REVIEW ARTICLE

Dicyclomine and Mefenamic Acid Dependence: A Case Report and Review of Literature

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Abstract

Anticholinergic medicines, such as dicyclomine, are frequently prescribed as antispasmodics. In addition to its effects on the peripheral nervous system, dicyclomine also induces central anticholinergic effects due to its high penetration into the central nervous system. There have been reports of abuse or misuse of anticholinergic medicines, such as procyclidine, biperiden, benztropine, and trihexyphenidyl (Benzhexol). In this case report and review, we describe a case of an adolescent female who came to us with complaints of right lower quadrant abdominal pain, with imaging and other tests ruling out any structural cause for the last 7 years. She even underwent appendectomy 12–16 months before presenting to the hospital with complaints of pain which shifted to the left lower quadrant post appendicectomy. At the time of presentation, she was taking 200 mg of Tramadol and 3–4 tablets of fixed dose combination (FDC) of 250 mg mefenamic acid and 10 mg dicyclomine by a local chemist without any prescription. According to ICD-10, patient met criteria for abuse of non-psychoactive substances with co-morbid mental and behavioral disorders due to the use of opioids-dependence and moderate depression without somatic syndrome. This case illustrates the need to give attention toward the addiction potential of anticholinergics and the need to formulate a treatment plan for effective outcome.

Keywords: Anticholinergics, Dependence, Dicyclomine.

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Introduction

Dicyclomine, an anticholinergic drug that can cross the blood–brain barrier due to its tertiary amine structure has been indicated for irritable bowel syndrome and dysmenorrhea, but poses a risk of abuse at higher doses due to its delirious effects.[1–4] Mefenamic acid belongs to non-steroidal anti-inflammatory drugs (NSAIDs), a class of drugs commonly used as an analgesic for dysmenorrhea.[4] There exist several formulations on the market that combine mefenamic acid and dicyclomine and are available as fixed dose combination (FDC).[4] The present report highlights the need for addressing anticholinergic dependence and to explore effective treatment options.

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Case Description

The current case is of an adolescent female, who finished her schooling 2 years ago and now pursuing her bachelors from Open University, is currently living in a joint family of lower-middle socioeconomic status. She is from an urban city in Northern India and came to the tertiary care hospital's outpatient department with a 7-year history of sharp pain and cramps in her lower right abdomen. On exploring the history, it was revealed that the total duration of pain was since the last 7 years. The pain would begin abruptly and would reach its peak intensity within 5–10 minutes of onset, the pain would be non-radiating and would be localized to the above-mentioned region. The pain was associated with cramps and it was associated with severe discomfort and would be persisting until the patient takes medication for it. The pain would be occurring two to three times in a week. Initially, when the patient started it would get resolved with intramuscular injection of 50 mg diclofenac. The patient would feel relaxed and would be able to resume her daily routine activity without any difficulty.

However, after 2–3 months, these injections were not sufficient in resolving the pain and she was at one instance given a FDC of 250 mg mefenamic acid and 10 mg dicyclomine by a local chemist without any prescription. The patient initially took 1–2 tablets of FDC, which increased to 3–4 tablets over the next 2 years as the pain did not subside with the previous dose of medication. Patient during this period consulted several gastroenterologists and multiple imaging studies were done. However, no organic cause or lesion was found and imaging studies were also completely normal. The patient continued to take the tablets due to the persistent pain in the abdomen. The frequency of the pain remained the same. She would constantly carry one or two strips of these pills in her luggage, and in situations when they were unavailable, she had even turned to thievery to get them. She would regularly have an intense desire to consume these tablets even when there would be no pain. She would be, however, able to control her urge to consume it for a maximum of 48 hours. After abstaining from these tablets for 24–48 hours, the patient complained of headache, stomach discomfort, anxiety, and intense irritability, all of which subsided after taking the pills. This pattern of FDC tablet consumption continued for the next 4 years.

After taking the tablets for 4 years, the patient's pain persisted and the patient started taking tablet tramadol 50 mg 1–2 tablets together with FDC tablets of 250 mg mefenamic acid and 10 mg

dicyclomine. She was introduced to tramadol by one of the chemists and she would be getting it without any prescription. The number of these FDC tablets further increased to 3–4 tablets daily. On a daily basis, the intake of tablets being 1–2 tablets of tramadol and 3–4 FDC tablets of mefenamic acid and dicyclomine. This pattern of drug use continued for the next 2–3 years. On stopping tablet tramadol due to some unavoidable reason, she would have complaints of pain in her joints, stuffy nose and lacrimation. All of these symptoms would resolve on taking tramadol.

Before presenting to the clinic, i.e., 12–14 months ago, she underwent appendectomy and there was mild reduction in pain at the right lower quadrant. She continued taking medication as usual. Post appendectomy she was diagnosed to have an episode of moderate depressive episode. There was a decline in her academic performance, weight loss, and deterioration in interpersonal relationships. Her mood would remain low and she would remain irritable throughout the day. There was a reduction in her appetite and also anhedonia which was corroborated by the family members. These symptoms were not present 12 months ago. She was prescribed capsule fluoxetine 20 mg but she was non-compliant. During this period, her daily consumption of tablets increased to 8–10 FDC tablets of mefenamic acid and dicyclomine and 2–4 tablets of tramadol 50 mg. During this, she was unable to control herself from taking the medication. Every attempt to stop the medication leads to withdrawal symptoms as mentioned above. She was initially treated as an outpatient for opioid dependence, but since no improvement was observed, she was admitted and managed as inpatient. Detail work up was done and she was diagnosed as per ICD-10 as a case of F11.22 mental and behavioral disorder due to use of opioid dependence syndrome, currently on clinically monitored maintenance therapy; F32.10 Moderate depressive episode without somatic syndrome; F55.2 abuse of non-dependence producing substance. She was started on tablet tramadol 200 mg and was gradually tapered off in the next 14 days along with capsule fluoxetine 20 mg for her depressive symptoms which was further increased to 60 mg. She would report of severe abdominal pain which would be similar in intensity and nature as described earlier and would be associated with anxiety which would resolve its own. The frequency of these episodes decreased during the course of hospital stay. Upon resolution of her depressive symptoms and reduction in her pain, she was discharged on capsule fluoxetine 60 mg and tablet naltrexone 50 mg.

She was on regular follow-up and personality assessment was done on OPD basis when her depressive symptoms subsided and the assessment revealed cluster B traits but a diagnosis of personality disorder was ruled out. She remained compliant to medication and there was improvement in her depressive symptoms and was also reported of minimal pain which if present subsided on its own. After 6 months she lost to follow-up.

Review of Literature

An electronic search was performed on PubMed, Scopus, and Web of Science (WoS) databases. The following search strategies have been used, respectively ("anticholinergic" OR "antimuscarinic" OR "scopolamine" OR "benztropine" OR "biperiden" OR "orphenadrine" OR "benzhexol" OR "trihexyphenidyl" OR "mefenamic acid" OR "dicyclomine") AND ("abuse" OR "misuse" OR "diversion"). Independent online search was also done for case reports. Literature review revealed that there are limited case reports for dicyclomine and/or mefenamic acid dependence. A total of three studies were found and all were reported from India.[5–7] The current case is the fourth reported case (Table 1).

Table 1: Case reports of dicyclomine with or without mefenamic acid dependence

No.	*Author*	*Age/Sex*	*Occupation*	*Dose, route*	*Indication for initiation*	*Time to dependence*	*Psychiatric co-morbidities*	*Comorbid substance use disorder*	*Treatment*
1	Das et al., 2013[5]	18 years/F	College student	20–120 mg IM	Acute infective enterocolitis	1–1½ years	None	NR	Physostigmine IV 2 mg, drug rehabilitation services
2	Sinha et al., 2020[6]	30 years/F	NR	Oral 20–200 mg (Mefenamic acid 250 mg + Dicyclomine 10 mg combination tablets)	Dysmenorrhea	10 years			Fluoxetine 20 mg PO Clonazepam 0.5 mg PO
3	Singh et al., 2020[7]	34 years/M	Skilled worker	Oral 20–200 mg (Mefenamic acid 250 mg + Dicyclomine 10 mg combination tablets)	Non-specific abdominal pain	8 months	None	Alcohol Benzodiazepine	Diazepam 7.5 mg PO Propranolol 40 mg PO Trazodone 50 mg PO Craving management and relapse prevention therapy

F, female; IV, intravenous; M, male; NR, not reported; PO, per oral

Discussion

Patients included in the review were two were females and one male with age ranging from 18 to 34 years. The conditions for which dicyclomine was started included dysmenorrhea, abdominal pain and one case for acute infective enterocolitis. The treatment ranged from benzodiazepine (diazepam, clonazepam), selective serotonin receptor inhibitors (SSRI) (fluoxetine), beta blockers (propranolol), trazodone and psychosocial interventions including relapse prevention therapy. There was no consensus or similarity in the treatment among the three patients reported.

Our patient met the criteria for dependence on substances not known to have psychoactive properties classically causing dependence. The fixed-dose combination tablet described in the case contained dicyclomine, which has been reported to have psychoactive properties due to which addiction develops and has been reported in various case reports.[5–7] Dicyclomine being selective M1 muscarinic receptor antagonist (similar to that of trihexyphenidyl) and by acting on the limbic system exerts reward and mood elevation.[8] Mefenamic acid does not appear to have any psychedelic properties, yet it has been observed that combining it with dicyclomine can lead to dependency. It is unknown, nevertheless, if using the combination increases the chance of developing dependence. Despite the propensity to lower the rate of excretion of dicyclomine, which may result in elevated serum levels.[1] It may also be assumed, based on neurobiological principles, that the alleviation of pain may serve as a positive reward, and that the subsequent reduction of withdrawal symptoms may serve as a negative reinforcement when using opioids.[8]

Cautious use of dicyclomine also becomes important in light of the fact that it is neither listed in the World Health Organization (WHO) list of psychotropic drugs in the Scheduled Drug category nor is it covered by the NDPS Act, 1985 and its subsequent amendments.[9] Therefore, it is not subject to regulation and is, therefore, difficult to control. However, it is a category H drug under the Drug and Cosmetics Act Amendment, 2006, which means it is easily available on prescription.[10] Our report highlights that healthcare professionals should be mindful of the risk of abuse of anticholinergics, a drug commonly prescribed in psychiatric hospitals and addiction clinics, particularly among those who use it continuously beyond the prescribed period or in over-therapeutic doses.[11]

Future Directions

This report highlights a case of problematic use of dicyclomine mefenamic acid for its euphorigenic effect. Our report adds to the available literature on anticholinergic abuse and especially to limited literature on dicyclomine abuse. Dicyclomine may cause dependence syndrome thus further systematic studies of anticholinergics dependence are needed to establish it as a valid diagnostic entity. In developing countries including India, unqualified medical practitioners wrongly prescribe dicyclomine to treat spasmodic pain symptoms, which may lead to dependence for dicyclomine and its harmful consequences. Appropriate legal measures to check dicyclomine misuse/abuse, more research and publications on harmful consequences of dicyclomine are needed to prevent such harmful practices in developing countries.

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