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Case Report
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Soft Tissue Abscesses Related to Repeated Intramuscular or Subcutaneous Cyclizine Injections

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Abstract

Cyclizine is an effective anti-emetic that has a variety of potential risks and side effects. These include reduced appetite, constipation, palpitations, postural hypotension and urinary retention, which are well recognized. There has been concern recently about regular intravenous use especially using central lines with extravasation and line erosion, probably due to the low pH of the preparation.

We present two patients with gastroparesis and persistent nausea unresponsive to oral anti-emetics treated with long term intramuscular or subcutaneous Cyclizine. This resulted in long-term skin and subcutaneous changes and the development of significant soft tissue abscess formation, each requiring extensive surgery for drainage.

Conclusion: Intramuscular or subcutaneous Cyclizine, in addition to other side effects and risks, may be associated with skin changes at the site of repeated injection and the development of abscesses. Regular intramuscular or subcutaneous Cyclizine should be avoided if possible.

Introduction

Cyclizine is a widely used histamine H1 receptor antagonist of the piperazine class which is characterized by a low incidence of drowsiness. It possesses anticholinergic and antiemetic properties [1]. Its proposed mechanism of action, as an anti-emetic, is by increasing lower esophageal sphincter tone and reducing the sensitivity of the labyrinthine apparatus. It may inhibit the part of the midbrain known collectively as the emetic centre.

Cyclizine has a variety of documented side effects, these include but are not limited to; reduced appetite, palpitations, postural hypotension, urinary retention and agitation *via* its anti-cholinergic properties. In addition, it has been recognized as a drug that can be abused; when taken orally or intravenously and causes a "high" and on occasions have a hallucinogenic effect.

Cyclizine has a low pH of approximately 3.3 to 3.7 when undiluted; this is thought to be contributory to its vascular irritating effects. Some guidelines have suggested that solutions with a pH<5 are unsuitable for peripheral administration due to the risk of vessel irritation; however, this has been debated [2].

The use of subcutaneous Cyclizine is widely recognized and studied within the palliative care setting. One retrospective study assessing the use of syringe drivers in palliative care denotes subcutaneous infusion of Cyclizine as high risk in relation to injection site reactions. This study proposes that infusions including Cyclizine are approximately five times more likely to cause injection site reactions, although the use of Cyclizine alone and/or the long term effects of such administration have not been greatly studied [3].

In patients with long term venous catheters there are increasing concerns over the effects of Cyclizine on the catheter with reports of increased line occlusion, fracture from unblocking and a signal of increased line infection rates. A recent BAPEN position statement advises, based on these risks, that other anti-emetics be used preferentially [4].

A search conducted of the yellow card drug analysis reports on the MHRA website revealed 29 reports of site reactions upon giving Cyclizine *via* the intramuscular or subcutaneous route. The reactions reported include but were not limited to skin necrosis, embolia cutis medicamentosa and chemical burns. From these reports 5 of are recorded as necrosis and 1 as ulcer, all of the 29 reports relating to skin reactions were single active constituent reports [5]. A literature review conducted

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using Medline, Embase and Pubmed demonstrated that the effects of long term subcutaneous Cyclizine injections have not been widely studied. However one other case report published in the American Journal of Dermatology makes reference to the potential risk of embolia cutis medicamentosa seen with a patient using subcutaneous Cyclizine, although no clear reference to Cyclizine is made when discussing the potential mechanism by which this reaction occurred [6]. The search terms used for the review included "Cyclizine", "subcutaneous", "intramuscular", "injection site reaction" and "abscess".

Case Presentation

We describe two patients who were taking regular intramuscular or subcutaneous Cyclizine for refractory, intractable nausea despite trials of oral medications. Both patients were advised against regular long-term use however they wished to continue initially due to the relief from this very troubling symptom. Both patients have given written permission for their details to be published.

First patient: EB is a 65 year old female who presented with nausea and vomiting leading to dehydration and admission to hospital. She had been fit and well following treatment for breast cancer until she had 4 episodes of pancreatitis. This left her with severe abdominal pain that only gained relief with opiate based painkillers. She was not diabetic. After thorough investigation a diagnosis of opiate induced pan-enteric gut dysmotility was made. Her gastroparesis persisted despite a gastric pacemaker. She maintained her nutritional state without the need for tube feeding or parenteral nutrition. Several anti-emetic regimes were trialed and the patient found symptomatic relief from intramuscular Cyclizine. She took this as required at least once a day if not more often.

After around 12 months the patient started to develop skin changes around the injection sites in her thighs, the skin being indurated and firm. The patient was advised to discontinue subcutaneous injections. An ultrasound scan of the areas suggested that fat necrosis secondary to the injections was the most likely diagnosis. Around 6 months later the patient developed a significant abscess of the right buttock that required drainage. An attempt was made to treat this conservatively. However she had ongoing discharge and abscess, the abscess culture grew *Klebsiella pneumoniae* and *Enterococcus faecalis*. She was referred to the plastic surgeons that performed a surgical excision and repair without grafting on this area, requiring an 8 day admission.

After this surgery she had a *Staphylococcus aureus* skin infection. Her right thigh wound then dehisced. Curettage and washout was attempted once but again she subsequently required excision of the abscess down to the muscle fascia and the histology showed "necrosis and inflammation and granulation tissue in keeping with an injection site". This resulted in a 6 day admission.

These abscesses were around the site of her intramuscular injections. The opinion of the operating surgeon, given the fat necrosis at the site, was that the cause of the abscesses was the Cyclizine. Through this period of time she was not immunosuppressed. The patient has subsequently been managed with oral anti-emetics and has not had any further problems with abscesses. The patient was around 75 kg in weight and so although this patient was prescribed intramuscular Cyclizine it is likely that much of the drug was delivered into the subcutaneous space.

Second patient: JR was at presentation a 68 year old female patient with Polyglucosan body myopathy causing Gastroparesis and small bowel dysmotility. Her past medical history was of osteoarthritis and hypertension. She had no obvious cause for immune-compromise or diabetes. Her malnutrition as a result of her gut dysmotility was initially managed *via* a surgically placed jejunostomy; however, she required progression to parenteral nutrition as she was unable to tolerate feeding *via* the jejunostomy. Nausea continued to be a prominent symptom despite adequate nutrition.

Oral anti-emetics had proven to provide very little benefit for treating her nausea. She had a trial of a variety of anti-emetics *via* subcutaneous infusion, with Cyclizine providing the best symptom relief. Over time the patient also developed skin changes with firm induration at the injection sites.

The patient subsequently developed an abscess on the left arm and the left lower quadrant of her abdomen. She was admitted for 8 days and treated with IV antibiotics (teicoplanin and clindamycin). These abscesses then required surgical drainage, culture from the abscesses was positive for *Staphylococcus aureus*. The patient has subsequently managed Octreotide as sub-cutaneous injections without problem.

Discussion

In addition to the known side-effects of Cyclizine these case reports demonstrate that long term Cyclizine use through the intramuscular or subcutaneous route can be associated with skin changes and then the risk of deep abscess formation requiring surgical drainage. The patients presented were not immunosuppressed and did not have diabetes. It is important to consider other potential factors such as poor injection technique although the patients in these cases had managed other subcutaneous drugs without issue.

The presumed mechanism of action is likely similar to the problems seen with intravenous use. Low pH causes skin necrosis and fibrosis and allows secondary infection. The pH of Cyclizine is 3.3 to 3.7 [1]. Intramuscular and subcutaneous preparations are typically not diluted to keep the volume to a minimum.

There are no current comments in the prescribing license for Cyclizine for its use subcutaneously. Anecdotal reports to the authors suggest that this complication of long-term subcutaneous Cyclizine injections may be relatively common although not reported in the medical or pharmacological literature.

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