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RESEARCH ARTICLE

Anticholinergics Stop the Pain and the Motions – A Lesson for Surgeons

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ABSTRACT

Background: Small bowel obstruction commonly presents to surgeons acutely. Adhesions and hernias are the commonest causes. However, medical ileus and gastroparesis are often overlooked.

Case report: This article presents a case of an 82-year-old woman on orthopaedic ward referred to the general surgeons with symptoms of small bowel obstruction: bilious vomiting and abdominal distension. Despite all conservative measures, symptoms did not improve. Oral contrast on cross-sectional imaging and gastrograffin follow-through consistently illustrated a transition point at the base of jejunum. No mass or mural lesion was seen. The patient was prescribed regular orphenadrine for cramps over her right periprosthetic femoral fracture. Surgical intervention was then considered on suspicion of adhesional small bowel obstruction. A day before the planned laparotomy, the general surgical team stopped orphenadrine as the last attempt to relieve her symptoms. Ceasing orphenadrine reversed her obstructive symptoms and signs within hours.

Conclusion: Orphenadrine has a broad range of anticholinergic effects that is known to cause gastroparesis and ileus, which is often overlooked. This article discusses the learning points of this case and reviews literature regarding its pharmacologic effects.

Keywords: Anticholinergics, bowel obstruction, ileus

Introduction

Small bowel obstruction is a common acute complaint necessitating urgent surgical consultation and even an emergency operation.^{1,2} In most cases, the obstruction resolves itself with gut rest and stimulant.³ The management of small bowel obstruction can be costly with the average hospital admission lasting 8 days.⁴ The Bologna guidelines advise that conservative management can be continued safely for 72 hours. Traditionally, surgery has been through laparotomy and adhesiolysis. The rise in laparoscopic techniques has significantly improved patient recovery and mortality. There is still significant mortality from small bowel obstruction requiring surgical intervention and it is as high as 4.9% for open adhesiolysis and 1.6% for laparoscopic surgery.⁵ These cost and consequences compel current medical practitioners to identify the correct aetiology of a patient, who presents with symptoms of bowel obstruction.

Adhesion, usually from previous operations, is one of the commonest causes of small bowel obstruction. Other less common causes of bowel obstruction, ileus and pseudo-obstruction are exacerbated or caused by factors such as immobility, metabolic disturbance, electrolyte imbalance and medications.⁶ These less common conditions may not be readily considered. Patients may face interventions and potential risk, which they would not require otherwise.

Orphenadrine is frequently used as an antispasmodic medication for muscular back pain and to relieve parkinsonian symptoms of neuroleptics in particular hyperkinesia. It is derived from diphenhydramine and has a wide range of known mechanisms of action. Orphenadrine mainly works as a non-selective anticholinergic centrally with a weak peripheral effect by antagonising N-methyl-D-aspartate (NMDA) receptors. This contributes to its anaesthetic properties.⁷ Among its other known mechanisms, it inhibits sodium dependent noradrenaline transporter causing a decrease in noradrenaline reuptake on presynaptic neurons⁸ thereby inducing a muscle relaxant effect for both skeletal and smooth muscle. The relaxant effect on smooth muscle leads to ileus being in orphenadrine's side effect profile. In clinical practice, this multitude of orphenadrine's pharmacological consequences are often overlooked.

This article presents a case of an elderly patient, who developed profound gastroparesis and ileus once commenced on orphenadrine. She was prescribed orphenadrine to treat her new symptom of cramps in the affected leg while it was in traction following a fracture of

her hip. It was only until this was ceased in the lead up to her laparotomy that her symptoms resolved and the operation was avoided. This case report will describe the details of the case and discuss the relevant literature. It will also serve as an important lesson for medication review when faced with clinical bowel obstruction.

Case Report

An 82-year-old woman was admitted with right femur periprosthetic fracture following a mechanical fall on background of an existing right total hip joint replacement. She complained of intractable crampy pain over her right leg. She was prescribed orphenadrine 100 mg twice daily for acute muscle spasm pain during admission whilst her leg was placed in traction waiting for her dabigatran to naturally wear off for right hip revision. On day 2, the patient developed episodes of bilious vomiting and absolute constipation accompanied by relatively painless abdominal distension.

The patient had a past medical history of mild cardiac failure with preserved ejection fraction of 51%, atrial fibrillation anticoagulated with dabigatran and rate controlled by metoprolol and digoxin, sick sinus rhythm that required a permanent pacemaker, oesophagitis, and diabetes on insulin. Despite the extensive medical history, the patient had a good performance status. There was no premonitory history of physical immobility or bowel inertia. Her surgical history included open emergency appendectomy. She was an ex-smoker with a 15 pack-year-history.

Examination revealed a non-tender abdomen but distended. Admission blood profiles showed a slight hyponatremia of 133 mmol/L, potassium level of 4.5 mmol/L and eGFR of 56. C-reactive protein was up to 67, thought to be a result of her trauma. Inpatient abdominal x-ray indicated faecal loading and gaseous distention of duodenum and stomach. Given her severe bowel symptoms, conservative management including nasogastric tube placement, intravenous rehydration, correction of electrolytes, meticulous diabetic control, enema and prokinetic (metoclopramide) were commenced. Contrast-enhanced cross-sectional computed tomography (CT) imaging of the abdomen showed marked stomach and proximal duodenum distention (Figure 1) with an apparent zone of transition in proximal jejunum consistent with diagnosis of midgut obstruction (Figure 2).

No mass or mural lesion was identified on CT scan. However, foregut outlet obstruction was considered and needed to be excluded. Upper endoscopy to the fourth part of the duodenum did not illustrate any luminal pathology. The duodenum was widely patent and fluid filled. A trial of oral

gastrografin was attempted on day 3 of admission but was unsuccessful in resolution. A femoral nerve catheter was also inserted for pain management of the right hip in order to come off any opiates but orphenadrine treatment continued.



Figure 1: CT Scan – markedly distended stomach and duodenum with greater curvature almost in the pelvis



Figure 2: CT Scan - indicating markedly dilation of stomach and proximal duodenum with a transition zone in proximal Jejunum

On day 4, the patient's dabigatran was close to being wearing off and all conservative measures had been instituted. Surgical exploration was being considered for the morning of day 5 as the nasogastric output remained high with imminent risk of malnutrition. Just as the patient was being referred for anaesthetic assessment, the general surgical team decided to stop the orphenadrine as the last attempt to improve symptoms. On the morning of day 5 of admission, there had been virtually no nasogastric content overnight and the patient defecated. Her symptoms of midgut outlet obstruction completely resolved. Her abdomen was flat and soft. She started oral fluids and introduced diet by the end of day 5, marking resolution.

Discussion

Bowel obstruction can occur when normal flow of intraluminal bowel contents is disrupted in small or large bowel. This can be either mechanical or functional. The commonest aetiology of large bowel obstruction in 60 percent of cases is colon cancer followed by volvulus and diverticulitis, with 11-15% and 4-10%, respectively.⁹ Post-surgical adhesions account for 75 to 80 percent of small bowel obstructions, with abdominal wall hernias being the second commonest cause (approximately 10-15%). Less common causes of small bowel obstruction include neoplasms, volvulus, intussusception, and gallbladder ileus.¹⁰ Differentials for small bowel obstruction that must always be

considered: large bowel obstruction, adynamic ileus, narcotic bowel, pseudo-obstruction (Ogilvie's syndrome) and mesenteric ischaemia. The pathophysiology of ileus is complex and not fully understood however the general principle is a failure of peristalsis. Causative or contributing factors to ileus such as prolonged immobility, electrolyte imbalance, sepsis, poorly controlled diabetes, opioid analgesics and anticholinergic drugs must not be overlooked. Prolonged ileus can viciously worsen electrolyte imbalances and effects of prokinetic medications worsening ileus.¹¹

Our patient exhibited many potential signs of adhesional small bowel obstruction likely from previous appendectomy. However, there were also other potential contributing factors to adynamic bowel function such as immobility from the periprosthetic fracture, analgesic medications like opiates and anticholinergics (orphenadrine), hyponatraemia, diabetic exacerbation and mesenteric angina from atrial fibrillation. The patient was virtually pain-free and had reasonable blood sugar levels, which exonerates the latter two causes.

The clinical management of this patient was supported by peer surgeons and international standards. These included appropriate correction of electrolytes, "drip and suck" nasogastric decompression, gastrograffin follow-through

and cessation of opiates. Early cross-sectional imaging is essential in prediction of early surgery against watch and wait approach, especially if a mechanical cause is identified such as internal herniation or mass lesion. A transition point delineates the likelihood of it being adhesional as opposed to ileus; although this is not always a reliable marker as seen in our patient's case. Cessation of orphenadrine and replacement with a regional nerve block eventually avoided an unnecessary laparotomy. A surgical intervention such as laparotomy in an elderly comorbid patient would pose significant risks and contribute to prolonged hospital stay. This success story may be possible for other patients.

A medication review for patients with clinical bowel obstruction is essential. It is cost-effective endeavour, which can utilise a pharmacist and treating clinician. Common medication known to cause ileus are opioids, tricyclic antidepressants such as amitriptyline, antipsychotics such as clozapine and quetiapine, antihistamines and anticholinergics.¹² The cessation of these medications is important to eliminate factors, which contribute to ileus. This is essential in making the correct diagnosis and treatment plan.

There is a paucity of literature to the potential adverse effects of anticholinergics. One previous case report from 1976 documented a similar presentation of a 77 year-old man on orphenadrine for his parkinsonism. That patient underwent a laparotomy but no cause for his clinical obstruction was found. The authors of this article attributed his case presentation to a combination of parkinsonism and atropinic properties of orphenadrine.¹³ Since then, there have been a handful of limited studies assessing the side effects of this medication. In 2021, a report came out accusing the effect of Benztropine, an anticholinergic drug for schizophrenia, causing ileus.¹⁴ This case study adds to build the knowledge and awareness of anticholinergic medications as a possible culprit in the patient with ileus.

Orphenadrine has a broad range of action both as an anticholinergic and a noradrenaline transporter inhibitor on

presynaptic neurons. This makes orphenadrine susceptible to a wide range of side effects and drug interactions. Ironically, often patients are prescribed hyoscine to relieve bowel spasm in cases of ileus after exclusion of a mechanical obstruction. Hyoscine is also an anticholinergic medication, which can have a synergistic effect with orphenadrine causing more bowel inertia.¹⁵ Our patient was initially prescribed opiates for pain, which were stopped following presentation of obstructive symptoms. Neither the orthopaedic nor general surgery considered orphenadrine as culprit medication causing this patient's ileus. Speaking to our peers in our institute, no one considered stopping orphenadrine as a first line approach to manage this patient's symptoms. The half-life of orphenadrine is 14 hours may also explain the rapid resolution in symptoms for our patient after the cessation of this medication. The real learning point of this case report is considering medications such as orphenadrine as a cause to ileus.

Conclusion

Anticholinergic medications have a wide range of pharmacological mechanisms of action and can lead to bowel obstructive symptoms and signs. Correction of metabolic causes and exclusion of mechanical causes remain imperative. Surgeons need to be vigilant of the side effects of anticholinergic medications being prescribed for pain or neuropsychiatric disorders.

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Consent:

Informed consent was signed by the patient with regards to use of her case and CT images for the purpose of educational publication.

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