Short Report

Acute severe depression following peri-operative ondansetron

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A 41-year-old woman with a strong history of postoperative nausea and vomiting presented for abdominal hysterectomy 3 months after a previous anaesthetic where ondansetron prophylaxis had been used. She had developed a severe acute major depression disorder almost immediately thereafter, possibly related to the use of a serotonin antagonist. Nine years before she had experienced a self-limited puerperal depressive episode. Anaesthesia with a propofol infusion and avoidance of serotonin antagonists provided a nausea-free postoperative course without exacerbation of the depression disorder.

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Ondansetron, a serotonin or 5-hydroxytryptamine-3 receptor ($5\text{-}HT_3$) antagonist, is often used as a potent anti-emetic during chemotherapy and anaesthesia. It is highly effective, with few side-effects. Oren[1] reported 1 patient who suffered the acute onset of short-lived severe depression following her third exposure to ondansetron for doxorubicin-induced nausea while concurrently taking a selective $5\text{-}HT_3$ or serotonin selective re-uptake inhibitor (SSRI), fluoxetine. The following is a report of a severe depressive incident following peri-operative ondansetron in a patient with a history of severe and debilitating nausea post-anaesthesia.

Case report

A fit 41-year-old woman weighing 75 kg was scheduled for an abdominal hysterectomy. She was normotensive, with no cardiovascular or respiratory problems, was not anaemic and had no allergies to medications.

Her past history of note revealed that she had previously undergone a reduction mammoplasty and a meniscectomy, which had both resulted in severe and debilitating postoperative nausea and vomiting (PONV) for 2 days after the event. She had subsequently undergone knee arthroscopy 3 months prior to the planned hysterectomy at another hospital and had been given ondansetron with induction of anaesthesia. She was not taking any regular medication at that time.

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On emergence from the arthroscopy she did not experience PONV, but she related that her affect had changed from that prior to the anaesthetic. She had become withdrawn and irritable, and slept poorly. Seven days after this previous anaesthetic she had become suicidally depressed. She had required intensive psychotherapy and medication in the intervening 3 months. Her medication at the time of presenting for her hysterectomy comprised fluvoxamine, alprazolam and flunitrazepam. At this stage, 3 months after the arthroscopy, she felt that she had improved markedly and was reducing her medication under professional guidance.

Further enquiry revealed that she had experienced a relatively mild and self-limiting puerperal depression 9 years previously. There was no history of any affective disorder in the intervening period.

She was prescribed midazolam 15 mg the night before the hysterectomy in place of the flunitrazepam, and a repeat prescription of midazolam 15 mg together with domperidone 10 mg orally was given as premedication 1 hour before surgery. An 18 g cannula was inserted intravenously in theatre and she was induced with a propofol infusion at 20 mg/kg/h, sufentanil 40 µg bolus and rendered immobile with vecuronium 0.1 mg/kg. Anaesthesia was maintained with a propofol infusion at 6 mg/kg/h. She was ventilated with oxygen-enriched air via a laryngeal mask. Additional medication included ketorolac 30 mg together with tenoxicam 20 mg. Anaesthetic time was 76 minutes and she did not require reversal of muscle relaxation. At skin closure, she was given tramadol 100 mg intravenously. Of note, tramadol, in addition to its effect on morphine receptors, also inhibits the re-uptake of 5-HT and noradrenaline.[2] This could well play a role in its central effects.

Postoperative analgesia with tramadol, ketorolac and oral analgesics was effective and she experienced no PONV at all. She experienced no deterioration of affect and in fact reported that she was feeling better than she had felt after any previous surgical or anaesthetic experience.

Her recovery was complicated by her developing an acutely tender abdomen with pyrexia (39°C) on the second postoperative day and she was treated with ceftriaxone and metronidazole. This settled rapidly (24 hours), and she was discharged 10 days after surgery in good spirits.

Discussion

Serotonin or 5-HT is widely distributed in nature in both animals and plants.[3] Among its diverse and ubiquitous roles, it functions as a neurotransmitter,[4] and has a structural similarity to hallucinogens (LSD, psilocybin, psylocin); this, together with the observation that reserpine (a potent tranquilliser as well as an antihypertensive drug) lowers brain 5-HT levels, suggests that 5-HT may play a role in mental illness. Only about 10% of 5-HT is found in the brain, specifically in the midline raphe regions of the pons and upper brainstem. The median raphe nucleus is closely linked to 5-HT innervation of the limbic system. Other regions of the brain demonstrating 5-HT innervation include the suprachiasmatic nucleus, amygdala and venterolateral geniculate body.[3]

5-HT is synthesised by hydroxylation of tryptophan with its subsequent decarboxylation. It is stored in secretory granules as a non-diffusible complex with adenosine triphosphate. Its release and re-uptake follow patterns similar to those seen with the catecholamines. Drugs that interfere with catecholamine storage and re-uptake also interfere with those of 5-HT, e.g. reserpine, monoamine oxidase inhibitors and tricyclic antidepressants.

Of particular relevance to the role of 5-HT in affective disorders has been the development of the SSRIs. These selectively block 5-HT re-uptake at presynaptic neurones, with a marked beneficial effect on mood and relatively few side-effects.

The specific 5-HT_3 receptor antagonists, such as ondansetron, are of particular use in countering nausea and vomiting. Their precise mechanism of action is uncertain but it would appear to be exerted both at central neuronal 5-HT_3 receptors (particularly the area postrema, which is rich in dopamine, opioid and 5-HT receptors)[5] and at peripheral receptors in the gut, inhibiting vagal afferent input to the brainstem and preventing nausea and vomiting.[5-7]

Studies concerned with the mechanism of action of the 5-HT_3 receptor antagonists have concentrated on the anti-emetic actions of these agents. These agents lack the centrally mediated dysphoria and extrapyramidal side-effects of certain other anti-emetics but are associated with mild sedation, dizziness and headache.[5] Theoretically, it may be possible that in certain susceptible patients central inhibition of 5-HT activity by SSRI drugs could lead to alterations in mood.

Oren's report[1] of an isolated case of severe depression following several exposures to ondansetron in a patient on SSRI treatment and concurrently receiving doxorubicin is the first. It is postulated that the patient in this report suffered from acute depression iatrogenically induced by a single exposure to the 5-HT_3 receptor antagonist, ondansetron, administered during her earlier anaesthetic. With this in mind, an anaesthetic plan to minimise the risk of PONV and provide adequate postoperative analgesia was adopted for this particular patient.

It is suggested that until more information is forthcoming about the central affective effects that drugs of this class may have, care should be taken in their use. Specific enquiry should be made about previous mood disorders in potential recipients. A positive history should perhaps be regarded as a relative contraindication to the use of 5-HT_3 receptor antagonists, e.g. ondansetron, for PONV prophylaxis.

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