BUDGET IMPACT ANALYSIS OF USING OMEPRAZOLE IMMEDIATE-RELEASE ORAL SUSPENSION IN REPLACE OF INTRAVENOUS PANTOPRAZOLE IN CRITICALLY ILL PATIENTS

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ABSTRACT

Objectives
The aim of the present study was to estimate the financial consequence of using omeprazole immediate-release (IR) oral suspension versus pantoprazole intravenous infusion for preventing stress-related upper gastrointestinal bleeding in critically ill patients from the perspective of the health care system.

Methods
An Excel-based model was developed to compare the cost of prevention of upper gastrointestinal bleeding early after intensive care admission using the current intravenous (IV) pantoprazole formulation versus omeprazole IR oral suspension. Total costs included the cost of acid suppressive drugs and related clinical outcomes. Inputs were obtained from a local clinical trial, the Ministry of Health database, insurance organizations, hospital and pharmacy registries, the relevant literature, and expert opinion. The robustness of the input data was investigated by one-way sensitivity analysis. The model was developed based on the results of a randomized control trial (RCT), in which experimental and control groups received omeprazole and pantoprazole, respectively.

Results
According to the proposed model, the cost of gastrointestinal (GI) bleeding prevention using pantoprazole IV was US$ 950,000 while US$ 750,000 was spent on receiving omeprazole oral suspension. These costs led to the annual cost-saving of almost US$ 200,000 (US$4 per member, per month) for the health care system.

Conclusion
In the present study, a budget impact analysis was performed to assess the financial consequences of using omeprazole IR oral suspension in place of pantoprazole IV for prevention of upper gastrointestinal bleeding. The better preventive effect of omeprazole IR oral suspension when compared with conventional therapy using pantoprazole IV was the major reason for the final comparative budgetary savings.

Key Words: *Budget impact, upper GI bleeding, proton pump inhibitors (PPIs), oral suspension, critically ill patients*

Stress-related gastrointestinal mucosal disease (SRMD) occurs among 75 to 100 percent of critically ill patients within 24 hours (h) of admission to intensive care units (ICU) and the related ulcers increase the risk of upper gastrointestinal bleeding (UGIB). Acid-suppressive drugs are effectively used in reducing the risk of UGIB by maintaining a pH above 4 almost always over time.[1,2]

On the other hand, nosocomial infection, which is a life-threatening, hospital-acquired complication, is correlated with intramucosal gastric pH. Ventilator-associated pneumonia (VAP), as a common nosocomial infection, is one of the costliest complications that occurs early after ICU admission and specifically refers to those patients who receive mechanical ventilation during ICU admission.[3] The exact amount of using acid-suppressive agents for increasing VAP incidence in patients in intensive care unit is still controversial. It is more likely that the higher the pH level, the higher the infection incidence would be. There are several acid-suppressive drugs that have been demonstrated to prevent UGIB. Histamine-2 receptor antagonist (H2RA) therapy has shown a significant decrease in the incidence of UGIB. Additionally, previous studies have shown that proton pump inhibitors (PPIs) are clinically much more effective in terms of inhibiting gastric acid production than H2RAs.[2,4] Due to the susceptibility of PPIs to the acidic environment, enteric-coated (EC) tablets are conventionally available in the market. However, since critically ill patients have difficulties in swallowing EC tablets, liquid formulations are highly recommended and thus acid-resistant PPI suspensions have been recommended by researchers. Philips et al. (1996) concluded that enteric-coated omeprazole granules, which were suspended in sodium bicarbonate, had an excellent gastric pH control.[5] Conard et al. (2005) demonstrated that immediate-release omeprazole suspension was more effective than intravenous cimetidine in terms of preventing UGIB in critically ill patients.[4] Moreover, a randomized controlled trial (RCT) in 2013 demonstrated better clinical outcomes using the oral suspension of omeprazole and pantoprazole versus intravenous pantoprazole among Iranian patients.[6]

In the current study, the above-mentioned RCT was considered as the main data reference, from which probabilities, clinical outcomes, and health care resource utilization were extracted. Primary objectives of the present work included evaluating the financial effect of using omeprazole oral suspension versus conventional pantoprazole IV infusion on preventing UGIB among critically ill patients from the perspective of Iranian health care system.

Materials and Methods

An Excel®- (Microsoft Corporation, Redmond, WA, USA) based model was made considering the results of the reference RCT which had been undertaken at Masih Daneshvari Teaching Hospital in 2012-2013.[6] Required data inputs such as probabilities, clinical outcomes, and resource utilization were mainly obtained from the RCT along with the literature. Standard clinical guidelines, practically applied at the intensive care units, were also considered as main reference to determine the most important and costly health care resource utilization.

Clinical outcomes related to the following specific key factors/events were included in the model calculations: acid-suppressive drugs (oral omeprazole versus pantoprazole IV), upper GI bleeding, and VAP. Drug costs were extracted from the Social Security Organization database and the hospital's pharmacy. As far as other health care resources were concerned, provider (hospital)–based prices were used in the model (2012–2013).

Data sources and population estimates

Required prevalence data were obtained from the ministry of health (MOH) database. The reference RCT was the main data source for probabilities. Health care utilization such as physician/specialist visits, laboratory tests, nursing services, and treatment options, which were similar in both groups, were excluded from the model calculations (Table 1).

TABLE 1 Model inputs and data sources for budget impact analysis

COMPONENTS	UNIT COST	SOURCE
Acid-suppressive drugs		
Omeprazole IR oral suspension	Price per bottle	Insurance organization's database
Pantoprazole (intravenous)	Price per vial	Insurance organizations' database
Clinical Outcomes		
Gastrointestinal bleeding		
Probability	-	Reference RCT (unpublished data)
Treatment		
Pantoprazole IV CBC test Washing with normal saline	Price per vial Price per test Price per bottle	Insurance organization's database Insurance organization's database Insurance organization's database
Ventilator- associated pneumonia (VAP)		
Probability	-	Reference RCT (unpublished data)
Treatment		
Ceftriaxone	Price per vial	Insurance organization's database
Ampicillin-sulbactam	Price per vial	Insurance organization's database
Levofloxacin	Price per tablet	Insurance organization's database
Imipenem	Price per vial	Insurance organization's database
Epidemiologic data	-	Ministry of Health database

IRR= Iranian Rials; USD= United States Dollars; CBC= Complete Blood Count

According to the MOH database, 4,150 ICU beds were active in Iran over the study period (from 2012 to 2013), which could be assumed as the maximum number of admission to intensive care units (in total at different provinces in Iran).

Time horizon and perspective

A 2-week time horizon (14 days) was considered for calculating the final budget impact from the perspective of health care system.

Comparison scenarios

According to the reference RCT, 56 critically ill patients referring to the intensive care unit at Masih Daneshvari Teaching Hospital randomly received intravenous pantoprazole (40 mg per day), omeprazole immediate-release oral suspension 2 mg / ml (40 mg per day), and pantoprazole oral suspension 2 mg / ml (40 mg per day). Results from the two groups of omeprazole oral suspension and pantoprazole intravenous infusion were included in the model calculation. Treatment duration was for at least 24 hours and up to 14 days. None of the patients completed the clinical trial. In the intravenous pantoprazole group only 3 patients continued the experiment to day 14. In the omeprazole group, only 5 patients continued the experiment to day 14. The most probable reason for leaving the trial could be intolerance of nasogastric tube or patients' death.

Analysis

The analytical model was made using Microsoft Excel® 2010. Costs of medical treatment and clinical complications were the main total cost components.

Cost of acid-suppressive drugs

According to the clinical guidelines, mean PPIs dose is 40 mg / day for UGIB prevention in ICU. Cost of omeprazole oral suspension (2 mg / ml, 100 ml) was 30,000 IRR (Islamic Republic of IRAN Rials) (US$ 1.2) per bottle or 7,500 IRR (US$ 0.3) per patient per day (each bottle containing 200 mg omeprazole, serving 5 dosages). Moreover, some devices were required for oral suspension, which included gavage syringe, gloves, etc. Total cost of treatment with omeprazole IR oral suspension was almost 1,200 million IRR (US$ 50) per patient over a 14-day course of therapy, which corresponded to the total annual cost of almost 5,000 billion IRR (US$ 200,000) to the health care system.

Cost of 40 mg pantoprazole intravenous was 1,680 million IRR (US$ 67) per patient over the 14-day course of therapy and the total annual cost of treatment with pantoprazole intravenous was almost 7,000 billion IRR (US$ 300,000) to the health care system (Table 2).

TABLE 2 Cost of acid-suppressive agents in omeprazole- versus pantoprazole-based therapies in Iran (2012-2013)

Maintenance Therapy	Dosage form	Dosage / day/ patient	Unit price (IRR)	Total cost/ day /patient (IRR)	Duration (D.)	Unit Cost (USD)	Total cost/ patient (IRR)	Total Cost (IRR) (n=4, 150)	Total Cost (USD)
1) Pantoprazole IV	For Inj 40 mg	40 mg qd	120,000	120,000	14		1,680,000	6,972,000, 000	278,880
2) Omeprazole PO	Oral Sus. 2mg/ml (bottle)	40 mg qd	30,000	7,500	14	105,000			-
Devices	Gloves	3	5,211	15,633	14	218,862			-
	Syringes	3	21,840	65,520	14	917,280	1,241,142	5,150,739, 300	206,030

D.= day; qd= once per day, every day

Cost of clinical complications

Major clinical events considered in the current model were clinically significant UGIB (6% versus 11%) and VAP (78% versus 89%) in omeprazole IR oral suspension and pantoprazole intravenous. As far as UGIB was concerned, pantoprazole IV infusion was administered over the 3-day therapy duration with the average treatment dose of 8 mg / h (in addition to the loading dose of 80 mg). Furthermore, complete blood count was tested every 6 h for the patients with GI bleeding. In case of VAP, the antibiotics of choice for hospital-acquired pneumonia were advised respectively (Tables 3 and 4). As it is shown in Table 3, cost of the management of the complications has been calculated for each patient. In Table 4, total cost of complications treatment has been calculated considering the rate of each complication occurrence and the number of patients.

Total cost and budget difference calculation

The total prevention cost in each scenario was calculated using both cost of medical treatment (acid-suppressive drugs) and cost of clinical complications related to each individual scenario.

Consequently, total cost difference between the new and current therapy strategies was calculated (as it is shown in Table 5) and was reported both in total and per-member per-month (PMPM) value, which was stated in both IRR and US$. Official exchange price for US$ 1 was 25,000 IRR over the study year (Table 5 and Figure 1).

One-way sensitivity analysis

To determine the robustness of the final results, a one-way sensitivity analysis was performed by evaluating changes of important variables, which were estimated price for omeprazole oral suspension, expected number of patients per year, pantoprazole market price, and cost of clinical outcomes for omeprazole- and pantoprazole-based regimens. Relative values mostly varied by 75% from the base-case, except in case of pantoprazole price (normally not becoming less than the base-case) and omeprazole price (varying between the current price and 60% of pantoprazole IV price).

RESULTS

Base-case scenario

Over the study period, 4,150 patients were admitted to the intensive care units at hospitals in Tehran. The study results demonstrated that final expected 1-year cost of UGIB prevention for receiving intravenous pantoprazole was almost 24, 000 billion IRR (US$ 950,000) versus 19,000 billion IRR (US$ 750,000) for the patients who received omeprazole as their prevention regimen.

These figures corresponded to both cost of acid-suppressive agents (28% versus 29% of total costs) and that of clinical complications (72% versus 71% of total costs) in omeprazole versus pantoprazole (Figure 1) and led to the cost-saving by almost 5,000 billion IRR (US$ 200,000) or 100,000 IRR (US$ 4) PMPM for the health care system (Table 5).

TABLE 3 Cost of clinical outcomes per patient for UGIB prevention in Iran (2012-2013)

AE/ drugs	Dosage form	Dosage/day/ patient	Nr. per day	Duration (D.)	Unit price (IRR)	Unit cost /patient (IRR)	Total cost/ patient (IRR)
GI Bleeding							
Pantoprazole	For infusion	Loading dose: 80 mg qd; Maintenance dose: 8 mg/h infusion	5.67	3	290,000	4,930,000	6,610,153
CBC test	-	q 6h	4	2	192,000	1,536,000	
Washing with normal Salin	-	-	1	3	48,051	144,153	
VAP							
Ceftriaxone	For Inj: 1g	2g qd	2	7	14,000	196,000	3,699,500
Ampicillin-sulbactam	For Inj: 1/ 2g	12g qd	6	7	22,000	924,000	
Levofloxacin	Tab: 500mg	750mg qd	1.5	7	19,000	199,500	
Imipenem	For inj: 500/500 mg	1g qd	2	7	170,000	2,380,000	

D.= day; hr= hour; VAP= ventilator-associated pneumonia; GI= gastrointestinal; (-)= not applicable

TABLE 4 Total cost of clinical outcomes related to omeprazole- versus pantoprazole-based therapies for UGIB prevention in Iran (2012-2013)

Adverse Events	Probability	Nr. of patients (n=4,150)	Unit cost (IRR)	Total cost (IRR)	Total Cost (USD)
			GI Bleeding		
Pantoprazole IV	0.111	461	6,610,153	3,044,966,979	121,799
Omeprazole PO	0.056	232		1,536,199,557	61,448
			VAP		
Pantoprazole IV	0.889	3,689	3,699,500	13,648,750,325	545,950
Omeprazole PO	0.778	3,229		11,944,575,650	477,783

TABLE 5 Budget impact results of conversion from pantoprazole IV infusion into omeprazole IR oral suspension for UGIB prevention in Iran (2012-2013)

Budget Components (base-case)	Omeprazole PO (IRR)	Pantoprazole IV (IRR)	Omeprazole PO (USD)	Pantoprazole IV (USD)
Costs of Treatment	5,150,739,300	6,972,000,000	206,030	278,880
Costs of Adverse Events	13,480,775,207	16,693,717,304	539,231	667,749
Total Costs	18,631,514,507	23,665,717,304	745,261	946,629
Difference (BI)	**-5,034,202,797**		**-201,368**	
PMPM	**-101,088**		**-4.044**	

PMPM= per-member per-month

FIG. 1 Budget impact of using omeprazole IR oral suspension instead of the current conventional therapy using pantoprazole (IV) in Iran (2012-2013).

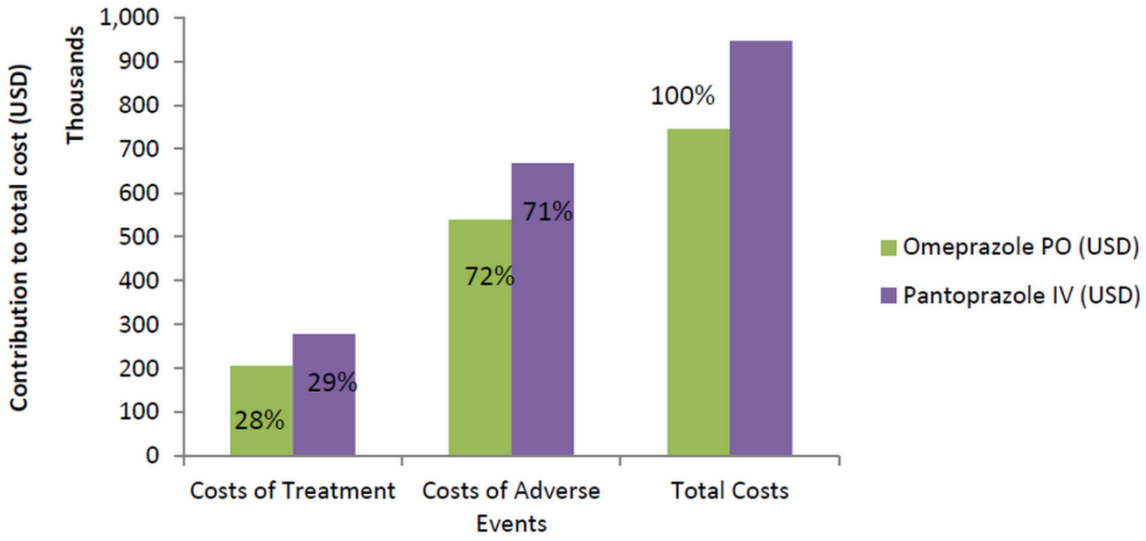
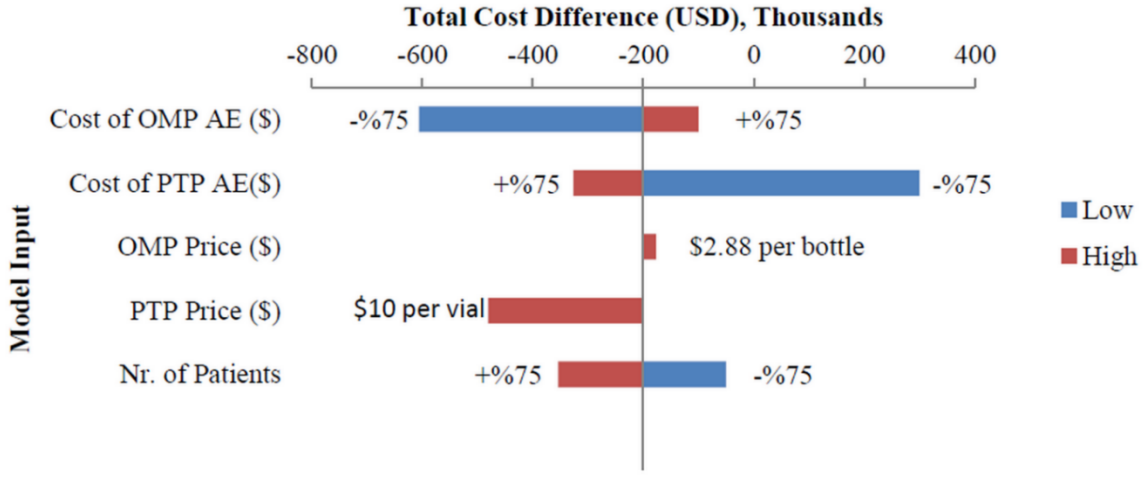


FIG. 2 Sensitivity analyses: Total BI difference between omeprazole IR oral suspension and pantoprazole (IV)-based therapies (2011–2012).



Note: *Values at the end of each bar indicate the change in BI from the base-case or the possible lowest and highest values of that input.*

One-way sensitivity analysis

According to the analysis, cost of adverse events related to pantoprazole IV and omeprazole IR oral suspension dramatically changed the budget required for the prevention of UGIB in the critically ill patients admitted to ICU. The final results demonstrated that the cost difference was not sensitive to the omeprazole IR oral suspension price. Thus, even by considering a price twice the base-case for omeprazole IR oral suspension, the budget difference would still result in a considerable cost-saving (Figure 2). The analysis also showed that cost of pantoprazole-based therapy and its relative clinical outcomes had an effective role in the total cost difference. As far as "the number of patients" was concerned, the results demonstrated that, the higher the number of patients, the higher the expected budget saving would be (Figure 2).

DISCUSSION

The term stress-related mucosal disease (SRMD) refers to a set of conditions which range from superficial mucosal damage to the stress ulcers caused by mucosal ischemia. It is commonly observed early in critically ill patients after ICU admission. Prophylaxis of stress ulcers, which mainly include acid-suppressive agents, may reduce major bleeding.[7]

Omeprazole, as the first PPI approved in the United States, keeps intragastric pH of ≥ 5 for up to 24 h. Only oral dosage forms of omeprazole are available in the market. Different studies have shown that omeprazole suspension that is normally administered through the nasogastric tube could safely prevent clinically significant GI bleeding.[7,8]

On the other hand, the majority of patients at ICU cannot usually tolerate the solid dosage forms of medications. Therefore, their care may be improved through using intravenous or oral liquid forms of the treatment as prophylaxis.[9]

Moreover, considering the fact that high-risk patients with SRMD in ICU usually require mechanical ventilation, one concern about the prophylaxis strategy of using acid-suppressive drugs is the increased risk of nosocomial pneumonia, which is the most common infection in mechanically ventilated patients and could be related to the increased gastric pH followed by aspiration.[10,11]

The model presented in this study was developed for estimating the financial effect (budgetary impact) of switching from intravenous pantoprazole IV to omeprazole oral suspension in terms of preventing UGIB from the perspective of health care system. Budget impact analysis generally demonstrates the financial impact of using a new therapy strategy or a new drug on the budget of the payers. Since omeprazole IR oral suspension is not covered by insurance organizations in Iran, the present work was developed to analyze the monetary value of switching to oral omeprazole formulation.[12] According to the results of the present study involving approximately 4,150 patients admitted to intensive care units in Iran over the study period, the budget impact of converting from the intravenous pantoprazole to omeprazole oral suspension was minus 5 billion IRR (US$ 200,000) or minus 100,000 IRR (US$ 4) PMPM.

The results also demonstrated that, mainly because of fewer cases of upper GI bleeding and ventilator-associated pneumonia over the 14-day stay at ICU, an omeprazole-based regimen would be less costly than the conventional intravenous pantoprazole-based therapies. Moreover, according to this analysis, an increase in the number of eligible patients would result in the subsequent increase in the amount of cost-saving.

Additionally, according to the local RCT and hospital registries, the extemporaneous omeprazole oral suspension formulation price (currently prepared at the hospital ward) was almost 30,000 IRR per bottle; however, its company price, with market authorization, would be quite different. In Iran`s health care system, there is a tight control on drug pricing by the MOH. Pricing system for locally-produced generic drugs is mainly cost-based unless the equivalent brand item is present in the market through importation.[13] In the last case the drug could get 60 to 80% of the price of the brand product. Currently there is no omeprazole IR oral

suspension formulation in either generic or brand forms in Iran`s drug market and thus the product would be marketed as a generic or brand generic product for the first time in the country. Therefore the applied pricing method could be the cost-based approach which corresponded to almost 30,000 to 40,000 IRR (US$ 1.2 to 1.6) per bottle. However, if the brand item was imported by the time of generic entry to the market, the product could get at least 60% of the brand or imported brand generic drug`s market price.

At present for the maximum price of omeprazole IR oral suspension in the model, as the next replaceable alternative, we took the pantoprazole IV brand price as the maximum probable price for the omeprazole IR oral suspension brand product assuming that in any case an oral suspension could not get a higher price than the intravenous formulation especially in the same therapeutic/ medical group. The price of pantoprazole was almost 120,000 IRR (US$ 4.8) per vial and calculating the 60% would make it almost 72,000 IRR (US$ 3) per bottle for the omeprazole IR oral suspension locally produced generic product. Having considered the above mentioned probable price window for omeprazole IR oral suspension in the market, and the fact that the total cost difference (budget impact) is not sensitive to the omeprazole IR oral suspension price (according to the SA results), a considerable budget saving would be always warranted using omeprazole IR oral suspension in replace to pantoprazole IV in UGIB prevention in critically ill patients at ICU (Figure 2).

CONCLUSION

Stress-induced upper gastrointestinal tract bleeding, as a serious complication in the immediate postoperative period, could increase the rate of mortality among critically ill patients. Drugs commonly used in the prophylaxis of stress-related GI bleeding include histamine receptor antagonists, sucralfate, antacids, and proton-pump inhibitors (PPIs).[15,16] Clinical studies have demonstrated that omeprazole suspension safely prevents clinically significant UGIB, maintains the perfect control of intramucosal pH, and is the least costly medication alternative.[16]

According to the present analysis, the annual saving budget impact of almost 100,000 IRR (US$ 4) PMPM would be expected in Iran as a result of using the new preventive strategy including omeprazole IR oral suspension. Less frequent costly adverse events (UGIB and VAP) related to omeprazole (IR) oral suspension compared to intravenous pantoprazole were the major reasons for the apparent final budgetary savings.

Company price of locally-produced omeprazole suspension in Iran could simply get the prices by almost 72,000 IRR (US$3) per bottle with no budgetary concerns to the payers. Moreover, the higher number of patients would result in the much higher value of savings than the base-case.

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