taking of blood samples must be carefully timed if the results of the assays are to be of maximum clinical value. Clinicians should contact their local laboratory to confirm the method in use and for recommendations on the handling and timing of specimens.

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Pneumocystis carinii pneumonia

Aerosolised pentamidine gives effective prophylaxis

As many as 85% of patients with AIDS will develop pneumonia due to *Pneumocystis carinii* at some stage in their illness, and the mortality of acute infections ranges from 9% to 35%.[1,2] Of those patients who survive, between 40% and 60% develop recurrent disease within one year in spite of the use zidovudine,[3,4] and the mortality of these recurrent episodes is high.[3,5,6] These figures provide a clear basis for the value of prophylactic treatment. Several systemic agents are effective,[6] but all are associated with adverse reactions in a high proportion of patients.[6,7] Against this background aerosolised pentamidine has been developed as a treatment directed against the site of the disease and one that reduces systemic adverse effects while maintaining therapeutic benefit both as a prophylactic agent[8] and as active treatment for mild infections.[8-10]

The effects of aerosolised pentamidine for acute mild to moderate *P carinii* pneumonia were first shown by Montgomery *et al.*[10] A dose of 600 mg was given daily for 21 days through a Respirgard II nebuliser, and 13 out of 15 patients responded. Plasma pentamidine concentrations were low and no serious systemic adverse effects were recorded, though the patients did have local symptoms such as cough. The results of other small scale uncontrolled studies were variable, perhaps because of the different doses of pentamidine and different nebuliser systems used.[9,11,12] Recently several larger studies have been presented (K Arasteh *et al*; J E Conte *et al*; P Dellamonica *et al*; L Flemholc *et al*; P-M Girard *et al*; A Meyer *et al*, Vth international conference on AIDS, Montreal, 1989; for the rest of this article all references given in parentheses are abstracts from that conference). In total these studies described the response of 155 patients given doses of 300-600 mg of pentamidine through various nebulisers. The success rates reported ranged from 61% (A Meyer *et al*) to 89% (J E Conte *et al*), and the overall figure for pooled results was 72%. The response to treatment seemed less rapid than with the use of systemic treatment (P-M Girard *et al*), and one study showed a lower cure rate with aerosolised pentamidine than with cotrimoxazole, though the difference was not signficant (P Dellamonica *et al*). The incidence of early relapse seemed higher, but adverse effects were less frequent than with cotrimoxazole. Aerosolised pentamidine seemed less effective in patients with abnormal chest radiographs at presentation (P-M Girard *et al*).

The use of aerosolised pentamidine as a secondary prophylaxis (after an acute episode of *P carinii* pneumonia) has been studied in greater detail. Early uncontrolled clinical studies showed a low incidence of breakthrough of pneumonia in patients given 30-300 mg pentamidine every one to four weeks with a variety of apparatus.[13-15] There was recurrence in only 8% of 382 patients over follow up periods of five to seven months—a substantial improvement over historical controls. Three recent studies are of particular importance: reductions in recurrence of *Pneumocystis carinii* pneumonia from 34·6% (placebo) to 6% (aerosolised pentamidine) were reported when 60 mg pentamidine was given every two weeks through a Fisoneb ultrasonic nebuliser in 84 patients over 24 months (J S G Montaner *et al*), and from 61% to 9% with 4 mg/kg pentamidine monthly (every two weeks for the first month) given through an Ultraneb 99 nebuliser in 51 patients over 8·7 to 10 months.[4] In a controlled study on 408 patients a substantial reduction in the incidence of recurrent pneumonia was shown with 150 mg every two weeks or 300 mg monthly in comparison with 30 mg every two weeks through a Respirgard II nebuliser (G S Leoung *et al*). These authors considered that even the 30 mg dose of pentamidine was of some benefit. The results of this study were instrumental in the decision of the United States Food and Drug Administration to license the use of nebulised pentamidine as secondary prophylaxis in a dose of 300 mg monthly given through Respirgard II.

Patients with evidence of profound immune deficiency (those with a count of CD4 lymphocytes $<200\times10^6$/l) have a probability of a first episode of *P carinii* pneumonia of 34% after six months and 61% after 18 months (R Weber *et al*), so many centres are now offering these patients primary prophylaxis. Few studies have been reported with enough patients and length of follow up to show conclusive benefit, but in one

study of 250 patients given pentamidine 150 mg every two weeks no episodes of pneumonia were documented over a follow up period of 21 months (J Weissman *et al*). Other smaller studies have also shown a low incidence of pneumonia in patients receiving primary prophylaxis with aerosolised pentamidine, with the disease occurring in 0-4% of patients over follow up periods of 2·5 to 11 months (E M Bernard *et al*; C Keyes *et al*; S D Nightingale *et al*; K Rodrigues *et al*).

On the other side of the equation were the adverse effects of aerosolised pentamidine. Local features related to pentamidine deposition in the upper respiratory tract include a foul taste, cough, sore throat, salivation, and bronchoconstriction.[16,17] More serious reported adverse effects include bronchial bleeding,[11] dysglycaemia,[18] and pancreatitis.[19] Pneumothorax has also been reported, but a causal relation has not been proved.[20] *P carinii* pneumonia may recur in the upper lobes because of poor deposition of the aerosol in this region,[21] but this risk may be reduced by inhalation in the supine position (M J O'Doherty *et al*). Non-pulmonary pneumocystosis seems to be uncommon but may occur more often with the increasing use of inhaled prophylaxis.[22]

Nebuliser apparatus

Another factor that affects the efficacy and tolerability of aerosolised pentamidine is the nebuliser apparatus used. Many centres and clinical trials have used the Respirgard II, which delivers particles of 1-2 μ diameter, an ideal size to maximise their deposition in the aleveoli and minimise deposition in the upper respiratory tract.[23] Other nebulisers should be compared with this standard. The Respirgard II incorporates a valve between the nebuliser and the mouthpiece that acts as a baffle and filters out larger particles. This reduces the overall efficiency of the nebuliser, and the dose of pentamidine reaching the lungs is low.[17] Pulmonary deposition of nebuliser doses of 50 mg (3 ml solution) and 300 mg (6 ml solution) have been measured as 1·4 mg[24] and 6·2 mg[25] respectively. Of this total, half to three quarters is deposited beyond the mucociliary apparatus ("alveolar deposition").[23,26]

Other nebulisers give better deposition rates. With nebuliser doses of 50 mg (3 ml solution), 50 mg (6 ml solution), and 300 mg (6 ml solution), pulmonary deposition using the System 22 Mizer is 2·7 mg, 3·7 mg,[24,27] and 12·6 mg[25] respectively, although a smaller fraction of this is thought to be alveolar.[24] The particles are, however, larger, resulting in increased central deposition and more frequent local adverse effects. Measurements of this sort are not available for many nebulisers. Until we know the lung dose of pentamidine required for effective treatment or prophylaxis of *P carinii* pneumonia and that delivered by any nebulisation process, the use of aerosolised pentamidine will remain empirical. A dose of 300 mg in 6 ml solution given with a Respirgard II nebuliser is effective and well tolerated, but a similar deposition may be achieved in a shorter time using a System 22 Mizer and 150 mg pentamidine.[26] The clinical efficacy of this regimen is, however, unproved.

Combination treatment

Though nebulised pentamidine is effective for treating acute mild episodes of *P carinii* pneumonia, in our view it should not be used as sole treatment for this purpose unless there is multiple drug intolerance, since the response to treatment seems slower and early relapse more frequent than with systemic treatment. In addition, there is the risk that systemic disease may be left untreated. Use in combination with systemic treatment may overcome some of these problems. All patients with a past episode of *P carinii* pneumonia, and perhaps also those with profound immune deficiency, should be offered prophylaxis. Aerosolised pentamidine seems to be effective but has disadvantages. Hospital supervision is required, at least at first, to assess the effect of the treatment on lung function and the need for pretreatment with a bronchodilator, and to instruct the patient on the method of self administration. The treatment is more expensive and may be less effective than oral treatment, though the results of comparative studies are awaited. On current evidence we suggest that aerosolised pentamidine is indicated as prophylaxis only for those patients intolerant of oral agents. We administer it monthly using a nebuliser dose of 150 mg (6 ml solution) given through a System 22 Mizer unless this is found to be intolerable, in which case a dose of 300 mg (6 ml solution) is given through a Respirgard II nebuliser.

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