

Effect of terbutaline on bronchoconstriction induced by nebulised pentamidine

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Abstract

The severity, duration, and reversibility of pentamidine induced bronchial narrowing was studied with and without pretreatment with nebulised terbutaline 10 mg in an open study of 40 patients seropositive for the human immunodeficiency virus (HIV). All subjects received pentamidine 300 mg in 5 ml water via an Acorn System 22 jet nebuliser. The forced expiratory volume in one second (FEV₁) fell in all 20 patients given pentamidine alone, the mean maximum fall being 20.6%. In the 20 patients given pentamidine preceded by nebulised terbutaline the mean maximum fall in FEV₁ was 4%; three subjects had a fall in FEV₁ of more than 10%.

Nebulised pentamidine isethionate is now established for the prophylaxis and treatment of *Pneumocystis carinii* pneumonia in patients with human immunodeficiency virus infection. It may, however, cause bronchial narrowing in these patients.^{1,2} The purpose of this study was to define the frequency, magnitude, duration, and response to terbutaline of airflow limitation induced in HIV positive patients by the inhalation of nebulised pentamidine isethionate.

Methods

We studied 40 homosexual, HIV positive men (mean age 35.6 (range 24-56) years) with no past history of chronic lung disease. Seventeen were cigarette smokers. All were receiving fortnightly treatment with pentamidine isethionate (Pentacarinat, Rhône-Poulenc-Rorer: 300 mg in 5 ml of water) delivered by an Acorn System 22 jet nebuliser (Medic-Aid, Pagham, Sussex) at a flow rate of 8 l/min (particle mass median diameter (MMD) 3 µm). Twenty patients received nebulised pentamidine alone, 13 for primary prophylaxis as they had not had pneumocystis pneumonia; the remaining 20 patients (16 for primary prophylaxis) inhaled 10 mg nebulised terbutaline sulphate in 2 ml normal saline 15 minutes before receiving nebulised pentamidine.

FEV₁ was measured before treatment (mean duration of pentamidine administration 10 minutes) and one, two, five, 10, and 30 minutes after completion of the inhalation.

Statistical analyses were performed with the Mann-Whitney and Wilcoxon rank sum tests.

Results

PRETREATMENT FEV₁

The forced expiratory volume in one second (FEV₁) was normal in most patients in both groups (mean FEV₁: pentamidine group 102% predicted (range 70-141%), pentamidine + terbutaline group 106% predicted (range 65-133%)). There was no significant difference in FEV₁ between patients having primary and those having secondary pneumocystis pneumonia prophylaxis (107% v 95% predicted).

EFFECT OF PENTAMIDINE WITH AND WITHOUT TERBUTALINE

FEV₁ fell in all 20 subjects treated with pentamidine alone (mean maximum fall 21%, range 8-62%; $p < 0.001$). The mean fall in FEV₁ was maximal five minutes after inhalation of pentamidine (mean fall 19%; $p < 0.001$), and it was still reduced by 16% at 30 minutes (figure). The fall in FEV₁ varied widely between patients; a fall of 15% or more occurred in 13 of the 20 patients at some time after they had pentamidine. The response was no different in patients having primary and secondary pneumocystis pneumonia prophylaxis, nor did the number of previous episodes of pneumocystis pneumonia make any difference.

There was a fall in FEV₁ in most of the group pretreated with terbutaline (mean maximum change in FEV₁ = -4.3%, range +16.6 to -22.6%, $p < 0.005$) but it was less than that seen with pentamidine alone ($p < 0.001$). Three of these patients had a 10% or greater fall in FEV₁; in two this was still present 30 minutes after the pentamidine inhalation.

Discussion

Bronchial narrowing with pentamidine isethionate may be partially abolished by pretreatment with nebulised beta agonists.^{2,3} A fall in FEV₁ occurred rapidly in all patients who did not receive terbutaline. The range and time course of bronchial narrowing was variable, but unrelated to the number of previous episodes of pneumocystis pneumonia. There was a trend suggesting that smokers might be more susceptible to the effects of pentamidine than non-smokers (mean fall in FEV₁ 25% v 19%), but this was not significant.

The mechanism of pentamidine induced bronchial narrowing is unknown, but is probably related to the deposition site and nature of the nebulised solution. The particle MMD of our nebuliser system was 3 µm. A smaller particle size would give greater distal deposition,⁴ and may account for reports of

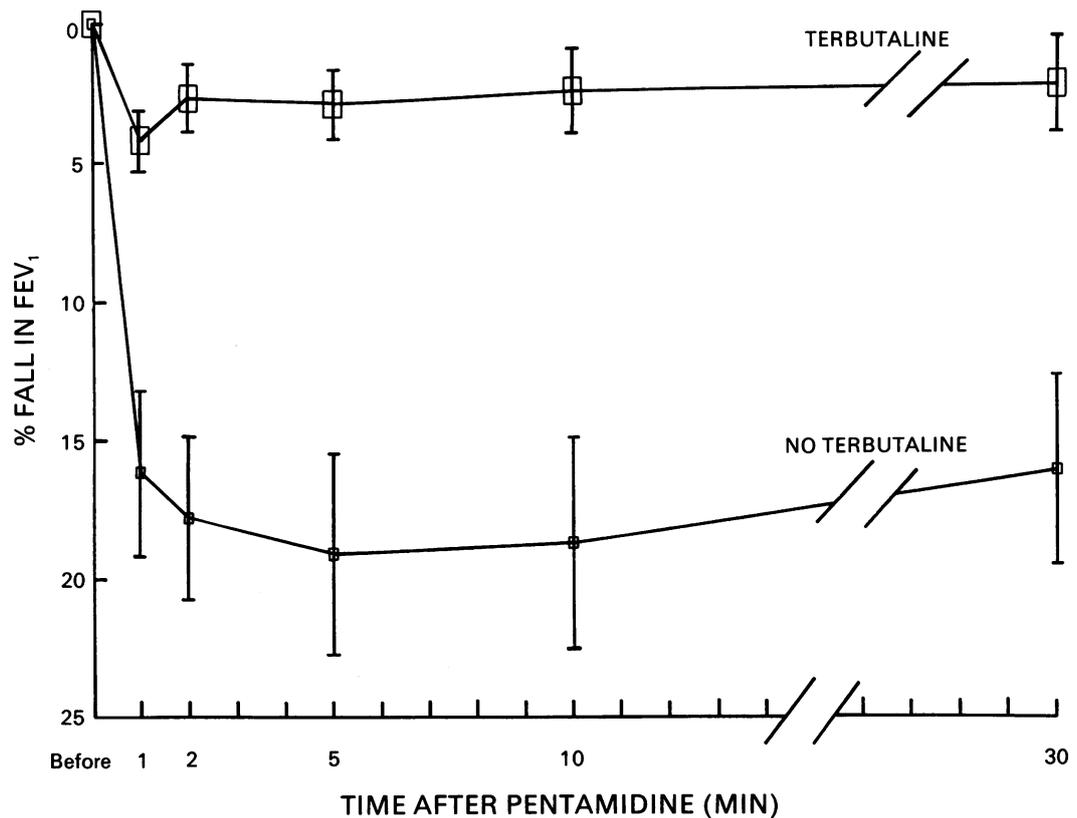
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Relation between percentage fall in FEV₁ and time after pentamidine inhalation with and without pretreatment with terbutaline. Each point represents the group mean result and vertical bars represent standard errors



fewer side effects from nebulisers that produce smaller particles.⁵ The changes in FEV₁ may result from rapid spasm of bronchial smooth muscle, local mucosal inflammatory response, direct histamine release, or platelet function inhibition.

Both moieties of pentamidine isethionate have been implicated in the genesis of airway narrowing, though in one study pentamidine isethionate and pentamidine gluconate caused no difference in toxicity,⁶ suggesting that pentamidine rather than isethionate is responsible for bronchial narrowing. The pH and osmolality of the nebulised solution might also be important.⁷ The pH of pentamidine isethionate is 4.5–6.0 (data on file, Rhône-Poulenc-Rorer), which is sufficiently acidic to cause bronchial irritation. Adjustment of this pH, possibly by inert buffers, may reduce unwanted effects. When pentamidine is made into solution as recommended by the manufacturer it is sufficiently hypotonic to cause airway narrowing. The osmolality ranges from 128 mosmol/kg (for 300 mg pentamidine isethionate in 10 ml water) to 294 mosmol/kg (for 300 mg pentamidine isethionate in 3 ml water)

(Leigh *et al*, unpublished observations).

Thus pretreatment with 10 mg nebulised terbutaline reduced the severity of falls in FEV₁ seen with nebulised pentamidine but did not totally abolish them. Whether modification of the pentamidine solution and its mode of administration will reduce side effects more requires further investigation.

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