Dear Editors,

Serotonin syndrome (SS) is a rare and potentially life-threatening condition. It results from excessive serotonin effect on the central and peripheral nervous system. Serotonin (5-HT) is an excitatory neurotransmitter involved in the regulation of wakefulness, affective behaviour, and regulation of autonomic functions such as vascular tone, gastrointestinal motility and thermoregulation [1,2].

The onset of SS ranges from several hours to several weeks after the administration of serotonergic drugs (Tab. 1). SS is difficult to detect as the signs can run from mild to life-threatening symptoms involving mental status changes (anxiety, agitation, visual hallucinations, restlessness, disorientation and coma), autonomic instability (hyper-/hypotension, tachycardia, tachypnea, diaphoresis, mydriasis, hyperthermia) and neuromuscular hyperactivity (muscle rigidity, tremors, nystagmus, myoclonus, ocular clonus, hyperreflexia). Several diagnostic criteria have been published (Sternbach’s Criteria, Radomski’s Criteria and more sensitive and specific Hunter’s Criteria in Tab. 2). The seven clinical features are associated with serotonin toxicity: clonus, agitation, diaphoresis, tremor, hyperreflexia and hypotension with temperature > 38 °C [2–4]. Mild symptoms usually resolve within 24 hours of cessation of the serotonergic drugs. Severe cases may manifest as severe hyperthermia, seizure, rigidity, respiratory arrest, or even death [1,5].

No specific laboratory abnormality is diagnosed in SS. The blood level of serotonin does not correlate with the severity of the condition as it does not reflect the intrasynaptic serotonin level. In cases of severe serotonin toxicity with muscular hyperactivity and rhabdomyolysis we can observe electrolyte derangements, metabolic acidosis, elevated creatinine levels and increased serum aminotransferase [4,6].

Selective serotonin reuptake inhibitors (SSRI) are the most frequently reported drugs associated with SS. When SS is recognised, immediate withdrawal of the causative drug is necessary. Supportive care is the mainstay of the treatment. Anxiety and agitation can be managed with benzodiazepines and serotonin symptoms can be managed with the 5-HT1A/2A receptor antagonist cyproheptadine or chlorpromazine. Severe cases of hyperthermia may require neuromuscular paralysis and intubation. Antipyretic agents do not help, because hyperthermia is caused by muscle hypermetabolism. Only early diagnosis and treatment can prevent complications such as the development of multiple organ dysfunction syndrome and death [1,2,6].

A 51-year-old female was presented to our emergency department early in the morning for dyspnoea, significant arthralgia, psychomotor unrest, and tremor. Physical examination showed mydriasis, tachycardia (110/min), arterial hypertension (160/100 mm Hg), elevated respiratory rate (24/min) and raised temperature (39 °C). According to the medical history, the patient had been repeatedly prescribed analgesic drugs (meloxicam, indomethacin and tramadol). She had asthma bronchiale treated with the inhaled corticosteroid budesonide in fixed combination with formoterol (160/4.5 mg). Further medication of the patient included ivabradine (10 mg/d) for sinus tachycardia, psychiatric medications paroxetine (60 mg/d), trazodone (300 mg/d), chlorprothixen (50 mg/d) and bromazepam (2 mg/d). According to the patient’s medical history confirmed lately by a family member, the patient had virtually housebound due to pain. She combined various analgesics and antidepressants, 2 days before admission she had even increased doses by herself. During the examination, the patient suffered from a collapse. An electromechanical dissociation was diagnosed and cardiopulmonary resuscitation (CPR) was initiated (lasting for 5 min). Severe metabolic acidosis was found. A nasogastric tube was passed and showed the presence of a variety of drugs in the stomach contents. Samples for toxicological testing were sent. The electrocardiography (ECC) showed 0.5-mm ST segment depression in I and aVL leads. Computed tomography (CT) of the chest was negative for pulmonary embolisms, while CT of the brain demonstrated an oedema.

The patient was admitted to the intensive care unit (ICU) after CPR for asystole of cardiac origin. Anticoagulation (sufentanil, midazolam) and artificial respiration were started and rescue therapy was initiated. We observed significant circulatory instability combined with...

M. Káňová1, J. Ďuricová2,3, J. Slonková4, V. Marcíán5, P. Ševčík5,6
University Hospital Ostrava, Czech Republic:
1 Department of Anaesthesiology and Intensive Care Medicine
2 Institute of Clinical Pharmacology
3 Department of Pharmacology, Faculty of Medicine, University of Ostrava
4 Department of Neurology
5 Department of Intensive Medicine, of Emergency Medicine and Forensic Studies, Faculty of Medicine, University of Ostrava

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MUDr. Marcela Káňová
Department of Anaesthesiology and Intensive Care Medicine
University Hospital Ostrava
17. listopadu 1790
708 52 Ostrava-Poruba
Czech Republic
e-mail: marcela.kanova@fno.cz
lin/ tazobactam) and antioedema therapy were administered (levofloxacin, piperacillin/tazobactam) and anti-oedematous therapy was applied to reduce cerebral oedema. Facial apoplexy (osmotherapy with 10% NaCl) was performed repeatedly, generalized triphasic waves were observed, but without specific epileptic discharges (Fig. 1). Tracheostomy was performed and sedation was subsequently reduced. Finally, on day 5 serotonin syndrome was diagnosed in cooperation with clinical pharmacologist and neurologists. The clinical triad characteristic for SS was confirmed: mental changes prior to sedation (agitation, delirium), vegetative instability (sweating, fever, tachycardia) and myoclonus accompanied by rhabdomyolysis and muscular rigidity. New potential serotoninergic drugs were stopped (opioid agent sufentanil and psychotropic agent metoclopramide, antibiotic levofloxacin-inhibitor CyP3A4), benzodiazepines continued and anti-serotonergic therapy (chlorpromazine plus cyproheptadine) were initiated. An initial dose of 12 mg of cyproheptadine was administered and then 2 mg every 2 h to a max. dose of 32 mg/day. Maintenance dosing of 8 mg every 6 h was administered on the following days. The patient’s clinical condition improved. However, the long-term prognosis was very unfavourable and 16 days later the patient appeared as coma vigil.

Severe SS toxicity may develop into a life-threatening condition with muscular rigidity, hyperthermia and coma. Symptoms with escalating toxicity, if left untreated, may result in complications including metabolic acidosis, rhabdomyolysis, disseminated intravascular coagulation, seizures and death [2]. The case report detailed above is an example of a severe case of SS which developed into coma vigil due to an untimely diagnosis of the condition. The patient’s medical history as well as serum toxicological analysis revealed the presence of several serotoninergic drugs, antidepressants (trazodone, paroxetine) and analgesics (tramadol, codeine) [3,4]. Antidepressants may be the most commonly implicated drugs associated with SS [7–9]. The lack of monitoring of the potential iatrogenic adverse in-

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TCA – tricyclic antidepressants, SSRi – selective serotonin reuptake inhibitors, SNRI – serotonin noradrenaline reuptake inhibitors, MAOI – monoamine oxidase inhibitors, LSD – lysergic acid diethylamide, 5-HT – 5-hydroxytryptamine

The laboratory evaluation excluded a systemic disease. She developed pneumonitis (Candida albicans and Aspergillus fumigatus) and voriconazole was added to the treatment.

By day 4, her white blood cell count started to decrease, the metabolic acidosis resolved, but myoglobinuria decreased only slowly. However, the patient’s circulatory system was still unstable. A transcranial Doppler (TCD) showed no signs of intracranial hypertension. Electroencephalography was performed repeatedly, generalized triphasic waves were observed, but without specific epileptic discharges (Fig. 1). Tracheostomy was performed and sedation was subsequently reduced. Finally, on day 5 serotonin syndrome was diagnosed in cooperation with clinical pharmacologist and neurologists. The clinical triad characteristic for SS was confirmed: mental changes prior to sedation (agitation, delirium), vegetative instability (sweating, fever, tachycardia) and myoclonus accompanied by rhabdomyolysis and muscular rigidity. New potential serotoninergic drugs were stopped (opioid agent sufentanil and psychotropic agent metoclopramide, antibiotic levofloxacin-inhibitor CyP3A4), benzodiazepines continued and anti-serotonergic therapy (chlorpromazine plus cyproheptadine) were initiated. An initial dose of 12 mg of cyproheptadine was administered and then 2 mg every 2 h to a max. dose of 32 mg/day. Maintenance dosing of 8 mg every 6 h was administered on the following days. The patient’s clinical condition improved. However, the long-term prognosis was very unfavourable and 16 days later the patient appeared as coma vigil.

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Tab. 1. Hunter’s Serotonin Toxicity Criteria (sensitivity 84%, specificity 97%).

In the presence of a serotoninergic agent, any one of:

1. spontaneous clonus
2. inducible clonus and agitation or diaphoresis
3. ocular clonus and agitation or diaphoresis
4. tremor and hyperreflexia
5. hyperpyrexia and temperature > 38 °C and ocular clonus or inducible clonus

Tab. 2. Hunter’s Serotonin Toxicity Criteria (sensitivity 84%, specificity 97%).

In the presence of a serotoninergic agent, any one of:

1. increased synthesis
2. increased release
3. decreased reuptake
4. decreased metabolism
5. serotonin 5-HT receptors agonism
6. increased 5-HT receptor sensitivity
7. others

Mechanism of increased serotonin activity

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Tab. 1. Mechanisms of serotonin excess.

Tab. 2. Hunter’s Serotonin Toxicity Criteria (sensitivity 84%, specificity 97%).

In the presence of a serotoninergic agent, any one of:

1. spontaneous clonus
2. inducible clonus and agitation or diaphoresis
3. ocular clonus and agitation or diaphoresis
4. tremor and hyperreflexia
5. hyperpyrexia and temperature > 38 °C and ocular clonus or inducible clonus

sinus tachycardia (up to 160/min) and administered high doses of norepinephrine and esmolol. The level of leukocytes was 20,000. Blood and urine samples were sent for cultivation. Additionally, antimicrobial agents were administered (levofloxacin, piperacillin/tazobactam) and anti-oedematous therapy (osmotherapy with 10% NaCl) was applied to reduce cerebral oedema. Facial myoclonus was observed as well as subsequent spasms of the entire body. Electroencephalography (EEG) revealed nonspecific epileptic discharges (Fig. 1). Tracheostomy was performed and sedation was subsequently reduced. Finally, on day 5 serotonin syndrome was diagnosed in cooperation with clinical pharmacologist and neurologists. The clinical triad characteristic for SS was confirmed: mental changes prior to sedation (agitation, delirium), vegetative instability (sweating, fever, tachycardia) and myoclonus accompanied by rhabdomyolysis and muscular rigidity. New potential serotoninergic drugs were stopped (opioid agent sufentanil and psychotropic agent metoclopramide, antibiotic levofloxacin-inhibitor CyP3A4), benzodiazepines continued and anti-serotonergic therapy (chlorpromazine plus cyproheptadine) were initiated. An initial dose of 12 mg of cyproheptadine was administered and then 2 mg every 2 h to a max. dose of 32 mg/day. Maintenance dosing of 8 mg every 6 h was administered on the following days. The patient’s clinical condition improved. However, the long-term prognosis was very unfavourable and 16 days later the patient appeared as coma vigil.

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teractions was a significant factor for the untimely diagnosis of SS. The presented case demonstrates the necessity to consider drug interactions. It is highly challenging for clinicians to identify therapeutic combinations that may increase the risk of SS. Serotonin toxicity presents as a triad of symptoms of mental-status changes, autonomic hyperactivity and neuromuscular abnormalities. Early recognition of SS and discontinuation of offending drugs are vital for successful management of this serious adverse reaction.

References