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Indexed in Current Contents and Index Medicus
Insulin-dependent diabetes mellitus following pentamidine therapy in a patient with AIDS

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Abstract. Pentamidine is known to cause severe dysglycaemia by damaging β-cell function of the pancreas. The exact mechanism still remains unclear. We report the case of a 53-year-old man infected with the human immunodeficiency virus who developed insulin-dependent permanent diabetes mellitus 3 days after starting intravenous treatment with pentamidine for pneumocystis carinii pneumonia. Discharged from hospital the daily need of insulin increased continuously over one year now requiring an average dose of 80 units per day. So far, a number of cases of insulin-dependent diabetes mellitus following pentamidine therapy has been reported, but long-term observations are rare.

Key words: Pentamidine – Diabetes mellitus – Human immunodeficiency virus

Insulin-dependent diabetes mellitus (IDDM) following parenteral pentamidine therapy in patients with the acquired immune-deficient syndrome (AIDS) has been described as a rare adverse event of the drug in a number of cases. Little is known about the exact mechanism of action, and there are no reports of long-term follow-up except one case with a follow-up of 8 months after the onset of diabetes mellitus. We report the case of a patient with AIDS developing IDDM after pentamidine treatment. His need of insulin increased continuously over 1 year.

Case report

A 53-year-old white man with known human immunodeficiency virus (HIV) infection since 1985 (current CD4 cell count 40/mm³) presented with fever, dyspnea, and cough requiring hospital admission. Physical examination revealed a patient in reduced general health with a respiratory rate of 42/min and a heart rate of 104/min. Blood gas analysis showed severe hypoxemia ($pO_2$ 49.4 mmHg). Life-threatening Pneumocystis pneumonia was suspected although the patient had used pentamidine inhalations for $P$. carinii prophylaxis during the past 6 months with very good compliance. After demonstration of $P$. carinii in the bronchoalveolar lavage fluid high-dose intravenous cotrimoxazole therapy was started. The patient developed severe skin rash after 1 day, and cotrimoxazole was therefore replaced by intravenous pentamidine (4 mg/kg). Methylprednisolone (100 mg/day) was added for 2 days to improve hypoxia. Within 2 weeks the pneumonia resolved; pentamidine was given for a total of 15 days.

After 3 days of pentamidine therapy asymptomatic hyperglycemia occurred, with serum glucose levels ranging up to 520 mg/dl requiring insulin therapy. Before pentamidine administration routine blood glucose tests had been normal. After discontinuation of pentamidine the hyperglycemia persisted, requiring increasing doses of insulin. The patient was discharged from hospital with an average daily dose of 16 U insulin per day. Within 12 months later the average daily dose had increased to 70 U (Fig. 1). No other risk factors for the development of diabetes mellitus were found. There was no family history of diabetes mellitus, hemoglobin Alc was within the normal range at the onset of hyperglycemia, and test results for antibodies against islet cells were negative. Low C peptide levels (1.5 ng/dl postprandial) indicated β-cell dysfunction.

Two weeks after discontinuation of pentamidine the patient had an episode of nausea and vomiting lasting for several days, accompanied by an increase in serum lipase to 490 U/l, serum amylase remaining within normal range. Over a period...
of 5 months lipase levels gradually returned to normal without further specific therapy.

**Discussion**

Pentamidine, an aromatic diamidine with antiprotozoal activity is used in the treatment of trypanosomiasis, leishmaniasis, and most importantly *P. carinii* pneumonia. It appears to affect oxidative phosphorylation, nucleic acid synthesis, glucose metabolism, and folic acid synthesis, but the exact mechanism of its antiprotozoal effect is not yet known [5]. The drug can be administered by inhalation, intramuscularly, and intravenously. Its volume of distribution is extremely high (3 l/kg) while the plasma half-life is very short (a few minutes) [12]. Experimental animal models show a high concentration of the drug in kidneys, liver, and lungs but also in other organs such as the pancreas after intravenous administration [6]. Seven days later the concentration of the drug in the organs remains almost unchanged [13]. Pentamidine is largely eliminated by renal excretion; a small proportion is also eliminated by liver and salivary glands.

Side effects of the drug are common, the most frequent of which are hypotension and hypoglycemia, the latter occurring in up to 26% of HIV-infected patients treated by intravenous pentamidine [7]. Persistent IDDM following pentamidine has been reported in about 25 cases so far [3, 4, 7, 8, 10, 14]. There are 12 case reports from India on patients treated for kala-azar [8]. Eleven of these developed IDDM, one of whom could be sufficiently treated by oral antidiabetics. All of these patients were followed up over the next 2–5 years and the diabetes persisted. The other reported cases of pentamidine-induced diabetes mellitus are AIDS patients treated with pentamidine for *P. carinii* pneumonia. There is only one case of non-insulin-dependent diabetes mellitus caused by pentamidine [1]. While this was the case with the shortest duration of therapy (9 days), the one with the longest duration (21 days) was accompanied by severe pancreatitis [14]. These clinical observations support the results of animal models in which the toxicity of pentamidine on the β-cells of the pancreas appeared time dependent, dose dependent, and irreversible [2, 3, 11]. Renal insufficiency has been shown to increase toxicity, but liver damage does not seem to affect toxicity of the drug [2]. A similar effect was observed after the administration of streptozotocin, alloxan, and certain rodenticides [9]. Histological examination of the pancreas was performed in one human who had developed diabetes mellitus after pentamidine treatment [14] and in rats exposed to pentamidine [2, 11]. Morphological changes differed from those found in the pancreas exposed to other toxic agents or in the pancreas of patients suffering from IDDM. The pancreas showed a decrease in β-cells and an increase in A-cells without β-cell necrosis or lymphocytic infiltration. There is no further information about the exact mechanism of action of the drug's damaging potential to β-cells.

The case described here emphasizes the toxicity of pentamidine to the pancreas. In this patient we found a slowly increasing need of insulin over 1 year after pentamidine therapy which cannot be explained by dietary failure. Although the drug is known for its persisting and extremely high concentrations in almost all organs [10], it remains unclear how pentamidine can cause an increase of need of insulin even months after discontinuation of therapy. Further investigations must be performed to ascertain the exact mechanism of action of pentamidine's high toxicity.

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