Postoperative opisthotonus and torticollis after fentanyl, enflurane, and nitrous oxide

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Most drug-induced extrapyramidal symptoms are due to blockade of dopaminergic receptors and are treated with anticholinergic drugs. We report a patient with severe postoperative extrapyramidal symptoms which responded to physostigmine and indicated a different aetiology. A young, healthy female outpatient developed severe extrapyramidal symptoms after an uneventful 50 min anaesthetic with thiopentone, fentanyl (100 μg), enflurane, and nitrous oxide. Although the trachea was not extubated until she obeyed commands, the patient developed opisthotonus, which resolved initially after treatment with thiopentone (40 mg), diazepam (5 mg), and diphenhydramine (50 mg). The opisthotonus recurred approximately 25 min later, in association with torticollis, obtundation, and periodic apnoea. A tentative diagnosis of central anticholinergic syndrome was proposed, and fentanyl was considered to have been responsible. Naloxone (0.4 mg) induced no improvement, but physostigmine (2 mg) reversed the dystonic symptoms and periodic apnoea and improved her mental status. The response to physostigmine may have been due specifically to increased levels of acetylcholine at the cholinergic receptors, or to a nonspecific analeptic effect.

La plupart des symptômes extrapyramidaux reliés à l'usage de médicaments sont causés par un blocage des récepteurs dopaminergiques et répondent bien aux anticholinergiques. Nous avons observé en postopératoire desmanifestations extrapyramidales répondant à l'usage de physostigmine, ce qui trahit une étiologie différente. Suite à une anesthésie de 50 minutes au thiopental, fentanyl (100 μg), enflurane et protoxyde d'azote et la détubation de la trachée après retour de la conscience, une jeune femme présenta un opisthotonos. Quarante mg de thiopental, 5 mg de diazépam et 50 mg de diphenhydramine parvinrent à contrer l'opisthotonos qui réapparu 25 minutes plus tard associé cette fois à un torticolis, de la stupeur et des pauses respiratoires. Avec un diagnostic présomptif de syndrome anticholinergique central attribuable au fentanyl, on essaya sans résultat 0,4 mg de naloxone. Deux mg de physostigmine suffirent à faire disparaître la dystonie et les pauses respiratoires et à améliorer l'état de conscience de la patiente. Cette réponse à la physostigmine peut être attribuable à une augmentation la quantité d'acétylcholine sur les récepteurs cholinergiques ou à un effet analeptique non-spécifique.

Key words

ANAESTHETICS, GASES: nitrous oxide;
ANAESTHETICS, INTRAVENOUS: fentanyl;
ANAESTHETICS, VOLATILE: enflurane;
ANTAGONISTS, NARCOTIC: naloxone;
ANTAGONISTS, MISCELLANEOUS: physostigmine;
CENTRAL NERVOUS SYSTEM: extrapyramidal system symptoms and central anticholinergic syndrome;
MUSCLE: rigidity.

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The unusual phenomenon of opisthotonus has recently been reported in the postoperative period after anaesthetics performed with propofol.[1–5] Also, postoperative myoclonic symptoms have been reported after the use of several inhalational anaesthetic agents, induction drugs, and narcotics.[6–11] Review of these reports revealed that postoperative myoclonic symptoms were frequently, but not always associated with the use of central excitatory drugs, such as propofol, enflurane, or etomidate, and were associated with the administration of potent narcotics. We report a patient who developed opisthotonus after anaesthesia.

Case report

A healthy, 32-yr-old, 59 kg, white female outpatient required surgical drainage of a breast abscess that had not responded to conservative treatment with antibiotics. She had a medical history of mitral and tricuspid valve prolapse, diagnosed by echocardiography. Nonexertional dyspnoea and chest tightness occurred occasionally, but

neither palpitations nor exercise intolerance were present. She had no history of seizures. Her only current medication was oral erythromycin for therapy of acne. She had a 14 pack-year smoking history and rarely used alcohol. She denied substance abuse at preoperative and postoperative interviews. She was employed as a psychiatric nurse. Two previous anaesthetics were uncomplicated.

Physical examination demonstrated a small left breast abscess and a left parasternal midsystolic click, which was accentuated by squatting. Preoperative electrocardiogram, complete blood count, and serum electrolytes were within normal limits.

Vital signs in the operating room were: blood pressure (BP) 130/80 mmHg, heart rate (HR) 70 beats · min^{-1}, respiratory rate (RR) 16 breaths · min^{-1} and oral temperature 37° C. Lactated Ringer's solution (800 ml) was infused with cefazolin (19) and gentamicin (80 mg) for endocarditis prophylaxis. Preinduction drugs included oxygen, d-tubocurarine (3 mg), lidocaine (100 mg), and fentanyl (100 mg). Tracheal intubation was performed after thiopentone (300 mg), succinylcholine (100 mg), and enflurane (2%) in oxygen. Anaesthesia was maintained with enflurane (1–2%) in 50% nitrous oxide (N_2O) and oxygen. Her BP ranged from 110–130/60–80 mmHg, HR 70–80, and end tidal PCO_2 ($PETCO_2$) from 35-40 mmHg, with assisted manual ventilation. Her trachea was extubated after 50 min of anaesthesia, when she obeyed commands and maintained a $PETCO_2$ of 42 mmHg with spontaneous ventilation.

Opisthotonus developed during transport to the postanaesthesia care unit (PACU). Her back and pelvis arched approximately 4–6 inches off the stretcher, and her extremities were extended. She was returned to the operating room for oxygen administration and evaluation. Vital signs were unchanged. She breathed 20 breaths · min^{-1}, without airway obstruction. The posturing recurred every one to two minutes. Because the muscular activity resembled a seizure, thiopentone (40 mg) and diazepam (5 mg) were infused and the opisthotonus resolved. Previous ingestion of phenothiazine-like drugs, with central cholinergic side-effects, was also considered, so diphenhydramine (50 mg) was administered.

The patient was returned to the PACU and initially was unresponsive. Mild horizontal and vertical nystagmus were noted 15 min after the initial onset of opisthotonus. The opisthotonus recurred ten minutes after return to the PACU, with spasms then developing every three to five minutes. In addition, intermittent torticollis (contraction of neck muscles with twisting of the neck and head) started. Recurrent episodes of intermittent apnoea lasting 10–15 sec developed after 20 min in the PACU. The RR varied between 6–16 breaths · min^{-1}, but she followed commands to breathe. She was lethargic and without spontaneous motor movement. Arterial blood gas analysis (FIO_2 50%) demonstrated pH 7.39, $PaOi_2$ 217 mmHg, and $PaCO_2$ 44 mmHg. Serum concentrations of electrolytes, glucose, calcium, phosphorous, and magnesium were normal.

A neurologist evaluated the patient within 30 min of entry into the PACU. He found external ophthalmoplegia in all directions, reactive pupils (3–4 mm), symmetrical, 3–4 + deep tendon reflexes, absence of clonus, and normal flexor plantar reflexes. Diffuse hypotonia was present between myoclonic contractions. The symptoms were attributed to central anticholinergic syndrome, probably induced by the fentanyl. Naloxone (0.4 mg) was given slowly *iv*, but it produced no improvement in 20 min. The tertiary anticholinesterase inhibitor physostigmine (2 mg) was slowly infused. The periodic apnoea, opisthotonus, and torticollis resolved over several minutes. The RR also increased to 12–16 breaths · min^{-1}, and the HR decreased to 60–70 beats · min^{-1}. The patient became more alert, expressed no complaints, and talked to her husband.

She was lethargic but arousable and oriented after admission to a closely monitored ward area. Mild nystagmus and muscular hypotonia persisted, but no muscular spasms recurred. Previous substance or drug abuse, topical exposure to antipsychotic medications, or ingestion of "over the counter" drugs were denied during extensive questioning the next day. She received a letter that listed the drugs administered and described her idiosyncratic reaction. Neurological evaluation two weeks later was normal.

Discussion

Our patient appears to be the first case of opisthotonus and torticollis following an anaesthetic that did not include propofol or drugs that produce extrapyramidal symptoms by antagonism of dopaminergic receptors (phenothiazine, droperidol, or metoclopramide). The contribution of other drugs administered to our patient and the possible role of central cholinergic receptors and potent narcotics are discussed, including details of the other reported cases of postanaesthesia myoclonus.

The dramatic extrapyramidal system (EPS) symptoms of opisthotonus, torticollis, and nystagmus, in conjunction with periodic apnoea and mental obtundation, were attributed to the central anticholinergic syndrome. Central anticholinergic syndrome can present after anaesthesia with mental obtundation or excitation.[12–14] Extrapyramidal symptoms are not a typical presentation but myoclonus, choreoathetosis, "truncal writhing and pelvic arching," symmetric decorticate posturing, and decreased muscle tone have been reported after overdoses of

tricyclic antidepressants (imipramine hydrochloride, amitriptyline) or angel's trumpet (Jimson weed). Physostigmine reversed these myoclonic and dystonic symptoms in the patients with the reported overdoses.[15,16]

Physostigmine has been utilized to antagonize sedation or delirium from anaesthetic drugs with central anticholinergic effects, such as atropine, scopolamine, phenothiazines, droperidol or antihistamines.[12,13] However, drugs with central nervous system (CNS) anticholinergic activity[14,17] were not administered to our patient, except for the diphenhydramine given after the opisthotonus started.

Physostigmine not only reverses central anticholinergic symptoms, but may also possess nonspecific analeptic properties. Physostigmine has reversed benzodiazepine-induced sedation[18,19] and hastened recovery from halothane and N_2O anaesthesia in patients premedicated with atropine and secobarbital.[20] Physostigmine has also reversed postoperative morphine-induced respiratory depression, without impairing analgesia, probably due to physostigmine's anticholinergic action in the medulla.[21] However, physostigmine did not alter morphine-induced respiratory depression in unpremedicated volunteers.[19]

Excitatory CNS phenomena following general anaesthesia have been documented previously. Hyperreflexia, positive Babinski signs, or sustained ankle clonus developed in 50% of patients receiving enflurane and N_2O and in 25% of patients given halothane and N_2O.[22] Certain anaesthetic agents may be more likely to induce postoperative CNS excitatory phenomena, including opisthotonus.

The role of individual perioperative drugs in causing the postoperative EPS symptoms needs to be considered. Enflurane possesses persistent, excitatory postoperative CNS effects. Reversible, mild electroencephalogram abnormalities occurred for 6–30 days after enflurane anaesthesia.[23] Seizures that developed days after enflurane anaesthesia were also attributed circumstantially, to enflurane.[24,25]

Volunteers receiving N_2O in a hyperbaric chamber (1.55 atm) demonstrated myoclonic movements, and one subject developed opisthotonus.[26] Mice developed jerking, grimacing, and excitation after cessation of N_2O. These withdrawal symptoms were considered analogous to central anticholinergic syndrome, and physostigmine reversed the symptoms in mice.[27] The complexity of the interactions is demonstrated by the observation, in mice, that naloxone pretreatment could prevent the excitatory symptoms, but that naloxone post-treatment could not.[27] Enflurane and N_2O have potential postoperative effects, which could have contributed to our patient's symptoms.

Synthetic narcotics, such as meperidine, with its "atropine-like" structure, may induce the central anticholinergic syndrome.[28] However, muscular rigidity is a more common neuromuscular complication following potent narcotic infusion. Electroencephalographic studies have demonstrated that the narcotic-induced rigidity was not associated with seizures, despite the extremely rapid onset of tonic-clonic movement and association with nystagmus.[29,30] Postoperative rigidity has occurred 3–24 hr after fentanyl (35–100 $\mu g \cdot kg^{-1}$), in association with recrudescence of high plasma concentrations of fentanyl. Naloxone reversed this postoperative rigidity.[31–35] However, narcotic-induced rigidity is an unlikely explanation for our patient's postoperative myoclonic symptoms, since she received an extremely low dose of fentanyl, had EPS symptoms and underlying hypotonia, and did not respond to naloxone.

Definitions and a differential diagnosis for dystonia and myoclonus are provided to help the aetiology of our patient's symptoms to be understood. Dystonic movements are involuntary movements that typically involve twisting movements of single or multiple parts of the body. The basal ganglia are the site of abnormality.[36] The differential diagnosis includes chronic neurological disorders (hereditary dystonia, Wilson's disease, Hallervorden-Spatz disease) and secondary dystonias, such as cerebral injury or tumour, CNS infections, toxicity from carbon monoxide or manganese, or drug-induced (levodopa, antipsychotics, metoclopramide, anticonvulsants) effects.[37] Our patient had no history of CNS disorders and had a normal neurological evaluation two weeks after the anaesthetic. Unacknowledged exposure to medicinal or recreational drugs was excluded by history from this intelligent, responsible patient. However, a toxicology screen was not performed on our patient or in any of the other reported patients with movement disorders.[1–11]

Myoclonus is characterized by either irregular or rhythmic muscle jerks, and it can either be epileptic or nonepileptic. Our patient's symptoms were not felt to be characteristic of seizures, due to EPS symptoms and periodic apnea. Myoclonus has a diffuse aetiology and can arise from a cortical, subcortical, or brainstem abnormality. The differential diagnosis for myoclonus includes encephalopathies from viral, toxic (heavy metals, strychnine), and metabolic causes (hypoxia, hypoglycaemia, or uraemia), storage diseases, basal ganglia or spinocerebellar degeneration,[36] and drugs (etomidate, ketamine, enflurane, levodopa, tricyclic antidepressants, lithium, and monoamine oxidase inhibitors, and toxic concentrations of cephalosporins and penicillins).[38] None of these factors was present in our patient.

The drugs and circumstances of the reported cases of postoperative myoclonus, not involving propofol, are summarized (Table I).[6–11] One case of myoclonic, postoperative symptoms has been reported after enflurane. However, the patient had focal symptoms, with right-sided headache and otalgia, a subjective feeling of

TABLE I Postoperative myoclonus after anaesthesia

Age, sex, procedure	*Inhalation*	*Pre-, intra-operative drugs*	*Narcotics*	*PACU symptoms*	*Diagnosis, treatment*
38, female,[6] knee arthroscopy	enflurane N_2O	*thiopentone 375 mg *iv*	—	Awake for 30 min then global myoclonic jerking which localized to left side for 48 hr	—
69, female,[7] knee arthroscopy	isoflurane N_2O	thiopentone 350 mg *iv*	—	Initially awake then upper extremity myoclonus 20 min after entry to PACU, responded to drugs	diazepam 10 mg, *iv*, twice diphenylhydantoin 400 mg *iv*
27, male,[8] hip synovectomy	isoflurane N_2O	diazepam 10 mg *po* glycopyrolate 0.2 mg *im* *thiopentone 400 mg *iv*	morphine 10 mg *im* fentanyl 100 mcg *iv* preop and 100 μg *iv* intraop	Global myoclonic movements starting intraop after fentanyl. Postop lower extremity myoclonus for >1 hr	thiopentone 150 m *iv* intraop
45, female,[9] D&C	—	scopolamine 0.2 mg *im* etomidate 35 mg *iv*	papaveretum 10 mg *im* fentanyl 150 μg *iv*	Initially awake then global clonic movements for 90 sec, resolved with drug therapy	diazepam 10 mg *iv*
75, male,[10] lumbar laminectomy	N_2O	diphenhydramine 50 mg *im* *etomidate 26 mg *iv* induction and 324 mg continuous infusion	fentanyl 475 μg *iv* infusion	Global myoclonus for 2.5 hr, resolved as patient gained consciousness	—
35, female,[11] C-section	—	epidural lidocaine 2% with epinephrine atropine 0.4 mg *iv* droperidol 1.25 mg *iv*	fentanyl 100 μg *iv* epidural fentanyl 100 mcg bolus and infusion 50 μg/hr postop	Asympotomatic for hours then global myoclonus, lethargy, delirium, nystagmus, responded to drug therapy	physostigmine 2 mg *iv* × 2 doses, CT normal

*Patients who received succinylcholine and/or nondepolarizing muscle relaxants with reversal; D&C = dilation and curettage; PACU = post-anaesthesia care unit; N_2O = nitrous oxide; CT = computerized tomography.

left-sided weakness, persistence of myoclonus for 48 hr, with no definite exclusion of CNS pathology.[6] Postoperative upper extremity myoclonus has been ascribed to isoflurane.[7] Intraoperative global myoclonic movements started after fentanyl (100 μg) was given during an isoflurane anaesthetic, with continuation of lower extremity myoclonus for more than one hr postoperatively.[8] Postoperative myoclonus also developed after anaesthetics performed with infusion of fentanyl and the CNS excitatory drug etomidate (premedication included drugs with anticholinergic properties).[9,10] A patient, undergoing a Caesarean section with epidural analgesia, received fentanyl and drugs with anticholinergic properties (droperidol and atropine). Epidural fentanyl was administered in the postoperative period.[11] This obstetrical patient was lucid and asymptomatic for three hours, but myoclonus and delirium developed one hour after discharge from the PACU. Physostigmine improved her mental status and reversed the myoclonus, but coarse tremors persisted.[11]

Dystonia, or more specifically opisthotonus, has been recently reported following propofol anaesthesia (Table II).[1–5] However, some of the patients developing opisthotonus after propofol also had a history of seizures[2,4] or received drugs with central anticholinergic properties (atropine[1,4,5] or droperidol[3]). The British Committee on Safety of Medicine reported that propofol has been associated with ten cases of opisthotonus, 16 cases of involuntary movements, and 37 cases of seizures (13 of the last had seizure histories).[40]

The exact cause of our patient's opisthotonus and torticollis and the other patients' myoclonic or dystonic symptoms cannot be determined retrospectively. Our patient's response to physostigmine does not definitely confirm central anticholinergic syndrome, since physo-

TABLE II Postoperative myoclonus with propofol

Age, sex, procedure	*Inhalation*	*Pre-, intra-operative drugs*	*Narcotics*	*PACU symptoms*	*Diagnosis, treatment*
44, female,[1] D&C	enflurane N_2O	atropine 0.3 mg *iv* propofol 114 mg *iv*	alfentanil 500 μg *iv*	Nystagmus, hyperreflexia ankle clonus, opisthotonus, weakness, sedated for 5 hr. Symptoms on right side at 10 hr	EEG, CT, and LP normal
24, female,[1] laparoscopy	enflurane N_2O	atropine 0.3 mg *iv* *propofol 114 mg *iv*	alfentanil 500 μg *iv*	Jerky movements, hypertonicity, hyperreflexia, ankle clonus, nystagmus. Sedated for 1 hr.	EEG normal
21, female,[1] laparoscopy	enflurane N_2O	atropine 0.3 mg *iv* *propofol 133 mg *iv*	alfentanil 500 μg *iv*	Initially awake then extensor jerks in all four limbs, hyperreflexia, hypertonicity	EEG normal
26, female,[1] myringotomies, seizure Hx	isoflurane N_2O	propofol 150 mg *iv*	—	Gasping then apnoeic, opisthotonus for 15–30 sec at three times, then awake	—
20, female,[2] D&C	—	temazepam 20 mg *po* propofol 140 mg *iv*	alfentanil 750 μg *iv*	Awake then opisthotonus ×7, triggered by noise and movement	Diazemuls 10 mg *iv* with response
55, female,[3] D&C	N_2O	droperidol 2.5 mg *iv* propofol 95 mg	alfentanil 250 μg *iv*	Violent writhing, opisthotonus, "marked" extrapyramidal signs, oculogyric crisis	procyclidine 10 mg *iv*, chlormethiazole infusion, EEG and brain scan normal
44, female,[4] D&C, Seizure Hx	N_2O	atropine 0.5 mg, *im* propofol 260 mg *iv*	meperidine 50 mg *im* preop fentanyl 50 μg *iv*	Initially normal, opisthotonus, myoclonic movement limbs, rightsided weakness, grand mal seizure five hr later	thiopentone 75 mg short respite from myoclonus, diazepam 2.5 mg and phenytoin to treat seizure
29, female,[5] toe arthrodesis	enflurane N_2O	atropine 0.6 mg *im* propofol 150 mg ankle block with bupivicaine 61.5 mg	morphine 10 mg *im*	Initially obeyed commands, opisthotonus followed by grand mal "seizure" with recurrent tonic-clonic "seizures", opisthotonic for 23 days	Diazemuls 10 mg *iv*, Brain scan, CT, LP, and EEG normal

*Patients that received succinylcholine and/or nondepolarizing muscle relaxants with reversal; Hx = History; PACU = post-anaesthesia care unit; D&C = dilation and curettage; N_2O = nitrous oxide; CT = computerized tomography; LP = lumbar puncture; EEG = electroencephalogram.

stigmine has direct receptor mediated effects and indirect analeptic effects. Our experience indicates that physostigmine should probably be considered for treatment of opisthotonus or other CNS dystonic postoperative phenomena, if seizure, metabolic cause, CNS disease, and use of drugs that antagonize dopamine receptors can be excluded.

It is not known if narcotics potentiate postoperative CNS excitatory phenomena, such as opisthotonus and myoclonus. However, a circumstantial association is suggested since fentanyl or alfentanil was utilized in four of the six reported cases of myoclonus not involving propofol[8–11] and in six of the eight reported cases of opisthotonus after propofol.[1–4] As discussed, synthetic narcotics such as meperidine can cause central anticholinergic syndrome.[28] Abundant animal research has shown the protean alterations in neurological mediator production and release following narcotics. Some of the mechanisms involved with narcotic-induced rigidity in animal models have been summarized.[39]

Extremely rare phenomena such as EPS symptoms after thiopentone, enflurane, fentanyl, and N_2O are difficult or impossible to study prospectively. Hopefully, the 37 cases reported of opisthotonus after propofol in Britain[40] will lead to prospective studies to examine the mechanism and to determine if potent narcotics are involved and if appropriate therapy includes physostigmine.

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