Nebulized pentamidine as prophylaxis for *Pneumocystis carinii* pneumonia

Up to 80% of patients with the acquired immune deficiency syndrome (AIDS) will experience an episode of *Pneumocystis carinii* pneumonia at some stage in their disease course and the mortality of acute infections ranges between 5% and 30% (Murray et al., 1984, 1987). The relapse rate after conventional therapy for a first episode of *P. carinii* pneumonia is about 35% at six months and may be as high as 60% at 12 months. This relapse rate appears to be reduced, but not eliminated, by therapy with zidovudine. For patients treated with zidovudine, the relapse rate is about 19% during the initial six months of therapy (Fischl et al., 1987; Girard et al., 1989). In those patients who develop recurrent episodes of *P. carinii* pneumonia the mortality is high (Brenner et al., 1987; Miller & Mitchell, 1990). There are therefore clear indications for using prophylactic treatment with a specific anti-*pneumocystis* regimen that is compatible with zidovudine. Patients who should receive prophylaxis include those who have already experienced an initial episode of *P. carinii* pneumonia (i.e., 'secondary' prophylaxis) and it is also reasonable to provide 'primary' prophylaxis for patients with CD4 cell counts $< 200$/mm$^3$ and also for those who have a history of either another life-threatening opportunistic infection or Kaposi's sarcoma.

Several oral medications are effective and include oral co-trimoxazole (Fischl, Dickinson & LaVoie, 1988), Fansidar (pyrimethamine and sulfadoxine) (Fischl & Dickinson, 1986) and dapsone (Metroka et al., 1988).

Several studies have shown that co-trimoxazole given daily or intermittent doses of co-trimoxazole may be as effective and less toxic. A recent study in immunosuppressed patients without AIDS showed that 960 mg twice daily, given three times a week, was effective in preventing *P. carinii* pneumonia (Hughes et al., 1987). Unfortunately data do not exist for the use of intermittent co-trimoxazole (or lower doses of daily co-trimoxazole) in AIDS patients. Despite this several regimens for prophylaxis with oral co-trimoxazole are in regular use (see Table I). Fansidar and dapsone also provide effective prophylaxis, although neither has been compared with co-trimoxazole in prospective studies. All three options are cheap (see Table I). Adverse reactions occur in a high proportion of patients (Gordin et al., 1984; Fischl, 1988; Fischl et al., 1988) but our experience suggests that rash with co-trimoxazole is not seen in the UK with the same high frequency as is reported from the USA. In those who do develop rash, therapy may frequently be continued with the use of anti-histamines. Against this background nebulized pentamidine has been developed as prophylaxis against *P. carinii* pneumonia, directed at the site of the infection, with an associated reduction in systemic toxicity (Girard et al., 1989; Golden et al., 1989).

The concept of nebulized antibiotic drug delivery is not new (Mutch & Hoskins, 1944), and nebulized antibiotics are now established as treatment for respiratory infections in patients with cystic fibrosis (Hodson, Penketh & Batten, 1981). Early uncontrolled studies of secondary prophylaxis showed a low incidence of recurrent *P. carinii* pneumonia in patients receiving 30–300 mg pentamidine every one to four weeks with a variety of nebulizers (Bernard et al., 1987; Fallat, Kandal & Feigal, 1988; Golden et al., 1989). In comparison with historical controls, there was a substantial improvement in relapse rates with only 31 of 382 (8%) of patients developing recurrence during follow-up periods of between five and seven months. A reduction in recurrence of *P. carinii* pneumonia from 34.6% (placebo group) to 6% (nebulized pentamidine group) has been reported when 60 mg of pentamidine was given fortnightly during 24 months in 162
Table I. Comparative monthly costs in the UK of *P. carinii* prophylaxis regimens. Monthly Index of Medical Specialities (MIMS) prices correct at August 1990 and including VAT at 15%

<table>
<thead>
<tr>
<th>Drug</th>
<th>Regimen</th>
<th>Cost per month</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Co-trimoxazole</td>
<td>(a) 960 mg alternate days</td>
<td>£4.35</td>
<td>Cost based on price of co-trimoxazole double strength (Septrin Forte) tablets.</td>
</tr>
<tr>
<td></td>
<td>(b) 960 mg once daily</td>
<td>£8.70</td>
<td></td>
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<tr>
<td></td>
<td>(c) 960 mg twice daily</td>
<td>£17.50</td>
<td></td>
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<tr>
<td>Fansidar (pyrimethamine 25 mg and sulfadoxine 500 mg)</td>
<td>(a) one tablet once a week</td>
<td>£1.16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(b) one tablet twice a week</td>
<td>£2.32</td>
<td></td>
</tr>
<tr>
<td>Dapsone</td>
<td>100 mg twice a week</td>
<td>£0.24</td>
<td></td>
</tr>
<tr>
<td>Pentamidine isethionate</td>
<td>(a) 300 mg/month via Respirgard II jet nebulizer</td>
<td>£27.32</td>
<td>Cost includes price of drug, nebulizer, air cylinder, water for reconstituting pentamidine and pre-treatment salbutamol inhaler.</td>
</tr>
<tr>
<td></td>
<td>(b) 150 mg/month via System 22 Mizer jet nebulizer</td>
<td>£28.46</td>
<td>Cost includes price of drug, nebulizer, air cylinder, water for reconstituting pentamidine and pre-treatment salbutamol inhaler. Cost may be decreased by 'pairing' two patients to share a 300 mg vial of pentamidine.</td>
</tr>
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Patients who used an ultrasonic nebulizer (Montaner et al., 1989). A reduction from 61% to 9% in recurrence rate was also reported with pentamidine at a dose of 4 mg/kg given monthly to 51 patients over a 8-7 to 10 months period with use of an ultrasonic nebulizer (Girard et al., 1989). A marked reduction in incidence of recurrent *P. carinii* pneumonia was demonstrated in a prospective controlled comparison of 488 patients receiving either 150 mg fortnightly or 300 mg monthly, compared with 30 mg monthly (Leoung et al., 1989).

Few studies have been reported with enough patients and sufficient length of follow up to show benefit from primary prophylaxis. In one study of 250 patients with CD4 counts less than 400/mm³ given nebulized pentamidine 150 mg fortnightly for six to 21 months there were no episodes of *P. carinii* pneumonia (Weisman et al., 1989).

Several adverse effects have been reported with nebulized pentamidine. Local problems caused by pentamidine deposition in the oropharynx and trachea include a metallic taste, hypersalivation, a sore throat, cough and bronchoconstriction (O'Doherty et al., 1988; Smith, Herd & Gazzard, 1988); bronchial bleeding occurs with bronchial deposition of aerosol droplets (Miller & Semple, 1988). These side effects are probably related to the physicochemical properties of pentamidine. When pentamidine is dissolved in water for nebulization at a concentration of 60–100 mg/ml the solution is hypotonic (osmolality 130 mOsmol/kg) and acid (pH 5.4) (Miller & Semple, 1988). In addition, pentamidine inhibits anti-cholinesterase activity (Alston, 1988) and inhibits platelet function. More serious side effects, which indicate that some pentamidine is absorbed systemically during nebulized delivery, include hypoglycaemia (Karboski & Godley, 1988), pancreatitis (Herer et al., 1989), acute renal dysfunction (Miller, Delany & Semple, 1989) and rash (Leen & Mandal, 1988). Recurrence of *P. carinii* pneumonia in the upper lobes may occur because of poor deposition of aerosol in this region (Abd et al., 1988; Jules-Elysee et al., 1990). Apical deposition of nebulized pentamidine is increased by inhalation in a supine position and this risk may thus be reduced (O'Doherty et al., 1989). Extra-pulmonary pneumocystosis, an uncommon presentation of *P. carinii* infection, appears to occur more frequently in patients receiving prolonged prophylaxis with nebulized pentamidine (Northfelt, 1989; Poblete et al., 1989). Because pentamidine given by an aerosol does not result in systemic distribution at therapeutic levels, it would not be expected to suppress potential extrapulmonary
jet nebulizers, many centres are now using continuously rated CR60 compressor. 

...continuously rated CR60 compressor. (particularly the systems used for pentamidine to patients. These have included perioral paraesthesiae (Green et al., 1989), bronchoconstriction (Doll, 1989), and abnormalities of lung function including impairment of carbon monoxide diffusion capacity (Gude, 1989).

The type of nebulizer used influences the efficacy and tolerability of nebulized pentamidine. The Respirgard II nebulizer which delivers particles of 1-2 μm diameter, the ideal size for maximal alveolar deposition and minimal upper respiratory tract deposition, has been used in many clinical studies (Miller, Godfrey-Faussett & Semple, 1989). This jet nebulizer incorporates a baffle between the nebulizer and the mouthpiece which filters out larger particles. Whilst creating an aerosol of droplets of the most appropriate size this unfortunately reduces the overall efficiency of the nebulizer and the dose of pentamidine reaching the lungs is low (O'Doherty et al., 1988). When doses of pentamidine of 50 mg (in 3 ml water) and 300 mg (in 6 ml water) are used, intrapulmonary deposition with the Respirgard II nebulizer has been measured as 1-4 mg (Thomas et al., 1989; O'Doherty et al., 1990) and 6-2 mg (O'Doherty et al., 1990), respectively; of this dose one half to three quarters is deposited in the alveoli (Simonds et al., 1989). Using the System 22 Mizer better deposition rates can be achieved. With doses of pentamidine of 50 mg (in 3 ml water) and 300 mg (in 6 ml water) intrapulmonary deposition is 2-4 mg (Thomas et al., 1989) and 12-6 mg (O'Doherty et al., 1990), although a smaller proportion is deposited in the alveoli (Thomas et al., 1989). The aerosol droplets produced by this nebulizer are larger than those produced by the Respirgard II nebulizer and this results in increased central deposition and more frequent local adverse effects. As an alternative to using bottled gases or wall-mounted hospital oxygen supplies to drive the jet nebulizers, many centres are now using portable mains driven compressors (which can also be used by patients at home). Very few compressors (particularly the systems used for nebulizing bronchodilators) have sufficient output to nebulize pentamidine adequately with Respirgard II or System 22 Mizer nebulizers. The exception to this is the high output continuously rated CR60 compressor.

Ultrasonic nebulizers have also been used to deliver nebulized pentamidine (Girard et al., 1989; Montaner et al., 1989). The Fisoneb and Ultraneb-99m tend to produce a heterogeneous aerosol with a droplet size larger than that produced by jet systems (O'Doherty et al., 1988; Smaldone, Perry & Deutsch, 1988). The Penta-sonic (called Portasonic in the USA) appears to produce droplets of a comparable size to the Respirgard II and is well tolerated by patients. Unfortunately comparative data are lacking on the clinical utility of this system. Until the optimal nebulizer system is identified and the intrapulmonary dose of pentamidine required for effective prophylaxis of P. carinii is known, the use of nebulized pentamidine remains empirical.

Prophylaxis with nebulized pentamidine appears to be effective but does have disadvantages. Close medical/nursing supervision is required at least initially to assess the need for pre-treatment with a bronchodilator and to instruct the patient on self-administration. Patients should receive their nebulized pentamidine in a well-ventilated room, away from other patients and members of staff. Treatment with nebulized pentamidine is more expensive (see Table I) and may be less effective than oral treatment. Our own experience suggests that with long term administration of nebulized pentamidine compliance with prophylaxis becomes a problem, although this has not been associated with a significant increase in relapse of P. carinii pneumonia—and compliance with oral prophylaxis may also be poor in the long term. On the basis of current evidence, dapsone 100 mg twice weekly, Fansidar one tablet twice weekly and co-trimoxazole 960 mg once daily provide cheap effective prophylaxis. Nebulized pentamidine should be given as prophylaxis only to patients who are intolerant of oral therapy. If nebulized pentamidine is used then either 150 mg (diluted in 6 ml water) given through a System 22 Mizer or 300 mg (diluted in 6 ml water) given through a Respirgard II nebulizer appear equally effective when given once a month; the former system delivers nebulized pentamidine in a shorter time, the latter system may well be better tolerated by patients.

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References


Continuous versus discontinuous antibiotic therapy: the role of the post-antibiotic effect and other factors

Delayed recovery of bacteria after exposure to antibiotics was described in the early days of the investigation of penicillin. This phenomenon has since been defined in vitro for most antibiotics and confirmed in vivo by various methods.

In the determination of the post-antibiotic effect (PAE) in vitro, the aim is to transfer the damaged, but surviving, bacteria to a drug-free medium. Methods such as dilution of the antibiotic-containing culture cannot guarantee that there is no persistent activity of the antibiotic, since partial inhibitory effects, some of which are reflected in morphological changes in the bacteria, may occur at concentrations well below the conventional MIC (Lorian, 1986). Moreover, drug that is bound to the bacterial cells may not be removed by dilution. For these reasons it may not always be possible to distinguish a true PAE from a sub-MIC effect.

If the two effects are to be detected and distinguished in vivo, the pharmacokinetic behaviour of the antibiotic must be precisely defined. In experimental animals, the pharmacokinetics at the infection site cannot be measured exactly in each animal, but they are inferred indirectly. The implantation of fibrin clots in rabbits allows the simultaneous determination of bacterial counts and drug concentrations in the clots (Weinstein, Daikos & Perin, 1951; Daikos & Weinstein, 1960a). As the clots are free of leucocytes, the interaction is simplified, even if the situation is somewhat artificial. The skin-blister technique allows the simultaneous measurement of drug concentrations in serum and tissue fluid (Wise et al., 1980). Other models that offer the possibility of pharmacokinetic determinations include the use of implanted chambers or of cotton threads as the site for the bacteria (Odenholt, Holm & Cars, 1988; Renneberg & Walder, 1989).

In early experiments with infection by Streptococcus pyogenes, injected into the leg muscle of intact mice, Eagle, Fleischman & Levy (1953) showed delay in bacterial recovery...