Hong Kong Journal of Nephrology
2003;5(1):15-18.

ORIGINAL ARTICLE

Risk of death in dialysis patients taking cisapride

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Abstract

Background: Cisapride is a prokinetic agent that is useful to relieve gastrointestinal symptoms that often occur in dialysis patients. However, sudden death has been reported and alarmed the use of cisapride in dialysis patients. This study was performed to identify whether the use of cisapride increases the risk of death.

Methods: We retrospectively analyzed all records of dialysis patients followed during the period November 1997 to March 2000. Cisapride dosage and risk factors associated with increased risk of sudden death such as cardiovascular disease, hypokalemia, and possible interacting drugs were recorded.

Results: Of 364 dialysis patients, 85 had been prescribed with cisapride (group A) whereas 279 had not (group B). Group A patients were older, with more female patients and longer duration of dialysis. There was no significant difference in mortality or causes of death between the two groups after adjusting for the baseline demographic differences. For group A, eight patients (9.41%) died while still on cisapride and 19 (22.4%) died after cisapride had been stopped. The causes of death were peritonitis (n = 2), infection (n = 2), ischemic heart disease (n = 1), malignancy (n = 1), sudden death (n = 1), and unknown (n = 1). Low serum albumin (p=0.013) and hypokalemia (p=0.066) were potential predictors of death while taking cisapride, but the presence of diabetes mellitus, maximum dosage of cisapride, and underlying cardiovascular disease were not. There was no drug interaction leading to cisapride toxicity.

Conclusions: Patients who were given cisapride were older, more often women, and had a longer duration of dialysis. Low serum albumin and hypokalemia were significant predictors of death in patients given cisapride. Although no excessive risk of death was documented, the use of cisapride in dialysis patients should still be cautious and potential drug interactions and electrolyte disturbances should be avoided.

Key words: Arrhythmia, Cisapride, Dialysis, Hypokalemia, Renal failure, Sudden death

中文摘要

背景：西沙必利（Cisapride）是一種胃腸促動藥，可用于緩解透析患者常見的胃腸道症狀。不過，曾有報道指出患者使用此藥後猝死。本研究旨在確定使用西沙必利會否增加死亡風險。

方法：本文回顧性地分析了1997年11月至2000年3月間所有隨訪透析患者的病歷，記錄了西沙必利劑量以及與猝死風險增大相關的風險因素，如心血管疾病、低鉀血症、和藥物之間可能存在的相互作用。

結果：在364例透析患者中，85例使用西沙必利（A組），其餘279例則不使用西沙必利（B組）。A組病人年齡較大，女性患者較多，透析的持續時間也較長。對患者基線一般資料的差異進行校正後，兩

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組間的死亡率或死因並不存在顯著差異。在A組中，八例（9.41%）在使用西沙必利時死亡，19例（22.4%）於停藥後死亡。死因包括腹膜炎（2例）、感染（2例）、缺血性心臟病（1例）、惡性腫瘤（1例）、猝死（1例）、和不明原因的死亡（1例）。低血清白蛋白（p=0.013）和低鉀血症（p=0.066）可能是在使用西沙必利時死亡的預測因素，但糖尿病、大劑量使用西沙必利、以及患者本身患有心血管疾病無關。未發現可導致西沙必利毒性的藥物相互作用。

結論：醫囑使用西沙必利的患者年齡較大、以女性較多、透析的持續時間也較長。低血清白蛋白和低鉀血症是西沙必利使用者死亡的顯著的預測因素。雖然本研究未證實死亡的風險增大，在透析病人中仍應慎用西沙必利，並應避免潛在的藥物相互作用和電解質紊亂。

INTRODUCTION

Anorexia, nausea, and dyspepsia are common gastrointestinal symptoms in uremic patients and would lead to malnutrition, a significant predictor of mortality. These symptoms may be related to delayed gastric emptying, which is frequently seen in patients with chronic renal failure (1). Cisapride, a prokinetic agent, is a useful drug to treat these symptoms (2). However, there have been reported cases of sudden death in patients taking cisapride. Most of the deaths were related to cardiac arrhythmia in association with certain drug combinations (3,4). Similar case reports have also been described in uremic patients (5) and have alarmed the use of cisapride in general. The current recommendation is that caution should be taken with the use of cisapride in patients with underlying renal failure, cardiac problems, and electrolyte disturbances. Although it was withdrawn from the United States market in July 2000 for safety reasons, there was a scarcity of data regarding mortality and safety of cisapride in dialysis patients. Because cisapride is an effective drug to treat dyspepsia and anorexia in uremic patients, we conducted this retrospective analysis to identify whether prescription of cisapride is linked to increased risk of death among dialysis patients and to identify possible factors associated with increased risk of death.

METHODS

Clinical data of chronic dialysis patients in our renal unit during the period November 1997 to March 2000 were retrieved and analyzed retrospectively. Patients were divided into two groups: those who had been prescribed with cisapride (group A) and those who had not (group B) during this period. Demographic factors including age, sex, presence of diabetes mellitus, mode of dialysis, and duration of dialysis were recorded. Data including indications, dosage and duration of cisapride use, and reasons for stopping cisapride were also obtained. The primary outcome was death. The causes of death in patients who died during the study period were also investigated. To study the risk of deaths associated with cisapride prescription, dosage of cisapride, concomitant use of medications including azole antifungals, macrolide antibiotics, class Ia/III antiarrhythmic agents, tricyclic antidepressants, antipsychotics and H1 antihistamines, serum albumin level, coexisting cardiovascular problems, presence of prolonged QT intervals, and electrolyte disturbances including hypokalemia and hypocalcemia were collected in the cisapride group for relative risk analysis.

Statistical analysis

The SPSS 10.0 program (SPSS, Chicago, IL, US) was used for statistical analysis. The chi-square test, Fisher's exact test, and Mann-Whitney's test were used where appropriate for comparison between various risk factors and number of deaths. General linear model with univariate analysis was used for adjustment of potential confounding factors. Continuous variables were expressed as mean (SD). A p value of 0.05 was taken as the level of statistical significance.

RESULTS

There were 364 dialysis patients in the study period including 314 patients on continuous ambulatory peritoneal dialysis and 50 patients on hemodialysis. There were 172 men and 192 women. The mean age was 58.48 (3.52) years and mean duration of dialysis was 54.13 (47.01) months. Among them, 85 patients had been prescribed with cisapride (group A) whereas 279 had not

Table 1. Baseline demographic data for both groups.

	Group A (n = 85)	Group B (n = 279)	*p* value
Age, years	63 ± 12	57 ± 14	0.000
Women, n (%)	55 (64.71)	137 (49.10)	0.013
Duration of dialysis, months (median)	21.48	46.00	0.000
Diabetes mellitus, n (%)	30 (35.29)	72 (25.81)	0.088
Peritoneal dialysis/hemodialysis ratio	74:11	240:39	0.808

(group B). There were more female patients and a tendency toward more diabetic patients in group A. They were also older with a longer duration of dialysis (Table 1). The most prevalent indication for cisapride was anorexia (n = 73, 85.9%) followed by dyspepsia (n = 11, 12.9%) and reflux symptoms (n = 1, 1.2%). The mean duration of cisapride use was 8.63 months (range, 0.2-56.9 months) and the average daily dosage of cisapride was 15.76 (6.05) mg. Sixty-eight patients stopped taking cisapride because it was no longer indicated, whereas only one patient stopped the drug because of diarrhea related to cisapride. Twenty-four patients (28.2%) had underlying cardiovascular disease in group A. Among them, 17 patients (20%) had ischemic heart disease, one patient (1.2%) had sick sinus syndrome, whereas six patients (7.1%) had a history of cardiac arrhythmia.

Nineteen patients (22.4%) from group A died during the period and among them eight patients died while still taking cisapride. In group B, 54 patients (19.4%) died during follow up. There was no statistically significant difference in the total number of deaths among the two groups (p=0.65) after adjusting for age, sex, and duration of dialysis. The causes of death from both groups were compared. There were only one cardiac related death and one sudden death from group A. The causes of death were similar in both groups as shown in Table 2. As for concomitant drug usage, 19 patients were taking H1-antihistamines (hydroxyzine and chlorpheniramine) concomitantly with cisapride whereas only two patients had taken antipsychotics (trifluoperazine and haloperidol, n = 1; pimozide, n = 1) and one patient had taken an antiarrhythmic agent (amiodarone) with cisapride. No patient had taken azoles or macrolides concomitantly with cisapride. No undue side effects were reported. No prolonged QT interval was found among all the patients prescribed with cisapride.

The relationship between potential risk factors related to death while taking cisapride was analyzed, which included serum albumin, age, presence of hypokalemia, maximum cisapride dosage, diabetes mellitus, and underlying cardiovascular disease. Patients who died while taking cisapride had a lower serum albumin compared with other patients from the cisapride group (27.42 vs 33.32 g/L; p=0.013). Higher serum albumin was associated with a decreased risk of death (relative risk, 0.813; p=0.016). There was also a trend that more patients who died while taking cisapride had hypokalemia compared with other patients in group A, although the difference was not statistically significant (p=0.066). However, the maximum dose of cisapride, diabetes mellitus, and cardiovascular disease were not significant predictors of death for patients taking cisapride (Table 3).

DISCUSSION

Cisapride is a serotonin (5-HT) receptor agonist that is specifically distributed to the gastric and intestinal tissues after oral absorption. It improves lower esophageal sphincter tone, esophageal peristaltic activity, gastric and duodenal contractility, as well as small bowel transit. It has also been reported to improve gastric emptying in dialysis patients (6). It is metabolized by hepatic cytochrome P450 enzyme. Case reports of sudden death related to cisapride use had been centered around prolonged QT interval and fatal cardiac arrhythmias. Because cardiac disease is the most important cause of death in dialysis patients on cisapride who would often present as sudden death (7), it is difficult to incriminate sudden death to cisapride use unless arrhythmia with typical QT prolongation or Torsades de pointes is documented (8,9). In our series, neither of these two phenomena was observed. There was only one sudden death in a patient taking cisapride. The number of cardiovascular or sudden deaths and the overall number

Table 2. Causes of death in both groups.

	Deaths		All deaths		
	While taking cisapride	After cisapride cessation	Group A	Group B	p value*
IHD	1	1	2	9	0.520
Sudden death	1	0	1	5	1.000
Peritonitis	2	2	4	8	0.528
Infection	2	3	5	15	0.902
Malignancy	1	0	1	2	1.000
CVA	0	2	2	4	0.647
Fluid overload	0	1	1	0	0.260
Others	0	2	2	5	0.872
Unknown	1	0	1	6	0.457
Total	8	11	19	54	0.651

IHD = ischemic heart disease; CVA = cerebrovascular accident.

*Adjusted for age, sex, and duration of dialysis.

Table 3. Potential predictors of death while taking cisapride.

Potential risk factors	Patients who died while taking cisapride (n = 8)	Other patients given cisapride (n = 77)	*p* value
Age, years	66.51 ± 8.14	62.85 ± 12.19	0.416
Diabetes mellitus, n (%)	4 (50)	26 (33.77)	0.444
Serum albumin, g/L	27.42 ± 4.93	33.32 ± 5.06	0.013
Hypokalemia, n (%)	6 (75)	30 (39.90)	0.066
Concomitant heart problem, n (%)	3 (37.5)	21 (27.27)	0.682
Maximum cisapride dose, mg	15.97 ± 6.28	13.75 ± 2.31	0.450

of deaths were similar between the two groups.

Our results showed no excessive risk of death in patients who took cisapride, and no potential drug interactions could be identified. However, this needs to be interpreted with caution because of the relatively small sample size in this retrospective analysis. Furthermore, because this study was only targeted at identifying the risk of death associated with cisapride, we have not studied the incidence of cardiovascular disease in patients not prescribed with cisapride. Hence, the possibility of a lower incidence of cardiac disease in group A leading to the observation of increased mortality in group A cannot be excluded. Conversely, because cisapride is often prescribed to malnourished patients with anorexia, selection bias is a distinct possibility because malnutrition is a strong predictor of death (10). A prospective study would give a more definitive answer, but the incidence of Torsades de pointes is only 1 in 120 000 according to the pharmaceutical package insert for cisapride, and a huge study sample size is required for the prospective study. Under the present stringent recommendation for cisapride use, it is almost impossible to conduct such a study. Caution in prescribing cisapride should be exercised in dialysis patients, and coexisting electrolyte disturbances and potential drug interactions should be avoided.

Patients who died while taking cisapride were found to have lower serum albumin levels and a tendency toward hypokalemia, both of which may be related to poor intake and malnutrition in this group of patients. There have been previous recommendations that uncorrected electrolyte disturbance should be avoided because it may increase the risk of Torsade de pointes during cisapride use (11). Given the fact that most deaths were not related to sudden death or cardiac arrhythmia in our series, the mortality in the cisapride group may be associated with the effects of poor nutrition or hypokalemia per se rather than the use of cisapride. It is established that malnutrition has adverse effects on survival (12,13). Our findings should alert caution in prescribing cisapride in patients with underlying malnutrition or tendency for hypokalemia because both are expected to be more common in this group of patients indicated for prokinetic agents.

In conclusion, no excessive risk of death was demonstrated for the use of cisapride in dialysis patients from our review. However, given the rare but potentially fatal cardiac complications associated with cisapride, its prescription in dialysis patients should still be cautious, and potential drug interactions and electrolyte disturbances should be avoided as far as possible.

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