A plausible explanation for this pattern of autonomic nervous dysfunction is the presence of long axons in cardiac parasympathetic and peripheral sympathetic systems, which are relatively more sensitive to the metabolic derangements as compared to the relatively short axons in the cardiac sympathetic system. Although it has not yet been shown that the treatment of hyperglycaemia in Type 2 diabetics will improve cardiac autonomic function, identification and treatment of CAN at the time of diagnosis of diabetes will improve the quality of life and should be a part of routine care for diabetic patients.

Kaveer N, Das AK, Agrawal A, Madanmohan, Veena N
Jawaharlal Institute of Post Graduate Medical Education and Research, Pondicherry, India.

Correspondence:
N Kaveer, MBBBS. E-mail: ramnarayankaveer@yahoo.com

References

Received : 16-12-03
Review completed : 02-02-04
Accepted : 03-04-04
PubMed ID : 15377815

Massive rhabdomyolysis with simvastatin precipitated by amoxicillin

Sir,
Currently, statins are being used extensively and more aggressively for the treatment of hypercholesterolemia. As more data gets pooled from newer trials, the threshold for statin use has been lowered and the potential for adverse events therefore has probably increased. But there are certain risks associated with the use of these drugs and many drug interactions can occur. Herein we describe a 75-year-old white male, a known patient of congestive heart failure (CHF) with a left ventricular ejection fraction of 30%, hypercholesterolemia and coronary artery disease (CAD). He was on optimum medications for CHF and CAD (lisinopril 10 mg / day, carvedilol 25 mg / day, aspirin 81 mg / day and frusemide 40 mg/day). His cholesterol-lowering medications included simvastatin 80 mg / day. He was on the same dose of these medications for the last 6 years. He was asymptomatic and the blood chemistry performed 3 weeks prior to admission showed normal liver and kidney functions. He was started on amoxicillin 500 mg TID by his doctor for cough, fever and sore throat as a treatment for upper respiratory tract symptoms. Immediately after taking the second dose of amoxicillin, he started feeling weak and excessively fatigued. He also started to have dull aches in the proximal muscles of the upper and lower limbs. He came to the emergency room where investigations revealed deranged kidney and liver functions and very high CPK levels. His haemoglobin level was 13.2 g/dl, leucocyte count was 8900 / cc, platelet count was 250000 / cc. AST/ALT were 701/520, serum alkaline phosphatase was 250 IU, serum bilirubin was 24.1 mg/dl with direct component being 22.4 mg/dl, BUN/ Serum creatinine were 162/5.3 and CPK was 29900 mg/dl with CKMB fraction of only 2.3%. His cardiac troponins were negative. He had metabolic acidosis with a serum bicarbonate level of 12.

Results of arterial blood gases revealed a pH of 7.12 and pCO2 of 31. A routine urine analysis revealed a large amount of blood and only 2-3 red blood cells/ HPF. Later on urine was found to be strongly positive for myoglobin. The patient was immediately started on high-dose intravenous fluid and bicarbonate to alkalinise the urine. He was given diuretics to treat his pulmonary oedema that developed due to underlying CHF. Subsequently, his condition improved, renal functions became better and the CPK levels came down to normal in 6 days and he was discharged.

Statins are associated with skeletal muscle complaints, including clinically important myositis and rhabdomyolysis, mild serum creatine kinase (CK) elevations, myalgia with and without elevated CK levels, muscle weakness, muscle cramps, and persistent myalgia and CK elevations after statin withdrawal. Thompson et al performed a review of the literature on statin-induced myopathy and found that cerivastatin was the most commonly implicated statin in rhabdomyolysis. The literature review found that reports of muscle problems during statin clinical trials are extremely rare. The FDA MEDWATCH Reporting System lists 3339 cases of statin-associated rhabdomyolysis reported between January 1, 1990, and March 31, 2002. Few data were available regarding the frequency of less serious events such as muscle pain and weakness, which may affect 1% to 5% of the patients. The risk of rhabdomyolysis and other adverse effects with statin use can be exacerbated by several factors, including compromised hepatic and renal function, hypothyroidism, diabetes, and concomitant medications.

The hepatotoxicity of the amoxicillin-clavulanic acid combination has been well documented in various studies. It has been associated with elevated AST (SGOT) and ALT (SGPT) levels, cholestatic jaundice, acute cytolytic hepatitis, and patterns of liver injury have been found to be consistent with immune-mediated hepatitis. On searching the literature we did not come across any description of hepatitis caused by amoxicillin use alone. But hepatic toxicity is described as one of the significant adverse effects associated with amoxicillin use by the manufacturers (Lexi-Comp).

Using the criteria reported by Naranjo et al to determine the likelihood of a drug being responsible for an adverse reaction, in the case described above it seems that amoxicillin taken by the patient was the possible cause of hepatic insult of some
form and it has a score of 3 on Naranjo ADR probability scale. Since simvastatin is metabolised by hepatic CYP3A4 enzymes, the liver injury probably compromised the metabolism of simvastatin resulting in high levels of this drug. These high levels of simvastatin could have caused the massive rhabdomyolysis seen in this patient. Another possibility could have been a viral infection that caused upper respiratory tract symptoms leading to severe hepatitis, and eventually causing rhabdomyolysis due to high levels of simvastatin. This raises concern regarding the use of statins as a very close monitoring for unexpected adverse drug interactions might be required for patients on statins and other drugs. Concerns have been expressed regarding the use of statins in octogenarians for primary prevention of CAD as there may be increased risks of myositis, rhabdomyolysis, and cancer in the elderly. The above described adverse event was reported to the Food and Drug Administration of USA.

Bhatia V
Department of Medicine, Mercy Hospital of Buffalo, Buffalo, NY - 14220, USA
Correspondence: Vishal Bhatia, MD. E-mail: vbhatia@buffalo.edu

References

Disseminated Penicillium marneffei infection in a human immunodeficiency virus-infected individual

Sir,

Prevention and treatment of opportunistic infections continues to be a major public health strategy among HIV-infected people in developing countries. Awareness of clinical manifestations and the cutaneous stigmata of opportunistic infections are pivotal in the diagnosis of many opportunistic infections in resource-limited areas. Increasing numbers of Penicillium marneffei infections have been documented in HIV-infected individuals from the northeastern part of India. This infection has been predominantly reported from Southeast Asia where it has been reported to be the third most common illness that defines Acquired Immuno Deficiency Syndrome.

We describe a patient who presented with fever, weight loss and typical umbilicated papules proven to have disseminated P. marneffei infection on histopathology and culture. A high index of suspicion in the presence of typical skin lesions can lead to early diagnosis.

A 43-year-old man from Assam presented with low-grade fever, weight loss and skin lesions. He had not previously been tested for HIV antibody or virus. On examination, he was wasted, pale with oropharyngeal candidiasis, and had multiple erythematous papules on the face, upper back and extremities. Most of the papules had a necrotic centre with scabs. Systemic examination was normal. His haemoglobin was 9.5 gm% and total white cell count was 4400/mm3 with normal differential count. The chest radiograph was normal. HIV-ELISA was reactive. Biopsy of the skin lesions revealed histiocytic granulomas with yeast-like organisms. Fungal culture grew pigment-producing fungus, Penicillium marneffei. Markers of immune suppression like CD4 counts and viral load were not done due to financial constraints. The patient showed clinical improvement with itraconazole 200 mg orally twice daily. The option of antiretroviral therapy was discussed with the patient but was deferred due to financial constraints.

Penicillium marneffei is a dimorphic fungus causing opportunistic infection, potentially life-threatening in immunocompromised individuals. P. marneffei was first isolated from a species of bamboo rat (Rhizomys sinensis) from Vietnam in 1956 and later, from other rodent species. The common clinical features are fever, weight loss, anaemia, hepatosplenomegaly, and popular skin lesions. The typical cutaneous papules with central necrotic umbilication may be present in about 70% of patients. While this a useful point, molluscum contagiosum and lesions of cryptococcosis can show similar features especially if they are inflamed or irritated. Hepatosplenomegaly, lung and bone involvement are other features of disseminated penicilliosis. Diagnosis is confirmed by fungal culture or histopathology. P. marneffei produces a distinctive red diffusible pigment and is the only dimorphic member of the genus Penicillium. As P. marneffei is an emerging pathogen, a high index of suspicion is warranted in areas which have geographic proximity to Southeast Asia, northeastern India and Bangladesh. History of travel and immigration from endemic areas are major clues to diagnosis as illustrated in this case.

In severe cases treatment with amphotericin B is necessary followed by prophylactic azole maintenance regimen. Itraconazole is an option to be considered in a less sick patient as corroborated in our case.

Varghese GM, Pise G, Michael SJ, Jacob M, George R

Letters