Case Reports/Case Series

Serotonin syndrome following methylene blue infusion during parathyroidectomy: a case report and literature review

[Syndrome sérotoninergique suite à une perfusion de bleu de méthylène pendant une parathyroïdectomie : présentation de cas et analyse bibliographique]

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Purpose: To report a case of autonomic, neurological and neuromuscular instability following methylene blue infusion for parathyroidectomy; to advance the argument for a diagnosis of serotonin syndrome; and to consider this diagnosis in previous, unexplained reports of adverse reactions amongst patients undergoing parathyroidectomy using methylene blue.

Clinical features: Methylene blue was administered to a 58-yr-old woman undergoing a parathyroidectomy under general anesthesia. The patient had a background of obsessive compulsive disorder treated with paroxetine. Postoperatively, she demonstrated symptoms and signs of serotonin syndrome; specifically tachycardia, agitation, dystonia and abnormal eye movements. These clinical findings spontaneously resolved themselves over the subsequent 48 hr.

Conclusion: An interaction between methylene blue and serotonergic agents may give rise to the serotonin syndrome. Consideration should be given to avoiding methylene blue in patients taking serotonergic agents. The diagnosis should be considered in patients with autonomic, neuromuscular or neurological changes and should be managed accordingly.

Objectif *: Présenter un cas d'instabilité autonome, neurologique et neuromusculaire suivant une perfusion de bleu de méthylène pendant une parathyroïdectomie ; développer les assises du diagnostic de syndrome sérotoninergique ; reconsidérer, à la lumière de ce diagnostic, des cas précédents de réactions indésirables inexpliquées chez des patients ayant subi des parathyroïdectomies et traités avec du bleu de méthylène.*

Éléments cliniques *: Du bleu de méthylène a été administré à une femme de 58 ans subissant une parathyroïdectomie sous anesthésie générale. La patiente présentait des antécédents de troubles obsessionnels compulsifs traités avec de la paroxétine. Après l'opération, elle a présenté des symptômes et signes d'un syndrome sérotoninergique, spécifiquement : tachycardie, agitation, dystonie et mouvements oculaires anormaux. Ces observations cliniques se sont résolues spontanément durant les 48 h suivantes.*

Conclusion *: Une interaction entre le bleu de méthylène et les agents sérotoninergiques pourrait provoquer un syndrome sérotoninergique. Il faudrait considérer l'option d'éviter le bleu de méthylène chez les patients traités avec des agents sérotoninergiques. Ce diagnostic devrait être envisagé chez les patients présentant des modifications autonomes, neuromusculaires ou neurologiques et ils devraient être pris en charge en conséquence.*

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A review of the literature reveals that seven reports have been published of patients who have experienced postoperative complications after the use of methylene blue in standard doses for intraoperative identification of the glands in elective parathyroidectomy. All of the patients experienced symptoms consistent with

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serotonin syndrome (or serotonin toxicity), including agitation, confusion, hypertonicity and clonus.[1–7] The most significant common feature of these cases is that five patients were concurrently taking a selective serotonin reuptake inhibitor (SSRI), or a serotonin norepinephrine reuptake inhibitor. One patient was receiving clomipramine, a tricyclic antidepressant with high serotonergic activity.[8] Despite this, four of the previous published cases did not consider the possibility of serotonin syndrome, two simply mentioned the possibility of an unspecified 'drug interaction' between methylene blue and SSRIs,[3,6] and only one report specifically mentioned serotonin syndrome but dismissed it as 'unlikely'.[7] We present an additional, similar case, and consider the evidence for a diagnosis of serotonin syndrome.

Case history

A 58-yr-old Caucasian woman underwent a right lower parathyroidectomy for a parathyroid adenoma. She had a history of an obsessive compulsive disorder for which she had been taking paroxetine 60 mg daily for several years. She was also taking omeprazole 40 mg *po* bid for gastroesophageal reflux, and simvastatin 20 mg *po* qhs for hypercholesterolemia. Her medical history was otherwise unremarkable. Her only previous drug reaction had been a rash in response to penicillin and sulfonamides. She had undergone multiple previous operations including, most recently, laparotomies for bowel resection and later, adhesiolysis. Anesthesia had been uncomplicated with no episodes of postoperative confusion and delirium.

On the morning of surgery she received her normal medications and was given methylene blue at a dose of 5 mg·kg^{-1} over one hour. Once the methylene blue had been administered she was taken to the operating room. Anesthesia was induced with midazolam 1 mg *iv*, fentanyl 100 mg *iv*, propofol 100 mg *iv* and rocuronium 40 mg *iv*. The procedure lasted 90 min, during which anesthesia was maintained with sevoflurane. There was a brief period of hypotension (blood pressure 75/45 mmHg) on induction which responded to boluses of ephedrine and metaraminol. The patient was otherwise stable throughout the procedure. She was positioned with her neck hyperextended throughout surgery. At the end of the procedure, neuromuscular block was reversed with neostigmine 2.5 mg and atropine 1.2 mg *iv*. The patient was transferred to the postanesthetic care unit (PACU) with a nasopharyngeal airway *in situ*.

On arrival in the PACU the patient was noted to be deeply sedated and, although arousable, she did not awaken for 25 min. Upon awakening the patient was agitated, unresponsive, disoriented and moving all limbs purposelessly. She had tachycardia at 100 beats·min^{-1}, an oxygen saturation of 99% and a stable blood pressure. A neurological examination revealed increased tone in all limbs and normal reflexes. She was noted to have rapid, fluid eye movements. She was treated with morphine 5 mg *iv* (in increments) and midazolam 2 mg *iv*, without effect. Postoperative electrolytes, complete blood count, glucose, calcium, and coagulation studies were within normal range. A computed tomography of the head (magnetic resonance imaging was unavailable) revealed no acute changes.

She was admitted to the intensive care unit where her dystonia and agitation resolved themselves slowly over five hours. She remained fearful and anxious, stating that she was 'alone', 'no-one will help me' and 'I am at the bottom of a big blue tank'. Her anxiety slowly resolved itself over the subsequent 48 hr. Consent from the patient was later obtained for publication of this report.

Discussion

Methylene blue (methylene blue trihydrate) is a derivative of phenothiazine, a compound that also formed the base for the first generation of antipsychotic medications.[9] It is the only dye in common use for intraoperative identification of parathyroid glands, and it relies on accurate timing to deliver the full dose via infusion, in the hour before the operation.[10]

The above case is the eighth reported occurrence of an adverse reaction following administration of methylene blue in standard dose for parathyroidectomy. In all eight cases the cause of the patient's condition was unclear. Referencing two of these patients (and one unpublished report), Gillman advanced the possibility that these cases were unrecognized examples of serotonin syndrome from a drug interaction between methylene blue and SSRIs.[11]

Early diagnoses considered in our patient included pain and anxiety and, after review by an anesthesiologist, she received opioids and then midazolam in the PACU. She was not hypoglycemic. Consults were obtained from general medicine, intensive care, neurology and psychiatry. Assessment was made difficult by the facts that the patient was poorly communicative and struggled to participate in a neurological or psychiatric assessment.

The possibility of a cerebral ischemic event was widely considered, particularly in the context of neck hyperextension during the case. She had no history of cerebrovascular disease, and hypercholesterolemia and age were her only risk factors. Vertebrobasilar insufficiency can cause nystagmus and limb ataxia, but

TABLE I Sternbach criteria for serotonin syndrome[13]

Recent addition or increase in a known serotonergic agent
At least three of the following clinical features
Mental status changes (confusion, hypomania)
Agitation
Myoclonus
Hyperreflexia
Diaphoresis
Shivering
Tremor
Diarrhea
Incoordination
Fever
Absence of other possible etiologies (infectious, metabolic, substance abuse or withdrawal, etc).
No recent addition or increase in a neurolpetic agent prior to the onset of the above features.

TABLE II Hunter serotonin toxicity criteria: decision rules for predicting serotonin toxicity[14]

In the presence of a serotonergic agent:
Spontaneous clonus
Inducible clonus OR ocular clonus AND agitation OR diaphoresis
Inducible clonus OR ocular clonus AND hypertonicity AND temperature > 38°C
Tremor AND hyperreflexia

would not explain her tachycardia or emotional lability. She did not suffer vertigo, visual disturbances, dysphagia, dysarthria or paraesthesias which commonly accompany vertebrobasilar insufficiency.

Atropine toxicity can present with ataxia, confusion and tachycardia, and has been known to occur even at normal doses.[12] The diagnosis was considered highly unlikely in our patient, given that she had tolerated atropine during a previous anesthetic. Methylene blue, like other phenothiazine derivatives, has an antimuscarinic effect. The antagonistic effect of both atropine and methylene blue on muscarinic receptors strengthened the possibility of anticholinergic syndrome. However, other associated symptoms, (mydriasis and dryness of the mouth and skin) were absent. None of the seven cases we reviewed reported atropine use.

The use of atropine in conjunction with neostigmine to reverse neuromuscular blockade remains widespread in New Zealand. This practice is largely driven by cost; in 1995 New Zealand hospitals paid 36-fold more for glycopyrrolate than American institutions,[13] and a large price differential still exists. Atropine, therefore, remains a common antimuscarinic for reversal of neuromuscular blockade, with many anesthesiologists reserving glycopyrrolate for patients intolerant of tachycardia or perceived to be at risk of mental status changes (notably the elderly or those with a background of postoperative confusion or agitation). These concerns were not applicable to this patient.

Other differential diagnoses, including acute alcohol withdrawal and neuroleptic malignant syndrome, were later dismissed after a thorough history was taken from the patient, family and general practitioner. The psychiatric service did not support a diagnosis of conversion disorder or malingering. Both diagnoses are dependent on the exclusion of possible organic causes, whereas this case report asserts that serotonin syndrome would reasonably explain this patient's condition. Ultimately, a definitive diagnosis was not made. Due to her ongoing clinical improvement, the patient was managed with supportive care only. By the time a literature review had raised the possibility of serotonin syndrome, her acute symptoms had resolved themselves.

A definitive diagnosis was never reached in the seven previously reported cases. As with our patient, cranial computed tomography and biochemistry values were unremarkable in all cases. Important differentials considered in previous reports included untoward effects from midazolam,[2] propofol[1] or opioid toxicity,[4,7] antimuscarinic effects,[4,7] methemoglobinaemia,[1,3,5–7] and malignant hyperthermia.[4] Four reports[1–3,7] cited Nadler's 1934 monograph on the toxicity of methylene blue.[14]

The morbidity which occurred in these patients should not be understated. Our patient, and four of the seven cases[1,4–6] required admission to an intensive care unit. Four patients required repeat tracheal intubation[1,4–6] and ventilatory support, and one required extended hemodialysis and management of myocardial ischemia.[4] Recovery times varied from 48 hr to a 14-day hospitalization. Although these cases are rare, the possibility that these undiagnosed episodes may be completely avoidable underscores their significance.

Serotonin syndrome is a clinical diagnosis based on a triad of mental status changes, autonomic hyperactivity and neuromuscular abnormalities.[15] Commonly used diagnostic criteria include the Sternbach criteria[16] (Table I) and the more recently developed Hunter decision rules[17] (Table II), the latter providing a simple diagnostic criteria with a high sensitivity of 84% and specificity of 97%. Despite increasing recognition, serotonin syndrome remains under-diagnosed due to a lack of clinician knowledge, applications of varying diagnostic criteria, the potential for early, mild or subacute presentations to be missed by clinicians or

TABLE III Clinical details of cases of postoperative complications after the use of methylene blue

Ref	*Patient*	*SSRI & other medications*	*Methylene blue dose*	*Diagnosis of serotonin syndrome (Sternbach)*	*Diagnosis of serotonin toxicity (Hunter)*	*Other clinical signs*	*Outcome*
[1]	60 yr female	Fluoxetine Coproxamol Beclamethasone Nasal spray	7.5 mg·kg^{-1}	Yes Agitation Hypertonicity Diaphoresis Rigid, jerky movements (possible spontaneous clonus)	Possible Possible spontaneous clonus	Reduced consciousness Aggression Rotational nystagmus Dilated and unreactive pupils Bilateral upgoing plantar reflexes	Intensive care unit admission and reintubation Complete recovery by day 4
[2]	59 yr male	Paroxetine Glyburide Metformin Verapamil Furosemide Potassium Simvastatin Rabeprazole	6 mg·kg^{-1}	Possible Confusion Forced foot dorsiflexion (possible spontaneous clonus)	Possible Possible spontaneous clonus	Aphasia	Complete recovery by day 2
[3]	52 yr female	Venlafaxine Mebeverine Ferrous sulphate	7.5 mg·kg^{-1}	Possible Confusion	Possible Confusion	Aphasia Nystagmus	Complete recovery by day 2
[4]	65 yr male	Citalopram Insulin Quinine sulphate Omeprazole Clopidogrel Atorvastatin Alfacalcidol Aluminium hydroxide Sildenafil	7.5 mg·kg^{-1}	Yes Agitation Fever (40.2°C) Diaphoresis	Possible Agitation Fever (40.2°C) Diaphoresis	Disorientation Reduced consciousness	Intensive care unit admission and reintubation. Hemodialysis used to remove methylene blue. Complete recovery by 2 weeks
[5]	48 yr male	Nil selective serotonin reuptake inhibitor	5 mg·kg^{-1}	No	No	Generalized tonic-clonic seizures leading to status epilepticus	Intensive care unit admission and reintubation. Commenced on antiepileptic medication and seizure free by day 7
[6]	65 yr female	Paroxetine Insulin Metformin Ramipril Atenolol Aspirin Simvastatin Carbimazole	1.75 mg·kg^{-1}	Possible Confusion Agitation	Possible Agitation	Reduced consciousness Aphasia	Intensive care unit admission and reintubation. Discharged on day 7
[7]	66 yr female	Clomipramine 50 mg Alverine citrate	5 mg·kg	Possible Confusion Agitation Jerky movements of all limbs (possible spontaneous clonus)	Possible Agitation Hypertonicity Possible spontaneous clonus	Nil	Complete recovery by day 4
Current case	58 yr female	Paroxetine 60 mg Omeprazole Simvastatin	5 mg·kg^{-1}	Possible Confusion Agitation Rapid fluid eye movements (possible ocular clonus)	Possible Agitation Hypertonicity Possible ocular clonus	Nil	Complete recovery by day 2

Diagnosis of serotonin syndrome: yes = definitely meets criteria; possible = insufficient data to rule out diagnosis; no = definitely does not meet criteria.

criteria, and the misattribution of symptoms to mental conditions or other medications.[15] Furthermore, both of the above criteria were developed from clinical populations whose serotonin syndrome occurred mainly in the context of SSRI overdose, rather than medication interactions.

A retrospective review of the seven published case reports (Table III) reveals that two cases met the diagnosis for serotonin syndrome according to at least one of the above criteria. In a further four, a triad of autonomic, neuromuscular and mental status signs suggested a possible diagnosis. Regrettably, relevant examination findings were not documented (and possibly not undertaken). This illustrates the importance of a high level of clinical suspicion and an appropriately focussed assessment. Only one of the seven case reports did not meet the diagnostic criteria, as a serotonergic agent had not been administered.[5]

There are no reports of serotonin syndrome occurring following the administration of methylene blue in isolation. Nonetheless, *in vivo* studies have shown that the dye increases serotonin levels in rats[18] and it has been shown to have a clinically significant effect as an antidepressant.[19] Despite this, methylene blue is considered to confer a low risk of serotonin toxicity but may cause problems when added to an SSRI.[11] Gillman has suggested that methylene blue has limited activity as a monoamine oxidase inhibitor.[11] In context of the high number of patients on SSRIs potentially exposed to methylene blue, he hypothesized that the rare occurrence of serotonin syndrome may be a consequence of variability in drug dosing or variability of cytochrome P450 enzyme activity between patients.[11] Of further relevance is the potential interaction of other drugs commonly used in anesthesia. Both fentanyl and ondansetron have been linked to serotonin syndrome,[15] although our patient only received the former medication.

These cases have important implications for future practice. Selective serotonin reuptake inhibitors are given for a range of indications (depression, bulimia, obsessive compulsive and other anxiety disorders, premenstrual dysphoric disorder). Given that serotonin syndrome has been described some five weeks after stopping an SSRI,[15] withholding these drugs perioperatively is unlikely to be a pragmatic solution. The use of methylene blue itself has been declining since the advent of preoperative radionuclide scanning and the use of targeted high-resolution ultrasound to localise glands. It has also been recognized that primary neck exploration by an experienced endocrine surgeon is successful in over 95% of cases.[20] An audit of practice in Australia showed methylene blue being used in 11% of initial neck explorations.[21] Avoidance of methylene blue in patients taking SSRIs should be discussed with surgical colleagues. If methylene blue is to be used in such patients, anesthesiologists should be aware of the possibility of serotonin syndrome, and assess and manage patients accordingly.

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