

Serotonin syndrome with tramadol and dextromethorphan

曲馬多與右甲嗎南導致血清素綜合症

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Serotonin syndrome is an iatrogenic drug-induced synaptic serotonin concentration related toxidrome. A 29-year-old man developed agitation, tachycardia and myoclonus of limbs after an intramuscular injection of 100 mg tramadol. He had recently been given multiple medications, including dextromethorphan (DXM) by a private doctor for flu-like symptoms. The patient was stabilised with diazepam, midazolam and supportive treatment. Both tramadol and DXM could cause the serotonin syndrome, but usually in combination with monoamine oxidase inhibitors or serotonin reuptake inhibitors. This was the first reported case in the English literature of serotonin syndrome with tramadol and DXM. Therefore, a detailed drug history and knowledge of potential serotonergic drugs are important. (*Hong Kong j.emerg.med.* 2007;14:48-52)

血清素綜合症是一種醫源性藥物引發突觸血清素濃度有關的中毒綜合症。一名 29 歲男子於肌肉注射 100 毫克曲馬多後顯現出焦急激動、心搏過速及四肢肌陣攣。因他近日有流行性感冒症狀而私家醫生給與多種藥物，包括右甲嗎南。病者經安定、咪達唑侖及支持性治療來穩定情況。曲馬多及右甲嗎南都可以引起血清素綜合症，但通常要聯同單胺氧化酶抑制劑或血清素再攝取抑制劑。這是英文文憲中曲馬多與右甲嗎南導致血清素綜合症的首個個案報告。因此，詳細的藥物病歷及理解有血清素能潛在性的藥物是重要的。

Keywords: Dextromethorphan, drug interactions, myoclonus, serotonin syndrome, tramadol

關鍵詞：右甲嗎南、藥物間相互作用、肌陣攣、血清素綜合症、曲馬多

Introduction

Serotonin syndrome (SS) is an iatrogenic drug-induced toxidrome, displaying the characteristics expected of a synaptic serotonin concentration related phenomenon.¹ The clinical triads are neuromuscular hyperactivity (tremor, clonus, myoclonus, hyperreflexia, pyramidal rigidity), autonomic hyperactivity (diaphoresis, fever, tachycardia, tachypnoea, mydriasis) and altered mental

status (agitation, excitement, confusion). Clonus, especially ankle clonus, is a characteristic sign of SS.^{1,2}

The clinical presentation is related to the degree of elevation of the intrasynaptic serotonin level. It can be raised by increased synthesis, increased release, reuptake inhibition, metabolism inhibition or postsynaptic receptor stimulation. SS is not an idiosyncratic reaction.

Life-threatening SS is commonly caused by a combination of monoamine oxidase inhibitors (MAOI) with serotonin reuptake inhibitors (SSRI), serotonin releasers (e.g. MDMA), some tricyclic antidepressants (e.g. clomipramine, imipramine) or venlafaxine.^{1,2}

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Case report

A 29-year-old Chinese gentleman was seen in the Accident and Emergency Department for epigastric pain in November 2005. He had asthma in his childhood period. He had on-and-off epigastric pain for three weeks. He had diarrhoea three times and vomited once in the last two days. His temperature was 37°C. His blood pressure was 161/91 mmHg, with pulse rate 136 beats per minute. His blood glucose was 7.1 mmol/L. He was fully alert. The examinations of his abdomen, cardiovascular system and central nervous system were normal. Hyoscine butylbromide 20 mg intramuscularly and antacid (Mylanta®) 10 ml orally were given. The pain did not improve. Tramadol 100 mg was given intramuscularly at 1 hour 35 minutes after presentation and morphine 2 mg was given intravenously at 2 hours 55 minutes after presentation for pain relief. Blood for complete blood count, liver function test, renal function test and amylase level were

taken. Normal saline 80 ml per hour was given for fluid replacement. Metoclopramide 10 mg was given intravenously at 3 hours 40 minutes after presentation.

Four hours after presentation, he developed irregular, asymmetric twitching of all four limbs for two minutes in the observation ward. He was agitated, confused, and not obeying command. He was afebrile. He had no cyanosis, hypotension or hypoglycaemia. His skin was not dry. His muscle tone was increased. There was no obvious focal neurological deficit elicited. Pupils and reflexes were difficult to assess because of his struggling. Electrocardiogram (ECG) showed a heart rate of 162/min, prolonged QTc interval of 552 msec, QRS interval of 104 msec and terminal 40 msec right axis deviation (prominent R in lead aV_R, deep S in lead I) (Figure 1).

Further history from his parent revealed multiple medications from a private doctor recently for

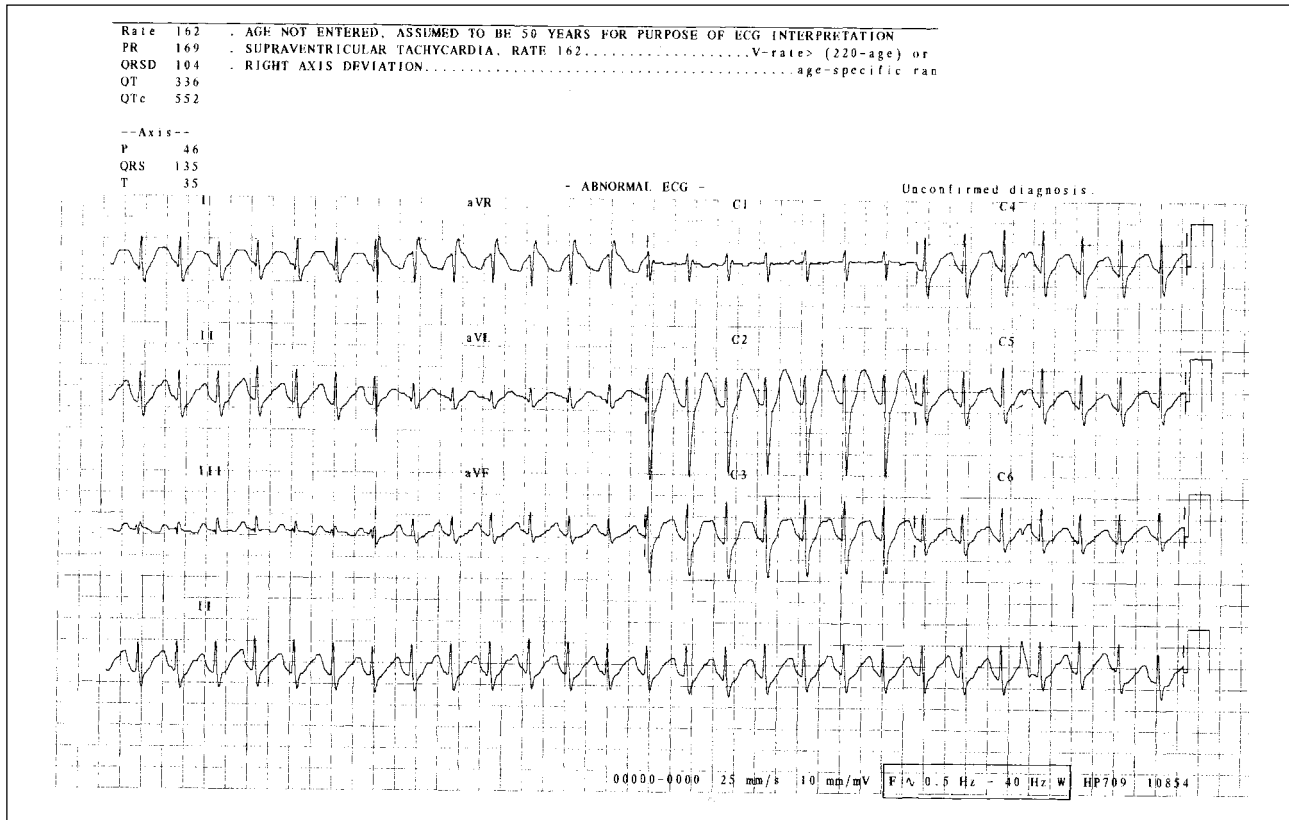


Figure 1. Electrocardiogram of the patient after myoclonus showing sinus tachycardia, prolonged QTc of 552 msec, QRS interval of 104 msec and terminal 40 msec right axis deviation (prominent R in lead aV_R, deep S in lead I).

abdominal pain and flu-like symptoms. The drugs included slow-releasing theophylline (Slobid®), domperidone (Motilum®), promethazine (Phenergan®), dextromethorphan (cough mixture), paracetamol, hyoscine butylbromide (Buscopan®) and sennoside B (Senokot®). He had no known psychiatric disease, drug abuse or overdose history.

The arterial blood gas taken after the twitching showed metabolic acidosis (pH 6.916, pCO₂ 4.85 kPa, pO₂ 19.24 kPa, base excess -25.1 mmol/L, O₂ saturation 97%). The liver and renal function tests were normal, except mild hyponatremia (Na 131 mmol/L). The amylase level was normal. The complete blood count showed white blood cell count 15.9 x 10⁹/L, neutrophil 14.2 x 10⁹/L, haemoglobin 14.6 g/dL and platelet count 382 x 10⁹/L. Plain computed tomography (CT) of brain showed no haemorrhage or intracranial mass. Diazepam 10 mg was given intravenously to control the recurrent twitching. Midazolam 12.5 mg was given intravenously to sedate the patient and to facilitate CT brain.

The differential diagnosis included drug effects (serotonin syndrome by tramadol and dextromethorphan, tricyclic antidepressant poisoning, neuroleptic malignant syndrome, tramadol or dextromethorphan overdose), infective causes (sepsis, central nervous system infection), thyroid storm, first convulsion in epilepsy or rarely carcinoid tumour.

With the clinical features (acute onset, agitation, tachycardia, myoclonus), drug history and ECG changes, serotonin syndrome and tricyclic antidepressant (TCA) poisoning were the most probable diagnoses. Terminal 40 msec right axis deviation was a sensitive but non-specific feature of TCA ingestion. As the patient had no psychiatric history, no TCA drug exposure, no precipitating factor for suicide and positive serotonergic drug exposure, serotonin syndrome was the most likely diagnosis. Neuroleptic malignant syndrome (NMS) was less likely because of the abrupt onset of symptoms, presence of myoclonus, absence of neuroleptic antipsychotic medications and no lead pipe rigidity.³ He was admitted to the hospital for close monitoring.

After admission, he had no further myoclonus. His conscious state and heart rate returned to normal six hours after admission. His blood sodium level was 140 mmol/L on rechecking. He had transient renal impairment, with peak blood creatinine 281 μmol/L one day after admission. Ultrasound of kidneys showed no obstruction or parenchymal disease. His white blood cell count normalised on day four after admission without antibiotic. His blood culture and Widal test were negative. Electroencephalogram showed normal background with non-specific isolated spikes over the right frontal lobe. Retrospective CT brain report showed a small area of low attenuation in the left external capsule. Follow-up magnetic resonance imaging (MRI) of brain done seven months later showed a 0.4 cm T1 hypointense, T2 hyperintense but FLAIR (fluid-attenuated inversion recovery) hypointense focus at the left subinsular region. There was no significant difference in size compared with the previous CT brain images. The MRI features were in favour of an indolent lesion. He had an uneventful recovery on follow-up nine days later.

Discussion

Adverse drug reaction could be assessed objectively by the Naranjo adverse drug reaction probability scale.^{4,5} The Naranjo score of the incident of this patient was five. It was a probable adverse drug reaction. Therefore, the probable diagnosis is serotonin syndrome with dextromethorphan, tramadol and metoclopramide.

Tramadol is a commonly used synthetic narcotic analgesic. It is a partial opioid μ agonist and serotonin reuptake inhibitor. It could cause SS in combination with SSRI (sertraline, citalopram, fluoxetine, paroxetine); MAOI (moclobemide), TCA (amitriptyline, clomipramine); venlafaxine or mirtazapine.⁶⁻¹² Tramadol could also cause SS alone in high 400 mg daily dose in the elderly or 2 g in overdose.^{10,13}

Dextromethorphan (DXM) is a d-isomer of 3-methoxy-N-methylmorphinan, a synthetic codeine analogue. It is an opioid receptor agonist, N-methyl-D-aspartate (NMDA) glutamate receptor antagonist

and serotonin reuptake inhibitor. It has euphoric and dissociative effects. DXM and codeine are the two common abusive ingredients in cough mixture. It is a common ingredient in cough mixtures in Hong Kong, including Phensedyl linctus[®], Actifed DM cough linctus[®], Promethazine compound linctus[®], Cocilla compound syrup[®], Cocillana DM syrup[®], U-DM-Cocillana syrup[®], etc.¹⁴ DXM could cause SS in combination with SSRI (fluoxetine with lithium, paroxetine, citalopram).¹⁵⁻¹⁷

There was no case report found in the English literature of SS with tramadol and DXM.

Metoclopramide has been mentioned as one of the drugs causing SS.³ There was only one case report of SS by metoclopramide with SSRI (sertraline).¹⁸ The mechanism might involve imbalance in the dopamine and serotonin neurotransmitters. Therefore, metoclopramide might play a role in SS in this patient.

Dr. Ken Gillman maintains an on-line drug list for SS.¹⁹ The common drugs that could cause significant SS are summarised in Table 1.^{1,2} Detailed drug history and knowledge of potential serotonergic drugs are

important in daily practice. Antidepressants are more commonly prescribed by private doctors recently. A high index of suspicion should be maintained in patients with depression, drug abuse, drug overdose, pain (acute or chronic), cough preparation or slimming agent.

Management of the serotonin syndrome includes removal of the precipitating drugs, provision of supportive care, control of agitation, autonomic instability and hyperthermia and occasionally administration of 5-hydroxytryptamine_(2A) antagonists.³ Benzodiazepine is useful to control agitation and excessive muscle activity. In severe cases, paralysis may be induced with non-depolarizing neuromuscular agent. Succinylcholine should be avoided because of the risk of arrhythmia from hyperkalemia associated with rhabdomyolysis. In SS associated with MAOI, the intrasynaptic adrenaline and noradrenaline concentrations are not under the control of monoamine oxidase. Indirect-acting sympathomimetic agents are metabolised to adrenaline and noradrenaline, which may cause an exaggerated haemodynamic response. Therefore, hypotension arising from SS associated with MAOI could be treated with low

Table 1. Examples of drugs with clinically relevant serotonergic effect

Mechanism	Drug group	Example	Clinical scenario
Monoamine oxidase inhibition	monoamine oxidase inhibitor	moclobemide selegiline	depression drug overdose
Serotonin re-uptake inhibition	selective serotonin reuptake inhibitor	paroxetine fluoxetine citalopram sertraline	depression drug overdose
	tricyclic antidepressant	clomipramine imipramine	depression drug overdose
	other antidepressant	venlafaxine	depression drug overdose
	narcotic analgesic	tramadol pethidine fentanyl dextropropoxyphene	iatrogenic hospital setting drug overdose chronic pain
	other opioid	methadone dextromethorphan	drug abuse cough preparation
	miscellaneous	sibutramine	slimming agent
Serotonin release	party drug	amphetamine MDMA	drug abuse

doses of direct-acting sympathomimetic agents. Cyproheptadine, a 5-HT_(2A) antagonist, could be used in severe SS at an initial dose of 12 mg.² Antipyretic agents are not useful in treating hyperthermia.

Prevention is better than cure. Patients on MAOI or SSRI should be educated to disclose actively the drug history during medical consultation.

This young healthy patient had abdominal pain and flu-like symptoms, but he was given multiple drugs by the private doctor. He was given four different parenteral drugs in the span of four hours in the emergency department. The combination of drugs caused the serotonin syndrome which could be potentially fatal. Therefore, polypharmacy should be avoided.

As there is no objective diagnostic test for SS, diagnosis is made by clinical features, serotonergic drug history and exclusion of other diseases. Developing a positive diagnostic test may be the way ahead.

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