Use of Cisapride with Contraindicated Drugs in the Netherlands

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OBJECTIVE: To investigate the prevalence of concomitant use and coprescribing of cisapride with potentially interacting drugs to evaluate the impact of these warnings from 1994 to 1998.

DESIGN: Retrospective follow-up study of patients using cisapride.

SETTING: Data for this study were obtained from the pharmacy database of the Dutch PHARMO record linkage system (n = 834 000).

RESULTS: From 1994 to 1998, the prevalence rate of the observed versus expected use of any potentially interacting drug decreased significantly over time ($p < 0.01$). However, the number of days-at-risk and number of coprescriptions of potentially interacting drugs among cisapride users increased on average by 13% and 9% per year, respectively. This increase was almost exclusively explained by a large increase in concomitant prescribing of clarithromycin, the most commonly used potentially interacting drug. Decreases in prevalence rates were observed for all individual potentially interacting drugs, except for concomitant use of fluconazole and miconazole.

CONCLUSIONS: Over the last few years, healthcare professionals have refrained from dispensing potentially interacting drugs to patients who use cisapride, probably as a result of drug warnings implemented during this period. The limited absolute effects result from an increase of coprescription and concomitant use of clarithromycin and fluconazole among cisapride users. Because therapeutically equivalent alternatives were available for both drugs, such combinations were avoidable. Communicating information on these drug–drug interactions to prescribers and pharmacists and inclusion of cardiovascular morbidity as a relative contraindication for prescribing cisapride with these drugs may substantially decrease the risk of potentially adverse events to cisapride.

KEY WORDS: cisapride, drug interactions, Netherlands.

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The gastrointestinal prokinetic drug cisapride has been licensed for marketing in the Netherlands since September 1989 for symptomatic treatment of epigastric and abdominal complaints, gastroesophageal reflux disease, and refluxoesophagitis.[1] Since the early 1990s, QTc prolongation, syncope, and nonsustained ventricular tachycardia have been associated with high doses of cisapride.[2,3] Gray[4] reported a case of QTc prolongation and syncope resulting from concomitant use of cisapride and agents known to inhibit the metabolism of cisapride. Several other reports and clinical studies have associated use of cisapride with QTc prolongation and torsade des pointes.[5-7] Cisapride has been removed from the market in the US, while its risks and benefits are now being reevaluated by the European Agency for the evaluation of Medicinal Products.

Warnings for QTc prolongation with respect to concomitant use of ketoconazole, miconazole, or itraconazole were included in the Dutch Summary of Product Characteristics since May 10, 1995. This change in labeling was followed by a "Dear Doctor" letter on October 20, 1995. A second modification in the labeling was issued August 30, 1996, regarding concomitant use of 3 additional drugs: fluconazole, erythromycin, and clarithromycin. The last label

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modification was issued December 23, 1997, and included nefazodone, ritonavir, and troleandomycin. No additional "Dear Doctor" letters have been posted. These modifications were communicated to prescribers and pharmacists in medical and pharmaceutical journals as well as major textbooks.

Besides the "Dear Doctor" letter, the warnings were included in package inserts and implemented in pharmacy medication surveillance systems. All Dutch pharmacies have medication surveillance systems that check for drug–drug and drug–disease interactions (including any contraindications) with each new prescription. Differences between surveillance systems exist with respect to the date these interactions were implemented.

The impact of warnings for drug–drug interactions may alter prescribing by minimizing concomitant prescribing of contraindicated drugs altogether or by minimizing the time (days-at-risk) patients use drugs that may interact. In this study, we investigated the prevalence of concomitant use and codispensing of cisapride and potentially interacting drugs as an evaluation of the impact of label changes in the period from 1994 to 1998. We hypothesized that the prevalence of concomitant use and codispensing of cisapride and potentially interacting drugs declines after the warnings were implemented in current practice.

Methods

SETTING

Data for this study were obtained from the pharmacy database of the PHARMO record linkage system.[8,9] This database prospectively collates the drug-dispensing records from 90 community pharmacies and hospital discharge records of all 834 000 community-dwelling inhabitants of 22 population-defined areas in the Netherlands and can be assumed to be a representative subset of the Dutch population. With exceptions, all inhabitants of the Netherlands are insured for health and pharmaceutical care and designate a single pharmacy to fill their prescriptions. Hence, drug-dispensing histories were virtually complete. The computerized drug-dispensing histories contained data concerning the type and quantity of the dispensed drug, type of prescriber, type of medication surveillance system, dispensing date, and prescribed dose/daily regimens. Prescription length was estimated from the total amount of dispensed drug and the prescribed units to be taken per day. In some pharmacies, the reason for prescribing was available, coded with an International Classification of Primary Care code.

DESIGN

We conducted a retrospective follow-up study of patients using cisapride. Subjects were followed from the first day of the first prescription of cisapride since September 1989 until the earliest of the following dates: 90th birthday, exit from the study population, death, or end of the follow-up (December 31, 1998). We excluded patients ≥90 years old who reside to a large extent in nursing homes and whose medication histories were rather incomplete. For each cohort member, the use of cisapride and the use of potentially interacting drugs were assessed every day of the follow-up period. Potentially interacting drugs included ketoconazole, miconazole, fluconazole, itraconazole, erythromycin, clarithromycin, nefazodone, and ritonavir. Troleandomycin, mentioned in the drug labeling, was never marketed in the Netherlands.

Looking at this subject from a general health point of view, we wanted to know whether the drug warnings managed to decrease the number of days-at-risk for QTc prolongation during the study period. Assuming that patients were at risk every day that they used cisapride and a potentially interacting drug concomitantly, we calculated the prevalence of combined use of both drugs to estimate the days-at-risk of cisapride users for effects attributable to the concomitant use of potentially interacting drugs in this study population.

Even if the prevalence of concomitant use of cisapride and potentially interacting drugs did not decline after the implementation of warnings, these warnings may still have been effective in preventing the prevalence of drug–drug interactions to increase further. In other words, it is possible that, even when the absolute number of days-at-risk rose over the years compared with what the expected number could have been, this observed prevalence (P_o) was relatively small.

The main outcome measure was the rate of the P_o of the use of potentially interacting drugs among patients taking cisapride divided by the expected prevalence (P_e) among these patients. These measures were the actual use of potentially interacting drugs among users of cisapride compared with the expected use among these patients based on the prevalence of potentially interacting drugs among the source population, assuming that the prescribing pressures among both populations were comparable. A ratio of <1 (observed vs. expected) indicated that patients taking cisapride use fewer potentially interacting drugs than would be expected among this population and, hence, that the general health concerns these drug–drug interactions have caused were smaller than they could have been.

The codispensing rate, defined as the number of cisapride prescriptions with at least a 1-day overlap of a potentially interacting drug, was also calculated. This measure was based on the decision to codispense both cisapride and potentially interacting drugs concomitantly and clarifies whether the drug warnings were able to make healthcare professionals refrain from dispensing potentially interacting drugs to patients taking cisapride. Prevalence and codispensing rates were calculated per calendar year.

STATISTICAL ANALYSES

The P_o of concomitant use of cisapride and potentially interacting drugs was estimated as the summarized person-days of concomitant use of those agents divided by the summarized person-days of use of all cisapride prescriptions: P_o = days-at-risk/days cisapride use.

The P_e represents the prevalence of concomitant use of cisapride and potentially interacting drugs that was expected based purely on the chance of combined prescribing of those drugs. It was estimated as $P_e = P_c \times P_p$, where P_c represents the prevalence of use of cisapride and P_p the prevalence of use of potentially interacting drugs among the source population. The expected prevalence was adjusted for age, gender, and calendar year by direct standardization with the study population.

The prevalence rate, defined as the quotient of the observed and expected prevalence (P_o/P_e), and 95% CIs were calculated using EGRET statistical software.[10]

Because of multiple dates of implementation of drug warnings in the healthcare system (drug labeling, "Dear Doctor" letters, pharmacy software), we did not think a simple comparison of prevalence before and after a certain date was an appropriate measure to evaluate the effect of drug warnings; therefore, we evaluated the prevalence per calendar year from 1994 until 1998. Trends in changes of the prevalence and prevalence rates were estimated using χ^2 analysis.

Results

Throughout the study period, a total of 30 051 patients were dispensed 95 578 prescriptions for cisapride. More than 60% of patients taking cisapride were women, and >38% of patients were 40–64 years of age. Of these patients, 944 (3.1%) used ≥1 potentially interacting drugs concomitantly with cisapride. Approximately 50% (n = 448) of these latter patients received clarithromycin. For all other individual potentially interacting drugs, the prevalence of concomitant use of cisapride was <0.6%. Nefazodone was used concomitantly with cisapride by only 2 patients, and ritonavir was never dispensed with cisapride

in our study population. Both drugs were excluded from further analyses. General practitioners prescribed cisapride in most cases (83.2%), followed by internists (11.4%) and pediatricians (3.0%). The median prescription length was 30 days, and the cumulative mean exposure time to cisapride varied from 60 days per patient in 1991 to 80 days per patient in 1998. Patients used cisapride and potentially interacting drugs concomitantly for a mean period of 14 days. Extrapolated to the Dutch population, approximately 800 000 patients were dispensed cisapride at least once in the Netherlands during the study period, of which 24 000–26 000 patients have been codispensed ≥1 potentially interacting drugs. Characteristics of the study population are presented in Table 1.

In Table 2, the P_o and P_e, as well as the prevalence rates (observed/expected), of the selected potentially interacting drugs from 1994 to 1998 are presented. The prevalence of use of any potentially interacting drug among patients taking cisapride increased from 40.0 to 63.1 per 10 000 person-days exposure to cisapride during the study period. On average, the prevalence increased 13% per year, while the P_e increased on average by 27% per year in the same period. The prevalence rate of the observed versus the expected use of any potentially interacting drug decreased significantly over time (χ^2, $p < 0.01$) to 0.55 (95% CI 0.53 to 0.57) at the end of the study period. This means that cisapride users experienced only about one-half of the days at risk that would be expected based on the prevalence of the drugs studied in the source population (Figure 1).

Decreases in prevalence rates were observed for all individual potentially interacting drugs, except for concomitant use of cisapride and fluconazole or miconazole. The prevalence of clarithromycin, fluconazole, and ketoconazole increased among users of cisapride from 1994 to 1998 (on average 43%, 23%, and 15%, respectively). The use of erythromycin decreased (11% on average), and the use of itraconazole and miconazole stayed rather stable. Large increases of the P_e were calculated for concomitant use of clarithromycin and itraconazole, indicating that, in general, both drugs were prescribed more frequently. The P_o was higher than the P_e only for fluconazole, suggesting a preference to coprescribe cisapride and fluconazole.

In Table 3, the prevalence of coprescriptions for the different potentially interacting drugs is presented. In 1998, approximately 2% of all prescriptions for cisapride had at least a 1-day overlap with prescriptions of potentially interacting drugs. Overall, the proportion of coprescriptions increased on average by 9% per year from 1994 until 1998. This increase can largely be explained by the major increase of the codispensing of clarithromycin with cisapride (34% per year on average). Besides clarithromycin, the number of coprescriptions with itraconazole also showed an increasing trend (12% on average). The largest decreases of codispensing of potentially interacting drugs was observed for ketoconazole (26% per year on average), while coprescriptions of erythromycin, fluconazole, and miconazole stayed rather stable.

The results in Tables 2 and 3 show differences that were explained by changes in average days of concomitant use of cisapride and the potentially interacting drugs. The average overlap of fluconazole and ketoconazole per cisapride prescription increased (from 4 to 11, and 9 to 17 d in the study period, respectively).

Table 1. Characteristics of Patients Taking Cisapride and Potentially Interacting Drugs

Characteristics	n	%
Gender		
men	11 848	39.4
women	18 203	60.6
Age (y)		
<14	2222	7.4
15–39	8972	29.9
40–64	11 635	38.7
≥65	7222	24.0
Concomitantly[a] dispensed		
any[b]	944	3.1
clarithromycin	448	1.5
erythromycin	187	0.6
fluconazole	131	0.4
itraconazole	83	0.3
ketoconazole	32	0.1
miconazole	120	0.4
nefazodone[c]	2	0
ritonavir[c]	0	0

PIDs = potentially interacting drugs.
[a]Patients may have been concomitantly exposed to several or single PIDs more than once.
[b]Patients may have been dispensed several different PIDs alone or concomitantly with cisapride during the follow-up period. Total number is not the sum.
[c]Excluded from further analyses.

Discussion

Since the introduction of cisapride on the Dutch market in 1989, more than 800 000 patients have been exposed to the drug; of these, 24 000–26 000 received it with ≥1 potentially interacting drugs for at least 1 day. During this study period, the prevalence rate of the observed versus the expected use of any potentially interacting drug decreased significantly over time, indicating that cisapride users took fewer potentially interacting drugs concomitantly than would be expected. The number of days-at-risk and number of coprescriptions of potentially interacting drugs among cisapride users, however, increased on average by 13% and 9% per year, respectively. This increase could almost exclusively be explained by a large increase of concomitant prescribing of clarithromycin. Excluding clarithromycin, the number of days-at-risk and coprescriptions stayed rather stable. The prevalence of contraindicated coprescriptions we found was somewhat lower than results from previous studies in the US[11] and Italy.[12] This could be explained by the fact that we limited the number of contraindications to the use of CYP3A4-inhibiting drugs mentioned in the drug labeling and did not include other drugs or diseases that could possibly increase the risk for cardiac adverse effects of cisapride. We limited the number of

drugs to specifically study the effects of drug labeling changes.

These findings show that patients were dispensed relatively fewer potentially interacting drugs, either due to the fact that physicians refrained from prescribing such agents to patients taking cisapride since warnings were implemented or perhaps due to automated pharmacy dispensing management. The warnings, however, did not seem to be effective in decreasing the absolute number of days-at-risk or coprescriptions. Efforts in preventing codispensing of cisapride and potentially interacting drugs should focus on fluconazole (for which there seems to be a preference to prescribe concomitantly with cisapride) and clarithromycin (for which absolute use among cisapride users increased dramatically).

The increase of coprescribing cisapride and clarithromycin could be explained by an overlap in indication. Cisapride is mainly prescribed as prokineticum, an agent that enhances gastrointestinal motility, to patients with dyspepsia and refluxoesophagitis, whereas clarithromycin is the first-choice antibiotic as part of *Helicobacter pylori* eradication regimens.[1] Since 1995, the number of *H. pylori* eradication courses increased from 2000 to 22 000 in 1998 in the Netherlands.[8] Subanalysis of the indication of prescribing, based on a sample of all prescriptions, showed that a substantial percentage (>25%) of clarithromycin prescriptions were prescribed as part of *H. pylori* eradication regimens. The frequent concomitant use of clarithromycin and cisapride for overlapping indications may have introduced bias in our study. Because full compliance was assumed, it was possible that the moment an eradication regimen was started, cisapride was stopped. We, however, had no data that permitted further exploration of this bias that may result in an overestimation of the days-at-risk and an underestimation of the impact of warnings. Another implication of the sharp increase of concomitant use of cisapride and clarith-romycin may be important in interpreting cardiovascular adverse events associated with cisapride. Patients taking these drugs at the same time probably experience more serious acid-related diseases than patients using cisapride alone. Further research should focus on this group of patients, because results from several studies[13,14] indirectly suggest that cardiovascular morbidity was 3–5 times more prevalent in this group of patients. Subanalyses of our data showed that >50% of all patients taking cisapride had a history of cardiovascular diseases. The risk of QTc prolongation is increased in these patients; therefore, cisapride can be considered a relative contraindication. On the other hand, the elevated baseline risk increases the probability of inappropriate association of QTc prolongation with cisapride. Reports of alleged adverse effects require careful evaluation because QTc prolongation or arrhythmia may be the result of an underlying cardiovascular disease rather than a direct effect of cisapride. A study[7] describing the interaction of clarithromycin and cisapride in healthy volunteers demonstrated a 3-fold increase in cisapride concentrations after combination of the recommended doses of the 2 drugs and an average increase in QTc intervals of about 25 msec, which could be clinically significant in patients with risk factors for cardiac arrhythmias.

An unexplained finding in our study was the association between fluconazole and cis-

Table 2. Observed and Expected Prevalence of Concomitant Use of Selected Potentially Interacting Drugs Per 10 000 Person Days of Exposure to Cisapride from 1994 to 1998

		Prevalence				
Drug	Year	Observed	Expected[a]	P_o/P_e	95% CI	Impact
Overall	1994	40.0	47.0	0.85	0.79 to 0.92	
	1995	48.7	48.0	1.02	0.95 to 1.09	
	1996	54.6	51.7	1.06	1.00 to 1.12	
	1997	49.3	71.4	0.69	0.66 to 0.73	
	1998	63.1	115.2	0.55	0.53 to 0.57	[c]
Clarithromycin[d]	1994	9.5	4.2	2.29	1.84 to 2.84	
	1995	13.9	8.5	1.64	1.42 to 1.90	
	1996	20.0	15.0	1.33	1.20 to 1.48	
	1997	18.3	22.4	0.82	0.75 to 0.89	
	1998	34.6	53.6	0.65	0.61 to 0.68	[c]
Erythromycin[d]	1994	12.1	16.2	0.74	0.65 to 0.86	
	1995	10.5	13.0	0.81	0.70 to 0.93	
	1996	13.4	14.8	0.91	0.81 to 1.02	
	1997	7.8	15.0	0.52	0.46 to 0.58	
	1998	6.5	9.8	0.66	0.58 to 0.75	[c]
Fluconazole[d]	1994	5.8	5.3	1.09	0.88 to 1.36	
	1995	5.1	6.1	0.84	0.68 to 1.03	
	1996	8.1	4.9	1.66	1.39 to 0.98	
	1997	12.1	6.6	1.85	1.62 to 2.11	
	1998	11.7	7.3	1.59	1.41 to 1.80	[e]
Itraconazole[f]	1994	5.2	7.2	0.72	0.58 to 0.89	
	1995	7.8	9.0	0.87	0.73 to 1.02	
	1996	6.5	9.1	0.72	0.62 to 0.84	
	1997	5.4	19.6	0.28	0.24 to 0.32	
	1998	4.3	21.7	0.20	0.17 to 0.23	[c]
Ketoconazole[f]	1994	4.1	6.2	0.66	0.53 to 0.84	
	1995	8.1	5.2	1.57	1.30 to 1.90	
	1996	1.8	4.9	0.36	0.28 to 0.47	
	1997	0.4	5.1	0.08	0.05 to 0.13	
	1998	0.9	4.9	0.18	0.14 to 0.25	[c]
Miconazole[f]	1994	4.6	4.0	1.16	0.90 to 1.49	
	1995	3.6	3.6	1.00	0.78 to 1.28	
	1996	5.1	3.6	1.40	1.14 to 1.73	
	1997	5.6	3.7	1.49	1.24 to 1.80	
	1998	4.3	4.4	0.97	0.82 to 1.16	[g]

P_{cisa} = prevalence of cisapride; P_e = expected prevalence; P_o = observed prevalence; P_{pid} = prevalence of individual potentially interacting drug; SPC = Summary of Product Characteristics.
[a]Expected prevalence estimated from P_{cisa} and P_{pid}, adjusted for age (5-y bands), gender, and calendar year. P_e estimated as $P_e = P_{cisa} \times P_{pid}$.
[c]Significant decrease ($p < 0.01$).
[d]SPC revision August 30, 1996.
[e]Significant increase ($p < 0.01$).
[f]SPC revision May 10, 1995; "Dear Doctor" letter, October 20, 1995.
[g]No change.

apride use. As shown in Table 2, the P_o doubled during the study period in contrast to expectations. This suggests that cisapride and fluconazole have an overlapping indication or that patients switched from other imidazoles for which warnings were issued earlier. In a sample of prescriptions used in this study, fluconazole was predominantly prescribed for treatment of candida vaginitis. The association of prescribing with patients using cisapride could be explained if fluconazole was prescribed for treatment of candida esophagitis or other gastrointestinal fungal infections. We had, however, no data that permitted further elaboration of this hypothesis. A single dose of fluconazole is often used for treatment of candida vaginitis in the Netherlands. One might question whether a single dose of this potentially interacting drug is able to cause a clinically significant effect. Studies[15] have shown, however, that the cytochrome P450 inhibitory effects of azoles may be seen after only a single dose. We assumed, therefore, that patients are at risk every day during concomitant administration of cisapride and a potentially interacting drug.

A limitation of this type of study was that warnings for different drugs are implemented at different points in time. It was therefore difficult to define clear-cut periods before and after the implementation of warnings.

In this study, we only investigated the concomitant use of cisapride and potentially interacting drugs mentioned in the Summary of Product Characteristics to learn whether these drug warnings are effective in preventing drug–drug interactions. One should, however, be aware that there can be potentially harmful pharmacokinetic as well as pharmacodynamic drug–drug interactions with drugs other than those investigated in this study.

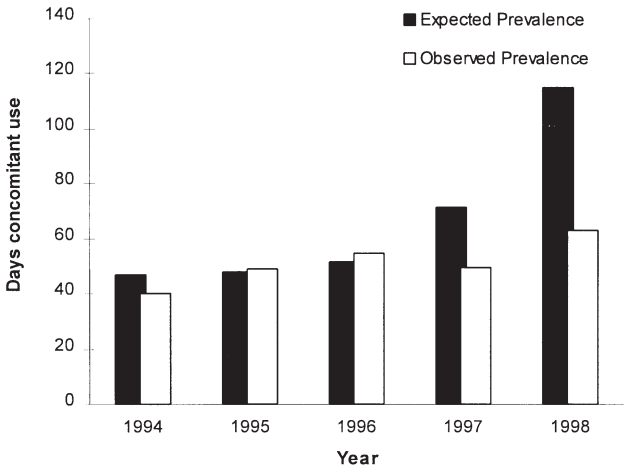

Figure 1. The prevalence of concomitant use of potentially interacting drugs (PIDs) among users of cisapride. The observed prevalence represents the true, measured prevalence in the PHARMO population from 1994 to 1998. The expected prevalence represents the prevalence of concomitant use of PIDs among patients taking cisapride, which is expected purely based on chance of concomitant use of both cisapride and PIDs. The difference between both types of prevalence is a measure of the effect of warnings.

Table 3. Coprescription Rate per 1000 Cisapride Prescriptions

Drug	1994	1995	1996	1997	1998	Per Year[a] (%)
Any[b]	16.4	15.9	20.1	19.2	22.3	9
Clarithromycin[c]	3.6	5.6	8.2	8.8	11.2	34
Erythromycin[c]	4.0	3.2	3.7	2.6	3.5	1
Fluconazole[c]	3.9	2.5	3.3	3.4	3.3	–1
Itraconazole[d]	1.0	1.4	2.0	1.8	1.3	12
Ketoconazole[d]	1.3	1.3	0.3	0.1	0.2	–26
Miconazole[d]	2.3	2.0	2.4	2.5	2.5	2

PIDs = potentially interacting drugs; SPC = Summary of Product Characteristics.
[a]Average difference per year.
[b]Patients may have been dispensed several different PIDs alone or concomitantly with cisapride during the follow-up period. Total numbers do not equal sums.
[c]SPC revision, August 30, 1996.
[d]SPC revision, May 10, 1995; "Dear Doctor" letter October 20, 1995.

Summary

Our findings show that, over the last few years, healthcare professionals have refrained from dispensing potentially interacting drugs to patients who use cisapride, probably as a result of drug warnings implemented during this period. The limited absolute effect on days-at-risk and coprescriptions resulted from increased coprescription and concomitant use of these drugs among patients taking cisapride. For both drugs, therapeutic equivalent alternatives are available and combinations with cisapride can be avoided. Furthermore, the risk of QTc prolongation or arrhythmias might be limited further by inclusion of such cardiovascular morbidity as a relative contraindication for prescribing cisapride. Despite these findings, one should realize that codispensing of potentially interacting drugs to patients taking cisapride was rare and affects <2% of cisapride users, approximately 5000 patients per year, in the Netherlands. By limiting concomitant dispensing of clarithromycin and fluconazole alone, this number will decrease to fewer than 1500 patients per year and minimize a potential risk of unwanted adverse effects.

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EXTRACTO

OBJETIVO: Investigamos la prevalencia del uso concomitante y la prescripción conjunta de la cisaprida con medicamentos que tienen el potencial de interactuar para evaluar el impacto de las advertencias durante el período de 1994–1998.

DISEÑO: Este es un estudio de seguimiento retrospectivo de pacientes que utilizan la cisaprida.

ESCENARIO: Los datos para este estudio se obtuvieron de la base de datos de farmacia del sistema de enlace de expedientes Dutch PHARMO (n = 834 000).

RESULTADOS: Durante el período de 1994–1998, la tasa de prevalencia de lo observado versus el uso esperado de algún medicamento con el potencial de interactuar se redujo significativamente con el tiempo ($p < 0.01$). El número de días a riesgo y el número de prescripciones conjuntas de medicamentos con el potencial de interactuar entre los usuarios de la cisaprida aumentó un promedio anual de 13% y 9%, respectivamente. Este aumento se explicó casi exclusivamente por un aumento sustancial de prescripciones concomitantes de claritromicina, el medicamento más comúnmente utilizado con el potencial de interacción. Considerando individualmente los medicamentos, se pudo observar una disminución en las tasas de prevalencia en cada uno de los medicamentos con potencial de interacción, excepto en el uso concomitante de la fluconazola y la miconazola.

CONCLUSIONES: Nuestros hallazgos demuestran que, durante los últimos años, los profesionales de cuidado de la salud evitan despachar medicamentos con el potencial de interacción a pacientes que utilizan la cisaprida, probablemente como resultado de las advertencias implementadas durante este período. Los efectos absolutos y limitados son el resultado de un aumento en la coprescripción y en el uso concomitante de la claritromicina y la fluconazola entre los usuarios de la cisaprida. Debido a que ambos medicamentos tienen opciones de equivalentes terapéuticos, estas combinaciones se pueden evitar. Informar las interacciones droga–droga a los médicos y a los farmacéuticos e incluir la morbilidad cardiovascular como contraindicación relativa al prescribir la cisaprida junto con estos medicamentos puede disminuir sustancialmente el riesgo de eventos adversos potenciales con la cisaprida.

Rafaela Mena de Giraldi

RÉSUMÉ

OBJECTIF: Nous avons étudié la fréquence d'utilisation concomitante et la prescription conjointe de cisapride avec d'autres médicaments ayant un potentiel d'interaction pour évaluer l'impact des mises en garde pour la période de 1994 à 1998.

DEVIS EXPÉRIMENTAL: Étude de suivi rétrospective des patients utilisant le cisapride.

LIEU DE L'ÉTUDE: Les données de cette étude ont été obtenues d'une base de données pharmaceutiques du système de dossiers hollandais PHARMO (n = 834 000).

RÉSULTATS: Pour la période de 1994 à 1998, la fréquence d'utilisation observée par rapport à celle prévue pour n'importe quel médicament avec un potentiel d'interaction a diminué de façon significative au fil du temps ($p < 0.01$). Le nombre de jours à risque et le nombre de prescriptions conjointes de médicaments avec potentiel d'interaction chez les utilisateurs de cisapride a cependant augmenté en moyenne de 13% et 9% par année, respectivement. Cette augmentation a été presque exclusivement expliquée par une forte augmentation de prescriptions concomitantes de clarithromycine, le médicament avec un potentiel d'interaction le plus utilisé. En regardant les médicaments de façon individuelle, des diminutions dans les fréquences d'utilisation ont été observées pour tous les médicaments individuels avec un potentiel d'interaction à l'exception de l'utilisation concomitante de fluconazole et de miconazole.

CONCLUSIONS: Nos découvertes démontrent que depuis quelques années les professionnels de la santé s'abstiennent de prescrire des médicaments avec un potentiel d'interaction aux patients utilisant le cisapride, probablement suite aux avertissements publiés pendant cette période. Les effets absolus limités résultent d'une augmentation de prescriptions conjointes et d'utilisation concomitante de clarithromycine et de fluconazole chez les utilisateurs de cisapride. Parce que des alternatives thérapeutiques équivalentes étaient disponibles pour les 2 médicaments, ces combinaisons étaient évitables. Communiquer ces interactions médicamenteuses aux prescripteurs et aux pharmaciens et inclure la morbidité cardiovasculaire comme une contre-indication relative lorsque le cisapride est prescrit avec ces médicaments pourraient réduire le risque d'effets adverses potentiels de façon substantielle avec le cisapride.

Chantal Guévremont