Clostridium difficile infection associated with bismuth-based quadruple therapy (Pylera®) for *Helicobacter pylori* eradication☆

Infección por *Clostridium difficile* tras tratamiento erradicador de *Helicobacter pylori* con cuádruple terapia con bismuto (Pylera®)

Dear Editor,

The main and best-known risk factor for *Clostridium difficile* infection (CDI) is antibiotic use. Other factors are the use of proton-pump inhibitors, older age and prolonged hospitalisation. Any antibiotic, even those effective in the treatment of CDI, such as metronidazole and vancomycin, can trigger this disease. We report a case of CDI after *Helicobacter pylori* eradication treatment with a ten-day course of quadruple therapy consisting of omeprazole, bismuth, tetracycline and metronidazole.

The patient was a 56-year-old woman, who smoked, had high blood pressure, undisclosed dyspepsia and *H. pylori* infection detected by positive antigen in faeces. A ten-day course of quadruple therapy eradication treatment was prescribed: omeprazole 40 mg before breakfast and evening meal, and three capsules of Pylera® (Forest Laboratories Ireland Ltd.) at breakfast, lunch, afternoon snack and evening meal. The Pylera® capsule contains: 140 mg bismuth subcitrate, 125 mg metronidazole and 125 mg tetracycline. The patient suitably completed this treatment, with no immediate adverse effects. She was admitted to hospital with a three-week history of liquid diarrhoea, up to ten bowel movements a day, with no particular predominant timing, containing mucus but no blood, preceded by abdominal pain. She reported no pyrexia or other relevant symptoms. The diarrhoea began seven days after finishing the eradication treatment. Physical examination showed no data of interest. Blood tests: no anaemia. Leukocytes 14,960/mm^3. c-reactive protein 123.9 mg/l. On day three after hospital admission, colonoscopy, advanced as far as the caecum, revealed areas of erythema throughout the colon. Biopsies: colon mucosa with normal architecture and acute cryptitis. Stool culture: no pathogenic germs detected. Faecal parasite examination was negative. CDI was detected after determination of the glutamate dehydrogenase antigen by immunochromatography (CerTest Biotec) and confirmed by polymerase chain reaction (Becton Dickinson). Treatment was started with oral metronidazole 500 mg/8 h, with no improvement, and so was stopped after six days of treatment. Oral vancomycin was then prescribed at 250 mg/6 h, with a good response; after four days of treatment both the diarrhoea and the abdominal pain had subsided. A total of 14 days of treatment was recommended.

The patient remained asymptomatic and repeat tests for CDI and *H. pylori* antigen in faeces four weeks after the end of the vancomycin treatment were negative.

The recommended eradication treatments for *H. pylori* infection have undergone changes in recent years in an attempt to achieve greater efficacy, which is currently over 90%. In the latest consensus documents, the recommendations are for quadruple therapy for 10–14 days, without bismuth (proton pump inhibitors, clarithromycin, amoxicillin and metronidazole) or with bismuth (proton pump inhibitors, bismuth, metronidazole and tetracycline), currently available with a new pharmaceutical formulation which includes these last three drugs in a capsule (Pylera®).[1] As eradication treatments include gastric antisecretory drugs and two or three antibiotics, and tend to involve a long course of treatment, they are theoretically a risk factor for CDI.[2] The virtual lack of references to CDI as a complication of eradication treatment is surprising.[2–5] Although usually well tolerated and self-limiting, diarrhoea is a known adverse effect of these treatments and there may be undiagnosed cases of mild CDI. There has been speculation about the metronidazole included in different eradication treatment guidelines having a possible protective role.[2] CDI has been reported after treatment with pantoprazole, clarithromycin and amoxicillin, but also, as in our case, with treatments that included metronidazole.[4,5] This does not necessarily stop metronidazole from being effective in curing the CDI, although it did not work in our case. The infection resolved after treatment with vancomycin which, according to the current consensus, should have been the first-choice treatment.

Our case illustrates a potential complication of *H. pylori* eradication treatment barely referred to in the literature and should be taken into account at least in patients who develop significant or prolonged diarrhoea during or after such treatment. It is interesting that the infection was triggered after treatment with antibiotics, metronidazole and tetracyclines, not usually associated with CDI.

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