized albuterol alone for the next two treatments.

Setting: Urban teaching hospital emergency department.

Results: We found no difference in pretreatment 1-second fractional expired volume (FEV₁) between the control and glycopyrrolate groups. There was no significant difference in the absolute value of the FEV₁ at 1 hour or at 3 hours between the two groups; however, patients who received combination therapy had a greater percent increase from the pretreatment value of FEV₁ (56%) as measured in milliliters than did control patients (19%; $P=.008$).

Conclusion: The combination of glycopyrrolate and albuterol produces a greater improvement in FEV₁ than does albuterol alone in the treatment of patients with acute exacerbation of COPD.

[Cydulka RK, Emerman CL: Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med* April 1995;25:470-473.]

INTRODUCTION

Anticholinergic agents have been widely used to treat patients with chronic obstructive pulmonary disease (COPD) exacerbations. Glycopyrrolate, a quaternary ammonium compound, is poorly absorbed from mucosal surfaces but otherwise has pharmacologic properties similar to those of atropine itself. Glycopyrrolate, when given by inhalation, should only affect the respiratory tract, thus limiting associated side effects.¹ It is available in solution and is easily used in nebulized form. The purpose of this study was to investigate the efficacy of combination treatment of glycopyrrolate and the β -agonist albuterol. In particular, we wished to determine whether the addition of a single aerosolized dose of glycopyrrolate would lead to greater improvement in pulmonary function over treatment with albuterol alone.

MATERIALS AND METHODS

This study was conducted from February 1991 through February 1992 in the emergency department of Metro-Health Medical Center, a large, urban, university-affiliated hospital. Patients with the self-reported diagnosis of COPD or patients with histories consistent with COPD, as defined by the American Thoracic Society², were eligible for the study if they presented to the ED with acute respiratory distress along with cough, wheezing, or both. Patients with asthma were excluded from the study, along with patients whose initial spirometry demonstrated a 1-second fractional expired volume (FEV_1) greater than 75% of predicted normal value. Patients were also excluded if they had clinical or radiographic evidence of pneumothorax, pneumonia, decompensated congestive heart failure, or history of lung cancer; if they were unable to perform spirometry; or if they had received prehospital aerosol treatment. Patients were also excluded if they had contraindications to the administration of glycopyrrolate, including glaucoma, obstructive uropathy, ileus, ulcerative colitis or megacolon, myasthenia gravis, autonomic neuropathy, liver disease, kidney disease, hiatal hernia with esophagitis, or cystic fibrosis. Patients younger than 18, pregnant women, nursing mothers, and prisoners were also excluded from this study.

After informed consent had been obtained, blood was drawn for CBC with differential, theophylline level, and arterial blood gases. Chest radiographs were also taken. Oxygen therapy was initiated at 3 L/minute through a nasal cannula and subsequently adjusted on the basis of the results of arterial blood gas or pulse oximetry, if available. Spirometry was performed with a computerized

portable Fleisch-pneumotach-type spirometer (SpiroScan 1000), with the patient seated and wearing nose clips. At least two forced expiratory maneuvers were obtained, with the highest forced vital capacity and FEV_1 used for analysis. The spirometer was calibrated at least three times a week by use of a 3-L syringe.

After initial evaluation, all patients received nebulized albuterol, 2.5 mg every hour for three aerosols. Patients received, in a randomized, double-blinded fashion, glycopyrrolate 2 mg or an equivalent volume of placebo solution mixed with their first albuterol aerosol. A block-design randomization scheme was devised before the study and used by the pharmacy to prepare coded vials. The patients, treating physicians, and investigators were all blinded to the contents of the vials. Patients did not receive any further glycopyrrolate or placebo solution after the initial aerosol. Spirometry was repeated 1 hour after the first aerosol and again 1 hour after the third aerosol treatment.

One hour after completion of the third aerosol (3 hours after initial treatment), patients were questioned as to the appearance of side effects to albuterol or glycopyrrolate. Patients then were admitted to the hospital or discharged from the ED without further therapy, at the discretion of the treating physician, on the basis of clinical assessment, including improvement in pulmonary function, disappearance of wheezing, and improvement in dyspnea. Patients who were discharged from the hospital were contacted by telephone after 48 hours to determine whether they had experienced relapse, defined as an unscheduled return for further treatment for bronchospasm within 48 hours after discharge. This study was approved by the hospital's human investigation committee.

Discrete variables were analyzed by means of the χ^2 test, whereas continuous variables were analyzed with Student's *t* test. Repeated-measures ANOVA was performed with a general linear model for ANOVA with post hoc comparisons of means by Tukey's test.³ A *P* value of less than .05 was considered significant. Data are reported as the mean $\pm$ SD.

RESULTS

Fifty-seven consecutive eligible patients, with an average age of 61.5 ± 11.3 years, were entered into the study (Table). Eighty-two percent of the patients were using outpatient β -agonist inhalers, 65% were taking theophylline products, and 18% were using steroids. Fifty-one patients were current or past cigarette users, with an average of 45.6 ± 23.6 pack-years. The WBC was $10,563 \pm 3,876$ cells/mm³; the theophylline level was 6.4 ± 6.5 μ g/mL.

There was no significant difference in the age (60 ± 10.3 years versus 62.4 ± 12.4 years), cigarette use (40.9 ± 23.0 pack-years versus 51.1 pack-years, WBC (10.3 ± 3.1 cells/mm³ versus 10.9 ± 4.6 cells/mm³), PaO₂ (62.4 ± 20.1 mm Hg versus 70.2 ± 15.8 mm Hg), initial FEV₁ ($29.5\% \pm 10.5\%$ versus $31.0\% \pm 12.8\%$ predicted normal), prednisone use (20% versus 15%), inhaler use (87% versus 78%), or ipratropium use (10% versus 7%) between the glycopyrrolate group and the control group. However, the theophylline level was significantly higher in the glycopyrrolate group (8.3 ± 7.3 mg/mL versus 4.3 ± 4.7 mg/mL, $P < .02$).

The pretreatment FEV₁ in the control group was 934 ± 424 mL ($31.0\% \pm 12.8\%$ of predicted normal); it was 892 ± 364 mL ($29.5\% \pm 10.5\%$ of predicted normal) in the glycopyrrolate group (NS). At 1 hour FEV₁ had increased to 963 ± 477 mL ($31.6\% \pm 12.6\%$ predicted) in the control group and $1,129 \pm 585$ mL ($37.4\% \pm 13.6\%$ predicted) in the glycopyrrolate group ($P = .22$ and $P = .11$, respectively). At 3 hours the FEV₁ in the control group was $1,095 \pm 573$ mL ($36.2\% \pm 15.8\%$ predicted) and $1,312 \pm 614$ mL ($42.8\% \pm 13.5\%$ predicted) in the glycopyrrolate group ($P = .19$ and $P = .11$, respectively). Repeated-measures analysis showed a significant difference in the percent of change in FEV₁ from pretreatment value (absolute value) between the control and glycopyrrolate groups both 1 hour and 3 hours after the start of treatment (Figure 1). Patients treated with glycopyrrolate and albuterol had a $28.2\% \pm 42.2\%$ increase in FEV₁ after treatment, whereas patients treated with albuterol alone had only a $6.0\% \pm 36.1\%$ increase in FEV₁ at 1 hour ($P = .04$). At

3 hours, patients treated with glycopyrrolate had a $56.0\% \pm 56.1\%$ increase in FEV₁, compared with a $19.3\% \pm 40.9\%$ increase in patients treated with albuterol alone ($P = .001$; Figure):

Overall, 30 (53%) of the patients required admission. Fifty percent of patients with COPD treated with glycopyrrolate were admitted, compared with 57% of patients treated with albuterol alone (NS). Follow-up information was available for 22 (81%) of the patients discharged from the ED. We noted no difference in the relapse rate between the glycopyrrolate and control groups (15.4% versus 11.1%).

Twenty-seven percent of the glycopyrrolate group experienced side effects, compared with 15% of patients treated with albuterol alone (NS). Side effects reported in the combination albuterol/glycopyrrolate group included dry mouth, headache, hypotension, and palpitations. Side effects reported in the albuterol group included tremors, anxiety, and palpitations. This study had a power of 20% to discern differences in the incidence of side effects between the two groups.

DISCUSSION

We found that patients with acute exacerbation of COPD who received combination glycopyrrolate and albuterol aerosol treatments had greater improvement in their percent change in FEV₁ at 1 hour ($29.2\% \pm 42.2\%$ versus $6.0\% \pm 36.1\%$, $P = .04$) and at 3 hours ($56.0\% \pm 56.1\%$ versus $19.3\% \pm 40.9\%$, $P = .001$) than did patients treated with albuterol alone. These results are distinctly different from

Figure.
Change in FEV₁ with treatment.

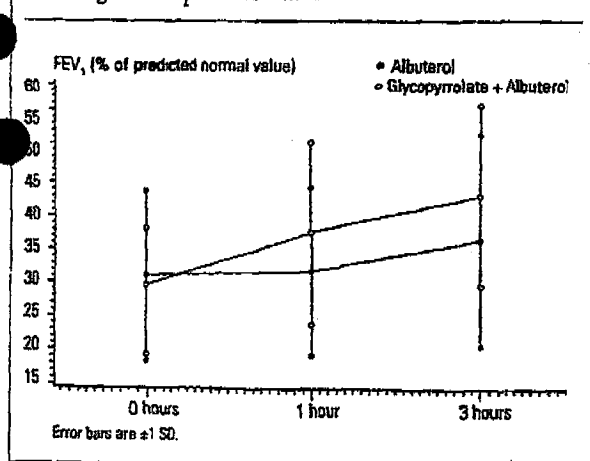


Table.
Results.

Parameters	Albuterol and Glycopyrrolate	Albuterol and Placebo
FEV ₁		
Initial absolute value (mL)	892±364	934±424
1 hour (mL)	1,129±585	963±477
Percent change in absolute value at 1 hour	29.1±42.2	6.0±36.1*
3 hours (mL)	1,095±573	1,312±614
After treatment (3 hours) (% of predicted normal)	42.8±13.5	36.2±15.8†
Percent change in absolute value of FEV ₁ at 3 hours	56.0±56.1	19.3±40.9‡
Percentage of patients admitted	50	57.1§
Side effects	26.7	14.8§

* $P < .05$ versus glycopyrrolate group.

† $P < .07$ versus glycopyrrolate group.

‡ $P < .01$ versus glycopyrrolate group.

§NS versus glycopyrrolate group.

those we reported in asthmatic patients treated with both albuterol and glycopyrrolate.⁴ Asthmatic patients treated with albuterol alone had greater improvement in their FEV₁ values than did asthmatic subjects treated with a combination of glycopyrrolate and albuterol. We believe this is best explained by the fact that in spite of airflow limitations due to destructive changes in the lungs, patients with COPD have some cholinergic tone, which can be abolished by anticholinergic agents, resulting in improved airflow.¹ Glycopyrrolate has been used for a variety of indications over the past 20 years, although only recently have investigators studied its use in the treatment of acute bronchospasm.⁵⁻⁹ Slovis et al⁴ reported a patient with COPD exacerbation in whom inhalation therapy with glycopyrrolate failed, presumably because of low tidal volumes, but who was successfully treated with intravenous glycopyrrolate. Because multiple studies have demonstrated that anticholinergic agents improve bronchodilation, even in patients who were considered nonresponders to adrenergic agents^{1,4}, we hypothesized that a long-acting quaternary ammonium compound such as glycopyrrolate had something new to offer in the treatment of acute COPD exacerbation.

This study is limited by the small sample size, which yielded a low power to discern differences in side effects. Other limitations include the large SDs accompanying our FEV₁ measurement. Unfortunately, large SDs are commonly found in research of obstructive airway disease. The one-tailed power of the study to determine a difference in post-treatment FEV₁ (as percentage of predicted normal value) was 49%. In addition, patients in the study group had higher theophylline levels than did patients in the control group. Because the levels in both groups were subtherapeutic, we do not think this influenced the outcome of the study. In this study we used only a single dose of glycopyrrolate. We cannot state whether other doses of the drug would be more or less effective. Similarly, we cannot determine the optimum dosing frequency. Finally, the maximum dose of albuterol that can be used in acute exacerbation of COPD has yet to be determined. The role of glycopyrrolate as a second agent in patients who receive maximal doses of albuterol may be different than that found with the dose employed here.

CONCLUSION

The addition of a single treatment with aerosolized glycopyrrolate to hourly treatments with albuterol produces a greater percent improvement in FEV₁ than does albuterol alone in the treatment of patients with COPD exacerbation.

The improvement in pulmonary function in patients with COPD did not lead, however, to a decrease in the hospitalization rate. Within the limitations discussed above, we feel that this drug should be considered for use in patients with acute exacerbation of COPD. The optimal doses and frequency for administration of glycopyrrolate for the patients remain to be determined.

REFERENCES

1. Gross NJ. Anticholinergic agents in COPD. *Chest* 1989;91(suppl):525-535.
2. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease and asthma. *Am Rev Respir Dis* 1987;134:225-243.
3. SAS Institute, Inc. *SAS/STAT User's Guide*, Release 8.00 edition Cary, North Carolina, SAS Institute, Inc. 1988, p 1028.
4. Slovis CM, Daniels GM, Wharton DT. Intravenous use of glycopyrrolate in acute respiratory distress due to bronchospastic pulmonary disease. *Ann Emerg Med* 1987;16:898-900.
5. Cydulka RK, Emerman CI. Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of asthma. *Ann Emerg Med* 1994;23:270-274.
6. Gilman MJ, Meyer I, Carter J, et al. Comparison of aerosolized glycopyrrolate and metaproterenol in acute asthma. *Chest* 1990;98:1035-1038.
7. Johnson BE, Suratt PM, Gal TJ, et al. Effect of inhaled glycopyrrolate and atropine in asthma. *Chest* 1984;85:325-328.
8. Schroederstein DC, Bush RK, Chervinsky P, et al. Twelve-hour bronchodilation in asthma with a single aerosol dose of the anticholinergic compound glycopyrrolate. *J Allergy Clin Immunol* 1988;82:115-118.
9. Walker FB, Kaiser DL, Kowal MB, et al. Prolonged effect of inhaled glycopyrrolate in asthma. *Chest* 1987;91:49-51.

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Comparison of nebulized glycopyrrolate and metaproterenol in chronic obstructive pulmonary disease

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Comparison of nebulized glycopyrrolate and metaproterenol in chronic obstructive pulmonary disease. G. Tzelepis, S. Komanapoli, D. Tyler, D. Vega, A. Fulambarker. ©ERS Journals Ltd 1996.

ABSTRACT: We assessed the bronchodilating effect of glycopyrrolate (GP) and compared it with that of metaproterenol (MP), alone and in combination (GP+MP), in patients with chronic obstructive pulmonary disease (COPD).

In a double-blind study, 11 patients (aged (mean±SD) 69±6 yrs; forced expiratory volume in one second (FEV₁) 1.2±0.4 L) with stable COPD inhaled nebulized GP 1.0 mg, MP 15 mg, or GP 1.0 mg + MP 15 mg. Spirometry was performed before inhalation and at hourly intervals for 8 h after inhalation.

It was found that GP produced a bronchodilating effect that was about equal to that of MP but lasted longer (8 vs 5 h). The combination of GP and MP produced a bronchodilating effect that was greater than that of either drug alone and was evident mostly during the effect of MP. The mean peak percentage improvement in FEV₁ over baseline was 35% for GP+MP and 25% for either drug alone.

These data suggest that nebulized glycopyrrolate is an effective bronchodilator in some patients with chronic obstructive pulmonary disease. Concurrent administration of glycopyrrolate and metaproterenol produces additional bronchodilation that is primarily apparent during the bronchodilator effect of metaproterenol.

Eur Respir J, 1996, 9, 100-103.

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Glycopyrrolate (GP), a quaternary ammonium compound, is an anticholinergic agent that has primarily been used with anaesthesia to reduce gastric acidity and salivary secretions or to reverse neuromuscular blockade [1]. Recently, GP has been used as a bronchodilator in patients with asthma [2-5]. This study was designed to investigate the bronchodilator effect of GP in patients with stable chronic obstructive pulmonary disease (COPD) and compare it with that of another commonly used bronchodilator, the β -adrenergic agonist metaproterenol (MP). In addition, we examined whether the concurrent administration of GP and MP provided any further bronchodilation than GP alone in this group of patients.

Methods

Eleven men with diagnoses of chronic bronchitis, emphysema, or both [6] were recruited from out-patient pulmonary clinics to participate in the study (table 1). Stability of their disease was defined as no hospitalizations or change in therapy over a 6 month period prior to the study. All patients had a forced expiratory volume in one second/forced vital capacity ratio (FEV₁/FVC) of less than 70%, and a history of cigarette smoking. A positive bronchodilator response following inhalation of metaproterenol, as defined by the American Thoracic Society (ATS) criteria [6], was documented during previous pulmonary function testing. None of the subjects

had a history of bronchial asthma or were on oral steroids. The study was approved by the institutional review committee and informed consent was obtained from all patients.

Measurements of FVC and FEV₁ were performed on a Collins Eagle One spirometer (Braintree, MA, USA). The medications were mixed with normal saline to a total volume of 7.5 mL and aerosolized using a Misty-Neb nebulizer (Airlife) with a flow rate of 10 L·min⁻¹ delivered over 15 min. GP, MP, or both were administered randomly and in double-blind fashion. Theophylline preparations and beta-agonists were discontinued 24 and 12 h prior to each study day, respectively. The subjects were studied in the pulmonary function laboratory on three separate days, at least three days apart. On each study day, baseline measurements of FEV₁ and FVC were obtained followed by inhalation of one of the following aerosols: 1) GP 1.0 mg; 2) MP 15 mg; or 3) GP 1.0 mg and MP 15 mg. Measurements of FVC and FEV₁ were subsequently performed at hourly intervals for 8 h. Blood pressure and pulse rate were measured before treatment and at the time of spirometry. Subjects were also questioned about any side-effects.

The largest FVC and FEV₁ of at least three reproducible values, as measured according to ATS standards [6], were analysed. The FEV₁ and FVC data were subjected to analysis of covariance (ANCOVA), where the drug regimen (drug) and time were within-subject variables and baseline performance was a covariate that was

Table 1. — Patient characteristics and pulmonary function testing data

Pt No.	Age yrs	Smoking Hx pack-yrs	FEV ₁ L	FEV ₁ % pred	ΔFEV ₁ % init	ΔFEV ₁ % pred	FVC L	TLC L	TLC % pred
1	70	56	0.84	21	21	5	1.8	6.4	101
2	60	60	1.26	44	23	10	2.6	6.4	106
3	63	98	0.58	19	15	3	1.3	7.2	115
4	59	120	1.53	46	22	10	3.2	6.3	97
5	68	50	0.81	24	25	6	1.7	6.2	90
6	75	26	1.18	35	33	11	2.1	8.5	118
7	70	92	1.46	46	26	11	2.9	7.2	108
8	72	110	0.87	26	16	4	1.7	6.8	199
9	70	46	1.99	61	19	11	3.3	6.9	96
10	70	92	0.86	32	18	4	1.8	7.9	122
11	80	67	1.82	70	11	9	3.1	6.4	115
Mean	69	74	1.2	38	21	8	2.3	6.9	108
±SD	±6	±30	±0.4	±17	±6	±3	±0.7	±0.7	±11

Pt: patient; Hx: history; FEV₁: forced expiratory volume in one second; % pred: percentage of predicted normal value; ΔFEV₁: change in FEV₁ in response to metaproterenol; % init: percentage of initial FEV₁; FVC: forced vital capacity; TLC: total lung capacity.

constant across time but changing across drug. Since the sphericity hypothesis was rejected (for both dependent variables), Greenhouse-Geisser probabilities are reported where appropriate. In addition, repeated measures analysis of variance (ANOVA) for single within-subject variable (drug) at each interval was performed for both FEV₁ and FVC data. A p-value <0.05 was considered to be statistically significant. All analyses were performed using the BMDP statistical program (Los Angeles, CA, USA) [7].

Results

Subject characteristics and baseline pulmonary function data are shown in table 1. Reversibility for the group was $8 \pm 3\%$ (mean $\pm$ SD) of predicted FEV₁. The ANCOVAs revealed significant effects for the covariate, drug, time, and drug-by-time interaction both for FEV₁ ($p < 0.01$) and FVC ($p < 0.05$). Thus, performance following treatment was shown to be affected by baseline (pre-treatment) performance, the drugs administered, and the time after administration. Furthermore, though there were overall drug effects, the magnitude of differences between drugs varied over time (drug-by-time interaction).

Figure 1 presents mean values for FEV₁ measured at each time interval for all regimens. In comparing the overall drug effects, GP was more effective than MP ($p < 0.05$), and the combination of GP and MP was more effective than either drug alone ($p = 0.014$ for GP; and $p = 0.0016$ for MP). Further analysis at each time period showed that GP and MP produced similar improvements in FEV₁ at 1–5 h; thereafter, the improvements in FEV₁ were greater with GP (approximately 13% above baseline) than with MP ($p < 0.05$). The combination of GP and MP produced an improvement in FEV₁ that was significantly higher than that of MP at every time-point ($p < 0.05$), and than that of GP during the first 5 h after

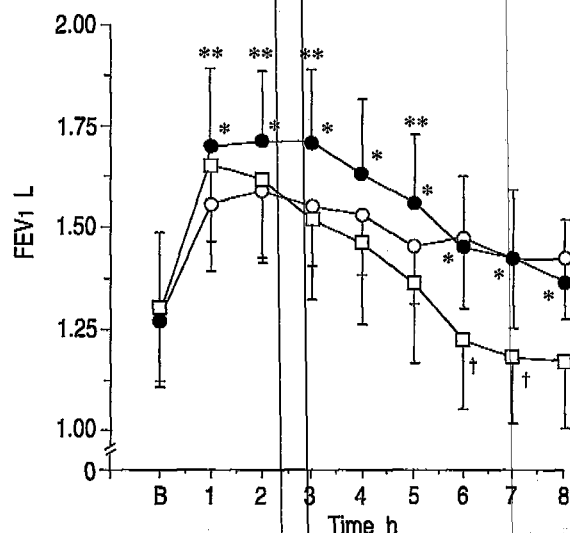


Fig. 1. — Increase in forced expiratory volume in one second (FEV₁) from baseline (B) following inhalation of metaproterenol (MP—□—), glycopyrrolate (GP—○—), or their combination (MP+GP—●—). Values are mean $\pm$ SEM. B: baseline; *: $p < 0.05$ when compared with MP; **: $p < 0.05$ when compared with GP; †: $p < 0.05$ when compared with GP.

administration ($p < 0.05$). The mean peak percentage increase in FEV₁ over baseline was approximately 35% for the combination and 25% for each drug alone.

The spirometric responses for FVC are shown in figure 2. Overall, GP was more effective than MP ($p = 0.0280$), and the combination of GP and MP was superior to MP ($p = 0.0012$) but as effective as GP ($p = 0.197$). Analysis at each time-point showed that the two drugs produced essentially similar improvements in FVC during the first 5 h, with the peak effect being about 20% above baseline; the improvement in FVC was higher at 4 h and 6–8 h with GP than with MP ($p < 0.05$). The combination of GP and MP produced a change in FVC that was greater than that of MP at 2–8 h ($p < 0.05$), and than that of GP only at 2, 3 and 5 h after administration ($p < 0.05$).

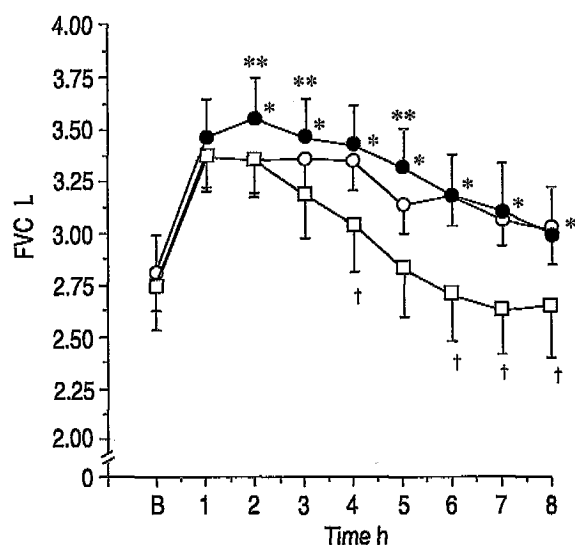


Fig. 2. — Increase in forced vital capacity (FVC) from baseline (B) after inhalation of metaproterenol (MP —□—), glycopyrrolate (GP —○—), or their combination (MP+GP —●—). Values are mean $\pm$ SEM. B: baseline. *: $p < 0.05$ when compared with MP; **: $p < 0.05$ when compared with GP; †: $p < 0.05$ when compared with GP.

No significant changes in blood pressure or pulse rate were noted. One patient reported tremors after inhalation of MP.

Discussion

In this study, clinically stable patients with COPD, some still having marked reversibility, were given nebulized GP, MP, or a combination of the two drugs. We found that GP produced a bronchodilating effect similar to that of MP, but of considerably longer duration. When inhaled concurrently, the two drugs produced an additive bronchodilating effect that was mainly apparent during the effect of MP.

The bronchodilating effects of GP were first noted in normal volunteers. GAL *et al.* [1] showed that GP, given intravenously or as an aerosol, produced a significant increase in FEV₁ which lasted up to 6 h. Subsequent studies confirmed the prolonged bronchodilating effect of GP in asthma, some studies [3, 5] demonstrating a bronchodilator effect up to 12 h. GILMAN *et al.* [2] also showed that the increase in FEV₁ produced by GP was comparable to that of MP. The present study extends these previous observations to patients with stable COPD. As in studies with asthmatic patients, we found that the peak bronchodilating response of GP occurred within 1–2 h, and the duration of action was 2–8 h.

The dose of GP used in the present study was selected on the basis of our own experience and also on studies in normals and in patients with asthma. In a preliminary study in COPD patients [8], we found that inhalation of 0.5 mg of GP produced a significant bronchodilation, yet smaller than that of 15 mg of MP. SCHROECKENSTEIN *et al.* [5] found that GP dosages of 0.5 or 1.0 mg produced equivalent bronchodilation. In a study comparing dose-response curves in normals, GAL *et al.* [1] found that the greater the dosage of GP the more sustained the

bronchodilating effect. However, the duration of bronchodilation produced by GP dosages greater than 1.5 mg was marginally better than that produced by a dose of 0.8 mg. Furthermore, the higher dosages were associated with more side-effects. GAL *et al.* [1], therefore, concluded that GP dosages of 1.0 mg could be used effectively with virtually no side-effects.

Unlike previous studies in asthmatics, we evaluated whether the bronchodilator effects of GP could be potentiated by a beta-agonist. We found that the concurrent inhalation of GP and MP enhanced the bronchodilating effect produced by either agent alone by an additional 10% improvement over baseline. This additive effect was evident only during the first 5 h after administration, an interval equal to the duration of action of MP.

The effects of concurrent administration of anticholinergic and adrenergic agents have been extensively evaluated and the results are controversial. Some studies have found synergistic effect [9–15], whereas others have not [16–19]. The additive effect of the two agents could be explained on the basis of differences in the mechanism of bronchodilation; anticholinergics act through the parasympathetic system whereas beta-agonists act through the sympathetic system. An alternative explanation for the additive effects may be related to submaximal dosages used rather than to enhanced effectiveness of the combined treatment. In patients with stable COPD, GROSS and SKORODIN [20] showed that addition of a beta-agonist to large dosages of an anticholinergic agent did not augment bronchodilation produced by the anticholinergic agent alone. In another study, EASTON *et al.* [21] found that addition of a second agent does not improve bronchodilation if large dosages of either adrenergic or anticholinergic agent are used. A potential advantage of the combined regimen is that it may reduce toxicity caused by each agent.

In the present study, all patients had partially reversible obstruction as measured following inhalation of a beta-adrenergic agonist. The question then arises as to whether GP is effective in patients not responding to beta-agonists. Previous studies have shown that COPD patients who do not respond to beta-agonists usually respond to anticholinergic bronchodilators, such as atropine or ipratropium bromide [9, 22]. Thus, as with atropine or ipratropium, a therapeutic trial of GP might be useful in patients with irreversible obstruction.

In conclusion, we found that glycopyrrolate achieved the same degree of bronchodilation as metaproterenol and had a duration of action that was longer than that of metaproterenol alone. Further studies involving larger numbers of patients are needed to establish the bronchodilator efficacy, safety and optimal dosage of glycopyrrolate in COPD.

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References

1. Gal TJ, Suratt PM, Lu JY. Glycopyrrolate and atropine inhalation: comparative effects on normal airway function. *Am Rev Respir Dis* 1984; 129: 871–873.

2. Gilman MJ, Meyer L, Carter J, Slovis C. Comparison of aerosolized glycopyrrolate and metaproterenol in acute asthma. *Chest* 1990; 98: 1095-1098.
3. Walker FB, Kaiser DL, Kowal MB, Suratt PM. Prolonged effect of inhaled glycopyrrolate in asthma. *Chest* 1987; 91: 49-51.
4. Johnson BE, Suratt PM, Gal TJ, Wilhoit SC. Effect of inhaled glycopyrrolate and atropine in asthma. *Chest* 1984; 85: 325-328.
5. Schroeckestein DC, Bush RK, Chervinsky P, Busse WW. Twelve hour bronchodilation in asthma with a single aerosol dose of the anticholinergic compound glycopyrrolate. *J Allergy Clin Immunol* 1988; 82: 115-119.
6. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991; 144: 1202-1218.
7. Dixon WJ (Ed.). BMDP statistical software manual. Berkeley, CA, University of California Press, 1990; Vol. 2.
8. Komanapalli S, Fulambarker A, Tyler D, Vega D, Patel J, Tzelepis G. Effects of glycopyrrolate and metaproterenol alone and in combination in COPD. *Am Rev Respir Dis* 1993; 147 (4): A316 (Abstract).
9. Dougals NJ, Davidson I, Sudlow MF, Fleney D. Bronchodilatation and the site of airway resistance in severe chronic bronchitis. *Thorax* 1979; 34: 51-56.
10. Lightbody LM, Ingram CG, Legge JS, Johnston RN. Ipratropium bromide, salbutamol and prednisolone in bronchial asthma and chronic bronchitis. *Br J Dis Chest* 1978; 72: 181-186.
11. Koyama H, Nishimura K, Ikeda A, Izumi T. A comparison of the bronchodilating effects of oxitropium bromide and fenoterol in patients with chronic obstructive pulmonary disease. *Chest* 1993; 104: 1743-1747.
12. Less AW, Allan GW, Smith J. Nebulized ipratropium bromide and salbutamol in chronic bronchitis. *Br J Clin Pract* 1980; 3: 340-342.
13. Leitch AG, Hopkin JM, Ellis DA, Merchant S, McHardy GJR. The effect of aerosol ipratropium bromide and salbutamol on exercise tolerance in chronic bronchitis. *Thorax* 1978; 33: 711-713.
14. Petrie GR, Palmer KNY. Comparison of aerosol ipratropium bromide and salbutamol in chronic bronchitis and asthma. *Br Med J* 1975; 1: 430-432.
15. Combivent Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. *Chest* 1994; 105: 1411-1419.
16. Rebuck AS, Chapman KR, Abboud R, Paré PD, Kreisman H, Wolkove N. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airway disease in the emergency room. *Am J Med* 1987; 82: 59-64.
17. Karpel JP, Pesin J, Greenberg D, Gentry E. A comparison of the effects of ipratropium bromide and metaproterenol sulfate in acute exacerbations of COPD. *Chest* 1990; 98: 835-839.
18. Karpel JP. Bronchodilator responses to anticholinergic and beta-adrenergic agents in acute and stable COPD. *Chest* 1991; 99: 871-876.
19. Lloberes P, Ramis L, Montserrat JM, et al. Effect of three different bronchodilators during an exacerbation of chronic obstructive pulmonary disease. *Eur Respir J* 1988; 1: 536-539.
20. Gross NJ, Skorodin MS. Role of the parasympathetic system in airway obstruction due to emphysema. *N Engl J Med* 1984; 311: 421-425.
21. Easton PA, Jadue C, Dhigra S, Antonisen NR. A comparison of the bronchodilating effects of a beta₂-adrenergic agent (albuterol) and an anticholinergic agent (ipratropium bromide), given by aerosol alone or in combination. *N Engl J Med* 1986; 315: 753-759.
22. Marini JJ, Lakshminarayan S. The effect of atropine inhalation in "irreversible" chronic bronchitis. *Chest* 1980; 77: 591-596.

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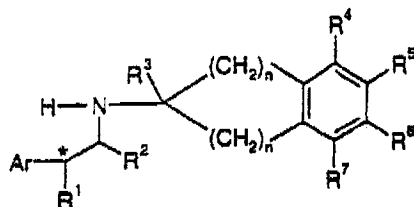
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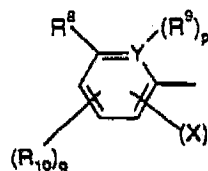
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ning of each regular issue of the PCT Gazette.*

(54) Title: **BETA2-ADRENOCEPTOR AGONISTS**



(I)



(II)

(57) Abstract: Compounds of formula (I) in free or salt or solvate form, where Ar is a group of formula (II) Y is carbon or nitrogen and R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, R⁹, R¹⁰, X, n, p, q and r are as defined in the specification, their preparation and their use as pharmaceuticals, particularly for the treatment of obstructive or inflammatory airways diseases. The compounds of formula (I) in free, salt or solvate form, have β 2-adrenoreceptor agonist activity.

189

The agents of the invention are also useful as co-therapeutic agents for use in conjunction with anti-inflammatory or bronchodilatory drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs. An agent of the invention may be mixed with the anti-inflammatory or bronchodilatory drug in a fixed pharmaceutical composition or it may be administered separately, before, simultaneously with or after the anti-inflammatory or bronchodilatory drug. Such anti-inflammatory drugs include steroids, in particular glucocorticosteroids such as budesonide, beclamethasone, fluticasone or mometasone, and dopamine receptor agonists such as cabergoline, bromocriptine or ropinirole. Such bronchodilatory drugs include anticholinergic or antimuscarinic agents, in particular ipratropium bromide, oxitropium bromide and tiotropium bromide. Combinations of agents of the invention and steroids may be used, for example, in the treatment of COPD or, particularly, asthma. Combinations of agents of the invention and anticholinergic or antimuscarinic agents or dopamine receptor agonists may be used, for example, in the treatment of asthma or, particularly, COPD.

In accordance with the foregoing, the present invention also provides a method for the treatment of an obstructive or inflammatory airways disease which comprises administering to a subject, particularly a human subject, in need thereof a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described. In another aspect, the invention provides a compound of formula I, or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore described for use in the preparation of a medicament for the treatment of an obstructive or inflammatory airways disease.

The agents of the invention may be administered by any appropriate route, e.g. orally, for example in the form of a tablet or capsule; parenterally, for example intravenously; topically to the skin, for example in the treatment of psoriasis; intranasally, for example in the treatment of hay fever; or, preferably, by inhalation, particularly in the treatment of obstructive or inflammatory airways diseases.

In a further aspect, the invention also provides a pharmaceutical composition comprising a compound of formula I in free form or in the form of a pharmaceutically acceptable salt or solvate thereof, optionally together with a pharmaceutically acceptable diluent or carrier therefor. Such compositions may be prepared using conventional diluents or excipients and techniques known in the galenic art. Thus oral dosage forms may include tablets and

147
190

capsules. Formulations for topical administration may take the form of creams, ointments, gels or transdermal delivery systems, e.g. patches. Compositions for inhalation may comprise aerosol or other atomizable formulations or dry powder formulations.

The invention also includes (A) a compound of formula I as hereinbefore described in free form, or a pharmaceutically acceptable salt or solvate thereof, in inhalable form; (B) an inhalable medicament comprising such a compound in inhalable form together with a pharmaceutically acceptable carrier in inhalable form; (C) a pharmaceutical product comprising such a compound in inhalable form in association with an inhalation device; and (D) an inhalation device containing such a compound in inhalable form.

Dosages employed in practising the invention will of course vary depending, for example, on the particular condition to be treated, the effect desired and the mode of administration. In general, suitable daily dosages for administration by inhalation are of the order of from 1 to 5000 µg.

The invention is illustrated by the following Examples. Compounds used in the Examples are prepared as follows:

Intermediate 1 - 5,6-Diethyl-inden-2-ylamine hydrochloride

Preparation 1 - 3-chloro-1-(3,4-diethylphenyl)- 1-propanone

1,2-Diethylbenzene (10.9 g, 74.6 mmol) and propionyl chloride (9.7 g, 74.6 mmol) are added dropwise to AlCl_3 (22.3 g, 167.8 mmol) in nitromethane (75 mL) over 30 min. The reaction mixture is stirred at room temperature for 2 hours, after which 70 g of ice and 14 mL concentrated sulphuric acid are added. The aqueous phase is extracted with ether, and the combined organic phases extracted with 2N HCl and saturated aqueous NaCl. The organic phase is further treated with activated charcoal, magnesium sulphate, and filtered, and the solvent removed *in vacuo*.

$^1\text{H-NMR}$ (CDCl_3) ppm: 7.8 (1H, s, Ar); 7.7 (1H, d, Ar); 7.2 (1H, d, Ar); 3.9 (2H, t, CH_2); 3.4 (2H, t, CH_2); 2.8 (4H, q, CH_2CH_3); 1.2 (6H, m, CH_3).

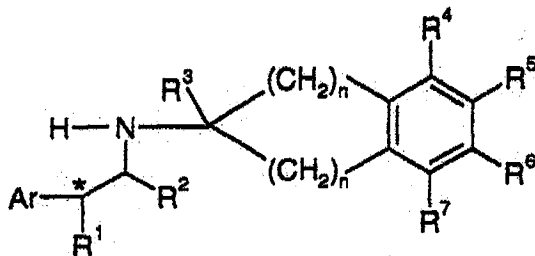
Preparation 2 - 2,3-dihydro-5,6-diethyl-1H-inden-1-one

3-chloro-1-(3,4-diethylphenyl)- 1-propanone (15.5 g) is dissolved in 66 mL concentrated sulphuric acid and heated to 90 °C for 4 hours. The reaction mixture is cooled, ice (70 g) is added, and the aqueous solution extracted twice with toluene. The organic layer is washed

10/14
191

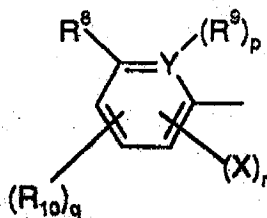
Claims

1. A compound of formula



in free or salt or solvate form, where

Ar is a group of formula



R^1 is hydrogen, hydroxy, or alkoxy,

R^2 and R^3 are each independently hydrogen or alkyl,

R^4 , R^5 , R^6 and R^7 are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, aryl, alkyl, alkyl substituted by one or more halogen atoms or one or more hydroxy or alkoxy groups, alkyl interrupted by one or more hetero atoms, alkenyl, trialkylsilyl, carboxy, alkoxycarbonyl, or $-\text{CONR}^{11}\text{R}^{12}$, where R^{11} and R^{12} are each independently hydrogen or alkyl, or R^4 and R^5 , R^5 and R^6 , or R^6 and R^7 together with the carbon atoms to which they are attached denote a carbocyclic or heterocyclic ring,

R^8 is halogen, $-\text{OR}^{13}$, $-\text{CH}_2\text{OR}^{13}$ or $-\text{NHR}^{13}$ where R^{13} is hydrogen, alkyl, alkyl interrupted by one or more hetero atoms, $-\text{COR}^{14}$, where R^{14} is hydrogen, $-\text{N}(\text{R}^{15})\text{R}^{16}$, alkyl or alkyl interrupted by one or more hetero atoms, or aryl and R^{15} and R^{16} are each independently hydrogen, alkyl or alkyl interrupted by one or more hetero atoms, or R^{13} is $-\text{C}(=\text{NH})\text{R}^{17}$, $-\text{SOR}^{17}$ or $-\text{SO}_2\text{R}^{17}$ where R^{17} is alkyl or alkyl interrupted by one or more hetero atoms, and R^9 is hydrogen, or R^8 is $-\text{NHR}^{18}$ where $-\text{NHR}^{18}$ and R^9 , together with the carbon atoms to which they are attached, denote a 5- or 6- membered heterocycle,

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Effects of Combined Treatment With Glycopyrrolate and Albuterol in Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Study objective: To investigate whether the addition of a single aerosolized dose of glycopyrrolate leads to a greater improvement in pulmonary function than treatment with albuterol alone for patients with acute exacerbation of chronic obstructive pulmonary disease (COPD).

Design: Prospective, randomized, blinded, controlled study. Fifty-seven patients with acute exacerbation of COPD were entered into the study. All patients received three aerosol treatments. Patients were randomized to receive 2 mg aerosolized glycopyrrolate (combination therapy group) or aerosolized placebo in addition to their first 2.5-mg albuterol aerosol treatment. All patients received 2.5 mg of aerosolized albuterol alone for the next two treatments.

Setting: Urban teaching hospital emergency department.

Results: We found no difference in pretreatment 1-second fractional expired volume (FEV₁) between the control and glycopyrrolate groups. There was no significant difference in the absolute value of the FEV₁ at 1 hour or at 3 hours between the two groups; however, patients who received combination therapy had a greater percent increase from the pretreatment value of FEV₁ (56%) as measured in milliliters than did control patients (19%; $P=0.008$).

Conclusion: The combination of glycopyrrolate and albuterol produces a greater improvement in FEV₁ than does albuterol alone in the treatment of patients with acute exacerbation of COPD.

[Cydulka RK, Emerman CL: Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med* April 1995;25:470-473.]

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193

INTRODUCTION

Anticholinergic agents have been widely used to treat patients with chronic obstructive pulmonary disease (COPD) exacerbations. Glycopyrrolate, a quaternary ammonium compound, is poorly absorbed from mucosal surfaces but otherwise has pharmacologic properties similar to those of atropine itself. Glycopyrrolate, when given by inhalation, should only affect the respiratory tract, thus limiting associated side effects.¹ It is available in solution and is easily used in nebulized form. The purpose of this study was to investigate the efficacy of combination treatment of glycopyrrolate and the β -agonist albuterol. In particular, we wished to determine whether the addition of a single aerosolized dose of glycopyrrolate would lead to greater improvement in pulmonary function over treatment with albuterol alone.

MATERIALS AND METHODS

This study was conducted from February 1991 through February 1992 in the emergency department of Metro-Health Medical Center, a large, urban, university-affiliated hospital. Patients with the self-reported diagnosis of COPD or patients with histories consistent with COPD, as defined by the American Thoracic Society², were eligible for the study if they presented to the ED with acute respiratory distress along with cough, wheezing, or both. Patients with asthma were excluded from the study, along with patients whose initial spirometry demonstrated a 1-second fractional expired volume (FEV₁) greater than 75% of predicted normal value. Patients were also excluded if they had clinical or radiographic evidence of pneumothorax, pneumonia, decompensated congestive heart failure, or history of lung cancer; if they were unable to perform spirometry; or if they had received prehospital aerosol treatment. Patients were also excluded if they had contraindications to the administration of glycopyrrolate, including glaucoma, obstructive uropathy, ileus, ulcerative colitis or megacolon, myasthenia gravis, autonomic neuropathy, liver disease, kidney disease, hiatal hernia with esophagitis, or cystic fibrosis. Patients younger than 18, pregnant women, nursing mothers, and prisoners were also excluded from this study.

After informed consent had been obtained, blood was drawn for CBC with differential, theophylline level, and arterial blood gases. Chest radiographs were also taken. Oxygen therapy was initiated at 3 L/minute through a nasal cannula and subsequently adjusted on the basis of the results of arterial blood gas or pulse oximetry, if available. Spirometry was performed with a computerized

portable Fleisch-pneumotach-type spirometer (SpiroScan 1000), with the patient seated and wearing nose clips. At least two forced expiratory maneuvers were obtained, with the highest forced vital capacity and FEV₁ used for analysis. The spirometer was calibrated at least three times a week by use of a 3-L syringe.

After initial evaluation, all patients received nebulized albuterol, 2.5 mg every hour for three aerosols. Patients received, in a randomized, double-blinded fashion, glycopyrrolate 2 mg or an equivalent volume of placebo solution mixed with their first albuterol aerosol. A block-design randomization scheme was devised before the study and used by the pharmacy to prepare coded vials. The patients, treating physicians, and investigators were all blinded to the contents of the vials. Patients did not receive any further glycopyrrolate or placebo solution after the initial aerosol. Spirometry was repeated 1 hour after the first aerosol and again 1 hour after the third aerosol treatment.

One hour after completion of the third aerosol (3 hours after initial treatment), patients were questioned as to the appearance of side effects to albuterol or glycopyrrolate. Patients then were admitted to the hospital or discharged from the ED without further therapy, at the discretion of the treating physician, on the basis of clinical assessment, including improvement in pulmonary function, disappearance of wheezing, and improvement in dyspnea. Patients who were discharged from the hospital were contacted by telephone after 48 hours to determine whether they had experienced relapse, defined as an unscheduled return for further treatment for bronchospasm within 48 hours after discharge. This study was approved by the hospital's human investigation committee.

Discrete variables were analyzed by means of the χ^2 test, whereas continuous variables were analyzed with Student's *t* test. Repeated-measures ANOVA was performed with a general linear model for ANOVA with post hoc comparisons of means by Tukey's test.³ A *P* value of less than .05 was considered significant. Data are reported as the mean $\pm$ SD.

RESULTS

Fifty-seven consecutive eligible patients, with an average age of 61.5 ± 11.3 years, were entered into the study (Table). Eighty-two percent of the patients were using outpatient β -agonist inhalers, 65% were taking theophylline products, and 18% were using steroids. Fifty-one patients were current or past cigarette users, with an average of 45.6 ± 23.6 pack-years. The WBC was $10,563 \pm 3,876$ cells/mm³; the theophylline level was 6.4 ± 6.5 μ g/mL.

147
194

There was no significant difference in the age (60 ± 10.3 years versus 62.4 ± 12.4 years), cigarette use (40.9 ± 23.0 pack-years versus 51.1 pack-years, WBC (10.3 ± 3.1 cells/mm³ versus 10.9 ± 4.6 cells/mm³), PaO₂ (62.4 ± 20.1 mm Hg versus 70.2 ± 15.8 mm Hg), initial FEV₁ ($29.5\pm10.5\%$ versus $31.0\pm12.8\%$ predicted normal), prednisone use (20% versus 15%), inhaler use (87% versus 78%), or ipratropium use (10% versus 7%) between the glycopyrrolate group and the control group. However, the theophylline level was significantly higher in the glycopyrrolate group (8.3 ± 7.3 mg/mL versus 4.3 ± 4.7 mg/mL, $P<.02$).

The pretreatment FEV₁ in the control group was 934 ± 424 mL ($31.0\pm12.8\%$ of predicted normal); it was 392 ± 364 mL ($29.5\pm10.5\%$ of predicted normal) in the glycopyrrolate group (NS). At 1 hour FEV₁ had increased to 963 ± 477 mL ($31.6\pm12.6\%$ predicted) in the control group and $1,129\pm585$ mL ($37.4\pm13.6\%$ predicted) in the glycopyrrolate group ($P=.22$ and $P=.11$, respectively). At 3 hours the FEV₁ in the control group was $1,095\pm573$ mL ($36.2\pm15.8\%$ predicted) and $1,312\pm614$ mL ($42.8\pm13.5\%$ predicted) in the glycopyrrolate group ($P=.19$ and $P=.11$, respectively). Repeated-measures analysis showed a significant difference in the percent of change in FEV₁ from pretreatment value (absolute value) between the control and glycopyrrolate groups both 1 hour and 3 hours after the start of treatment (Figure 1). Patients treated with glycopyrrolate and albuterol had a $28.2\pm42.2\%$ increase in FEV₁ after treatment, whereas patients treated with albuterol alone had only a $6.0\pm36.1\%$ increase in FEV₁ at 1 hour ($P=.04$). At

3 hours, patients treated with glycopyrrolate had a $56.0\pm56.1\%$ increase in FEV₁, compared with a $19.3\pm40.9\%$ increase in patients treated with albuterol alone ($P=.001$; Figure):

Overall, 30 (53%) of the patients required admission. Fifty percent of patients with COPD treated with glycopyrrolate were admitted, compared with 57% of patients treated with albuterol alone (NS). Follow-up information was available for 22 (81%) of the patients discharged from the ED. We noted no difference in the relapse rate between the glycopyrrolate and control groups (15.4% versus 11.1%).

Twenty-seven percent of the glycopyrrolate group experienced side effects, compared with 15% of patients treated with albuterol alone (NS). Side effects reported in the combination albuterol/glycopyrrolate group included dry mouth, headache, hypotension, and palpitations. Side effects reported in the albuterol group included tremors, anxiety, and palpitations. This study had a power of 20% to discern differences in the incidence of side effects between the two groups.

DISCUSSION

We found that patients with acute exacerbation of COPD who received combination glycopyrrolate and albuterol aerosol treatments had greater improvement in their percent change in FEV₁ at 1 hour ($29.2\pm42.2\%$ versus $6.0\pm36.1\%$, $P=.04$) and at 3 hours ($56.0\pm56.1\%$ versus $19.3\pm40.9\%$, $P=.001$) than did patients treated with albuterol alone. These results are distinctly different from

Figure.
Change in FEV₁ with treatment.

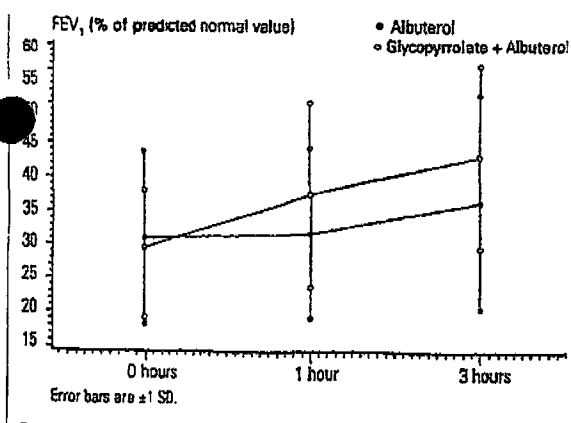


Table.
Results.

Parameters	Albuterol and Glycopyrrolate	Albuterol and Placebo
FEV ₁		
Initial absolute value (mL)	892±364	934±424
1 hour (mL)	1,129±585	963±477
Percent change in absolute value at 1 hour	29.1±42.2	6.0±36.1*
3 hours (mL)	1095±573	1,312±614
After treatment (3 hours)		
(% of predicted normal)	42.8±13.5	36.2±15.8†
Percent change in absolute value of FEV ₁ at 3 hours	56.0±56.1	19.3±40.9‡
Percentage of patients admitted	50	57.1§
Side effects	26.7	14.8§

* $P<.05$ versus glycopyrrolate group.

† $P=.07$ versus glycopyrrolate group.

‡ $P<.01$ versus glycopyrrolate group.

§NS versus glycopyrrolate group.

10/10
198

those we reported in asthmatic patients treated with both albuterol and glycopyrrolate.⁴ Asthmatic patients treated with albuterol alone had greater improvement in their FEV₁ values than did asthmatic subjects treated with a combination of glycopyrrolate and albuterol. We believe this is best explained by the fact that in spite of airflow limitations due to destructive changes in the lungs, patients with COPD have some cholinergic tone, which can be abolished by anticholinergic agents, resulting in improved airflow.¹ Glycopyrrolate has been used for a variety of indications over the past 20 years, although only recently have investigators studied its use in the treatment of acute bronchospasm.⁵⁻⁹ Slovis et al⁴ reported a patient with COPD exacerbation in whom inhalation therapy with glycopyrrolate failed, presumably because of low tidal volumes, but who was successfully treated with intravenous glycopyrrolate. Because multiple studies have demonstrated that anticholinergic agents improve bronchodilation, even in patients who were considered nonresponders to adrenergic agents¹⁻⁴, we hypothesized that a long-acting quaternary ammonium compound such as glycopyrrolate had something new to offer in the treatment of acute COPD exacerbation.

This study is limited by the small sample size, which yielded a low power to discern differences in side effects. Other limitations include the large SDs accompanying our FEV₁ measurement. Unfortunately, large SDs are commonly found in research of obstructive airway disease. The one-tailed power of the study to determine a difference in post-treatment FEV₁ (as percentage of predicted normal value) was 49%. In addition, patients in the study group had higher theophylline levels than did patients in the control group. Because the levels in both groups were subtherapeutic, we do not think this influenced the outcome of the study. In this study we used only a single dose of glycopyrrolate. We cannot state whether other doses of the drug would be more or less effective. Similarly, we cannot determine the optimum dosing frequency. Finally, the maximum dose of albuterol that can be used in acute exacerbation of COPD has yet to be determined. The role of glycopyrrolate as a second agent in patients who receive maximal doses of albuterol may be different than that found with the dose employed here.

CONCLUSION

The addition of a single treatment with aerosolized glycopyrrolate to hourly treatments with albuterol produces a greater percent improvement in FEV₁ than does albuterol alone in the treatment of patients with COPD exacerba-

tion. The improvement in pulmonary function in patients with COPD did not lead, however, to a decrease in the hospitalization rate. Within the limitations discussed above, we feel that this drug should be considered for use in patients with acute exacerbation of COPD. The optimal doses and frequency for administration of glycopyrrolate for the patients remain to be determined.

REFERENCES

1. Gross NJ: Anticholinergic agents in COPD. *Chest* 1989;91(suppl):525-555.
2. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease and asthma. *Am Rev Respir Dis* 1987;134:225-243.
3. SAS Institute, Inc: *SAS/STAT User's Guide*, Release 8.03 edition Cary, North Carolina, SAS Institute, Inc, 1988, p 1028.
4. Slovis CM, Daniels GM, Wharton DR: Intravenous use of glycopyrrolate in acute respiratory distress due to bronchospastic pulmonary disease. *Ann Emerg Med* 1987;16:898-900.
5. Cydulka RK, Emerman CL: Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of asthma. *Ann Emerg Med* 1994;23:270-274.
6. Gilman MJ, Meyer L, Carter J, et al: Comparison of aerosolized glycopyrrolate and metaproterenol in acute asthma. *Chest* 1990;96:1035-1038.
7. Johnson BE, Suratt PM, Gel TJ, et al: Effect of inhaled glycopyrrolate and atropine in asthma. *Chest* 1984;85:325-328.
8. Schroederstein DC, Bush RK, Chevinsky P, et al: Twelve-hour bronchodilation in asthma with a single aerosol dose of the anticholinergic compound glycopyrrolate. *J Allergy Clin Immunol* 1988;82:115-118.
9. Walker FB, Kaiser DL, Kowal MB, et al: Prolonged effect of inhaled glycopyrrolate in asthma. *Chest* 1987;91:49-51.

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199-196

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES**

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE
Apoderado

ASUNTO	Radicación	06-113683
	Trámite	002
	Evento	001
	Actuación	430 000460
	Oficio	
	Folios	12

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐

No. Sol. Internacional PCT/EP2005/005354
Fecha de Presentación Internal. 17 de mayo de 2005

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

<u>Descripción:</u>	Folios: <u>50</u> a <u>98</u> y <u>113</u> como se radicó inicialmente
<u>Reivindicaciones:</u>	Folios <u>99</u> a <u>112</u> como se radicó inicialmente
	Folios <u>171</u> a <u>172</u> modificadas
<u>Prioridad:</u>	Folios: <u>1</u> 18/05/2004, GB, 0411056.5
<u>Respuesta del solicitante:</u>	Folios <u>165</u> a <u>170</u>

2. Análisis de la Prioridad

La fecha de prioridad del 18 de mayo de 2004 y su correspondiente documento, corresponden con la materia solicitada de protección.

3. Objeto de la invención

Título de la solicitud: Combinación de glicopirrolato y (R)-5-[2-(5,6-dietil-indan-2-ilamino)-1-hidroxi-etil]-8-hidroxi-1H-quinolin-2-ona maleato (indacaterol maleato)

El problema planteado es obtener combinaciones útiles para la enfermedad pulmonar obstructiva crónica, de larga duración que minimice o evite dosis diarias a repetición; preferiblemente una vez por día.

Para solucionar este problema técnico la solicitud en estudio, el solicitante proporciona una combinación de glicopirrolato y (R)-5-[2-(5,6-dietil-indan-2-ilamino)-1-hidroxi-etil]-8-hidroxi-1H-quinolin-2-ona maleato (indacaterol maleato)

Expediente 06-113683-2o 45

IPC: A61K 31/402, 31/4704, 31/428

4. De la solicitud de Patente

Reivindicaciones (artículo 30 D 486)

Se sugiere restringir en las reivindicaciones el compuesto glicopirrolato, que se encuentra sustentado en la descripción y con el cual se evidencia el efecto técnico superior.

La reivindicación 5, contiene la palabra y/o, lo cual da a entender que las composiciones pueden encontrarse en forma separada.

5. Determinación del Estado de la Técnica

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

- Fecha de la publicación en fase internacional: 18 de mayo de 2004

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 18/05/2004 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
D1	WO 00/75114	Beta2-adrenoceptor agonists	14/12/2000
D2	Annals of emergency medicine, 25:4, 1995	Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of chronic obstructive pulmonary disease	1995

D1 enseña compuestos que tienen actividad beta 2 adrenoreceptora y los cuales son útiles en enfermedades pulmonares.

D2 enseña los efectos de combinar glicopirrolato con un beta2 adrenérgico como es albuterol

6. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo 18 D486)

La reivindicación 1 consiste en:

Una composición farmacéutica que comprende:

(A) Glicopirrolato

(B) (R)-5-[2-(5,6-dietil-indan-2-ilamino)-1-hidroxi-etil]-8-hidroxi-1H-quinolin-2-ona maleato (en adelante indacaterol maleato), junto con al menos un vehículo farmacéuticamente aceptable.

El Estado de la Técnica más cercano es **D2**, que da a conocer la eficacia en el volumen espiratorio forzado en el primer segundo (FEV1) cuando se combina glicopirrolato y albuterol (Ver Folio 191, conclusión), y que es administrada al paciente en una mezcla

líquida de ambos activos en un aerosol. (Ver Folio 192, columna 2)

Las composiciones farmacéuticas, objeto de esta solicitud se diferencian de **D2**, en que en la combinación emplea indacaterol maleato en lugar de albuterol, en un polvo seco para inhalación.

El hecho de intercambiar inadacaterol por albuterol en las composiciones de **D2** para el tratamiento de la enfermedad pulmonar obstructiva crónica, no evidencia un efecto técnico inesperado frente a las de **D2**, en cuanto a su duración donde se minimice o evite dosis diarias a repetición, preferiblemente una vez por día

El Problema Técnico Objetivo era obtener composiciones útiles para la enfermedad pulmonar obstructiva crónica, de larga duración que minimice o evite dosis diarias a repetición, preferiblemente una vez por día.

D1 sugiere cómo resolver el problema técnico mediante composiciones en polvo seco para inhalación (Ver página 18, líneas 3-9) de los compuestos de fórmula I, donde al realizar los reemplazos sugeridos en dicha estructura química se obtiene el indacaterol de la solicitud presentada y donde además se sugiere que pueden estar presentes en su sal maleato. Estos compuestos además se pueden combinar con agentes anticolinérgicos para ser utilizados en el tratamiento del asma, en particular de la enfermedad pulmonar obstructiva crónica.

La reivindicación es obvia, porque el Experto en la Materia enfrentado al problema de obtener composiciones útiles para la enfermedad pulmonar obstructiva crónica, de larga duración que minimice o evite dosis diarias a repetición, preferiblemente una vez por día utilizaría los compuestos de fórmula I (los cuales incluyen indacaterol), en combinación con un agente anticolinérgico como se enseña en **D1**, en las composiciones farmacéuticas combinadas que tienen glicopirrolato como **D2**, logrando de esta forma las partículas objeto de esta solicitud. Por tanto, la reivindicación 1 no tiene Nivel Inventivo. Las reivindicaciones dependientes 2-11, no mencionan alguna característica que haga inventivo al procedimiento de la reivindicación 1, por lo cual se considera que no tienen nivel inventivo.

7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO 00/75114	1-11	Nivel Inventivo
D2	Annals of emergency medicine, 25:4, 1995	1-11	Nivel Inventivo

8. Respuesta a los argumentos del solicitante

8.1. El solicitante en los Folios 165 a 167 a las modificaciones realizadas al capítulo reivindicatorio y al título, las cuales son aceptadas por esta oficina para su correspondiente estudio de patentabilidad.

8.2. El solicitante en el Folio 167 se refiere a novedad.

De acuerdo con las modificaciones realizadas al capítulo reivindicatorio, la solicitud frente a **D1** tiene novedad. Sin embargo, este documento afecta el nivel inventivo de la solicitud

puesto que las combinaciones de un agente anticolinérgico y un beta 2 adrenérgico ya se encontraban divulgadas en el estado de la técnica, como se mencionó en nivel inventivo.

8.3. El solicitante anexa en el Folio 169, los resultados obtenidos de la combinación, los cuales evidencian la eficacia de la terapia combinada de indacaterol maleato y glicopirrolato.

Este resultado es esperado frente a las enseñanzas de D1 y D2, sin considerarse superior. (Ver figuras D2)

8.4. El solicitante en el Folio 169 se refiere a los documentos citados por artículo 46 y donde menciona: "el indacaterol es llamado agonista beta de ultracción (uLABA por sus siglas en inglés), que es el primer compuesto de este tipo aprobado en Europa".

El problema objetivo de la solicitud son las combinaciones y no los compuestos. La combinación de un agente anticolinérgico como glicopirrolato y un beta 2 adrenérgico, ya enseñaban el aumento en la eficacia en los FEV₁, tal como lo hacen las composiciones de la solicitud presentada. Es obvio para el experto en la materia, que si el compuesto es de larga acción, de esta forma también va a actuar en las composiciones. La característica de larga acción es del compuesto y no de las composiciones, lo cual evidencia la falta de actividad inventiva.

8.5. El solicitante concluye en el Folio 170: "la combinación particular reivindicada no se deriva de las enseñanzas de Sidulka o Tzelepis, puesto que dichos documentos, motivan expresamente al apersona versada en la materia a combinar glicopirrolato con agentes tipo SABA y revelan o siquiera sugieren la existencia de agonistas uLABA como el indacaterol"

La combinación que menciona el solicitante, la está basando en el uso de los compuestos (larga acción) y no en los elementos técnicos de la composición. El principio usado para el tratamiento en EPOC, para combinaciones de un agente anticolinérgico y un beta 2- adrenérgico con eficacia mejorada, ya es ampliamente conocido en el campo terapéutico, siendo estas composiciones combinadas, obvias para el experto en la materia.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

JOSÉ LUIS SALAZAR LÓPEZ

Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista, de fecha

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CONCEPTO TÉCNICO No. 04353	EXAMINADOR TÉCNICO Código No. 202070
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