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Serotonin syndrome due to co-administration of linezolid and methadone

Antonio Mastroianni[1], Gianfranco Ravaglia[2]

[1]U.O. Malattie Infettive, Presidio Ospedaliero, "G.B. Morgagni - L. Pierantoni", Forlì, Italy;
[2]U.O. Farmacia, Presidio Ospedaliero "G.B. Morgagni - L. Pierantoni", Forlì, Italy

SUMMARY

Serotonin syndrome (SS), a potentially life-threatening adverse drug reaction caused by excessive serotonergic agonism in central and peripheral nervous system serotonergic receptors, may be caused by a single drug or a combination of drugs with serotonergic activity. The syndrome results in a variety of mental, autonomic and neuromuscular changes, which can range in severity from mild to life-threatening. To our knowledge, we present the first reported case of SS associated with linezolid and methadone with a brief review of the literature.

Keywords: serotonin syndrome, linezolid, methadone, methicillin-resistant *Staphylococcus aureus.*

INTRODUCTION

Serotonin syndrome (SS) is a toxic state caused mainly by excessive serotonergic activity in the nervous system, nearly always caused by a drug interaction involving two or more "serotonergic" drugs [1]. These include serotonin precursors, serotonin agonists, serotonin releasers, serotonin reuptake inhibitors, monoaminoxidase inhibitors (MAOIs) and some herbal medicines. Linezolid is a weak, nonselective, reversible inhibitor of MAOIs, and potentially may interact with MAOIs and adrenergic and serotonergic agents. SS has been reported in patients receiving linezolid concomitantly with serotonergic drugs [2]. Methadone is a serotonin re-uptake inhibitor which may be involved in serotonin toxicity reactions [3].
To the best of our knowledge, we present the first reported case of SS associated with linezolid and methadone. This serious adverse interaction between linezolid and methadone inducing SS was reported in a drug-addict HIV-positive man with sepsis, osteomyelitis and multiple muscle abscesses and metastatic skin abscesses caused by methicillin-resistant *Staphylococcus aureus* (MRSA), under combined antibiotic treatment.

Corresponding author
Antonio Mastroianni
E-mail: antoniomastroianni@yahoo.it

CASE REPORT

A 39-year-old drug-addict male was admitted to our department with fever (up to 39.5°C) and a deterioration of the general conditions associated with pain in the abdomen, the dorsal and lumbar-sacral spine, and lower limbs two months duration, with fatigue, hypotension and oliguria during the last 24 hours reported by his family.
In previous months, for the persistence of a sciatica he had taken anti-inflammatory therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) and steroids, with a self-administration. The patient had a remarkable medical history because of a surgery for right iliac-femoral arterial bypass about 1 year ago. The patient assumed

methadone 40 mg/day, as maintenance therapy for opioid dependence. Antiretroviral therapy included lamivudine 300 mg daily, tenofovir 245 mg daily and darunavir 800 mg / ritonavir 100 mg daily.

On admission, clinical examination revealed a dehydrated patient with high fever, blood pressure of 90/50 mmHg, heart rate 125/min, and respiratory rate 35/min, as well as the presence of multiple erythematous and tender swellings over the right elbow and arm, left side of the chest wall, and abdomen. Respiratory examination revealed bilateral coarse crepitations. The neurological examination was negative, the patient was collaborative, oriented and responsive even if very suffering. Laboratory findings included: hematocrit 37.6%, white blood cell count 15.15×10^9/l, platelet count 95×10^9/l, C-reactive protein 340 mg/l, and creatinine 1.2 mg/dl. The chest X-ray displayed bilateral opacities, while computed tomography (CT) revealed the presence of multiple cavitated nodular infiltrates in both pulmonary fields. Ultrasound of the swellings showed the presence of fluid attenuation into the muscles. A transthoracic echocardiogram was negative for endocarditis. Supportive care, including aggressive rehydration with normal saline and empiric antibiotics (ceftriaxone 2 g once daily intravenously and amoxicillin and potassium clavulanate 1000 mg/200 mg every 8 hours daily intravenously) was initiated immediately.

A CT scan of the abdomen showed multiple muscle abscesses and a pyomyositis of the left psoas muscle. The kidneys showed some hypodense areolas with lamellar morphology, the largest in the middle third of the left kidney (finding compatible with areas of initial pyelonephritis). There was also evidence of edematous imbibitions of subcutaneous and adipose tissue of the left lower limb tissue, multifocal dorsal-lumbar chronic osteomyelitis and a bilateral abscess in suprapatellar recess. Blood cultures obtained on admission were positive for MRSA sensitive to daptomycin (MIC<0.25 mg/L), levofloxacin (MIC<=0.12 mg/L), linezolid (MIC<1 mg/L), teicoplanin (MIC<=0.5 mg/L), tigecycline (MIC<=0.12 mg/L), rifampicin (MIC<=0.03 mg/L) and vancomycin (MIC<1 mg/L). Cultures obtained from the blood and the purulent material aspirated after guided drainage from the swelling of the right arm were positive for MRSA. On the basis of blood and pus cultures, on the fifth day of hospitalization antibiotic treatment was changed to linezolid 600 mg twice daily plus clindamycin 600 mg four times daily intravenously, suspending the previous antibiotic combination, while repeated surgical drainage of the muscle abscesses was performed during his hospital stay. However, the patient was febrile (39°C) and sweating and three days after the introduction of new antibiotic therapy has become increasingly confused, disoriented and agitated. His pulse fluctuated between 95 and 120 beats/minute, and his blood pressure between 110/70 and 100/60 mm Hg. He had a score of 10 on the Glasgow Coma Scale and was unable to sustain conversation; he had generalised abdominal tenderness. Neurological examination revealed dilated reactive pupils, an increased tone in both legs, with brisk reflexes and clonus at both ankles but no meningism. Investigations revealed a white cell count of 21.1 x 10^9/l, predominantly neutrophils, and a C-reactive protein of 15 mg/dl. Chest and abdominal X-rays and urine were normal.

An urgent evaluation raised the suspicion of a serotonin syndrome and after a neurological consultation linezolid was immediately suspended; the patient was subjected to rehydration therapy, steroids and benzodiazepines, with a progressive improvement in the next 48 hours. The patient's clinical condition gradually improved and a different antibiotic therapy including ciprofloxacin, 400 mg twice daily intravenously, and rifampicin 600 mg daily intravenously was reintroduced on the twelfth day of hospitalization. A repeated CT of the chest (day 20) showed a significant improvement of the infiltrates, while the muscle abscesses had reduced in size. The patient was followed up at the clinic; he received ciprofloxacin 750 mg twice daily plus oral rifampin 600 mg daily for three months, with disappearance of the muscle abscesses (40 days after his discharge).

DISCUSSION

SS, a potentially life-threatening adverse drug reaction caused by excessive serotonergic agonism in central and peripheral nervous system serotonergic receptors, may be caused by a single or a

combination of drugs with serotonergic activity, and it results in a variety of mental, autonomic and neuromuscular changes, which can range in severity from mild to life-threatening [4,5].
A variety of single or a combination of drugs with excessive serotonergic agonism on central nervous system and peripheral serotonergic receptors can be involved as a cause of SS, including MAOIs, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), opiate analgesics, over-the-counter cough medicines, antibiotics, weight-reduction agents, antiemetics, antimigraine agents, drugs of abuse, H2-antagonist and herbal products) can be involved as a cause of SS [5].
Most cases will involve either an SSRIs or an MAOIs and at least one other medication. Most reported cases of SS are in patients using multiple serotonergic drugs or who have had considerable exposure to a single serotonin-augmenting drug [6].
Most cases of SS are mild and may be treated by withdrawal of the offending agent and supportive care; however, critically ill patients may require neuromuscular paralysis, sedation, and intubation [6]. In recent years, some opioid analgesics including phenylpiperidine series opioids, pethidine (meperidine), tramadol, methadone and dextromethorphan and propoxyphene appeared to be weak serotonin re-uptake inhibitors and may infrequently precipitate dose-dependent serotonin toxicity reactions with monoamine oxidase inhibitor (MAOIs) drugs [3, 7].
Methadone, a synthetic piperidine opioid, is a racemic mixture of R/S methadone enantiomers. It exerts its analgesia through opioid receptor agonism by R enantiomer and N-methyl-D-aspartate antagonism by S enantiomer, it is metabolized by hepatic enzymes and it is a CYP2D6 enzyme inhibitor [3, 8].
In vitro studies of methadone show a greater tendency toward serotonin reuptake inhibition compared with other opiates, which may explain methadone-mediated precipitation of SS [7]. A case of SS has been associated with methadone overdose and with fentanyl and methadone use in a burn injury [9, 10].
A patient was seen on the palliative care service at Buffalo General Hospital who developed SS and mutism associated with methadone use [11].
Linezolid is a synthetic antimicrobial agent of the oxazolidinone class with weak, nonspecific inhibitor of monoamine oxidase enzymes. Concomitant therapy with an adrenergic or serotonergic agent or consuming tyramine (>100 mg/day) may induce SS [12].
In a recent critical review serotonergic agent dose and duration of coadministration with linezolid did not appear to influence the occurrence of SS. The Authors stated that time of onset ranges from <1 to 20 days, and effect resolves in <1 to 5 days after discontinuation of offending agents [3]. SS in a chronic-pain patient receiving concurrent methadone, ciprofloxacin, and venlafaxine has been reported [13].
In our case report we hypothesized the patient has suffered from a SS due to the interaction between linezolid and methadone, blocking serotonin reuptake and the serotonin presynaptic release, causing increased levels of serotonin in the central nervous system (CNS).
As a matter of fact, mental, autonomic and neuromuscular symptoms resolved after discontinuation of linezolid and the administration of benzodiazepines. We ruled out the possibility of other CNS pathology or other drug interaction. The case reported is the first report of SS associated with linezolid and methadone without the co-administration of other serotonergic agents.
The present case suggests that clinicians should be aware of the potential drug interaction between linezolid and some opioids that have serotonergic activity as methadone, to avoid the risk of life threatening serotonin toxicity which may result from this drugs combination.
We can therefore predict that combination of linezolid with methadone, a weak serotonin re-uptake inhibitor, might possibly precipitate serious serotonin toxicity.
A knowledge of the properties of these drugs may help to ensure that serious reactions can be avoided in methadone-maintained people.

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