

Retrospective Analysis

Incidence of Serotonin Syndrome in Patients Treated with Fentanyl on Serotonergic Agents

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Background: There has been a recent surge in the literature highlighting the association of fentanyl as precipitating serotonin syndrome in patients on a serotonergic agent.

Objective: The purpose of our study was to understand the incidence of serotonin syndrome in patients who receive fentanyl while on serotonergic agents.

Study Design: This retrospective analysis was conducted from 2012 to 2013 after approval from the Institutional Review Board. We searched for all patients that had received a serotonergic agent and were admitted to the hospital during the study period. Next, we split these patients into 2 groups by placing all patients who had received fentanyl and a serotonergic agent into one group. We then searched for any of the Hunter Serotonin Toxicity Criteria in the records of patients that had received both fentanyl and a serotonergic agent. Further, we searched for all patients with serotonin syndrome mentioned in their records.

Setting: This study was conducted at a 900 bed tertiary care academic center.

Results: Over the 2 year study period, 112,045 patients were on a serotonergic agent, and 4,538 of these patients were treated with both fentanyl and a serotonergic agent. A search for Hunter's Criteria through the records of the patients receiving both fentanyl and a serotonergic agent revealed 23 patients had been documented with some of these symptoms. On detailed chart review, only 4 [95% CI 1 – 10] of these patients truly met Hunter's Criteria for serotonin syndrome. We then searched all admissions for a diagnosis code of serotonin syndrome during the study period. Five additional cases of serotonin syndrome were found, but none of these patients were treated with fentanyl.

Limitations: Some of the limitations of our study include that it represents a single institution, although it is a large academic center. An inherent limitation may be the under diagnosis of serotonin syndrome.

Conclusion: The incidence of serotonin syndrome in patients who receive both fentanyl and a serotonergic agent is low.

Key words: Fentanyl, serotonin syndrome, serotonergic drugs, opioids, SSRI, antidepressant

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There has been a recent surge in the literature, primarily case reports, highlighting the association of fentanyl as a serotonin syndrome enhancing drug in patients on a serotonergic agent (1-5). While other opioids, including methadone, have been implicated as well (6), a particular emphasis on

fentanyl as a serotonin syndrome enhancing drug appears to be emerging.

Phenylpiperidine opioids, such as fentanyl, have serotonergic activity and thus in combination with other serotonin reuptake inhibitors can cause serotonin syndrome.

Fentanyl is commonly used in anesthesia as an induction agent in a balanced technique. It is also used for procedural sedation with benzodiazepines and in intensive care units. Fentanyl patches are used for the treatment of chronic pain. Per the Centers for Disease Control, 11% of Americans aged 12 and over take antidepressants (7). There has been a 145% increase in the aggregate production of fentanyl from 2003 to 2013 (8). Given this, it appears a reasonable proportion of the population may be on both fentanyl and a serotonergic agent at the same time.

The purpose of our study was to understand the incidence of serotonin syndrome in patients who receive fentanyl while on serotonergic agents.

METHODS

This retrospective analysis received approval from the Massachusetts General Hospital Institutional Review Board. The Research Patient Database Registry maintained at our institution was queried for a 2 year period, from January 2012 to December 2013.

We queried the database for all patients admitted to the hospital, during the study period, who had received a serotonergic agent. We then split these patients into 2 groups by placing all patients that had

received fentanyl and a serotonergic agent into one group (Table 1). The records of the patients who were treated with fentanyl and a serotonergic agent were further queried for key words from the Hunter's Serotonin Toxicity Criteria (Table 2). We then conducted detailed chart reviews of these records to confirm that these patients had serotonin syndrome.

We also queried the database for all patients admitted to the hospital who had serotonin syndrome in any part of their medical record. Further analysis of these records was done to reveal the true incidence of serotonin syndrome.

The statistical results reported in this article were calculated using the exact binomial 95% confidence interval and a chi-squared test.

RESULTS

Over the study period from January 2012 to December 2013, we found that 112,045 patients were taking serotonergic agents. Four thousand five hundred and thirty-eight of these patients, which is about 4%, received fentanyl while on a serotonergic agent, and 107,507 patients did not receive fentanyl while on a serotonergic agent. A search for Hunter's Criteria through the records of the 4,538 patients receiving fentanyl and a serotonergic agent revealed 23 patients had been documented with some of these symptoms. On detailed chart review, only 4 [95% CI 1 – 10] of these patients truly met Hunter's Criteria for serotonin syndrome (Table 3). Of interest, 3 of the 4 patients were on fentanyl patches and one patient received intravenous fentanyl while in the hospital.

There appeared to be no pattern as far as number of serotonergic or serotonin enhancing agents used by the same patient, dose of drugs used, or duration of therapy that could be considered predictive of developing serotonin syndrome.

We then searched all admissions given a diagnosis code of serotonin syndrome during the study period. This yielded 292 records. Further analysis of these re-

Table 1. Serotonergic drugs used for data query.

Serotonergic Drugs	Serotonin Syndrome Enhancing Drugs
Antiemetics Granisetron Ondansetron Metoclopramide	Opioids Alfentanil Fentanyl Methadone Meperidine Remifentanil Sufentanil Tramadol
Serotonin-norepinephrine reuptake inhibitor Duloxetine Venlafaxine	Others Dextromethorphan Dextroamphetamine
Serotonin specific reuptake inhibitors Citalopram Escitalopram Fluoxetine Imipramine Paroxetine Sertraline	
Others Trazodone Mirtazapine Monoamine oxidase inhibitors Buspirone	

Table 2. Hunter's criteria used for data query (9).

Hunter Serotonin Toxicity Criteria
Spontaneous clonus
Inducible clonus and agitation or diaphoresis
Ocular clonus and agitation or diaphoresis
Tremor and hyperreflexia
Hypertonic and temperature > 38 degrees Celsius and ocular or inducible clonus

Incidence of Serotonin Syndrome in Patients Treated with Fentanyl on Serotonergic Agents

Table 3. Serotonin syndrome cases with fentanyl, other opioids, and serotonergic agents.

Subject	Fentanyl	Other Opioids	Serotonergic Agents
1	Fentanyl Patch 50 mcg/hr; Fentora 100 mcg PO Q4H PRN	Dilaudid 6 mg PO TID	Mirtazapine 15 mg PO QID; Methylphenidate Hcl Tablet 10 MG
2	Fentanyl Citrate	Oxycodone 5 – 15 mg PO	Ondansetron 4 mg IV
3	Fentanyl Patch 100 mcg	Hydromorphone* (Dilaudid*) 6 – 8 mg	Amphetamine-dextroamphetamine 30 mg tab BID; Venlafaxine xr 150 mg BID; Sumatriptan 100 mg PO PRN
4	Fentanyl Patch 12 mcg/hr	Oxycodone 5 mg/5 mL Solution, 2.5 – 5 mL PO PRN	Ondansetron 8 mg PO

cords revealed that only 153 had serotonin syndrome discussed as a differential in their medical records during the study period. On detailed chart review, 6 cases had a true diagnosis of serotonin syndrome. One of these patients was treated with fentanyl and was previously identified. Of the remaining 5 patients, all of which were on serotonergic agents, 2 were cases of drug overdose on serotonergic drugs and 2 were on opioids, specifically tramadol (Table 4).

Overall, we found that the incidence of serotonin syndrome is 0.09% in patients that received both fentanyl and a serotonergic agent, in comparison to 0.005% in patients that did not receive fentanyl while on a serotonergic agent ($P < 0.01$).

DISCUSSION

There has been a recent increase in case reports and some studies associating serotonin syndrome with opioids, especially fentanyl, when given to patients on serotonergic agents. Fentanyl is a very commonly used opioid in the hospital setting, especially in the peri-operative and procedural areas. In addition, fentanyl patches are used to treat chronic pain. Since the use of serotonin reuptake inhibitors and other serotonergic agents is relatively common in the population (6), we undertook this study to ascertain the incidence of serotonin syndrome in patients receiving both drugs.

Based on our results, less than one in 1,000 patients receiving both drugs was diagnosed with serotonin syndrome. We were unable to ascertain a relationship to number of serotonergic agents used, dose of drugs given, or duration of use of the drugs that could be attributed as risk factors.

Some of the limitations of our study include that it represents a single institution, although it is a large academic center. An inherent limitation may be the under diagnosis of serotonin syndrome. Further, we only had

Table 4. Serotonin syndrome cases with opioids other than fentanyl and serotonergic agents.

Subject	Opioids other than fentanyl	Serotonergic agents	Comments
1	N/A	Zoloft 150 mg qd, Concerta d/c at discharge	Drug Overdose
2	Tramadol 50 mg	Fluoxetine HCL 40 mg	N/A
3	N/A	Citalopram 20 mg	Drug Overdose
4	Tramadol 25 mg Q4H	Fluoxetine 40 mg daily	N/A
5	N/A	Citalopram 20 mg	N/A

a small number of cases that could support an association; hence, we were unable to further study the association of number of agents used, dose, or duration of therapy as potential risk factors.

CONCLUSION

Our results suggest that the incidence of serotonin syndrome is significantly higher in patients receiving fentanyl and a serotonergic agent. However, the low incidence of serotonin syndrome in patients receiving both fentanyl and serotonergic agents raises the need for additional research before establishing this association. Further research is required to assess the role of doses used or use of multiple agents.

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