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Comparison of nebulized and intravenous terbutaline during exacerbations of pulmonary infection in patients with cystic fibrosis

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Comparison of nebulized and intravenous terbutaline during exacerbations of pulmonary infection in patients with cystic fibrosis. M.J. Finnegan, D.V. Hughes, M.E. Hodson.

ABSTRACT: Twenty three patients completed a double-blind study, comparing intravenous and nebulized terbutaline, during the first four days of a pulmonary exacerbation of cystic fibrosis (CF), with follow-up to day 10. Routine treatment with chest physiotherapy and appropriate intravenous antibiotics was given to all patients.

The best peak flow rate (PF), forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), in the past year and at entry to the study, revealed no significant difference between the groups. However, on day 10, PF, FEV_1 and FVC, of the nebulizer group remained significantly reduced compared to best values in the previous year, whereas the PF and FEV_1 in the intravenous group were not significantly reduced compared to the best values in the previous year. Comparison of regression lines showing the overall rate of improvement of PF, FEV_1 and FVC between the two groups showed that the rate of improvement of each parameter was more rapid in the group receiving intravenous terbutaline. This was statistically significant for PF.

It is possible that during acute exacerbations of infection, sputum retention makes it more difficult for the inhaled bronchodilators to reach the airways and intravenous therapy is, therefore, more beneficial.

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Most patients with cystic fibrosis (CF) have airways obstruction, which often increases during infective exacerbations of their condition [1]. For this reason, it is common practice to treat adult patients with CF, attending the Royal Brompton Hospital, with nebulized bronchodilators, in addition to appropriate intravenous antibiotics and intensive physiotherapy, when these patients are admitted with infective pulmonary exacerbations.

Pharmacological means to stimulate mucociliary clearance of excess secretions would be helpful, especially during pulmonary exacerbations. Reports differ as to whether $beta_2$-agonists stimulate mucociliary clearance in asthma and chronic bronchitis [2, 3], but in CF, subcutaneous injection of terbutaline was shown to stimulate tracheal mucociliary transport [4].

Because of the large amounts of purulent secretions in the bronchi of patients with CF in exacerbation, it is quite possible that nebulized $beta_2$-agonists do not reach their site of action, especially in the first few days of treatment, when the largest amounts of secretion are produced. For this reason, we attempted to determine whether intravenous terbutaline given for the first four days of treatment was beneficial when compared to standard treatment. If intravenous therapy has an advantage over aerosol terbutaline, one would expect to see this at the beginning of a course of treatment, when the sputum load in the lung is highest.

Patients and methods

All patients had typical features of CF and a sweat sodium concentration of >70 $mmol \cdot l^{-1}$ by pilocarpine iontophoresis. All were admitted because of an exacerbation in their pulmonary condition (increasing dyspnoea and sputum production and reduction in spirometric tests). Exclusion criteria were: pregnancy, uncontrolled hypertension, thyrotoxicosis, ischaemic heart disease, known terbutaline allergy and previous paroxysmal tachycardia. Patients with extreme symptomatic tachycardia during the study had a reduction of dosage, as did patients with asymptomatic tachycardia at rest >130 $\cdot min^{-1}$. Withdrawal criteria were: patients' request, persistent tremor or tachycardia despite dosage reduction, angina, or a sharp rise in blood pressure. The study was passed by the hospital Ethics Committee and all patients gave signed informed consent.

The study protocol was as follows: routine active treatment, with intensive physiotherapy and intravenous antibiotics, as indicated by sensitivity testing of micro-organisms cultured in sputum, was given to all patients. In addition, patients were randomized to receive either intravenous terbutaline sulphate (3 $\mu g \cdot min^{-1}$ for three days followed by 1.5 $\mu g \cdot min^{-1}$ for 1 further day, given by syringe pump), or nebulized terbutaline sulphate respiratory solution (10 $mg \cdot ml^{-1}$), 0.5 ml nebulized with 2.5 ml of normal saline 6-hourly. In order to blind the study, all subjects were given both a syringe pump and a nebulizer solution to use for these four days. One of these contained the active drug and one contained normal saline only. The route of active drug delivery was not known by patient or doctor. For the remainder of the admission, standard treatment with physiotherapy, intravenous antibiotics and nebulized bronchodilators was given.

On admission to hospital and on days 1, 2, 4, 6 and 10 of the course of intravenous antibiotics, peak flow (PF), forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) (Vitalograph spirometer) were recorded by a physician. Each recorded value was the best of three attempts and each record was made at the same time of day. For purposes of comparison each patients' best peak flow and spirometric values from the previous year were recorded from the notes.

Statistical analysis

For the purpose of analysis, the code was not broken, but the two treatment groups were identified as groups X and Y. The data were found to be "non-normal" in distribution and therefore Mann-Whitney analysis was used for between group comparisons and, the, Wilcoxon matched pairs signed rank test for intra-group comparisons. The rate of improvement in peak flow and spirometric values was compared by plotting the percentage of the predicted value on entry and on day 10 of the study for each subject, and for each treatment group the "best fit" regression line was determined and the slopes compared.

Results

Twenty seven patients were recruited to the study. One (from group X) withdrew from the study on day 2 because she did not like the syringe pump. Three subjects were excluded (all from group X): one because her FEV_1, FVC and PF were not significantly reduced on entry to the study from her best in the previous year, and two because they deteriorated on treatment and required a prolonged stay in hospital (over a month in each case), with two or more changes in antibiotics and with no appreciable improv-ement at 10 days. Twenty three patients completed the study: 11 in group X and 12 in group Y. Group X was the group treated with intravenous (*i.v.*) normal saline and nebulized terbutaline, and group Y the group treated with *i.v.* terbutaline and nebulized normal saline.

There was no significant difference between the groups in terms of age (mean age: group X 25.3 yrs, group Y 24.4 yrs), sex or percentage predicted PF, FEV_1 or FVC, either in the previous year or on entry to the study. Compared with the best in previous year values, the PF, FEV_1 and FVC were significantly reduced on entry to the study in both groups. Compared with the entry data, PF, FEV_1 and FVC were significantly improved by day 10 of the study in both groups. In group X (*i.v.* saline/nebulized terbutaline) the day 10 levels of PF, FEV_1 and FVC remained significantly lower than the best in previous year results, whereas in group Y (*i.v.* terbutaline/nebulized saline) the day 10 levels for both PF, and FEV_1 were not significantly different from the best in previous year values, but the day 10 FVC remained significantly reduced (table 1).

The rate of improvement in PF in each treatment group is shown graphically in figure 1, which demonstrates a significantly faster rate of improvement in group Y ($p<0.05$). For FEV_1 and FVC, the rates of improvement were more rapid in group Y but neither reached statistical significance (FEV_1: $0.05<p<0.1$; FVC: $p>0.1$).

None of the patients experienced tremor, local thrombophlebitis or other side-effects from the intravenous or aerosol beta-agonists.

Table 1. – Comparison of mean percentage predicted peak flow and spirometry on entry to the study and at day 10 with best recorded value in previous year in groups X and Y (Wilcoxon matched-pairs signed-rank test)

	Previous year			Entry to study			Day 10		
Treatment group	PF	FEV_1	FVC	PF	FEV_1	FVC	PF	FEV_1	FVC
Group X n=11, 6M	67.3	55.6	73.4	51.4†	31.7$^{\#}$	44.5$^{\#}$	61.7*	43.9†	66.3†
Group Y n=12, 7M	65.4	47.2	68.6	51.2°	32.2$^{\#}$	46.7$^{\#}$	68.3^{+}	45.5^{+}	60.4†

$^{+}$: $p>0.05$; *: $p<0.05$; †: $p<0.01$; $^{\circ}$: $p<0.005$; $^{\#}$: $p<0.001$. PF: peak flow; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; M: male.

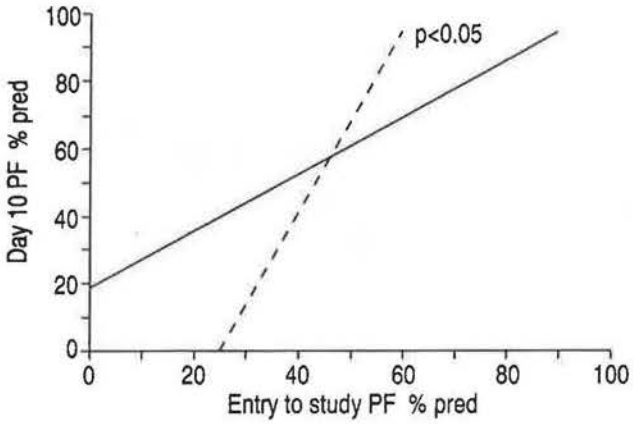

Fig. 1. – Comparison of regression lines for entry and Day 10 percentage predicted (% pred) PF in Groups X and Y ($p<0.05$). PF: peak flow. —— : Group X; – – – : Group Y.

Discussion

Adrenergic agents have been shown to stimulate mucociliary transport in normal subjects [5] and in patients with a variety of respiratory conditions, including bronchial asthma [6], chronic bronchitis [3] and cystic fibrosis [4]. In humans, stimulating effects on mucociliary transport have been observed using beta-agonists *via* the oral, inhaled, subcutaneous and intravenous routes [7].

The literature is not conclusive concerning whether intravenous or nebulized $beta_2$-agonist is more effective in severe or moderately severe attacks of asthma [8, 9]. In severe attacks of asthma, there is widespread plugging of the small airways with mucus, so that there would seem to be some theoretical advantage to giving intravenous therapy, but in practice this has not always proven to be the case.

At least part of the increase in airways obstruction which occurs in infective exacerbations of CF is due to sputum retention. There seems little doubt that with many of the airways full of secretions, nebulized therapy would not reach its site of action, whereas intravenous therapy may penetrate the inflamed bronchial mucosa better than in the non-inflamed state. This may account, at least in part, for the observed difference between the two groups.

In conclusion, we have shown, in a double-blind, randomized study, that an initial four days treatment with intravenous terbutaline results in more rapid and complete reversal of airways obstruction than does nebulized terbutaline, in patients with infective exacerbations of CF, all of whom were also treated with intensive physiotherapy and appropriate intravenous antibiotics.

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