Occup. Med. Vol. 49, No. 4, pp. 243–245, 1999

0962-7480/99

Exposure of health care workers to pentamidine isethionate

J. R. Beach, M. Campbell and D. J. Andrews
Institute of Occupational Health, University of Birmingham and Departments of Occupational Health and Clinical Biochemistry, University Hospital Trust, Birmingham, UK

Pentamidine isethionate is currently used for the prophylaxis and treatment of *Pneumocystis carinii* pneumonia. Its use has been associated with a number of symptoms in staff administering treatment, and there are some additional concerns about possible adverse health effects of long term exposure. The aim of this study was to quantify exposure of health care staff administering nebulized pentamidine to patients. Personal breathing zone and static air samples at the height of the patient's head were collected during the nebulization of pentamidine to nine sequential out-patients attending a haemophilia unit. These were analysed using a standard method allowing the exposure of staff to be estimated. The duration of treatment varied between 15 and 60 min. Personal breathing zone samples showed exposure to be between 2 and 100 μg/m^3. Static samples showed the concentration of pentamidine in the room varied from 15 to 2,100 μg/m^3. While these exposures were relatively low, they were higher than some other studies have reported, and may pose some risk of adverse effects to staff. Some simple measures could reduce staff exposure.

Key words: Aerosol; nebulized; occupational exposure; pentamidine.

Occup. Med. Vol. 49, 243–245, 1999

Received 13 July 1998; accepted in final form 15 December 1998

INTRODUCTION

Pentamidine isethionate is an aromatic diamidine anti-protozoal agent which acts by interfering with DNA and folate transformation, and by inhibiting RNA and protein synthesis. It has proved to be useful in the treatment and prophylaxis of *Pneumocystis carinii* pneumonia (PCP), an opportunistic infection which gives rise to a rate of high mortality in immuno-suppressed people, most notably patients with HIV infection. Thus it has become more widely used in recent years, often being administered as a nebulized solution to out-patients. The usual treatment regime is 600 mg once daily for three weeks *via* nebulizer, while for prophylaxis smaller doses of either 150 mg every two weeks or 300 mg monthly are usually given. Inhalation of the drug targets it specifically to the lungs and allows higher doses to be administered without the adverse effects seen when high doses are used systemically.

Occupational exposure to the drug occurs during nebulization mainly due to release of the aerosolized pentamidine into the general atmosphere. This release raises concerns about the potential risk of passive exposure to the drug and possibly to respiratory pathogens of health care personnel.[1,2] Anecdotally, health care staff in the West Midlands area of the UK who regularly administer prophylactic treatment to immuno-suppressed patients have reported a variety of symptoms associated with exposure to aerosolized pentamidine. We therefore conducted an investigation to evaluate and quantify the levels of occupational exposure to aerosolized pentamidine in health care staff working in the unit where this drug was administered. Samples were collected over a period of several weeks as patients attended for their monthly prophylactic treatment.

MATERIALS AND METHODS

Nurses working in the haemophilia unit of the Queen Elizabeth Hospital in Birmingham, UK were asked to participate in the study. Each was asked to wear a personal sampling train whilst administering pentamidine to subjects in their normal way. Sampling was performed during a number of sequential visits to the unit by patients requiring prophylactic pentamidine. The majority of the nurses eventually wore the sampler during at least one treatment period although the actual selection

Correspondence and reprint requests to: J. R. Beach, Institute of Occupational Health, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. Tel: (+44) 121 414 6048; Fax: (+44) 121 414 6217.

of the nurse to wear the sampling device depended simply on which one was administering treatment at the time of sampling. The duration of sampling was fixed as the time taken to treat a single patient, the sampling equipment being started at the beginning of the treatment episode and switched off immediately afterwards.

Patients received their treatment in a room within the haemophilia unit which was also used for other procedures, and which included refrigerated storage facilities. Patients usually sat in a chair positioned near a window which was kept open whenever possible. At the time of the survey the unit used a System 22 nebulizer and 'Mizer' reservoir device (Medic Aid, Pagham, UK) connected to a compressor to aerosolize the drug. Patients usually inhaled using a mouthpiece rather than a mask, and exhaled air was exhausted *via* a 'T' piece with one-way valves through a large bore tube directly out of the adjacent window. Theoretically, all exhaled pentamidine was released outside the treatment room. The room had no mechanical ventilation, the only source of fresh air being the window which was kept closed during bad weather. The duration of treatment was usually 20–30 min.

Staff caring for patients did not usually remain in the room during treatment but did enter intermittently to check on progress, and occasionally had to enter to remove supplies from the refrigerated storage. It was sometimes necessary for staff to stay with patients throughout treatment if they were particularly ill or became distressed because of coughing or other symptoms. Patients were given additional instructions aimed at reducing pentamidine release into the room. These included switching off the compressor when removing the mouthpiece or mask, for example when taking a drink or when they needed to cough.

Personal samples were collected from the breathing zone (PBZ) of the nurses to quantify exposure of staff during treatment. The nurses wore a harness carrying a pump drawing air at 2 L/minute through an open faced cassette holding a 37 mm, 5 μm pore polyvinyl chloride membrane filter.[3,4] Additional static (S) samples were collected using a similar technique from a position at the patient's head-level, one metre each side of the patient, to evaluate the amount of pentamidine released into the room due to equipment leakage during coughing bouts, nose breathing or other 'improper' use of the nebulizer. Control samples were also collected from the treatment room when not in use and from the library at the Institute of Occupational Health.

After sampling the filters were collected and pentamidine isethionate extracted using 3 ml aliquots of 50:50 ethanol:water with 0.085% phosphoric acid and 0.04% tetramethylammonium chloride in an ultrasonic bath for 10 min. Quantification was performed using high performance liquid chromatography (HPLC) using a Techsphere 5 μm C8 column, acetonitrile:water (30:70 v/v) mobile phase containing 0.085% phosphoric acid and 0.04% tetramethylammonium chloride, and fluorescence detection.[3,4]

Table 1. Results of personal breathing zone (PBZ) and static exposure assessments in the treatment room

Patient	PBZ ($\mu g/m^3$)	Right side of patient ($\mu g/m^3$)	Left side of patient ($\mu g/m^3$)	Sample time (mins)
1	100	300	2,100	15
2	100	20	400	30
3	20	100	200	15
4	20	400	400	20
5	60	100	50	20
6	2	70	130	60
7	6	150	130	35
8	7	140	170	15
9	90	400	150	40
Geometric mean	23	140	224	(20)[a]

[a] Arithmetic mean.

RESULTS

Samples were collected during a total of nine treatment periods with nine separate patients. Results for each sample are shown in Table 1. The duration of treatment ranged from 15–60 min depending upon how often the treatment needed to be interrupted by the patient to maintain comfort. The nurses wearing the sampling equipment felt that these treatment episodes were typical of their working practice. None of the control samples taken from the treatment room when not in use or from the library at the Institute of Occupational Health, contained any detectable pentamidine.

DISCUSSION

The results obtained in the study showed that there was quantifiable exposure to pentamidine isethionate in health care staff working in this unit. In other health care settings with comparable work practices there is likely to be a similar level of exposure. However it is difficult to quantify the risks to health that might result from this exposure, as only limited information is available on the health effects of long-term exposure to pentamidine isethionate, particularly at the relatively low levels typical of occupational exposure, and exposure in this study was relatively variable, with no clear relationship being apparent between the results of personal sampling and static sampling. We do not believe this is due to any methodological problems but simply reflects the true distribution of the data. Unfortunately, the number of samples was not sufficient to identify the factors which might contribute to greater or lesser exposure.

Currently, the Health and Safety Executive has set no occupational exposure limit for pentamidine.[5] Exposure levels were below a provisional control limit which has previously been recommended by the manufacturer (1 mg/m^3 as an 8-hour time weighted average),[6] although the supplier does not currently recommend any such limit. It was unclear which adverse effects had been considered in arriving at this putative exposure limit, but any such exposure limit must be relatively imprecise given the paucity of available data on occupational exposure.

One previous study has reported similar levels of exposure when sampling was performed immediately after a treatment,[7] whereas others have reported somewhat lower levels and it is relevant that in these studies an exhaust filter was used.[8,9] Acute bronchospasm following low-level exposure to pentamidine has been reported to occur in a nurse observing the administration of nebulized pentamidine to a patient, and in a visitor of a patient receiving similar treatment.[10] Additionally, in a group of nurses with broadly comparable occupational exposures to these (< 0.03 μg/m^3 to 62.2 μg/m^3) a mean cross-shift decrease in FEV1 of 140 mls was detected.[11]

It has also been suggested that low doses of pentamidine may carry a risk of teratogenesis as it is able to inhibit the enzyme dihydrofolate reductase.[12,13] The manufacturer's hazard safety data sheet does advise that the exposure of pregnant women to pentamidine should be minimized.[6] It must also be borne in mind that unlike patients, staff receive no benefit from their exposure to pentamidine, and thus a lower level of risk of adverse effects is likely to be acceptable for staff than that for patients. COSHH (Control of Substances Hazardous to Health Regulations) assessments have been completed, but again, perhaps because of the paucity of available information about the adverse health effects of occupational exposure to pentamidine, sufficient emphasis may not have been given to some risks.

Assessment of the work practices in the haemophilia unit indicated that some simple controls were already in use in an attempt to reduce exposure. For example, staff were aware that they should spend a minimum amount of time during the room during patient treatment, and that they should avoid entering to collect supplies from the refrigerators until treatment had finished whenever possible. A number of measures were recommended to help reduce exposure both to pentamidine and airborne pathogens including: the use of an exhaust filter; increasing the general ventilation in the room; regular checks of equipment seals; building an observation window into the wall or door of the room; not using the room for a period after each nebulization and moving the refrigerated storage elsewhere. Establishing a negative pressure within the room relative to the adjacent room and corridor would help reduce the risk of exposure to staff not in the treatment room, and the introduction of a device to time nebulization to inhalation (an inhalation dosimeter) may also be useful. In addition to airborne exposure there is the potential for some skin contamination and ingestion of pentamidine. The potential for exposure *via* this route is unclear as surface wipes were not performed, but again some simple housekeeping measures could help control this. Finally, many of the staff, although concerned, were unsure of possible health risks and appropriate control measures, emphasizing the importance of information and training in the management of chemical hazards in the workplace. A complete account of effective control measures is contained in the guidance recently provided by the British Occupational Hygiene Society.[14]

Although the quantity of data here is limited, we believe it is important. Many health service staff work with a wide variety of toxic chemicals used specifically because they are biologically active. Limited resources, time pressures, the prioritization of patient care and complacency arising from familiarity may all contribute to poor control in some circumstances. This data emphasizes that risks to health care staff arising from pharmaceutical agents continue to exist, but that relatively simple and inexpensive measures may significantly reduce these risks.

ACKNOWLEDGEMENTS

We are grateful to T. Chando for her help with the collection and analysis of data.

REFERENCES

1. Dupon M, Malou M, Rogues AM, Lacut JY. Drug points. Acute eosinophilic pneumonia induced by inhaled pentamidine isethionate. *Br Med J* 1993; 306: 109.
2. Leigh TR, Millett MJ, Jameson B, Collins JV. Serum titres of *Pneumocystis carinii* antibody in health care workers caring for patients with AIDS. *Thorax* 1993; 48: 619–621.
3. National Institute for Occupational Safety and Health. *NIOSH Manual of Analytical Methods, Fourth Edition. Pentamidine Isethionate: Method 5032*. Cincinnati, OH (USA): NIOSH, 1992.
4. Tucker SP, Belinky BR, Seitz TA, Foley GD. Determination of pentamidine isethionate in air. *Am Ind Hyg Assoc J* 1993; 54: 628–632.
5. Health and Safety Executive. *Occupational Exposure Limits 1998*. London, UK: HSE Books, 1998. EH40/98.
6. Rhone Poulenc Rorer Ltd. *Material Safety Data Sheet, Pentacarinat Ready-To-Use Solution*. January, 1991.
7 Ros JJ, Langen MC, Stallen PC, Lenderink AW. Pentamidine aerosols and environmental contamination: healthcare workers at risk. *Pharm World Sci* 1996; 18: 148–152.
8. Montgomery AB, Corkery KJ, Brunette ER, Leoung GS, Waskin H, Debs RJ. Occupational exposure to aerosolized pentamidine. *Chest* 1990; 98: 386–388.
9. Decker JS, Seitz TA, Shults RA, *et al.* Occupational exposures to aerosolized pharmaceuticals and control strategies. *Scand J Work Environ Health* 1992; 18(Suppl 2): 100–102.
10. Doll DC. Aerosolised pentamidine [letter]. *Lancet* 1989; ii: 1284–1285.
11. Balmes JR, Estacio PL, Quinlan P, Kelly T, Corkery K, Blanc P. Respiratory effects of occupational exposure to aerosolized pentamidine. *J Occup Environ Med* 1996; 38: 330–331.
12. Waalkes TP, Makulu DR. Pharmacologic aspects of pentamidine. *Natl Cancer Inst Monogr* 1976; 43: 171–176.
13. Ito S, Koren G. Estimation of fetal risk from aerosolized pentamidine in pregnant healthcare workers. *Chest* 1994; 106: 1460–1462.
14. British Occupational Hygiene Society special interest group for the NHS. *COSHH Guidance Note 0396: Pentamidine*. Derby, UK: BOHS, 1997.