CASE REPORT

High dose of prokinetics for refractory hiccups after chemotherapy or the return to a simple drug

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SUMMARY

Hiccups in patients with cancer might be difficult to treat, impacting negatively on the quality of life. Many therapies are available, but they are usually started empirically, and often they are unsuccessful. We report a case of a man with metastatic colon cancer who after the first cycle of chemotherapy developed persistent hiccups refractory to neuroleptics and low dose of metoclopramide. After searching for the potential cause, a high dose of prokinetics was initiated in the hospital and his symptoms disappeared. This case shows how searching for potential causes helps start the right treatment immediately, and therefore it is relevant for the prompt relief from this bothersome symptom. So far, no cases reporting high doses of prokinetics to treat persistent hiccups after chemotherapy have been published. This option should be taken into account when developing hiccups and gastro-oesophageal reflux after chemotherapy, especially if low doses of prokinetics have already been tried.

BACKGROUND

Hiccups are sudden involuntary and spasmodic diaphragmatic and intercostal muscle contractions with early glottis closure at the end of the inspiration.^{1 2} The name comes from the 'hic' sound emitted by the air rushing into the lungs. The prevalence of hiccups in cancer is unknown as most research reports on cancer chemotherapy have shown no data on the occurrence of hiccups as an adverse reaction. However, several reports^{3–5} have disclosed a high incidence of more than 30% of treated patients during chemotherapy. The problem is that most cancer chemotherapy regimens consist of multiple drugs including steroids, antisickness, etc; therefore, identifying the causative drug is very difficult⁶ and the best treatment could be considered still a challenge.

Though often a self-limited disorder, sometimes hiccups last for more than 48 h, becoming persistent and bothersome.⁷ In these cases, the symptom might be extremely uncomfortable and impact negatively on the patient's quality of life by interfering with a normal conversation or oral intake; eventually, they can lead to frustration, insomnia and fatigue.^{7 8} It is in such cases that the prompt and right management of the symptoms would be crucial to rapidly return to a good quality of life.

CASE PRESENTATION

A 54-year-old man without any known comorbidities was diagnosed with colon cancer stage IV with multiple, small, non-resectable liver metastases

affecting both the lobes. He was started on palliative chemotherapy with a combination of intravenous FOLFOX-6 (oxaliplatin, leucovorin 400 mg/m², 5-fluorouracil 2400 mg/m² continuous infusion over 46 h) and bevacizumab 5 mg/kg. He also received the standard antiemetics with dexamethasone (4 mg daily for 2 days) and low doses of metoclopramide (10–30 mg/daily) only if required (the patient did not take it).

One day after the 5-fluorouracil pump was removed, the patient developed various spells (>10) of hiccups, gradually increasing in number and intensity and becoming exhausting with a rate of 35–45 hiccups/min. He called the open access phone for emergencies and was recommended to take metoclopramide 10 mg/8 h and haloperidol 2.5 mg three times a day. The symptoms improved slightly several hours after taking the first dose of metoclopramide and haloperidol but finally got gradually worse, becoming more persistent. They were exacerbated after drinking or eating small amounts of food. The patient phoned again, and this time the recommendation was to stop all current medications and to switch to a subcutaneous infusion of levomepromazine 6.25 mg daily as monotherapy. At the same time, he decided to reduce his oral intake aiming at stopping the hiccups.

After 24 h, his clinical condition deteriorated even more with uncontrollable hiccups, and he decided to go to the hospital. At admission, the hiccups were continuous and the patient seemed to be mildly dehydrated and extremely worried and depressed. Unable to sleep properly for the past 36 h, he was exhausted and frustrated.

He also reported having gastro-oesophageal reflux after chemotherapy, which was causing much discomfort and upper odynophagia, although his mouth and throat were fine on examination.

INVESTIGATIONS

Blood tests including haematological and biochemistry tests (liver and renal function, calcium, magnesium, sodium and potassium).

DIFFERENTIAL DIAGNOSIS

Potential causes were taken into account: pharmacological origin (chemotherapy, steroids, etc), phrenic irritation by liver metastases, gastroparesis after chemotherapy or gastro-oesophageal reflux.

TREATMENT

The treatment then focused on the reflux as the most likely cause, and was managed with a high

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dose of prokinetics from the beginning. The first step consisted of intravenous metoclopramide 20 mg to be able to start an oral therapy to discharge him from hospital. As soon as the intensity of the hiccups reduced (approximately 40 min later), 70 mg of domperidone per mouth was given.

After an initial improvement lasting for 1 h approximately in which the hiccups disappeared completely, the symptoms reappeared again though not as intense as previously with a rate of 10–15/min in several spells (2–4/h) but not continuously. Finally, we decided to admit him as an inpatient and started a subcutaneous infusion with high doses of metoclopramide (90 mg in 24 h, 1.5 mg/kg; 62 kg). Approximately 2.5 h after starting the infusion, the hiccups reduced dramatically and he had a good sleep.

OUTCOME AND FOLLOW-UP

The next day, he had a completely normal breakfast with high amount of liquids without any trouble with the hiccups.

In addition, the patient had not passed urine for the previous 28 h, but after a normal intake and some intravenous fluids, the problem was solved and his renal function which showed dehydration at admission was resolved.

After observation for another 12 h, the patient was discharged with 60 mg/daily of oral domperidone. He was also recommended to double the dose for 3 days before his next chemotherapy and continue it for a further 3 days. He received his second cycle of chemotherapy without any trouble except for less than three episodes of mild, brief, self-limited spells which did not affect his life at all.

DISCUSSION

Hiccups might be extremely uncomfortable and impact negatively on the patient's quality of life, and thus an expedient treatment is advisable.^{1 2 7 8} There are no large randomised controlled trials addressing this symptom, and therefore no consensus on how to treat them has been reached.^{9 10}

Moreover, the pathophysiology of hiccups is still being elucidated, though it seems to involve a complex reflex arc among the peripheral phrenic, vagal and sympathetic pathways and central midbrain.⁷ Therefore, any irritant affecting this arc can cause the symptom (ie, invasive neoplasia), and thus there are many potential aetiologies. Some authors have reported a gastro-oesophageal reflux disease as a potential cause, though various drugs have also been blamed, such as antiparkinsonism agents, steroids and cytotoxic drugs.³

An effective treatment of persistent hiccups may be established on the correct diagnosis of the lesion responsible for this serious event,⁷ though sometimes it is really difficult to determine and the pharmacotherapy of hiccups includes a broad spectrum of drugs such as chlorpromazine, gabapentin, baclofen, serotonergic agonists, prokinetics, dexamethasone and lidocaine.^{7 10}

Thus, this picture opens the window to a wide selection of pharmacological options, some of them completely empirical and useless for some patients. This reinforces the need for us to seek potential causes every time we treat these symptoms, instead of prescribing mechanically.

Whenever the cause is suspected, it should be treated specifically^{9 10} and strongly from the beginning to increase the chances of success and to speed up the process of controlling this uncomfortable symptom.

This short case pretends to be a call to attention to all the professionals dealing with this bothersome symptom, which

could be troublesome for many patients. It also pretends to be a reminder about the necessity for decisive treatment without hesitation from the beginning to avoid nutritional and physical complications and to improve the patients' quality of life as soon as possible.

There are several protocols dealing with hiccups, and metoclopramide has been observed for so long to induce dramatic relief to intractable hiccups when given orally or parenterally to patients with different illnesses. The effect was observed within 30 min and the relief lasted up to 8 h, indicating a direct relation to the duration of action of the drug.¹¹ This drug has in fact been recommended for symptomatic relief of hiccups associated with serious organic illnesses or anaesthetic-induced hiccups,¹² without any fear of undesirable effects, but no one to our knowledge has reported so far a case with a high dose of prokinetics in a patient with hiccups after chemotherapy.

In our case, improvement was experienced after intravenous metoclopramide but not maintained through oral domperidone at the beginning, which makes us think about the potential benefit of using these drugs parenterally to achieve a quick and positive result and leaving oral therapy as maintenance. However, to confirm this point, other serious studies should be carried out.

Learning points

- ▶ Though the prevalence of hiccups in cancer is unknown, several reports have disclosed a high incidence of more than 30% of treated patients during chemotherapy.
- ▶ Hiccups are usually easy to treat but could become extremely uncomfortable, persistent and impact negatively on the patient's quality of life, leading to frustration and depression.
- ▶ Searching for the potential cause and treating it accordingly and strongly is the best way to proceed to restore the patient's quality of life as soon as possible.
- ▶ Gastro-oesophageal reflux could be the cause for early hiccups after chemotherapy, and a high dose of prokinetics could be the best way to treat this symptom.

Contributors Both authors made substantial contributions to the conception and preparation of this manuscript, as well as a careful revision of the literature. EU wrote the introduction, discussion and conclusion. PA wrote the first draft of the case report and EU revised it critically and gave approval for the final version.

Competing interests None.

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