Serotonin toxicity caused by an interaction between fentanyl and paroxetine

[Toxicité sérotoninergique provoquée par une interaction entre le fentanyl et la paroxétine]

Simon T. Rang FRCA, Jennifer Field MB BS, Colm Irving FRCA

Purpose: To report a case of serotonin toxicity, presenting in the postoperative period, caused by an interaction between paroxetine (a selective serotonin reuptake inhibitor, SSRI) and fentanyl (a phenylpiperidine opioid). Serotonin toxicity precipitated by fentanyl is unusual and has not previously been described in combination with SSRIs in the perioperative setting.

Clinical features: A 60-yr-old woman, established on paroxetine for depression, underwent excision of a chest wall myxofibrosarcoma and chest wall reconstruction. Fentanyl was administered for intraoperative and postoperative analgesia (1 mg intraoperatively, and 2.5 mg by infusion in the first 36 hr, postoperatively). She developed a vague affectation, intermittent agitation, bilateral hyper-reflexia, inducible clonus, and a period of hypertension, suggestive of serotonin toxicity. There was complete resolution after cessation of fentanyl and paroxetine.

Conclusion: The co-administration of SSRIs and fentanyl may precipitate serotonin toxicity. There must be consideration of this unusual interaction when administering fentanyl to patients established on SSRIs. Physicians should be vigilant of the features of serotonin toxicity developing in such patients.

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***Objectif** : Nous rendons compte d'un cas de toxicité sérotoninergique apparue en période postopératoire et provoquée par une interaction entre la paroxétine (un inhibiteur sélectif du recaptage de la sérotonine, SSRI) et le fentanyl (un opiacé de type phénylpipéridine). La toxicité sérotoninergique provoquée par le fentanyl est inhabituelle et n'a jamais été décrite auparavant en association avec des SSRI dans un contexte périopératoire.*

***Éléments cliniques** : Une femme de 60 ans traitée avec de la paroxétine pour une dépression, a subi une excision d'un myxofibrosarcome sur la paroi thoracique et une reconstruction thoracique. Le fentanyl a été utilisé pour l'analgésie peropératoire et postopératoire (1 mg pendant l'opération, et 2,5 mg en perfusion durant les 36 premières heures suivant l'opération). Une vague affection s'est manifestée, évocatrice d'une toxicité sérotoninergique et présentant des symptômes d'agitation sporadique, d'hyperréflectivité bilatérale, de clonus inductible et une période d'hypertension. Les symptômes se sont complètement résorbés une fois que le fentanyl et la paroxétine ont été cessés.*

***Conclusion** : L'administration combinée de SSRI et de fentanyl pourrait provoquer une toxicité sérotoninergique. Cette interaction inhabituelle doit être prise en compte lorsque le fentanyl est administré à des patients traités avec des SSRI. Les médecins devraient être particulièrement vigilants si des caractéristiques d'une toxicité sérotoninergique apparaissaient chez de tels patients.*

SEROTONIN (5-hydroxytryptamine, 5-HT) is a neurotransmitter concentrated in the raphe nuclei of the brainstem reticular formation of the central nervous system (CNS). It is involved in regulating the sleep-wakefulness cycle, mood, appetite, emotion, temperature, and the motor system.[1] The serotonin syndrome, or serotonin toxicity, is a well-documented series of clinical features resulting from drug-induced serotonergic hyperstimulation in the CNS.[2] Many drugs, including selective serotonin reuptake inhibitors (SSRIs, e.g., paroxetine), exert their primary clinical effect by

From the Royal Marsden Hospital, London, United Kingdom.
Address correspondence to: Dr. Simon Rang, Specialist Registrar in Anaesthesia, Department of Anaesthesia, Royal Marsden Hospital, Fulham Road, London, SW3 6JJ, United Kingdom. Phone: +44 207 352 8171; E-mail: simonrang@gmail.com
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TABLE I Laboratory investigations

	Reference range	*Preop*	*Day 1*	*Day 2*	*Day 3*	*Day 4*
Hemoglobin ($g \cdot dl^{-1}$)	11-18	12.9	*9.7*	*10.4*	*9.3*	*9.7*
White blood cells ($x10^9\ L^{-1}$)	4-11	5.7	6.0	*3.2*	5.7	7.4
Platelets ($x10^9 \cdot L^{-1}$)	130-450	195	*94*	*63*	*119*	147
Sodium ($mmol \cdot L^{-1}$)	135-145	139	138	140	140	135
Potassium ($mmol \cdot L^{-1}$)	3.5-5.0	3.8	4.1	4.1	4.2	4.3
Urea ($mmol \cdot L^{-1}$)	2.5-6.4	4.5	3.0	4.7	2.6	2.5
Creatinine ($\mu mol \cdot L^{-1}$)	54-98	81	68	82	57	*50*
Bilirubin ($\mu mol \cdot L^{-1}$)	< 17	9	13	8	10	12
Alanine transferase ($U \cdot L^{-1}$)	< 40	20	11	15	21	26
Alkaline phosphatase ($U\ L^{-1}$)	24-110	*16*	25	*18*	34	42
Albumin ($g \cdot L^{-1}$)	30-50	40	*14*	*12*	*18*	*22*
Magnesium ($mmol \cdot L^{-1}$)	0.65 – 1.05		1.28	0.89	0.75	0.81
Adjusted calcium ($mmol \cdot L^{-1}$)	2.1-2.6		2.34	2.31	2.31	2.28
TSH ($mU \cdot L^{-1}$)	0.43-0.67				0.03	
Tri-iodothyronine, T3 ($nmol \cdot L^{-1}$)	2.51-5.3				3.9	

Hematological and biochemical investigations eight days preoperatively, postoperatively on the evening of the day of surgery (day 1), and for three days thereafter. Values in italics are outside the reference range. Preop = preoperative; TSH = thyroid stimulating hormone.

enhancing serotonin neurotransmission in the CNS. Others influence serotonergic pathways as a secondary effect that is often not anticipated. Patients established on SSRIs frequently present for anesthesia and surgery, to critical care units and to pain medicine physicians. Therefore, an understanding of the potential interactions of SSRIs with agents used in these areas is important. Fentanyl, a phenypiperidine opioid in widespread use in anesthesia, critical care, and pain management, has previously been implicated in serotonin toxicity,[3–5] but never in association with SSRIs *in the perioperative setting*. We present a case of postoperative serotonin toxicity caused by an interaction between paroxetine and fentanyl.

Patient consent for publication

Written informed consent, in accordance with local institutional guidelines for publication of this case report, was obtained from the patient described.

Case report

A 60-yr-old woman underwent extensive resection of a recurrent left chest wall myxofibrosarcoma with chest wall reconstruction. Her other medical history included hypothyroidism and depression, for which she was taking thyroxine and paroxetine, her only preoperative medication. Physical examination and routine preoperative laboratory investigations (Table I) were normal. Her chest radiograph clearly demonstrated the left chest wall sarcoma but no underlying pulmonary abnormalities.

She had an uneventful ten-hour surgical procedure. Anesthesia was induced with propofol and fentanyl 200 µg. Atracurium was used to facilitate orotracheal intubation with a double-lumen, endotracheal tube. Anesthesia was maintained with isoflurane in oxygen and air, and a further 800 µg of fentanyl was administered in intermittent, 50 µg boluses for intraoperative analgesia; the mean rate of fentanyl administration, intraoperatively, was 100 $\mu g \cdot hr^{-1}$. The estimated intraoperative blood loss was 3 L, and 3 U of packed red blood cells were transfused, titrated to blood hemoglobin concentration.

Postoperatively, the patient was electively admitted to the intensive care unit. Initially, sedation was maintained with infusions of propofol 100 $mg \cdot hr^{-1}$ and fentanyl 100–200 $\mu g \cdot hr^{-1}$, and her ventilation was supported via a single-lumen endotracheal tube. Propofol was stopped after 12 hr, in preparation for tracheal extubation, but fentanyl infusion was continued for postoperative analgesia. This was stopped after a further 24 hr because the patient remained over-sedated for tracheal extubation. At that time, neurological examination revealed bilateral hypertonia and hyper-reflexia, more severe in the lower limbs and on the right, with marked, inducible ankle clonus, bilaterally. Her expression remained detached and vague with intermittent periods of agitation and a Glasgow coma scale score of 9/15 (E4, V1, M4). The only other abnormal examination finding was a period of hypertension (180/90 mmHg) for the first 24 hr postoperatively, which then spontaneously settled to her preoperative blood pressure of 130/65 mmHg. She remained apyrexial. Postoperative laboratory investigation results were unremarkable (Table I), except for a transiently low blood platelet count for the first two postoperative days, probably resulting from platelet consumption following intraopera-

TABLE II Sternbach's suggested diagnostic criteria for serotonin syndrome[2]

A. Coincident with the addition of, or increase in, a known serotonergic agent to an established medication regimen, at least three of the following clinical features are present:
1) Mental state changes (confusion, hypomania)
2) Agitation
3) Myoclonus
4) Hyper-reflexia
5) Diaphoresis
6) Shivering
7) Tremor
8) Diarrhea
9) Poor coordination
10) Fever
B. Other etiologies (e.g., infectious, metabolic, substance abuse or withdrawal) have been ruled out.
C. A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above.

tive hemorrhage. Serum albumin concentration was acutely reduced in the postoperative period, consistent with a hemodilution effect. Thyroid function tests confirmed appropriate chronic thyroxine replacement therapy. A computed tomography radiograph of her brain demonstrated no abnormality.

She had received a total of 2545 μg of fentanyl during this 36 hr perioperative period, an overall mean administration rate of 71 $\mu g \cdot hr^{-1}$. Her neurological abnormalities improved 24 hr after cessation of fentanyl, and she underwent tracheal extubation on the third postoperative day. On discharge from the intensive care unit on the fourth postoperative day, she had made a full neurological recovery. She was discharged from hospital on the tenth postoperative day with no further complications.

Discussion

Serotonin toxicity involving fentanyl

An occurrence of serotonin toxicity requires a pharmacologically mediated enhancement of serotonin neurotransmission in the CNS. This may be caused by single-agent overdose[6,7] or, more commonly, by drug combinations that interact to synergistically increase synaptic serotonin. Examples of causative agents include monoamine oxidase inhibitors (MAOIs), and the SSRIs.[2] The phenylpiperidine opioid analgesics have weak serotonergic activity,[8] and therefore, it is unsurprising that there are several reports of serotonin toxicity related to interactions between MAOIs or SSRIs, and phenylpiperidines. Pethidine and tramadol have been particularly implicated, whilst early literature suggested that fentanyl was "safe".[9] Subsequently, there have been two reports implicating fentanyl. Noble and Baker[5] described a patient, chronically taking the MAOI tranylcypromine, who received 7 mg of fentanyl for intraoperative analgesia during cardiac surgery. He demonstrated features of severe serotonin toxicity in the immediate postoperative period, and he died 18 hr after onset of these symptoms. Ailawadhi *et al.*[4] described a case of serotonin toxicity that occurred 24 hr after administering a fentanyl patch for chronic back pain (25 $\mu g \cdot hr^{-1}$, total dose of 600 μg prior to symptom onset) to a patient established on the SSRI citalopram. The symptoms resolved 24 hr after cessation of fentanyl. Serotonin toxicity, caused by pharmacological stimulation of serotonergic pathways, is thought to be dose-related.[10] The combination of SSRIs and fentanyl, administered for perioperative analgesia, has not previously been reported to precipitate serotonin toxicity. However, one case report has described postoperative muscular rigidity, hyper-reflexia, and inducible clonus, following intraoperative fentanyl (500 μg) with chronic exposure to venlafexine.[11] The authors attributed these symptoms to opioid-induced rigidity due to their rapid reversibility with naloxone, but this may have been an atypical presentation of serotonin toxicity.[10] We believe that the case presented in our report is unique, by demonstrating definitive features of serotonin toxicity in the postoperative period following an interaction between an SSRI (paroxetine) and perioperative fentanyl.

Presenting features and diagnosis of serotonin toxicity

The diagnosis of serotonin toxicity is clinical. Sternbach[2] originally proposed a set of diagnostic features (Table II). As each case has a variable presentation with a wide spectrum of severity, rigid adherence to Sternbach's diagnostic criteria may exclude mild cases.[12] A more generalized description of the condition as a triad of neuroexcitatory features (altered mental state, neuromuscular hyperactivity, and autonomic disturbance) has also been suggested.[13,14] This allows for the wide variation in presenting symptoms, from mild affectation disturbance with a subtle tremor through to a severe, confusional state with muscular

rigidity, hyper-pyrexia, and life-threatening autonomic instability. By analyzing symptoms in over 2,000 consecutive cases of the condition, that had either been given or had not been given an accepted "gold standard" diagnosis, i.e., ascribed by a medical toxicologist, Dunkley *et al.*[7] proposed a set of diagnostic decision rules, based on simple clinical features, that predicts the "gold standard" toxicologist's diagnosis more closely than Sternbach's original criteria. The patient described in our report exhibited features of moderate severity, including agitation, marked inducible clonus, hyper-reflexia, and hypertension. According to the decision rules, a combination of inducible clonus and agitation, in the presence of a serotonergic agent, confirms a diagnosis of serotonin toxicity.

Differential diagnosis

The differential diagnosis includes other drug-induced conditions, such as propofol neuroexcitation, opioid-induced rigidity, and the neuroleptic malignant syndrome (NMS). Primary neurological conditions, namely, hypoxic brain injury, cerebrovascular injury, and epileptic seizures were also considered. Propofol neuroexcitation is unlikely, as there was not a strong temporal relationship between symptoms and propofol administration (in contrast to fentanyl). Rigidity was never a feature, particularly during the intraoperative and the initial postoperative period when the rate of fentanyl administration was greatest. There was no previous history of epilepsy or other neurological disease and no features suggesting acute, seizure activity. Hypoxic brain injury and cerebrovascular injury were considered unlikely for several reasons: there were no preoperative risk factors for thrombotic or embolic cerebrovascular disease; there were no intraoperative periods of hemodynamic instability; and a postoperative brain computed tomography radiograph was normal. Neuroleptic malignant syndrome was excluded for several reasons: there was no evidence of "lead pipe" rigidity; the main features of hyper-reflexia and clonus in this patient were much more typical of serotonin toxicity than of NMS; and the patient was not taking any drugs that are commonly implicated in NMS. In support of serotonin toxicity, it was noted that the patient had been well established on paroxetine, which continued until the morning of surgery. She received relatively large doses of fentanyl, intra- and postoperatively, prior to the onset of symptoms, and she made a full neurological recovery two days following cessation of fentanyl.

Management of serotonin toxicity

Treatment of serotonin toxicity is both non-specific and specific. Non-specific treatment is supportive and includes withdrawal of serotonergic drugs, support of end-organ function, and control of autonomic instability. Sedation has been beneficial in animal models[15] and may be used to treat agitation.[16] Severe cases involving hyperpyrexia (> 38.5°C), marked hypertonia, or rigidity require aggressive, supportive treatment, including active cooling and consideration of neuromuscular paralysis with mechanical respiratory ventilation.[7]

Severe cases of serotonin toxicity have a well documented mortality; therefore, the use of specific 5-HT_{2A} antagonists is recommended.[16] Cyproheptadine[17] is only available in an oral formulation, but may be given crushed via a nasogastric tube. Chlorpromazine is the only intravenous 5-HT_{2A} antagonist available for humans, and this has been successfully used in the treatment of severe serotonin toxicity.[16] Chlorpromazine may exacerbate cardiovascular instability due to α_1 antagonist effects. The patient in this report responded to supportive treatment and withdrawal of serotonergic drugs. However, if serotonin toxicity is diagnosed by the diagnostic decision rules described above,[7] accepted guidelines recommend commencing specific treatment, and this patient may have benefited from treatment with a 5-HT_{2A} antagonist.

Conclusion

The use of serotonergic agents is increasing in many diverse medical fields. Many of these drugs are not primarily known for their serotonergic effects (e.g., phenylpiperidine opioids); hence, there is inevitably an increased risk of serotonergic drug interactions and toxicity. A list of all drugs with serotonergic properties is available online.[18] In this report, we have highlighted an unusual interaction between two serotonergic drugs, paroxetine and fentanyl, frequently encountered in anesthesia, critical care, and pain medicine. To simply advise against this drug combination would be over-cautious. Importantly, there have been no reported cases of serotonin toxicity in association with low doses of fentanyl that are commonly used during induction of anesthesia. The aim of this report is to raise awareness of serotonin toxicity as a potential complication of co-administering large doses of fentanyl with other SRIs and to foster an understanding of the presentation, diagnosis, and appropriate management of this potentially fatal, iatrogenic condition.

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