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ORIGINAL ARTICLE

Assessment of the use of clopidogrel associated with gastroprotective medications in outpatients

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KEYWORDS
Clopidogrel;
Proton pump inhibitors;
Drug interaction

Abstract
Objectives: Check the progress of hospitalization and death of the patients that use clopidogrel associated with omeprazole and the patients that do not.
Methods: A retrospective cohort was conducted between January 2007 and November 2009 to evaluate patients that were using clopidogrel in association or not with omeprazole.
Results: The study included 2823 patients. Of these patients, 36% were female and 64% were male, the mean age was 63 years. Regarding the association of drugs for gastric protection, omeprazole was prescribed to 45%, ranitidine for 9%, while 46% of patients were not receiving gastroprotective medication. As for the analysis by groups, 35.5% of the omeprazole group was hospitalized after starting treatment with clopidogrel, compared with 25.7% in the group without omeprazole. In evaluating the deaths among patients using clopidogrel in the study period, we found the occurrence of 36 deaths, 22 in the omeprazole group and 14 in the other group.
Conclusions: In our study, we did not evaluate the clinical status of the patients and the rates of reinfarction. And, as our study data showed, there are not any statistically differences between the groups that used clopidogrel associated with omeprazole, with ranitidine or that did not use any gastroprotective medication.

PALABRAS CLAVE
Clopidogrel;
Inhibidores de la bomba de protones;
Interacción medicamentosa

Valoración del uso de clopidogrel asociado a medicamentos gastroprotectores en pacientes ambulatorios

Resumen
Objetivos: Comprobar el incremento en la tasa de hospitalización y fallecimiento de los pacientes que reciben clopidogrel asociado con omeprazol y los pacientes que no lo reciben.

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Métodos: Entre enero de 2007 y noviembre de 2009 se realizó un estudio de cohorte retrospectivo para evaluar a los pacientes que recibían clopidogrel, independientemente de si estaba asociado o no a omeprazol.
Resultados: El estudio incluyó a 2823 pacientes, de los cuales, 36% eran mujeres y 64% eran hombres, con una media de edad de 63 años. En cuanto a la asociación de medicamentos gastroprotectores, al 45% se le había recetado omeprazol y al 9% ranitidina, mientras que al 46% de los pacientes no se le administraba este tipo de medicación. Si evaluamos el uso de los medicamentos por grupos, observamos que el 35,5% del grupo del omeprazol se encontraba hospitalizado tras comenzar el tratamiento con clopidogrel, al igual que el 25,7% del grupo al que no se le administraba omeprazol. Al evaluar los fallecimientos entre pacientes que recibían clopidogrel durante el periodo de estudio, observamos que se produjeron 36 fallecimientos, 22 en el grupo del omeprazol y 14 en el grupo que no tomaba omeprazol.
Conclusiones: En nuestro estudio no evaluamos el estado clínico de los pacientes ni las tasas de reinfarto. Como demuestran nuestros datos, no existen diferencias estadísticas entre los grupos que recibían clopidogrel asociado con omeprazol, ranitidina o que no recibían ningún tipo de medicamento gastroprotector.

Introduction

Atherosclerosis is a chronic degenerative disease and the treatment beyond the control of risk factors and drug therapy are myocardial revascularization or percutaneous coronary intervention (PCI).[1]

The PCI were comparable to myocardial revascularization in patients with multivessel disease, with less cost and similar mortality.[1] Thrombosis is still the most feared complication associated with PCI, occurring in 0.5–2% of patients. Despite being a relatively rare occurrence, the overall clinical impact is substantial, due to the high risk of myocardial infarction and death associated with the event. Mortality after stent thrombosis can reach 45%.[2]

With the introduction of the stent in the coronary circulation, the drug protocol administered to patients before, during and after the procedure was greatly modified. The fear of the occurrence of thrombosis in the coronary circulation, promoted a new clinical pharmacology which had never been seen before. Thus, patients who were undergoing PCI received aspirin, dipyridamole, dextran, warfarin and heparin, administered orally or intravenously for 30 days. Certainly, this is one of the most aggressive pharmacological regimens of anticoagulation and antiplatelet therapy used in modern cardiology.[3]

In August 2001, clopidogrel arose and it began to be prescribed commonly to prevent coronary thrombosis after interventions.[3] Clopidogrel has an antiplatelet effect for about six hours after a loading dose of 300 mg and about two hours after a dose of 600 mg orally. This inhibition reaches a steady state between 3 and 7 days with repeated doses.[4]

About the duration of the treatment, we have little information about the benefits and risks of continuing treatment with clopidogrel for 15 months. Most studies have recommended at least one year of antiplatelet therapy after the procedure.[5]

Today, the therapy of choice to prevent thrombosis in patients undergoing PCI is the use of a dual scheme, with aspirin and clopidogrel.[6]

Clopidogrel compared to aspirin, showed a decrease of 8.7% in the relative risk of ischemia, myocardial infarction, stroke and death by vascular causes in patients with cardiovascular disease. When using the two drugs (aspirin and clopidogrel), there was a decreased risk of cardiovascular death, stroke and reinfarction by 20% compared to aspirin alone.[7]

The response to treatment with clopidogrel can be very variable.[8] In a study conducted with 60 patients after acute myocardial infarction who were treated with a loading dose of clopidogrel and maintenance, 25% of patients showed resistance to inhibition of platelet aggregation.[9] Therefore, clinical, cellular and genetic factors are also shown as being causes of a low efficacy of clopidogrel.[8]

When stent thrombosis occurs, the physician should also suspect non-adherence to medication, early cessation of drug therapy[2] and drug interactions.[10]

Medications that reduce the activation of clopidogrel by drug interaction may trigger stent thrombosis, a new coronary syndrome, and a need for new revascularization.[9,10]

Clopidogrel can cause dyspepsia (including pain, burning and nausea), gastric ulceration and gastrointestinal bleeding, especially when used in combination with aspirin.[10] Therefore, during the period in which patients use the dual scheme antiplatelet therapy, treatment involves proton pump inhibitors.[11]

Proton pump inhibitors: omeprazole, lansoprazole, dexlansoprazole, rabeprazole, pantoprazole and esomeprazole effectively block acid secretion by inhibiting the hydrogen bomb-potassium ATPase that resides on the luminal surface of the parietal cell membrane of the stomach.[10]

Studies show that when comparing patients who used only clopidogrel with others that used clopidogrel and a proton pump inhibitor, which inhibits the cytochrome P450 2C19, the patients that used the combination of drugs have a 40% increased relative risk of recurrence of a myocardial infarction.[12] Moreover, it is estimated that the cause of reinfarction for 7.4% of elderly patients who have suffered an acute myocardial infarction and were readmitted

for reinfarction within 90 days after discharge is using the combination of clopidogrel and inhibitors proton pump.[13]

Pezalla et al.[14] conducted a retrospective study that lasted one year and assessed the rate of reinfarction in patients using clopidogrel. The results were as follows for acute myocardial infarction: 1.38% (66 in 4800 patients) in patients who used only clopidogrel, 3.08% (22 out of 712 patients) in patients that used clopidogrel and associated omeprazole for six months, and 5.03% in patients who used clopidogrel and omeprazole for more than six months.

Methods

A retrospective cohort was conducted to evaluate patients undergoing PCI that used drugs to prevent thrombosis (clopidogrel and aspirin) in association or not with proton pump inhibitors (omeprazole). The patients' progress was checked for cases of hospitalization and death after the procedure.

The survey was conducted through the hospital management system to identify the patients treated with clopidogrel 75 mg, between January 2007 and November 2009, who were attended to by the pharmacy department of the Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

The study excluded patients who used, in addition of clopidogrel, omeprazole 20 mg and ranitidine 150 mg during the study (even at different times).

Results

During the study period, the pharmacy department of the Heart Institute (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo provided the drug clopidogrel for the treatment of coronary artery disease to 2913 patients. However, the study included 2823 patients because the others used two different gastroprotective medications, omeprazole and ranitidine, during the study.

Of these patients, 36% (1020) were female and 64% (1803) were male. The mean age was 63 years (12–97), with a standard deviation of 12.

The average service time of the drug clopidogrel for patients was 6 months with a minimum of one month and maximum of 34.6 months (Table 1).

In relation to hospital admissions during the study, after initiation of clopidogrel treatment, 30% (851) of patients had an average of two hospitalizations each. Of these 851 patients, 452 were using omeprazole, 90 were ranitidine and 309 were not using gastroprotective medication. Data analysis showed a relative risk of hospitalisation of 0.928 (95% confidence interval = 0.895–0.962) by comparing the patients that were treated with omeprazole to those that were not treated with omeprazole.

From patients that used clopidogrel plus aspirin who were evaluated for hospital admissions during the study, we found 366 patients that used omeprazole, 86 patients that used ranitidine, and 276 patients that did not use gastroprotective medication. Comparing the data of rehospitalization in the omeprazole and ranitidine groups, the relative risk was 1.009 (95% confidence interval = 0.934–1.089). When we compare the data of the omeprazole group with those for the group without any gastroprotective medication, the relative risk was 0.888 (95% confidence interval = 0.852–0.924).

As for deaths during the study, we found that 36 patients died, 22 of whom were treated with omeprazole, 4 with ranitidine and 10 received no gastroprotective medication. Comparing the group that was treated with omeprazole with the group that was treated with ranitidine, the relative risk of death was 0.999 (95% confidence interval = 0.982–1.015). In addition, the relative risk of death for the omeprazole group, compared with the group that did not use any gastroprotective medication, was 0.990 (95% confidence interval = 0.982–0.999).

Table 1 Baseline medications from the study population.

	No./total no. (%)
Clopidogrel plus omeprazole	1273/2823 (45)
Clopidogrel plus ranitidine	255/2823 (9)
Clopidogrel without gastroprotective medicine	1295/2823 (46)
Clopidogrel plus aspirin	2456/2823 (87)
Clopidogrel plus aspirin and omeprazole	977/2823 (34.6)
Clopidogrel plus aspirin and ranitidine	222/2823 (7.8)

Discussion

To prevent thrombosis and ischaemic events after PCI, the drugs most used in the antiplatelet therapy are aspirin with clopidogrel. As demonstrated by the study of Gaspoz et al.[7], clopidogrel reduced by 8.7% the relative risk of ischemia, myocardial infarction and stroke in patients with cardiovascular disease, and when combined with aspirin, by 20%.

The disadvantages of the combination of clopidogrel and aspirin are gastrointestinal adverse reactions, such as dyspepsia, gastric ulceration and bleeding. Therefore, during the period in which patients use the dual antiplatelet therapy regimen treatment is given with gastroprotective drugs.

The results of our study showed that 54% of patients with clopidogrel received a gastroprotective drug 45% received a proton pump inhibitor (omeprazole) and 9% received a H2 receptor antagonist (ranitidine).

Lau and Gurbel[12] revealed in their studies that the use of a proton pump inhibitor, which inhibits the P450–2C19 associated with clopidogrel, increases the relative risk of recurrence of a myocardial infarction by 40%. Furthermore, Juulink et al.[13], estimated in 2009 that 7.4% of elderly patients with prior infarction and readmission for reinfarction within 90 days after discharge can be attributed to the use of the combination of clopidogrel and proton pump inhibitors.

Not all proton pump inhibitors have shown interaction with clopidogrel. In their experiments Cuisset et al.[14] showed that pantoprazole does not interfere with the action of clopidogrel as omeprazole.

Regarding rates of reinfarction, Pezalla et al.[15] found a higher incidence in patients using clopidogrel associated with omeprazole (3.08%), while the group that used clopidogrel alone was 1.38%.

In our study, we did not evaluate the clinical status of the patients and the rates of reinfarction and, as our study data shows, there is no statistical difference between the groups that used clopidogrel associated with omeprazole, with ranitidine or that did not use any gastroprotective medication.

Conflict of interest

The authors have no conflict of interest to declare.

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