Short-term side effects during *H. pylori* eradication therapy

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Introduction

Knowledge of side effects related to drugs administered for the eradication of *H. pylori* will allow (i) to increase the adherence of patients to prescribed regimens by informing them about common side effects, and (ii) to avoid the prescription of drugs contraindicated in specific cases. This review will detail side effects of different drugs administered for *H. pylori* eradication, and compare the incidence of side effects associated with various drug regimens used in this indication.

Side effects of different drugs included in current regimens

Proton-pump inhibitors (PPI)

Side effects related to the intake of PPI are very rare. Those related to omeprazole are better known than those related to more recent PPI. They include diarrhoea (which accounts for half cases of all side effects reported with omeprazole), headache, fatigue, dizziness, gynecomastia (most often observed during prolonged treatments with high doses for Zollinger Ellisson's syndrome), thrombocytopenia and skin rash (1).

Metabolic interactions of omeprazole and lansoprazole (but not pantoprazole) with other drugs have been reported both *in vitro* and in volunteer studies. Interactions which may be of clinical relevance include a decreased clearance of phenytoin, of carbamazepin, and of warfarin during omeprazole therapy (2).

Bismuth preparations

Ranitidine bismuth citrate and tripotassium dicitrato bismuthate may cause headache, gastrointestinal disorders (e.g., diarrhoea, constipation, nausea), discoloration of the tongue, and darkening of the stools in about 10% of patients (3). Bismuth-associated encephalopathy has exceptionally been reported after the administration of tripotassium dicitrato bismuthate (4), but not, to our knowledge, of ranitidine bismuth citrate. Bismuth preparations are contraindicated in patients with a clearance of creatinine smaller than 25 mL/min.

Antibiotics

Side effects common to amoxycillin, clarithromycin and metronidazole include gastrointestinal disorders, a decreased efficacy of oral contraceptives, pseudomembranous colitis (even with regimens including metronidazole) (5), and moniliasis.

Amoxycillin

Hypersensitivity reactions are by far the most common side effect noted with this drug. Their incidence varies from 0.7 to 10% in different studies. The most severe type of reaction, i.e. anaphylaxis, is rare and causes death of about 0.001% of patients treated with penicillins. Desensitization is not recommended if the use of penicillin is not essential, since it is a heavy and dangerous procedure of unproven efficacy. Other side effects include bone marrow depression, hepatitis, and "toxic" skin rash (in case of concurrent administration of allopurinol, or of infectious mononucleosis). In these two latter circumstances, the administration of amoxycillin should be avoided.

Clarithromycin

Disturbance of taste affects 10% of patients. Hepatitis and auditory impairment may complicate the course of erythromycin therapy but have not, to our knowledge, been reported with clarithromycin.

Clarithromycin is contraindicated in patients taking ergotamine or dihydroergotamine. Interaction of clarithromycin with theophylline and carbamazepine (decreased clearance) may be clinically significant (6).

Metronidazole

Patients should be advised against alcohol consumption during treatment with metronidazole, since disulfiram-like reactions may occur. Other side effects include a metallic taste and temporary neutropenia. Central nervous system toxicity as well as peripheral neuropathies have been reported after prolonged or high-dose metronidazole therapy (7). However, mental

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status changes have been noted as early as 72 h after the onset of metronidazole 2 g/day (8).

Clinically relevant interactions have been reported between metronidazole and phenytoin (decreased clearance), warfarin (prolonged prothrombin time) as well as lithium (increased serum concentration).

Side effects associated with different drug regimens administered for *H. pylori* eradication

A meta-analysis (9) summarised the experience gained in 5751 patients treated with triple therapy (publication dates of the original reports, from January 1990 to October 1995). The result of this analysis, supplemented by these observed with ranitidine bismuth citrate (10-11) are indicated in the table below.

Conclusion

The frequency of adverse events reported during *H. pylori* eradication therapy is high. This frequency may have been overestimated, due to the designs of protocols. To date, the incidence of side effects reported has been the highest with standard triple therapy and the lowest with the association of omeprazole, clarithromycin, and tinidazole. Patients should be informed by the prescribing physician (i) about the most common side effects (possibly with the help of a standard form), and (ii) that any of their medical worries appearing during *H. pylori* eradication therapy will receive a prompt answer. Patients receiving some drugs with a low therapeutic index (i.e., theophylline, carbamazepine, phenytoin, warfarin) should be advised against potential development of side effects related to these drugs. Women potentially pregnant should be screened with a pregnancy test before initiating *H. pylori* eradication therapy and those taking oral contraceptives should be advised to take additional measures to prevent unwanted pregnancy during *H. pylori* eradication.

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Table I. — **Side-effects during *H. pylori* eradication therapy**

	All side-effects* % (95% CI)	Side-effects stopping therapy % (95% CI)
Standard triple therapy		
Bismuth + amoxycillin + nitroimidazole	23 (20-26)	5 (3-7)
Bismuth + tetracycline + nitroimidazole	40 (38-42)	4 (3-5)
PPI triple therapy		
Omeprazole + amoxycillin + clarithromycin	22 (18-26)	1 (1-2)
Omeprazole + amoxycillin + metronidazole	39 (36-42)	2 (1-3)
Omeprazole + clarithromycin + tinidazole	7 (4-10)	0.4 (0-1)
Ranitidine bismuth citrate (RBC)		
RBC + clarithromycin	29	5

* Including side-effects graded as minor, moderate, and severe.