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CASE REPORT: SEROTONIN SYNDROME IN AN INJURED SERVICEMAN DURING TREATMENT OF BLAST INJURY

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ABSTRACT

Background. Serotonin syndrome is a life-threatening condition that may be caused by an unanticipated interaction of serotonergic drugs. Medications of this category are routinely prescribed during treatment of blast injury. Their effect on serotonin receptors should be taken into account to prevent the development of serotonin syndrome.

Case description. A patient was transported from another hospital directly to the ICU to continue treatment of consequences of multiple blast injuries of lower limbs and abdomen, complicated by wound infection and clinical depression. Treatment with linezolid and duloxetine combined with repeated surgical interventions with opioid-based anesthesia has resulted in development of the serotonin syndrome, manifesting as tremor and frequent clonic seizures. Complete revision of the prescribed pharmacological therapy as well the approach to sedation and anesthesia has led to a complete resolution of clinical symptoms of this complication.

Conclusion. In this case, improvement was achieved through discontinuation of fluoxetine and linezolid. All unfavorable drug interactions must be taken into account in management of complex blast injury. Limiting opioid use through regional anesthesia and prescription of sedative agents that do not promote serotonin accumulation may prevent the development of serotonin syndrome in such patients.

Keywords: serotonin syndrome, blast injury, sedation, fluoxetine, linezolid, seizures.

INTRODUCTION

Serotonin syndrome is a condition caused by an accumulation of serotonin, commonly caused by an excessive use of serotonergic medications, either through overdose of a single drug or due to an unanticipated interaction of multiple agents [1]. Its milder symptoms, such as tremor, hyperthermia, hypertension, and mental status alteration often get misattributed to other diseases, which may lead to both initiation of inappropriate treatment and continuation of serotonergic medications, eventually leading to manifestation of severe complications: clonic seizures, coma and life-threatening hyperthermia [2]. True incidence of serotonin syndrome is difficult to estimate, with US-based studies reporting 0.07 %-0.19 % among patients receiving at least one serotonergic agent with a decrease of prevalence during the study period [3]. At the same time, overall incidence is projected to increase with an increasing use of serotonergic drugs in clinical practice [4]. A similar trend may be expected in Ukraine, owing to the sharp rise in psychological trauma caused by the experiences related to war, often requiring prescription of serum serotonin reuptake inhibitors.

Excessive stimulation of serotonin (5-HT) receptors may occur through the following mechanisms: increased serotonin synthesis, increased serotonin release from the presynaptic vesicles, inhibited serotonin metabolism, sensibilization of postsynaptic receptors, effect of serotonin agonists [5]. It should be noted that medications that produce such effects are not necessarily used in clinical practice for their serotonergic properties and may therefore go unrecognized as a potential trigger. Such medications

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include, but are not limited to fentanyl, procaine, linezolid, dextromethorphan, diphenhydramine.

No single laboratory test may confirm the diagnosis of serotonin syndrome. An approach to its identification is usually aimed at identification of a potential cause (for example, detection of a serotonergic agent in serum or markers of impaired drug metabolism which may have resulted in accumulation of a properly prescribed medication) supplemented by an objective evaluation of the patient. Multiple standardized tools have been developed to confirm the diagnosis – Sternbach, Radomski and Hunter criteria, with the latter being the most prominent, although not necessarily superior [6, 7].

Table 1. Hunter Serotonin Toxicity Criteria. One fulfilled criterion confirms the diagnosis.

In the presence of a serotonergic agent:
1. Spontaneous clonus.
2. nducible clonus AND (agitation OR diaphoresis).
3. Ocular clonus AND (agitation OR diaphoresis).
4. Tremor AND hyperreflexia.
5. Hypertonia AND temperature > 38°C AND (ocular clonus OR inducible clonus).

CASE DESCRIPTION

A 40-year-old male patient was transferred directly to the ICU on June 24th, 2024, via medical evacuation following battlefield injury on June 18th 2023. Initial diagnosis – blast injury, gunshot wound of the anterior abdominal wall, shrapnel injury and bilateral perforating gunshot fractures of the middle third of both femurs, external fixation devices, soft tissue defects. Multiple surgical interventions, repeated debridement and VAC placements were performed during the following two months, with fentanyl being the chief analgesic agent during interventions and within the ICU. Changes in patient's mood were noted and he was evaluated using the Hospital Anxiety and Depression Scale (HADS), scoring 16 points, which warranted the prescription of duloxetine 60 mg daily on July 30th, 2023. Wound infection was suspected and confirmed via bacteriological examination of an intraoperatively collected sample. A. baumannii, K. pneumoniae susceptible to polymyxin E as well as C. striatum susceptible to linezolid were isolated. Antibiotic therapy prescribed on August 4th, 2023, consisted of colistin 2g / day, rifampicin 2g / day and linezolid 600 mg/day.

On August 6th, 2023, 20:40 an intention tremor was noted, which has transitioned into a rest tremor within an hour with no alteration in mental status. Intravenous infusion of diazepam 10 mg has resulted in a mild improvement in patient's condition. Following examination by a neurologist has confirmed the persistence of the intention tremor, polyneuropathic sensitivity disorder, end-point nystagmus with no other remarkable findings. Interpreting available data, patient's condition was initially attributed to posttraumatic encephalopathy with focal seizures.

Similar seizures have then occurred on August 7th, 18:30 and 22:45, August 8th 2:00, each temporarily treated with diazepam 20 mg and magnesium sulfate 25 % 10 ml. A multidisciplinary consilium was conducted and serotonin syndrome was diagnosed based on the presence of focal seizures, recent initiation of treatment with SSRI and MAO inhibitors, fulfillment of Sternbach and Hunter criteria. Duloxetine and linezolid were immediately discontinued.

In the following three days, a total of 10 seizure episodes were observed, some occurring consecutively and lasting up to 20 minutes in total. Diazepam was used to interrupt those episodes with thiopental being supplemented in select cases. A continuous intravenous infusion of dexmedetomidine 1 mcg/kg/hr was initiated, titrated to maintain a RASS score of -1/-2, resulting in a gradual regression in duration and frequency of seizures, with the last episode being registered on August 12th, lasting less than a minute. Treatment of gunshot injuries was continued with minimal use of opioid agents, now favoring single-shot peripheral nerve blocks for surgical interventions and on-demand analgesia within the ICU. Additional diagnostic methods employed during the period between 8th and 12th of August included: psychiatrist's consultation – PTSD suggested as an additional diagnosis; CT scan – unremarkable; EEG – disorganized bioelectrical activity, unspecific diffuse slowing, diminished reactivity to afferent stimuli. Absence of typical epileptiform activity.

DISCUSSION

The drugs that are not viewed primarily as serotonergic are easy to dismiss as "minor" factors in a problem, caused first and foremost using antidepressants. Discontinuation of such secondary triggering agents may in certain scenarios appear unjustified when considering the risks and benefits (e.g. an ongoing antibiotic therapy of a resistant bacterial infection). In our report, we would like to highlight the role of one of these miscellaneous drugs (linezolid) as a likely major component in SS development. Similar cases of rapid onset of SS shortly after the initiation of linezolid treatment have been described [8], although a broader analysis did not detect an increased risk for this category of patients [9]. Another point of concern is demonstrated by a delay in recovery in our patient, with life-threatening seizures persisting for several days despite an immediate and complete discontinuation of all serotonergic agents following diagnosis. Such possible clinical course must be

considered when weighing the risks of selective or late trigger withdrawal.

Despite its rarity, SS is relatively well understood, with a wide range of data on high-risk populations easily available. A new category of vulnerable patients is now emerging in Ukraine, where a unique mixture of conditions facilitates the creation of a perfect scenario for iatrogenic SS development. These are: the nature of a protracted ground invasion, inevitably contributing to a large amount of complex blast injury susceptible to infection and pain chronification; liberal and often uncoordinated use of antibiotics and opioids on all stages of medical evacuation; prevalence of psychoneurological disturbances that are now being treated with widely available antidepressants. While this blend of risk factors is being commonly observed in wounded Ukrainian soldiers, reports of SS are extremely rare, possibly owing to misattribution of mild symptoms to other diseases, particularly PTSD, cranial injury, sepsis, and substance withdrawal. In-depth research involving this group of patients is hardly feasible in current conditions, but individual vigilance in serotonergic drug prescription may still improve patient outcomes.

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ПРОКОПІВ М.М. , СОЛЯРИК С.О., БОДАК Л. О., ОРЕЛ М.Я., ФРАНК М.С.

КЛІНІЧНИЙ ВИПАДОК СЕРОТОНІНОВОГО СИНДРОМУ У ВІЙСЬКОВОСЛУЖБОВЦЯ ПІД ЧАС ЛІКУВАННЯ МІННО-ВИБУХОВОЇ ТРАВМИ

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Резюме

Вступ. Серотоніновий синдром є життєзагрозливим станом, що може виникнути унаслідок непередбаченої взаємодії серотонінергічних препаратів. Медикаменти цієї категорії рутинно призначаються при лікуванні мінно-вибухової травми у рамках стандартної терапії. Урахування їх впливу на серотонінові рецептори може дозволити попередити розвиток серотонінового синдрому у пацієнтів високого ризику. Опис випадку. Пацієнт був доставлений у ВАІТ для продовження лікування наслідків множинних мінно-вибухових уражень нижніх кінцівок та черевної стінки, ускладнених інфекцією та проявами депресії. На тлі призначеної антибактеріальної та антидепресантної терапії в умовах частих повторних хірургічних втручань з опіоїдним знеболенням, у пацієнта розвинувся сертоніновий синдром, що переважно проявлявся як тремор та клонічні судоми. Повний перегляд фармакотерапії та підходу до седації та анестезії сприяв повному розрішенню клінічних проявів цього ускладнення. Висновки. У описаному випадку до покращення стану призвела відміна флуоксетіну та лінезоліду. При довготривалому лікуванні наслідків бойових травм слід враховувати усі потенційні небажані взаємодії лікарських засобів. Обмеження використання опіоїдів за рахунок реґіонарної анестезії та надання переваги седативним засобам, що не сприяють накопиченню серотоніну можуть попередити розвиток серотонінового синдрому у пацієнтів цієї категорії.

Ключові слова: серотоніновий синдром, мінно-вибухова травма, седація, флуоксетін, лінезолід, судоми.

УЧАСТЬ АВТОРІВ В ПІДГОТОВЦІ СТАТТІ:
ПРОКОПІВ М.М. – лікування хворого, коректура рукопису, загальне керівництво,
СОЛЯРИК С.О. – лікування хворого, аналіз даних, загальне керівництво,
БОДАК Л. О. – лікування хворого, збір даних, написання рукопису,
ОРЕЛ М.Я. – збір та обробка даних, написання рукопису,
ФРАНК М.С. – редагування та написання рукопису.