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Original article

Polysorbate 80 add-on therapy in the treatment of *Helicobacter pylori* infection
Polysorbate 80 and HP antibiotic resistance

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SUMMARY

Polysorbate 80, a sorbitan derivate, is a surfactant used as an emulsifier in some foods in concentrations of up to 0.5%. It was recently shown *in vitro* that polysorbate 80 decreases the minimum bactericidal concentrations of clarithromycin and metronidazole and may also revert antibiotic resistance. We report the case of an adult man, suffering from symptomatic *Helicobacter pylori* (HP) infection resistant to two courses of treatment with PPI plus amoxicillin and clarithromycin, and PPI plus clarithromycin and metronidazole. He was treated with a further antibiotic approach consisting of two-week administration of clarithromycin, metronidazole, PPI and polysorbate 80 as an add on therapy. Eradication of infection was confirmed by ^{13}C-urea breath test two and five months after completion of the treatment course. Complete regression of symptoms was also achieved. To our knowledge, this is the first case of HP infection eradicated with a combination therapy based on polysorbate 80 added to antibiotics.

1. Core tip

The worldwide increase of antibiotic resistance reduces the efficacy of *Helicobacter pylori* eradication therapies. Consequently non antibiotic molecules may represent a very useful approach to bacterial infections. This is the first case of an HP infection successfully treated with a combination of antibiotics and polysorbate 80.

2. Introduction

The treatment of *Helicobacter pylori* (HP) infection is mainly based on the combination of antibiotics and proton pump inhibitors (PPI). However, although the standard triple therapy was characterized by an eradication rate >90% until 1998 [1], it subsequently dropped significantly to below 80% due to the increasing resistance to antibiotics. In Europe, the resistance to clarithromycin is estimated to reach 15% and resistance to metronidazole to range from 10% to 50% of strains [2,3]. These figures do not differ from those reported in the USA where, respectively, metronidazole resistance ranges from 20% to 40% and clarithromycin from 6% to 12% of isolates [4–6]. In Italy, the prevalence figure of primary metronidazole and clarithromycin resistance is variable among the different geographic areas, as it is lower in the North (14.9% and 1.8%, respectively) than in Central and Southern areas (35% and 24.1%, respectively) [7–9]. In Italian areas with high antibiotic resistance, eradication rate by using standard guidelines and a PPI-claritromycin-metronydazole protocol may be lower than 70% [10]. To solve this important clinical problem, different antibiotic schedules were tested and various associations of amoxicillin, clarithromycin and metronidazole, known as sequential, concomitant and hybrid therapy, were suggested [11]. Here, we described the first case of an HP infection, resistant to two courses of therapy, successfully treated with the same antibiotics used earlier plus polysorbate 80.

Polysorbate 80 is a sorbitan derivate with a surfactant activity, used as an emulsifier in some foods, such as ice creams, in concentrations of up to 0.5%. It was recently shown *in vitro* that polysorbate 80 exerts a bactericidal activity against HP and that may improve the minimum bactericidal concentrations of

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clarithromycin and metronidazole, reverting in some cases the resistance of HP strains to these antibiotics [12]. Should this effect be observed also *in vivo*, the association of polysorbate 80 with antibiotics could increase the efficacy of antibiotics, even in patients with HP infection repeatedly resistant to treatment.

3. Case report

A 48-year old man complained of epigastric pain, burning and nausea. Symptom onset was dated at September 2013 and discontinuous proton pump inhibitor (PPI) treatment was followed for the next two years to control the symptoms. In October 2013, the histological examination of gastric biopsies obtained by endoscopy showed a mild superficial gastritis and the presence of HP organisms. The patient underwent the first one-week oral course of antibiotics to eradicate HP infection with amoxicillin 1 g bid, clarithromycin 500 bid and omeprazole 20 mg bid. Two months after the discontinuation of this treatment he underwent a breath test with ^{13}C-labelled urea, which proved to be still positive. During this two-month period the patient reported symptom recurrence, in particular epigastric pain and burning, which were treated with antacids and magaldrate. In January 2014, he underwent a second one-week oral course of antibiotic treatment with clarithromycin 500 bid, metronidazole 500 bid, and omeprazole 20 bid. Two months after the discontinuation of the treatment, the urea breath test still confirmed the persistence of infection.

In agreement with the patient, who gave his informed consensus, a further course of antibiotic treatment was therefore prescribed: a two-week oral course of clarithromycin 500 bid, metronidazole 500 bid, and omeprazole 20 bid, associated with polysorbate 80, contained in a capsule at the dosage of 350 mg bid. The No Adverse Effect Level for polysorbates is 1000 mg/kg/die, accordingly, by introducing a safety factor of 100, ADI for man was fixed at 10 mg/kg/day, endorsed by the Food Safety Commission of European Community [13]. At the end of the treatment, the patient was re-evaluated for the occurrence of side effects. Mild nausea with a metallic taste in the mouth was present (i.e., common side effects of metronidazole). Two months after the discontinuation of the treatment, the patient underwent a breath test and this time the result was negative. Moreover, the patient did not report symptom recurrence on discontinuation of the antibiotic treatment. Urea breath test (Infrared Spectrometer IR200, Richen Force, Beijing) carried out after two and five months proved to be negative for HP infection and also dyspeptic symptoms were still absent. Routine blood tests were normal both before and after the treatment.

4. Discussion

To the best of our knowledge, this is the first case of an HP infection successfully treated with a combination of antibiotics and polysorbate 80. Polysorbates are sorbitan-derivate molecules known as Tween. Polysorbate 80 is a safe and well tolerated substance and it is used as an emulsifier in certain foods in concentrations up to 0.5%.

Some of our group recently found that polysorbate 80 exerts an antimicrobial activity against HP strains [12]. An ultrastructural study showed that polysorbate 80, at concentration corresponding to its minimum bactericidal concentration, causes derangements of the outer membrane of bacteria [12]. The effects on bacteria were more evident in organisms treated with antibiotics in association with polysorbate 80, but at concentrations reduced by approximately four-times respect to when polysorbate 80 and antibiotics were used alone. Macro molecules such as clarithromycin, which hardly penetrate into bacteria using the lipid layer, might exploit the alterations of the bacterial outer membranes to diffuse into microorganisms and reach high concentrations. As far as strains resistant to metronidazole are concerned, some researchers assert that the first stage leading to the development of metronidazole resistance consists in the overexpression of *hefA* gene, which encodes an efflux pump [14]. Efflux pumps are common amongst strains of *H. pylori*, and protect organisms from the possible lethal effects of antibiotic and metabolite accumulation [14]. One component of a family of multidrug efflux transporters is localised in the outer membranes [15]. It was recently demonstrated that the inactivation of any efflux mechanism constituent can abrogate the function of the entire group of efflux systems [14]. Thus, we have speculated that the destruction or the detachment of the HP outer membrane, caused by polysorbate 80, could have determined the loss of efflux transporter, impairing the mechanism of metronidazole resistance of our strains.

It is very difficult to suggest a recommendation on the basis of a case report. However, if the effect of polysorbate will be confirmed in future studies, in particular the reversal of the resistance to metronidazole and clarithromycin, the administration of polysorbate could be reasonable in patients undergoing a failure of the eradication with first-line therapy: in these growing subgroup of patients a re-treatment with the same antibiotic association (amoxicillin plus metronidazole or amoxicillin plus clarithromycin) and an add-on polysorbate might prevent the adoption of second-line treatment.

In conclusion, the use of non-antibiotic compounds that can facilitate antibiotic penetration into bacteria seems a rational approach toward improvement of the HP infection eradication rate. Polysorbate 80 is an optimally tolerated compound which proved to be effective in the treatment of an HP infection repeatedly resistant to two courses of treatment. Further studies, in which a more numerous group of patients are treated with this protocol, are needed to confirm this promising result.

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Author's contribution

Michele Di Stefano designed the protocol, performed data analysis and prepared the manuscript; Natale Figura designed the protocol and prepared the manuscript; Manuela Bergonzi, Elisabetta Pagani, Eugenia Vittoria Pesatori, collected patient's data and prepared the manuscript; Gino Roberto Corazza and Antonio Di Sabatino critically revised the manuscript.

Conflict of interest

The authors have no conflict of interests to declare.

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