

## CASE REPORT

## PAIN MANAGEMENT

# Is central anticholinergic syndrome linked to opioid use for cervical cancer pain?

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## Abstract

Central anticholinergic syndrome (CAS) presents with central and/or peripheral neurological symptoms after exposure to anticholinergic medication. Pain management is a challenge for patients who have CAS and concurrent cancer-related pain. We present a patient who became lethargic and unresponsive after receiving butorphanol, with persistent symptoms despite administration of an opioid antagonist. This case report is the first to suggest a causal relationship between opioids and CAS without the presence of confounding anticholinergic medications. CAS should be considered for patients who develop neurological symptoms after opioid exposure and have an incomplete response to an opioid antagonist.

**Key words:** Central Anticholinergic Syndrome; Butorphanol; Opioids; Cancer-Related Pain; Anticholinergic Toxicity; Case Report

**Abbreviations:** CAS - Central Anticholinergic Syndrome; IV – intravenous; IM – intramuscular; ED - Emergency Department; WHO - World Health Organization; MRI - Magnetic Resonance Imaging; MED - Morphine Equivalent Dosing; ICU - Intensive Care Unit

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## 1. Introduction

Anticholinergic agents block the binding of acetylcholine, a neurotransmitter at the muscarinic or nicotinic receptors at the neuron synapses.<sup>1</sup> These interactions affect the parasympathetic functions in the central and peripheral nervous systems, which ultimately influence neurologic function and smooth muscle in the respiratory tract, vascular system, urinary tract, gastrointestinal tract, pupils of the eyes, and other parts of the body. “Anticholinergic” term is often used to describe the adverse effects of medications with anticholinergic properties e.g., delirium, respiratory depression, urinary retention, drug mouth, constipation, orthostatic hypotension etc. Anticholinergic medications can also be used to manage certain diseases e.g., depression, cardiovascular disease, chronic obstructive

pulmonary disease, overactive bladder or incontinence, nausea/vomiting, and allergies etc.

Central anticholinergic syndrome (CAS) presents after exposure to anticholinergic medication with nonspecific symptoms such as delirium, agitation, rigidity, respiratory depression and coma. Diagnosis is made when all other reversible causes have been addressed and symptoms resolve with physostigmine (Box 1).<sup>2</sup> Physostigmine is an acetylcholinesterase inhibitor that has been used to treat anticholinergic toxicity since the 1800s when it was first extracted from the Calabar bean *Physostigma venenosum*.<sup>3</sup> It has a rapid onset of action of within 10 min intravenously (IV) and 20-30 min when given intramuscularly (IM).<sup>4</sup> The usual dose of physostigmine for anticholinergic toxicity is 1-2 mg IM or 0.02 mg/kg IV with additional doses depending on clinical response.<sup>5</sup>

### Box 1: Differential diagnosis of anticholinergic toxicity<sup>6</sup>

- Agitated depression
- Alcohol withdrawal
- Delirium
- Dementia
- Hepatic encephalopathy
- Malignancy with or without brain metastasis
- Malignant hyperthermia
- Neuroleptic malignant syndrome
- Salicylate toxicity
- Sepsis
- Serotonin syndrome
- Thyroid storm

Opioids are widely used for acute and chronic pain, as they are part of the World Health Organization (WHO) analgesic ladder for cancer-related pain.<sup>7</sup> Opioids have anticholinergic properties, which can lead to adverse effects such as nausea and urinary retention.<sup>8</sup> This poses a challenge to patients with concurrent cancer and CAS as they may require opioids to manage cancer-related pain. The current literature regarding opioids and CAS is limited, with only a few case reports describing exposure after fentanyl or buprenorphine.<sup>9-11</sup> However, these case reports involve other anticholinergic medications as confounders (Table 1). Here, we discuss a patient with known CAS who exhibited possible CAS after opioid exposure only.

## 2. Case Description

A 39-year-old female with history of CAS and Stage IB1 cervical cancer presented to the Emergency Department (ED) with abdominal pain. Vital signs were within normal limits. Physical exam showed mild abdominal tenderness. Pelvic magnetic resonance imaging showed a fluid collection adjacent to the sigmoid colon, concerning for possible abscess. Her pain in the ED was controlled with as needed acetaminophen, ibuprofen, and butorphanol. Butorphanol is a kappa/delta agonist and mu antagonist, which was selected previously for its partial agonist/antagonist property due to the patient's known history of CAS. Her first CAS episode was after exposure to fentanyl (full mu-agonist opioid), midazolam, and propofol, and resolved with physostigmine.

An abdominal drain was placed under moderate sedation with 15 ml of purulent fluid removed with no complications. Peri-procedure, the patient received acetaminophen, ketorolac, and butorphanol. Post-procedure, her pain was controlled with as needed doses of butorphanol 0.5mg IV once or twice a day. Post-procedure day 3, she received butorphanol 0.5 mg IV

twice, with the second dose close to midnight. Ten hours later, on day 4, she became lethargic and unresponsive to noxious stimuli. Vital signs were within normal limits with a respiratory rate of 18 breaths per minute. Blood glucose was within normal limits. Naloxone, a mu/delta/sigma opioid antagonist, 0.04 mg IV was given with no effect. Two hours later, a second dose of naloxone 0.04 mg IV was given with no effect. Finally, 30 minutes later, a third dose of naloxone 0.4 mg IV was given with patient showing improvement in mental status.

The treatment team considered several differential diagnoses. Her family history included malignant hyperthermia, but this was thought to be less likely as her symptoms manifested several days after drug exposure. Administration of physostigmine was also considered after naloxone for possible CAS, but ultimately decided not to pursue this in the setting of her partial response to naloxone; additionally, physostigmine was restricted to ICU patients at the time due to a nationwide shortage. Acute Pain Service was consulted, who noted miotic pupils (2 mm bilaterally) and considered the incident an atypical response to opioids.

Pain control was ultimately achieved with non-opioid medications for the remainder of the hospital admission. However, she continued to have a "brain fog" with intermittent delirium and urinary retention requiring intermittent catheterizations. She was discharged on post-procedure day 6, with ibuprofen 800mg PO every 8 hours as needed for pain.

In comparison, she had an admission two months ago for surgical debulking of her cervical cancer under general anesthesia. Post-procedure, she received acetaminophen and ketorolac. Her pain remained uncontrolled so she was given butorphanol (2 mg IV in divided doses), a partial agonist/antagonist opioid due to her known history of CAS to full agonist opioids. Twenty minutes after receiving butorphanol, she was noted to be lethargic. Vital signs were within normal limits with respiratory rate of 14 breaths per minute. Physical exam showed she was drowsy and able to withdraw from painful stimuli. Blood glucose was within normal limits. Opioid overdose was suspected due to multiple breakthrough doses administered overnight. Naloxone 0.4 mg IV was given and her symptoms resolved with no remaining symptoms.

## 3. Discussion

The majority of current research on CAS are case reports in the perioperative setting where patients were exposed to anticholinergic anesthetics. Our literature search found six case reports that suggest CAS after opioid exposure (Table 1).

Table 1: Summary of CAS case reports

| Author/<br>Year     | Age | Gender | Procedure                  | Associated Symptom   | Associated<br>Opioid/Indication                          | Other Associated Medication  | Other Diff.<br>Diagnosis                        | Intervention  |
|---------------------|-----|--------|----------------------------|--|--|--|---|---|
| Jost et al., 1982   | 72  | N/A    | Varicose surgery           | Central - stupor, unable to awake, amnesia, tired  | Buprenorphine 0.3 mg IV for postoperative pain           | Pre/periooperative medication – atropine, promethazine, pethidine, bupivacaine, mepivacaine, and benzocaine  | N/A   | Physostigmine 4mg IV with associated symptom(s) resolution  |
|                     | 50  | N/A    | Paraumbilical hernia       | Central - not responsive   | Fentanyl 0.4 mg IV for general anesthesia and sedation   | Pre/periooperative medication – atropine, promethazine, pethidine, midazolam, and pancuronium  | Opioid toxicity                                 | Neostigmine, atropine, naloxone IV with no effect<br>Physostigmine 4mg IV with associated symptom(s) resolution   |
|                     | 27  | N/A    | Chronic appendicitis       | Central - not responsive   | Fentanyl 0.1 mg IV for general anesthesia and sedation   | Pre/periooperative medication – atropine, promethazine, pethidine, midazolam, succinylcholine, alcuronium, and fluothane                                 | N/A   | Neostigmine, levallorphan, atropine IV with no effect<br>Physostigmine 4mg IV with associated symptom(s) resolution   |
|                     | 27  | N/A    | Cholecystectomy            | Central - not responsive   | Fentanyl 0.5 mg IV for general anesthesia and sedation   | Pre/periooperative medication – atropine, promethazine, pethidine, midazolam, fentanyl, and pancuronium  | Opioid toxicity                                 | Naloxone IV with no effect<br>Physostigmine 4mg IV with symptom resolution  |
| Carras et al., 1992 | 23  | M      | Right radial styloidectomy | Central - coma, bradypnea, drowsy, dizziness, headache, hyperthermia, asthenia, anorexia, behavior disturbances, inhibition phase – slowness of ideation, prostration) and excitement phase - insomnia, nocturnal agitation, manic disorders, confusion<br>Ocular - fixed gaze | Fentanyl 0.075 mg IV for general anesthesia and sedation | Pre/periooperative medication – loperazolam, flunitrazepam, lidocaine, and midazolam   | Central hyperthermia<br>Benzodiazepine toxicity | Flumazenil IV with no effect<br>Physostigmine 2mg IV with associated symptom(s) resolution  |
| Cho et al., 2018    | 37  | F      | Laparoscopic appendectomy  | Central - agitation, aphasia, respiratory depression<br>Ocular - periorcular swelling<br>Skeletal muscle changes - myoclonus, lower limb rigidity<br>Dermis - facial flushing<br>Other - neck swelling   | Fentanyl 0.1 mg IV for postoperative pain                | Pre/periooperative medication – lidocaine, propofol, rocuronium, remifentanyl, and desflurane<br>Post-operative medication – nefopam and glycopyrrrolate | Opioid toxicity                                 | Naloxone IV with no effect<br>Midazolam IV for agitation<br>Dexamethasone IV for ocular/facial swelling<br>Physostigmine 1mg IV with associated symptom(s) resolution |

Abbreviations: central anticholinergic syndrome (CAS), male (M), female (F), intravenous (IV), postoperative day (POD), intensive care unit (ICU), and not available (N/A); Google Translate was used to interpret Jost et al., 1982 and Carras et al., 1992.

**Table 2: Comparison of medications received, clinical changes, interventions, and responses between admission two months ago and current admission**

| Variable  | Admission two months ago   | Current admission   |
|---|--|---|
| Reason for admission  | 3-day admission for surgical debulking   | 4-day admission for pelvic abscess  |
| Opioids received prior to clinical change   | <b>MED 10.5mg</b><br>•Butorphanol 0.5 mg IV x 3 (last dose 20 minutes prior to clinical change)                    | <b>MED 7 mg</b><br>•Butorphanol 0.5 mg IV x 2 (last dose 10 hours prior to clinical change)   |
| Non-opioid medications received prior to clinical change  | •Acetaminophen 975 mg PO x 2<br>•Heparin 5000 units SC x 1<br>•Ibuprofen 600 mg PO x 2<br>•Ondansetron 4 mg IV x 1 | •Ketorolac 30 mg IV x 1<br>•Acetaminophen 975 mg PO x 4<br>•Famotidine 20 mg PO x 2<br>•Ibuprofen 600 mg PO x 2<br>•Ondansetron 4 mg PO x 2 |
| Clinical change   | Lethargy   | Lethargy  |
| Interventions   | Naloxone 0.4 mg  | Naloxone 0.04 mg x2, naloxone 0.4 mg  |
| Response  | Resolution of associated symptoms in both episodes   | Improvement in mental status but persistent delirium and urinary retention  |
| Likely cause  | Opioid toxicity  | CAS with or without opioid toxicity   |
| <b>Abbreviations:</b> Morphine Equivalent Dosing (MED), oral (PO), subcutaneous (SC), intravenous (IV); for opioid conversion, used GlobalRPH opioid calculator <sup>12</sup> |  |   |

These six case reports share several important clinical characteristics of CAS. First, all patients exhibited primarily central symptoms. Second, five cases involved fentanyl, a full mu-agonist

opioid, while one case involved buprenorphine, an agonist/antagonist opioid. Third, opioid toxicity and benzodiazepine toxicity were part of the differential diagnosis in three and one patient(s), respectively. They were given reversal agents with no significant effect and only had complete symptom resolution after administration of physostigmine. Our case shares all these characteristics as the patient exhibited central symptoms of lethargy, received butorphanol, and was given naloxone due to concern for opioid toxicity.

Opioid toxicity may explain some of her symptoms, but several factors suggest a stronger possibility of CAS. During her prior admission, she received higher Morphine Equivalent Dosing (MED) of 10.5 mg and showed complete resolution of her symptoms with naloxone (Table 2). During the current admission, she received a lower MED of 7.5mg and had a partial response to naloxone. Moreover, the last opioid dose in the current admission was 10 hours prior to her clinical change, compared to 20 minutes in the prior admission. Chart review showed her kidney and liver function tests were within normal limits, which further implicate that her symptoms in the current admission were not due to opioid toxicity alone. In addition, she had urinary retention and persistent delirium, which are symptoms of

anticholinergic toxicity. These findings suggest that the patient's symptoms were more likely an exacerbation of her CAS and would have benefited from physostigmine.

We recognize several limitations to our case analysis. The most notable is that the patient did not receive physostigmine to establish the diagnosis of CAS. As a result, other differential diagnoses such as opioid sensitivity and psychogenic response remain valid. Nonetheless, our case stands out by the fact that the patient received opioids and no other anticholinergic agent while exhibiting symptoms similar to those described in prior studies.<sup>9-11</sup> This would have been the first case to document a cause-and-effect relationship between opioid and CAS exacerbation. Furthermore, our case report is the first to describe a possible CAS episode outside the perioperative setting. These points highlight the need to increase awareness of CAS beyond the perioperative setting and to educate all providers who prescribe opioids. Lastly, our literature search did not include all journals in foreign languages where the majority of CAS case reports were found. We also did not utilize formal translation service to interpret the case reports included in our search.

The next step would be to develop a pain plan for this patient. As first-line treatment, we recommend non-pharmacologic interventions and/or non-opioid medications. If pain is poorly controlled, then opioid should be added. Although she was given butorphanol, a partial agonist/antagonist opioid, there is no published

evidence of utilizing partial agonist/antagonist opioids for patients with CAS, and in this case butorphanol may have been the cause of her CAS. There are no studies investigating if certain opioids have higher anticholinergic properties than others. As a result, we suggest three treatment options. First, an opioid with a different receptor affinity profile could be used, such as butorphanol (partial mu antagonist and kappa/delta agonist).<sup>13</sup> or buprenorphine (mu partial agonist and kappa/delta antagonist).<sup>14</sup> The second option would be an opioid with different pharmacodynamic properties. Opioids can be organized by chemical class, e.g. phenanthrenes (butorphanol) and phenylpiperidines (fentanyl).<sup>15</sup> We could consider a diphenylheptane (methadone) or phenyl propylamines (tapentadol, tramadol). Third, we could consider medications with dual mechanisms of action such as tramadol (weak mu agonist and serotonin-norepinephrine reuptake inhibitor) or tapentadol (weak mu agonist and norepinephrine reuptake inhibitor).

## 4. Conclusions

Although the incidence of CAS is rare, it is a condition that significantly affects the quality of life in patients with life-limiting illnesses. CAS should be considered as a differential diagnosis in patients who present with neurological symptoms after opioid ingestion who exhibit an incomplete response to opioid antagonists. More studies are warranted to provide guidance for advanced pain management in this vulnerable population.

### 5. Conflict of interests

The authors have no conflicts of interests to be declared.

### 6. Disclosures

The authors have no disclosures.

### 7. Authors' contributions

AC: Main contributor in writing the manuscript and designing tables.

EP: chart review and contributed to discussion section.

TB: literature review.

MO: manuscript editing.

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