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British Intestinal Failure Alliance (BIFA) Position Statement

The use of cyclizine in patients receiving parenteral support

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Summary

Cyclizine is a piperazine derivative that was discovered in 1947 while researching new antihistamine drugs (H1 blockers) and was first sold 1965. It is marketed for the treatment or prevention of nausea, vomiting, and labyrinthine disorders including vertigo and motion sickness. This includes nausea after a general anaesthetic and that caused by opioid use. In the United Kingdom the oral formulation is classified as a Pharmacy (P) medicine and can be sold from a registered pharmacy premises by or under the supervision of a pharmacist. The intravenous formulation is classified as a Prescription Only Medicine (POM). There is increasing recognition that the intravenous formulation of cyclizine may cause euphoria and dependence (addiction) and was reported in patients with cancer in 2008 (1). These side effects may not be reported by patients and be under recognised by healthcare professionals. It has many associated problems when used by patients receiving long-term parenteral support. This position paper

Actions/pharmacology (1)

Cyclizine has both antihistamine (H1) and anti-cholinergic (anti-muscarinic M1) effects. It is a class 1 drug in the biopharmaceutical classification (high permeability and solubility) with a peak plasma concentration of about 70 ng/ ml reached approximately 2 hours after oral ingestion, as measured in healthy adults. Its quoted elimination (biological) half-life is 20 hours when given orally (2) and 13 hours when given intravenously (3). Cyclizine is metabolised to its N-demethylated derivative, norcyclizine, which has little anti-histaminic (H1) activity compared to cyclizine. Its therapeutic mechanism of action may primarily be by blocking histamine (H1) and muscarinic cholinergic receptors in the vomiting centre (which includes the chemoreceptor trigger zone). It also has other actions as a central nervous system depressant and a local anaesthetic. Licensed formulations available in the United Kingdom include those that can be administered via the oral, intravenous, intramuscular, and subcutaneous routes all at a dose of up to 50 mg three times a day for patients over the age of 18 years (4).

Undesirable effects relevant to this document (see table 1) (3-4)

Side effects of cyclizine relate mainly to its anti-cholinergic effects and include reduced appetite, constipation, palpitations, postural hypotension, and urinary retention. These are particularly relevant as cyclizine is often prescribed to patients with gastrointestinal dysmotility who may have a poor nutritional state, constipation, postural orthostatic tachycardia syndrome (PoTS) and urinary problems. The prescribing of cyclizine in this patient group makes it very hard to distinguish between disease-related and drug related symptoms and signs. Extrapyramidal motor disturbances can occur with chronic use. Agitation is reported especially at high doses and especially in children and the elderly. Liver disease exacerbates its sedative effects as it is metabolised by the liver.

Intravenous cyclizine may precipitate at concentrations above 10 mg/mL or in the prolonged presence of sodium chloride 0.9%. It is extremely irritating due to its low pH (3.3-3.7) and can result in vein tracking, erythema, pain, rash, thrombophlebitis and blisters. Central and peripheral vein damage may lead to a loss of venous access. Concerns have been raised by some home parenteral support (HPS) and intestinal failure (IF) centres that the regular use of cyclizine via a central venous catheter (CVC) can increase the risk of occlusion and traumatic fracture secondary to patients attempting to unblock the CVC. Patients receiving intravenous cyclizine may have more episodes of catheter-related blood stream infections (CRBSIs). Clinical staff should check for drug interactions, cautions and contraindications that may affect the patient by using the British National Formulary (BNF).

Cyclizine abuse

There have been reports of abuse of cyclizine, either taken orally or intravenously, for its euphoric ("high") or hallucinatory effects (1,6-10). As with most anticholinergic medication, death has been reported in overdose (11). The concomitant misuse of cyclizine with large amounts of alcohol is particularly dangerous, since the anti-emetic effect of cyclizine may increase the toxicity of alcohol. Some people using methadone recreationally combine it with cyclizine to enhance the psychoactive effect. The anti-cholinergic effects may induce hallucinations. Addictive behaviour, drug-seeking behaviour and dependence have been documented in some patients needing parenteral support (mainly those with dysmotility) (9).

Table 1

Potential problems of intravenous cyclizine when used by patients receiving long-term parenteral support (PS)

- Dependence.
- Impaired judgement that may affect the safe completion of the aseptic procedures required for setting up and taking down PN.
- Damage to central and peripheral veins.
- Damage to central venous access devices.
- Increased episodes of catheter-related blood stream infections.

Note: Oral preparations of cyclizine may not be absorbed in patients with intestinal failure. However, oral cyclizine is a BCS class 1 drug with a Tmax of less than 2hrs. Thus, there is a good probability that after being taken orally enough is absorbed to elicit a pharmaceutical response even in those with a short bowel.

Alternatives to cyclizine

Although ondansetron or granisetron are more expensive, they may be preferable agents to prescribe as they are equally or more efficacious than cyclizine (12-14). However, constipation is a common adverse effect of all formulations of both ondansetron and granisetron and this should be taken into consideration. In one study of post-operative nausea, cyclizine was less effective than ondansetron or metoclopramide (15). Licensed formulations available in the United Kingdom for ondansetron include those that can be administered via the oral, intravenous, intramuscular, and rectal routes and via the oral, intravenous and transdermal route for granisetron. Please check local formularies to see which formulations are available. Both oral ondansetron and granisetron are BCS class 1 drugs that have a Tmax of less than 2hrs. This means that there is a good probability that sufficient amounts will be absorbed after an oral dose to elicit a pharmaceutical response (16-17).

Recommendations for Healthcare Professionals

1. Cyclizine should be regarded as a medication that may cause dependence (like opiates).
2. Counsel all patients on the undesirable side effects profile of cyclizine especially the euphoric/addictive effects before prescribing. Healthcare professionals should ask patients if they areexperiencing these symptoms after prescribing has commenced.
3. Intravenous cyclizine may be used acutely but should not be used in the long-term.
4. Cyclizine should be used with extreme caution in patients with nausea/vomiting secondary to GIdysmotility.
5. Patients already receiving intravenous cyclizine should be weaned off and other anti-emeticmedicines should be considered.
6. Cyclizine impairs judgement so should be used with extreme caution if ever prescribed to patientsreceiving long-term parenteral support.
7. In patients with recurrent catheter occlusion and or traumatic catheter fracture cyclizine useshould be considered as a potential cause.
8. The central catheter must be flushed before and after cyclizine and care should also be taken if it isgiven after any other drug as precipitation may occur (especially if they have a high pH).
9. Any case of dependence should be reported via the MHRA yellow card scheme either using the paperforms found in the back of the British National Formulary or electronically via yellowcard.mhra.gov.uk.
10. Ensure there is only one named prescriber for cyclizine per patient (or per department). The prescriber should be informed at the start of an in-patient episode and any prescriptions should be placed on hold until discharge. On discharge only the smallest amount needed should be supplied until the named prescriber can continue the prescription. Patients should be told that they will notbe supplied with additional stock if ampoules are damaged, stolen or lost.

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