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*RAPID COMMUNICATION*

# Drug utilization of clarithromycin for gastrointestinal disease treatment

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## Abstract

**AIM:** To evaluate the patterns of use of clarithromycin for gastrointestinal disease treatment and promote its rational use.

**METHODS:** Using a structured pro forma, we conducted a two-month survey of the electronic prescriptions containing immediate-release (IR) or sustained-release (SR) product of clarithromycin for outpatients with gastrointestinal diseases in a 2200-bed general hospital. Suitability of the prescription was audited retrospectively.

**RESULTS:** One hundred and sixty-four prescriptions of SR product and 110 prescriptions of IR product were prescribed for gastrointestinal disease treatment. Among prescriptions for anti-*Helicobacter pylori* (*H pylori*) therapy, triple therapy take the dominant position (91.8%), followed by quadruple therapy (4.3%) and dual therapy (3.9%). Amoxicillin was the most frequently co-prescribed antibiotic. Furazolidone and levofloxacin are used more widely than metronidazole or tinidazole. Clarithromycin SR was administered at inappropriate time points in all prescriptions. Fifty percent of all prescriptions of clarithromycin SR, and 6.4% of prescriptions of clarithromycin IR, were prescribed at inappropriate dosing intervals. Surprisingly, disconcordance between diagnoses and indications was observed in all prescriptions of clarithromycin SR which has not been approved for treating *H pylori* infection although off-label use for this purpose was reported in literature. On the contrary, only one prescription (0.9%) of clarithromycin IR was prescribed for unapproved indication (i.e. gastro-oesophageal reflux disease). 1.4% of prescriptions for chronic gastritis or peptic ulcer treatment were irrational in that clarithromycin was not co-prescribed with gastric acid inhibitors. Clinical significant CYP3A based drug interactions with clarithromycin were identified.

**CONCLUSION:** There is a great scope to improve the quality of clarithromycin prescribing in patients with gastrointestinal disease, especially with regard to administration schedule, concordance between indications and diagnoses and management of drug interactions.



**Key words:** Clarithromycin; Drug utilization; Prescriptions; *Helicobacter pylori*; Gastrointestinal diseases; Drug administration schedule; Drug interactions; Polypharmacy

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## INTRODUCTION

Clarithromycin is a semi-synthetic macrolide antibiotic

that inhibits bacterial protein synthesis. It is more acid-stable, better absorbed, and is widely used as a component of anti-*Helicobacter pylori* (*H pylori*) regimens[1,2]. The oral clarithromycin formulations available on the market include immediate-release (IR) clarithromycin and sustained-release (SR) clarithromycin. The two formulations have different administration schedule, clinical indications and therapeutic cost. The SR clarithromycin has obvious advantages over the IR product when they are prescribed for the same indications. These advantages are as follows: (1) higher antimicrobial activity in that clarithromycin is a time-dependent antibiotic; (2) better tolerability, fewer gastrointestinal adverse reactions and reports of abnormal taste[3,4]; (3) bioequivalence between the SR (1000 mg *qd*) and IR (500 mg *bid*)[4]; and (4) enhanced medication compliance due to its convenience.

The patterns of combination use of clarithromycin for *H pylori* infection have not been reported in literature. Meanwhile, many patients with *H pylori* infection also suffer from other diseases and hence may receive polytherapy regimens, which may exert complex, significant drug interactions[5]. Up to now, drug utilization of clarithromycin for gastrointestinal disease treatment has not been available. Targeting inappropriate prescribing is one means of trying to reduce drug costs and promote rational use of drug. The aim of this two-month drug utilization study was to assess the extent and appropriateness of clarithromycin by examining prescribing practice for outpatients in a general hospital.

## MATERIALS AND METHODS

The setting of this study is a 2200-bed general hospital in Zhejiang Province, China. The pharmacy has two products of clarithromycin [Klaci® (clarithromycin IR tablets, Abbott S.P.A.) and Nuobang® (clarithromycin SR tablets, Jiangsu Hengrui Medicine Co., Ltd, China)]. Each tablet of BIAXIN® contains 250 mg of clarithromycin. Each tablet of Nuobang® contains 500 mg of clarithromycin. Prescribing information for these products along with BIAXIN® XL Filmtab® (clarithromycin SR tablets, Abbott S.P.A.) were referenced[6]. Relevant literature was identified by performing Pubmed searches until the end of 2007. A structured pro forma was used to perform a survey of electronic prescriptions containing IR or SR product for outpatients with alimentary disease covering the period from December 2007 to January 2008. The pro forma included details of the patient's age and sex, indication for clarithromycin therapy, the type of clarithromycin product prescribed, the dose and duration of therapy and details of other prescribed medications. Suitability of the prescription was audited retrospectively.

Differences between patient groups were tested for statistical significance using $\chi^2$ analysis. A $P$-value $< 0.05$ was considered significant.

## RESULTS

Over a two-month period clarithromycin SR was prescribed for 949 patients whereas clarithromycin IR product was prescribed for 197 patients (Table1). With respect to use for alimentary disease treatment by gastroenterologists, 164 patients (17.3%) were on SR product compared to 110 patients (55.8%) on IR product ($P < 0.05$). The mean age of these patients was 45.9 years (range: 18-82 years). The number of male patients was equal to that of female patients. Among prescriptions for anti-*H pylori* therapy, triple therapy take the dominant position (91.8%), followed by quadruple therapy (4.3%) and dual therapy (3.9%).

**Table 1 Details of prescriptions of the two clarithromycin products**

| | Clarithromycin | |
|---|---|---|
| | Sustained-release | Immediate release |
| Total number of prescriptions | 949 | 197 |
| Number of prescriptions for alimentary disease | 164 | 110 |
| Mean age (range) yr | 45.9 (18-82) | |
| Male:Female | 137:137 | |
| Number of prescriptions for anti-*H pylori* therapy | 159 | 96 |
| Triple therapy | 151 | 83 |
| PPI/Clarithromycin/Amoxicillin | 43 | 58 |
| PPI/Clarithromycin/Furazolidone | 44 | 21 |
| PPI/Clarithromycin/Levofloxacin | 63 | 1 |
| PPI/Clarithromycin/Metronidazole | 1 | 1 |
| PPI/Clarithromycin/Tinidazole | 0 | 2 |
| Quadruple therapy | 5 | 6 |
| PPI/Bismuth/Amoxicillin/Clarithromycin | 0 | 2 |
| PPI/Bismuth/ Furazolidone/Clarithromycin | 1 | 3 |
| PPI/Bismuth/Levofloxacin/Clarithromycin | 4 | 1 |
| Dual therapy | 3 | 7 |
| Clarithromycin/PPI | 2 | 7 |
| Clarithromycin/Ranitidine bismuth citrate | 1 | 0 |

PPI: Proton pump inhibitor.

### *Administration schedule*

Post-meal dosing of clarithromycin was specified in all investigated electronic prescriptions. According to the prescribing information, Nuobang® should be taken with food whereas Klaci® may be given irrespective of food intake. Thus, Nuobang® in all prescriptions was administered at inappropriate time.

Eighty-two prescriptions of Nuobang® (50%) were prescribed twice daily, which was inconsistent with the once-daily dosing method according to its prescribing information. Klaci® was given twice daily according to all prescriptions, which met the requirements for triple therapy. However, dual therapy requires clarithromycin IR 500 mg to be given three times daily[6]. Thus, 7 prescriptions of dual therapy containing clarithromycin IR tablet (500 mg *bid*) and PPI were identified as irrational.

### *Diagnoses of patients on clarithromycin-based therapy*

For patients with alimentary disease receiving clarithromycin-based therapy, diagnoses were summarized in Table 2. The diagnoses were various. Combining the results of upper gastrointestinal

**Table 2 Diagnoses of patients on clarithromycin-based therapy**

| Diagnoses | Clarithromycin | |
|---|---|---|
| | SR | IR |
| Chronic gastritis | 90 | 87 |
| Peptic ulcer | 40 | 5 |
| Duodenal ulcer | 9 | 5 |
| Gastro-oesophageal reflux disease | 5 | 1 |
| Chronic gastritis, *H pylori* infection | 4 | 3 |
| Gastric ulcer | 1 | 4 |
| Chronic gastritis, Gastric ulcer | 2 | 1 |
| Gastro-oesophageal reflux disease, Gastric ulcer | 1 | |
| *H pylori* infection | 2 | |
| Chronic gastritis, Peptic ulcer | 1 | 3 |
| Peptic ulcer, *H pylori* infection | | 1 |
| Mesenteric lymphadenitis | 7 | |
| Abdominal pain of unknown origin | 2 | |

SR: Sustained-release; IR: Immediate release.

**Table 3 Concomitant drugs used in clarithromycin-based triple therapy**

| Comedicated drugs | Clarithromycin | |
|---|---|---|
| | SR | IR |
| PPI | | |
| Omeprazole | 17 | 6 |
| Lansoprazole | 68 | 6 |
| Pantoprazole | 30 | 66 |
| Esomeprazole magnesium | 15 | 11 |
| Rebeprazole | 23 | 21 |
| Antibiotics | | |
| Amoxicillin | 38 | 63 |
| Furazolidone | 47 | 24 |
| Levofloxacin | 67 | 2 |
| Metronidazole | 1 | 1 |
| Tinidazole | 0 | 13 |
| Amoxicillin/clavulanate potassium | 5 | 0 |

SR: Sustained-release; IR: Immediate release.

**Table 4 CYP3A based clinical significant drug interactions with clarithromycin**

| Concurrent medications primarily metabolized by CYP3A | Clarithromycin | | References |
|---|---|---|---|
| | SR | IR | |
| Alprazolam and zolpidem | 1 | | [6,7] |
| Midazolam | 1 | | [6,8] |
| Amlodipine | 1 | 2 | [9] |
| Levoamlodipine | | 1 | |
| Nifedipine | | 1 | [10] |
| Carbamazepine | | 1 | [11] |
| Nifedipine, clopidogrel and atorvastatin | | 1 | [10,12-14] |
| Amlodipine and ergoloid mesylate sustained release capsules | | 1 | [9,15] |
| Prednisone | | 1 | [16] |

SR: Sustained-release; IR: Immediate release.

endoscopy or $^{13}$C-urea breath test, concordance between diagnoses and indications were examined. Except for patients with mesenteric lymphadenitis or abdominal pain of unknown origin, 90.6% of other patients test positive for *H pylori* infection prior to initiation of anti-*H pylori* regimen. Surprisingly, disconcordance between diagnoses and indications was observed in all prescriptions of clarithromycin SR. On the contrary, only one prescription (0.9%) of clarithromycin IR was prescribed for unapproved indication (i.e. gastro-oesophageal reflux disease).

### Drug interactions

Concomitant PPIs and anti-*H pylori* agents used in clarithromycin-based triple therapy were listed in Table 3. The PPIs included omeprazole, lansoprazole, pantoprazole, esomeprazole magnesium and rebeprazole. The antibiotics co-presribed with clarithromycin included amoxicillin, furazolidone, levofloxacin, metronidazole, tinidazole and amoxicillin/clavulanate potassium. Amoxicillin was the most frequently co-prescribed antibiotic. Furazolidone and levofloxacin were used more widely than metronidazole or tinidazole. The CYP3A dependent clinical significant drug interactions with clarithromycin in this survey were summarized in Table 4.

Clarithromycin plays its role of anti-*H pylori* only under the circumstance of pH more than 4.0 and thus it usually needs concomitant use of anti-gastric-secretion drugs. However, 4 prescriptions for chronic gastritis or peptic ulcer treatment did not contain gastric acid inhibitors, and thus were judged as irrational.

## DISCUSSION

### Administration schedule

Food has no significant effects on pharmacokinetics of IR clarithromycin and thus the product may be given irrespective of food intake. With regard to Nuobang®, administration under fasting conditions is associated with approximately 30% lower area under the plasma concentration-time curve (*AUC*) for clarithromycin relative to administration with food. Therefore, it should be taken with food to maximize bioavailability. Physicians and pharmacists should pay attention to this biopharmaceutical requirement and strengthen patient education.

Compared to the triple therapy, the dual therapy has a lower eradication rate of *H pylori*. Moreover, regimens which contain clarithromycin as the single antibiotic are more likely to be associated with the development of clarithromycin resistance among patients who fail therapy. When the IR clarithromycin tablet is combined with PPI as dual therapy, the dose needs to be tailored to 500 mg three times daily[6].

The SR clarithromycin has obvious advantages over the IR product when they are prescribed for the same indications[3,4]. However, the novelty of the SR product and its administration of only once a day would decrease the benefit for patients and their compliance if given twice daily as detected in most prescriptions.

### Concordance between indications and diagnoses

Chronic gastritis is an inflammation of the lining of the stomach that occurs gradually and persists for a prolonged time. It can be classified based on the underlying etiologic agent (e.g. *H pylori*, bile reflux,

nonsteroidal anti-inflammatory drugs, autoimmunity, allergic response) and the histopathological pattern. Diagnosis of chronic gastritis is broad and disconcordant with indications described in the package insert of clarithromycin. It should be further specified if patients test positive for *H pylori* (i.e. *H pylori*-associated chronic gastritis instead of chronic gastritis) and the rationale also applies to diagnoses of gastric ulcer, peptic ulcer and duodenal ulcer.

Gastro-oesophageal reflux disease (GERD) is an unapproved indication for IR or SR clarithromycin. Although a significant proportion of patients with GERD have *H pylori* infection, it is unclear whether or not *H pylori* should be treated. Eradication therapy is currently not recommended for most of GERD patients with *H pylori* infection[1,2]. Relief of abdominal pain of unknown origin was also an unapproved indication for clarithromycin-based therapy. Seven prescriptions for mesenteric lymphadenitis treatment included monotherapy with clarithromycin ($n$ = 1), dual therapy with clarithromycin-levofloxacin ($n$ = 3), clarithromycin-cefdinir ($n$ = 1), clarithromycin-amoxicillin/clavulanate potassium ($n$ = 2). Given the predominance of *Y. enterocolitica* in mesenteric lymphadenitis infection, initial oral antibiotic selection from third-generation cephalosporins, broad spectrum penicillins, fluoroquinolones and doxycycline may be considered. Recently, association of mesenteric lymphadenitis with mycoplasma was revealed by Tao *et al*[17]. Among 108 patients with mesenteric lymphadenitis in that study, 36 patients (33%) were Mycoplasma-IgM positive. The switch to macrolide azithromycin provided a benefit for patients with an unsatisfactory response to third-generation cephalosporins or broad spectrum penicillins. In our survey, follow-up indicated that the combination of macrolide clarithromycin with levofloxacin, amoxicillin/clavulanate potassium or cefdinir showed satisfactory results in patients suffering from mesenteric lymphadenitis.

Clarithromycin IR based triple therapy or dual therapy is indicated for the treatment of patients with *H pylori* infection. However, the efficacy and safety of clarithromycin SR treatment for *H pylori* infection have not been established, as indicated in the prescribing information for Biaxin Xl Filmtab®. There have been three studies on clinical efficacy of clarithromycin SR -based triple therapy to cure *H pylori* infection. Coelho *et al*[18] observed that the combination of lansoprazole 30 mg, clarithromycin SR 500 mg and furazolidone 400 mg, once daily for 7 d, was inexpensive, safe and an effective alternative for anti-*H pylori* therapy in family members of gastric cancer patients. Chu *et al*[19] proved that one-week once-daily course of lansoprazole 30 mg, clarithromycin SR 500 mg and metronidazole 800 mg was a safe, well-tolerated, easy to comply with, and efficacious treatment for *H pylori* infection. A randomized controlled trial study by Liou *et al*[20] provided the direct evidence that clarithromycin SR 1000 mg once daily can be used as an alternative to clarithromycin IR 500 mg twice daily for the treatment of *H pylori*-associated peptic ulcer disease. In that study, 161 patients with *H pylori*-associated peptic ulcer were randomized to receive one-week triple therapy with either clarithromycin SR 1000 mg once daily or clarithromycin IR 500 mg twice daily combination with amoxicillin 1000 mg twice daily and esomeprazole 40 mg once daily. The eradication rates were comparable in the two groups. Further clinical trials with a larger sample size are required to establish the efficacy and safety of clarithromycin SR. Effective communication between patients and gastroenterologists are rather necessary prior to initiation of off-label use of clarithromycin SR.

### Drug interactions

The combination of clarithromycin with omeprazole has a synergic effect. The $C_{max}$, $AUC$0-24, and $T_{1/2}$ derived from omeprazole increased by 30%, 89%, and 34%, respectively by the concomitant administration. The mean 24-h gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when co-administered with clarithromycin[6]. On the other hand, by concomitant administration of omeprazole, clarithromycin concentrations in the gastric tissue and mucus increased (e.g. clarithromycin mucus concentrations 2 h after application increased by about 9-fold)[21]. Simultaneous administration of lansoprazole, amoxicillin and clarithromycin increases the serum concentrations of lansoprazole and the active 14-OH-clarithromycin metabolite significantly[22]. Compared to treatment with esomeprazole alone, the mean steady state $AUC$ and $C_{max}$ of esomeprazole increased by 70% and 18%, respectively, during triple therapy (esomeprazole magnesium 40 mg *qd*, clarithromycin 500 mg *bid* and amoxicillin 1000 mg *bid* for 7 days)[23]. The $AUC$ and $C_{max}$ of rabeprazole and 14-hydroxyclarithromycin (active metabolite of clarithromycin) increased, although the $AUC$ and $C_{max}$ for clarithromycin were not different following combined administration consisting of rabeprazole, amoxicillin and clarithromycin compared to values following single administration[24]. Although there is no significant pharmacokinetic interaction between clarithromycin and pantoprazole, clarithromycin has a better effect in *H pylori* treatment when pantoprazole is used concomitantly[25].

Clarithromycin is a potent inhibitor of CYP3A4 and P-gp. Concomitant administration of clarithromycin and any of the following CYP3A4 substrates is contraindicated: cisapride, pimozide, astemizole, terfenadine, and ergotamine or dihydroergotamine, as described in standard information sources. In this survey, such prescriptions were not found. Coadministration of clarithromycin and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both the therapeutic and adverse effects of the concomitant drug. Dosage adjustments may be considered, and when possible, plasma concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

Triazolobenziodidiazepines (e.g. triazolam

and alprazolam) and related benzodiazepines (e.g. midazolam) have been observed of CYP3A based drug interactions with erythromycin products and/or with clarithromycin in postmarketing experience. For example, intestinal and hepatic CYP3A inhibition by clarithromycin can significantly reduce the clearance of midazolam, resulting in an increase in the *AUC* of midazolam by 8-fold following oral dose in the elderly[8]. Zolpidem is extensively metabolized, mainly by CYP3A4[7]. Thus, a prescription containing alprazolam, zolpidem and clarithromycin has a high risk for excessive sedation (Table 4). Pharmacotherapy monitoring and dosage adjustment for these sedative drugs should be implemented accordingly.

Clarithromycin may increase the levels/effects of amlodipine[9]. Levoamlodipine is an eutomer of amlodipine and the first enantiomerically pure dihydropyridine calcium channel blockers. Levoamlodipine is also mainly metabolized by CYP3A4, so its levels/effects may also be affected by clarithromycin. A case of vasodilatory shock possibly resulting from a clarithromycin-nifedipine interaction was reported by Gerónimo-Pardo *et al*[10]. A potentially significant pharmacokinetic interaction between clarithromycin and carbamazepine was identified in two patients with long-standing epilepsy who were given omeprazole/clarithromycin therapy for *H pylori* gastritis[9]. Serum carbamazepine levels were augmented by clarithromycin and returned to the therapeutic range following cessation of clarithromycin therapy. Empirically in such cases carbamazepine dose need to be tailored by 30% to 50%.

Clarithromycin did have a significant effect on atorvastatin pharmacokinetic parameters. When coadministered, clarithromycin raised atorvastatin *AUC* by 82% and $C_{max}$ by 56%. Hence, clarithromycin should be avoided in patients taking atorvastatin and similarly metabolized HMG-CoA inhibitors[12]. Sipe *et al*[13] reported a case of rhabdomyolysis causing AV blockade due to possible atorvastatin, esomeprazole, and clarithromycin interaction. The antiplatelet effects of the prodrug clopidogrel can be reduced by concomitant administration of erythromycin or troleandomycin. The proposed mechanism is inhibition of CYP3A4 activity, which is responsible for the conversion of clopidogrel to its active metabolite. Clarithromycin also inhibits CYP3A4 activity and is also expected to affect clopidogrel metabolism[14]. Until more information is available, monitoring for altered efficacy of clopidogrel may be advisable if clarithromycin is co-administered with clopidogrel.

In a combination of clarithromycin, nifedipine, clopidogrel and atorvastatin (Table 4), at least 4 clinical significant pharmacokinetic interactions are involved, e.g. clarithromycin-nifedipine, clarithromycin-clopidogrel, clarithromycin-atorvastatin and atorvastatin-clopidogrel[26]. Such a prescription with high risk of adverse drug interactions is irrational. Considering the short course of clarithromycin therapy, close monitoring and proper dose adjustment may be more practicable than to switch to alternatives not mainly metabolized by CYP3A4.

Clarithromycin may increase levels of ergoloid mesylate by inhibiting CYP3A4 metabolism, resulting in toxicity (ischemia, vasospasm) and the combined use is contraindicated[15]. So the combination therapy of clarithromycin with amlodipine and ergoloid mesylate at conventional dosage is irrational. A case of mania due to prednisone-clarithromycin interaction was reported by Finkenbine *et al*[16], suggesting that pharmacotherapy monitoring should be performed during the concurrent therapy.

Triple therapy with a PPI, clarithromycin and either amoxicillin or metronidazole is the first-line treatment regimen to eradicate *H pylori* infection[1,2,27]. Significant differences are observed in the prevalence of metronidazole resistance between developed and developing countries[28-30]. High levels of resistance to metronidazole mainly relates to the wide application in parasite infection, dental infection and gynecological diseases in developing countries. Antimicrobial susceptibility tests performed in Zhejiang Province of China indicated that the antibiotic resistance rate increased perceptibly during the period of 2003-2007[31,32]. Among six antibiotics (metronidazole, amoxicilin, gentamycin, levofloxacin, furazolidone and clarithromycin), the rate of resistance to metronidazole (99.32%) appeared to be the highest and the levofloxacin resistance rate (0.51%) was the lowest. Amoxicillin rarely induces resistance[33]. Fluoroquinolones are active against *H pylori* in vitro and have a synergistic effect with PPIs[34]. Strains resistant to furazolidone are rare. Furthermore, there is no cross-resistance to metronidazole and furazolidone is effective in populations with a high prevalence of metronidazole resistance[35]. The resistance status may explain the pattern of antibiotic use in this hospital, i.e. furazolidone and levofloxacin are used more widely than are metronidazole or tinidazole. Guo *et al*[28] reported that *H pylori* eradication rates were significantly different in patients receiving OAC (omeprazole/amoxicillin/clarithromycin) and OFC (omeprazole/furazolidone/clarithromycin) compared to those receiving OMC (omeprazole/metronidazole/clarithromycin). The eradication rate for *H pylori* infection was 90.3%, 90.9% and 70.9% in OAC, OFC and OMC groups, respectively. Based on these results, one-week of triple therapy with OAC or OFC were recommended for Chinese patients with duodenal ulcers and chronic gastritis. Since furazolidone is cheap and the *H pylori* eradication rate is high, OFC regimen is recommended to be one of choices for *H pylori* eradication.

PPI-based double combinations were clearly inferior to triple regimens, which is in accordance with the evidence-based data and they are not recommended in the first-line treatment. However, concurrent therapy of ranitidine bismuth citrate and clarithromycin have a similar efficacy compared to the triple regimens[36-38]. Thus, the prescription of a combination of clarithromycin and ranitidine bismuth citrate in our survey is rational. A 7 d

quadruple therapy based on PPI, bismuth, tetracycline and metronidazole is the more frequently accepted[1,2]. Our survey found that some patients received quadruple therapy regimens containing PPI, bismuth, clarithromycin, and one of antibiotics including amoxicillin, furazolidone or levofloxacin.

In conclusions, a retrospective utilization study of clarithromycin for gastrointestinal disease treatment was conducted. There is a great scope to improve the quality of clarithromycin prescribing, especially with regard to administration schedule, concordance between indications and diagnoses and management of drug interactions.

## COMMENTS

### Background

The oral clarithromycin formulations available on the market include immediate-release (IR) clarithromycin and sustained-release (SR) clarithromycin. Due to difference in pharmaceutical forms, the IR and SR formulations have different administration schedule, clinical indications and therapeutic cost. Meanwhile, the patterns of combination use of clarithromycin for *Helicobacter pylori* (*H pylori*) infection have not been reported in literature. Many patients with *H pylori* infection also suffer from other diseases and hence they may receive polytherapy regimens, which may exert complex, significant drug interactions if clarithromycin is used. In order to promote its rational use in gastrointestinal disease treatment, it is essential to assess the extent and appropriateness of clarithromycin by examining prescribing practice.

### Research frontiers

Drug utilization studies can provide useful information to improve the appropriate and effective use of pharmaceuticals in populations. In recent years many such studies have been performed to monitor prescribing patterns and assess adherence to standard therapeutic guidelines in clinical practice.

### Innovations and breakthroughs

This is the first drug utilization study of clarithromycin for gastrointestinal disease treatment and the article critically compares the prescribing patterns of clarithromycin with different pharmaceutical forms.

### Applications

The significance of this article is: (1) it provides insights into the aspects of drug use and prescribing pattern; (2) it helps to improve the quality of clarithromycin prescribing, especially with regard to administration schedule, concordance between indications and diagnoses and management of drug interactions; (3) it helps doctors to attach equal importance to other medicines for gastrointestinal disease treatment and finally promote rational drug use in clinical practice.

### Terminology

Drug utilization: The study to describe the extent, nature and determinants of drug exposure, consider clinical appropriateness and cost effectiveness, and facilitate rational use of drugs in populations. Drug administration schedule: time schedule for administration of a drug in order to achieve optimum effectiveness and convenience. Drug interactions: The action of a drug that may affect the activity, metabolism, or toxicity of another drug. Polypharmacy: The use of multiple drugs administered to the same patient, most commonly seen in elderly patients.

### Peer review

This retrospective utilization study is well designed. It is of particular interest to the practical medicine and can improve the quality of clarithromycin prescribing in patients with gastrointestinal disease.

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