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Trimethoprim-sulfamethoxazole-associated severe hypoglycaemia: a sulfonylurea-like effect

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Abstract. – *Aim:* **To report hypoglycaemia, a life-threatening adverse event, associated with trimethoprim-sulfamethoxazole. A sulfonylurea-like effect, leading to insulin raise, was investigated.**

Methods: **Two cases of trimethoprim-sulfamethoxazole-associated hypoglycaemia in 2 patients with a diagnosis of new HIV-1-infection presenting with Pneumocystis jiroveci pneumonia are reported. The patients had no predisposing factors, such as renal or liver impairment, interfering with trimethoprim-sulfamethoxazole elimination, thus leading to hypoglycaemia. Insulin plasma levels were measured in both patients.**

Results: **Severe hypoglycaemia was associated with increased serum levels of insulin up to 84 μU/ml (normal values <10 μU/ml). Continuous dextrose infusion was necessary, further suggesting the sulfonylurea-like effect of sulfamethoxazole. Interestingly, plasma levels of insulin progressively raised after trimethoprim-sulfamethoxazole administration.**

Conclusions: **Only 18 cases of trimethoprim-sulfamethoxazole associated hypoglycaemia are reported in the literature. Hypoglycaemia is a life-threatening condition, likely underreported, to consider when trimethoprim-sulfamethoxazole administration is required, even in the absence of predisposing factors or other hypoglycaemic agents. Physician should bear in mind the potential trimethoprim-sulfamethoxazole-associated adverse event especially when prolonged treatments and elevated dosage are used.**

Key Words:

Co-trimoxazole, Hypoglycaemia, Insulin, HIV, Pneumocystis jiroveci pneumonia.

Introduction

Trimethoprim-sulfamethoxazole (co-trimoxazole) (TMP-SMX) is a widely and commonly used chemotherapeutic agent and a first-line drug for the treatment of *Pneumocystis jiroveci* (formerly *Pneumocystis carinii)* pneumonia (PCP). It is also used for the prophylaxis of *Pneumocystis jiroveci* in Human Immunodeficiency Virus type I (HIV-1) infected individuals.

Among the co-trimoxazole side effects, hypoglycaemia, although rare, can be severe and protracted leading to a loss of consciousness and seizures[1].

We report two cases of hypoglycaemia in two HIV-1-infected patients treated with co-trimoxazole for *Pneumocystis jiroveci* pneumonia.

Case Report 1

In October 2008, a 44 years old woman was admitted to our Infectious Diseases Unit with symptoms of fever and dyspnea. Respiratory rate was 28/minute, heart rate was 120 b.p.m., O_2 saturation on room air was 80%, blood pressure was 120/80 mmHg, LDH was 487 IU/L, CD4 T-cell count was 17/μl. A diagnosis of HIV-1 infection was made on the basis of 2 positive ELISA tests, western blot positivity and positive HIV-RNA.

Chest X-ray showed ground-glass opacities bilaterally. A diagnosis of *Pneumocystis jiroveci* pneumonia was made and prednisone (40 mg b.i.d. IV.) and co-trimoxazole (1600 mg sulfamethoxazole, 320 mg trimetoprim IV, every 6 hours) were initiated.

Seven days after co-trimoxazole initiation the patient developed symptoms of hypoglycaemia such as sweating, asthenia, dizziness, with a plasma glucose value of 59 mg/dl and plasma insulin level of 40 μU/ml (normal values: <10 μU/ml). Intravenous bolus administration of 10% glucose

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solution was effective in raising the levels of glycaemia to normal values.

The next day the early morning level of insulin, before co-trimoxazole administration, was 27 μU/ml (blood glucose was 50 mg/dl). After co-trimoxazole administration insulin levels raised to 62 μU/ml one hour later and to 84 μU/ml 3 hours later.

Liver and renal function were normal. Serum creatinine levels were always within normal limits with most values around 0.8 ± 0.1 mg/dl. Her body weight was 75 kg and creatinine clearance was 106 mL/min (Cockcroft-Gault for GFR calculation). AST and ALT were slightly above normal values (68 and 88 IU/L, respectively), although liver function was within normal limits and hepatitis C virus and hepatitis B virus tests were negative. The patient was not diabetic and her family history for diabetes was negative.

The patient continued the therapy for PCP under strict surveillance, frequent blood glucose tests, 10% glucose solution administration and avoiding prolonged fasting periods.

Case Report 2

In February 2007, a 24 years old man was admitted to our Infectious Diseases Unit with symptoms of left hemiparesis and diarrhea. A new diagnosis of HIV-1 infection was made. His CD4 T-cell count was 48/μl and the plasma HIV-1 RNA viral load was above 100,000 copies/ml. Cranial computed tomography (CT) with contrast revealed typical cerebral lesions of neurotoxoplasmosis. CT contrast had no impact on renal function which remained within normal limits. Treatment with sulfadiazine (1 g every 6 hours) and pyrimethamine 50 mg/day was started, as well as highly active antiretroviral therapy (HAART) with tenofovir, lamivudine and lopinavir/ritonavir. Seven days later the patient had a fever, dyspnea (respiratory rate 36/minute), tachycardia (120 b.p.m.) and dry cough. A chest X-ray showed ground-glass opacities bilaterally, LDH was 487 IU/L (normal values: 125-243), O_2 saturation on room air was 86% and PO_2 was 70 mmHg. A diagnosis of *Pneumocystis jiroveci* pneumonia was made and prednisone (40 mg b.i.d. IV.) and co-trimoxazole (1200 mg sulfamethoxazole, 240 mg trimetoprim IV, every 6 hours) were initiated, while sulfadiazine and pyrimethamine were interrupted.

Two weeks later a cytomegalovirus (CMV) chorioretinitis was diagnosed and ganciclovir 300 mg bid IV was started.

Twenty days after co-trimoxazole initiation the patient developed symptoms of hypoglycaemia such as sweating, asthenia, confusion, nausea and dizziness, with a plasma glucose value of 56 mg/dl and plasma insulin level of 80 μU/ml (normal values: <10 μU/ml). The patient was not diabetic and his family history for diabetes was negative. Antiretroviral therapy, ganciclovir and co-trimoxazole were stopped. Renal and liver function were normal. Serum creatinine levels have been tested daily and were always within normal limits with most values around 0.8 ± 0.1. His body weight was 60 kg and creatinine clearance was 107 mL/min (Cockcroft-Gault for GFR calculation). Upon a bolus administration of 10% glucose solution, glycaemia levels raised temporarily and dropped again to even lower levels (46 mg/dl) one hour later, accompanied by the same symptoms. Continuous administration of 10% glucose solution seemed to be effective, with the lowest plasma glucose level of 66 mg/dl in one occasion. Eighteen hours later a plasma glucose level of 40 mg/dl led us to augment the glucose solution to 33%. Thereafter, the plasma glucose levels remained in the normal range. Of importance, the levels of plasma insulin decreased from 80 μU/ml to 30 μg/ml in the subsequent 36 hours, and to normal values in 48 hours. The PCP resolved and ganciclovir was restarted within 72 hours. After 20 days a new HAART regimen with boosted atazanavir, tenofovir and lamivudine was initiated.

Discussion

Eighteen cases of co-trimoxazole-induced hypoglycaemia have been described in the literature[1-16]. Of note, a predisposing factor, such as impaired renal or hepatic function and or the contemporary use of drugs that decrease plasma glucose levels, was present in all patients. Since co-trimoxazole is renally excreted, decreased renal function was the main risk factor.

In our cases, there were no predisposing factors. In our first case report, the patient was treated with co-trimoxazole only and we were also able to show that upon co-trimoxazole administration the plasma levels of insulin increasingly

raised, further demonstrating the sulfonylurea-like effect of sulfamethoxazole.

In the second case, the treatment course with co-trimoxazole was longer and was preceded by sulfadiazine, which, like other sulfonamides, may induce hypoglycaemia through a sulfonylurea-like effect[1]. Sulfamethoxazole and sulfonamide are similar to the oral hypoglycemic molecule sulfonylurea, which is a secretogogue drug that stimulates the release of insulin. In fact, in our cases, as well as in other reports, we have documented increased levels of plasma insulin that lowered gradually upon interruption of co-trimoxazole. It is likely that this phenomenon is dose and time dependent. Moreover, we also had to augment the glucose supplementation to more than 10 g per hour. This further supports the sulfonylurea-like effect of co-trimoxazole[1].

As for ganciclovir, there is just one report of drug-induced hypoglycaemia, in 2 children[17]. In the second case report, the patient was treated with both co-trimoxazole and gancyclovir for six days before the onset of hypoglycaemia**.** As such, the synergistic effect of the two drugs cannot be excluded. As for tenofovir, lamivudine and lopinavir/ritonavir, hypoglycaemic events have not been reported in the medical literature. Nor drug-drug interactions have been reported with co-trimoxazole, potentially leading to hypoglycaemia (PUBMED search of the literature has been performed using several combinations of the following terms: tenofovir, lamivudine, lopinavir/ritonavir, hypoglycaemia, co-trimoxazole).

We believe that hypoglycaemia is probably underestimated and underreported. It is likely that hypoglycaemia is associated with prolonged co-trimoxazole administration and/or elevated dosage of the drug, along with severe infections. Since drug-induced hypoglycaemia is a life-threatening condition, it should be carefully considered especially in HIV-1-infected individuals due to the multiplicity of drugs, infections, and diverse organ dysfunction that they experience along the course of HIV-1-infection.

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