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Original article

The inadvertent consequences of drug recalls: A case study of a recall of pantoprazole generics from the markets

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ABSTRACT

Introduction: Drug recalls may impact treatment plans or access to suitable therapies. Thus, they inadvertently affect treatment outcomes.
Objective: We aimed to examine the impact of recalls on patients' safety using pantoprazole-containing products recall as a case study in terms of the occurrence of potential drug-drug interactions (pDDIs).
Methods: This retrospective study used de-identified electronic health records of adult patients who had a prescription for oral proton pump inhibitors (PPIs) including pantoprazole, esomeprazole, lansoprazole, or omeprazole from April 2020 through September 2021 from a large tertiary care hospital. The study outcome definition was the prevalence of pDDIs in PPIs users before and after the recall date (March 2021). Changes in the prevalence of pDDIs were modeled using interrupted time-series. The rate ratio of pDDIs in the 12 months before and 6 months after the recall was modeled using negative binomial regression.
Results: A total of 1,826 pDDIs were identified, and the median monthly prevalence of pDDI before the recall was 102.5 which increased to 115.5 after the recall. A change in the level of pDDIs occurred immediately after the recall date, followed by a gradual decrease over time. The rate of pDDIs was 69% higher after the recall compared to the baseline (rate ratio 1.69; 95% confidence interval, 0.75–1.91).
Discussion: Recall of pantoprazole-containing products was associated with a higher rate of pDDIs. However, the prevalence of pDDIs gradually decreased over time. We highlight the importance of planning of recall process and coordinating all potential stakeholders to avoid potential harms.
Word count: 1450.

1. Introduction

Drug recalls due to quality issues in Saudi Arabia have increased six-folds since 2010 (Alquadeib et al., 2010). This sharp increase is possibly due to the improvement of the Saudi Food and Drug Authority (SFDA) regulations including post-marketing surveillance programs and reporting systems (Alquadeib et al., 2010). Drug recalls in healthcare settings may contribute to treatment disruptions, especially in the absence of safe and accessible therapeutic alternatives (Farrukh et al., 2019; Jackevicius et al., 2020; McAlister and Youngson, 2020). In some cases, recall of medications may be associated with an increased risk of adverse health outcomes (Jackevicius et al., 2020; McAlister and Youngson, 2020).

One of the most PPIs prescribed to patients with gastric acid-related disorders is Pantoprazole. Pantoprazole as other PPIs works on the same mechanism of gastric acid secretion suppression through binding to the proton pump (L, 2009). However, it has a relatively longer duration of action compared with other PPIs (L, 2009). Moreover, studies have found that pantoprazole has fairly fewer drug-drug interactions compared with other PPIs (Table S1 in the appendix) (H et al., 2006; L, 2009). This is an important

Abbreviations: PPIs, proton pump inhibitors; pDDIs, potential drug-drug interactions; SFAD, Saudi Food and Drug Authority; DDIs, drug-drug interactions; EHRs, electronic health records.

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consideration especially among patients with comorbidities who are affected by polypharmacy that increase their risk of drug-drug interactions (Scarpignato et al., 2016; Schepisi et al., 2015). Pantoprazole as it lacks inhibition of CYP2C19 preferred to be prescribed among some patients (S et al., 2013). For example, pantoprazole has no significant interactions with clopidogrel compared with other PPIs (Schepisi et al., 2015). Studies have also found that pantoprazole does not affect the pharmacokinetics or pharmacodynamics of phenytoin and warfarin (PW, 2000; RS and H, 2014). Thus, pantoprazole might be preferred over the other alternatives to relieve the symptoms of acid-related disorders.

In March 2021, the SFDA issued a patient-level withdrawal of two pantoprazole-containing products from the markets. Patients were instructed to contact their healthcare providers for possible alternatives for their conditions. Alternatives to pantoprazole were other proton pump inhibitors (PPIs) including rabeprazole, esomeprazole, lansoprazole, or omeprazole (Edwards et al., 2006). Their clinical effectiveness might be comparable; however, their safety profiles are different; especially pharmacokinetic profiles (Ahmed and Clarke, 2022; Jarchow-Macdonald and Mangoni, 2013). Therefore, switching might be problematic for polypharmacy patients as drug-drug interactions (DDIs) may arise (Scarpignato et al., 2016; Schepisi et al., 2015).

Drug recalls are an increasingly common problem that has an impact on patient outcomes and healthcare system access (BN et al., 2016; Fenna et al., 2021). Studies have highlighted the need to assess and monitor the impact of these recalls on patients, clinicians, and healthcare systems especially for drugs impacting a wide population (Jackevicius et al., 2020; Office of Healthcare Inspections, 2022).

With the recent recall of two generic pantoprazole-containing products from the Saudi markets treatment disruption may have occurred due to unavailability of suitable alternatives especially in hospitals, where no more than one product with the same active substance and dosage form is procured. Thus, we hypothesized that switching patients to alternative therapies may increase their risk of potential DDIs. To the best of our knowledge, the impact of the recall of pantoprazole-containing products on patients' safety has never been examined. Thus, the aim of this study was to assess the impact of drug recalls on patients' safety using pantoprazole withdrawal on the occurrence of potential DDIs as a case study.

2. Methods

2.1. Study design and data source

This retrospective study used de-identified electronic health records (EHRs) of adult patients (18 years or older) who had a prescription for any of the available oral PPIs including pantoprazole, esomeprazole, lansoprazole, and omeprazole. Data collection was from a large tertiary care hospital, where pantoprazole was a formulary item, covering 12 months before recall date (April 2021) and six months following the recall date (April 2020 to September 2021). The EHR has information about patient demographics, prescriptions, and dates and duration of dispensed drugs. We excluded the parenteral use of any study drugs and emergency patients in an attempt to reduce the possibility of episodic treatment not reflecting changes in treatment plan.

2.2. Measurements

The study outcome was the number of potential DDIs associated with PPIs use, which was calculated based on the concurrent use. Concurrent use is defined as using one or more interacting medications that overlap with a PPI prescription (Fig. 1). This included complete or partial overlap with at least one day of overlapping. To identify potential DDI, we used the products' Summary of Product Characteristics and the online Drug Interactions Checker database ('Drug Interactions Checker', n.d.; Saudi Food and Drug Authority, n.d.). These two sources were used to search for drugs that when used with PPIs might cause unwanted health effects. Table S1 in the appendix shows the interacting drugs included in the study analysis.

Patients' demographics (age and sex) and PPIs prescriptions data (including the number of prescriptions, duration of prescriptions, and frequency of dispensing). The number of potential DDIs associated with PPIs use was counted per calendar month to assess trends and variations over the study period. The prevalence of potential DDIs associated with PPIs use was calculated by dividing the counted number of potential DDIs per month by the number of interacting drugs' prescriptions per month.

2.3. Statistical analysis

Patient' demographics and PPIs prescriptions data during the study period were summarised using descriptive analysis. Changes in the number of potential DDIs throughout the study period were examined through an interrupted time-series analysis and were controlled for seasonal variation. The number of potential DDIs 12 months before and 6 months after the recall was assessed using a negative binomial regression model as there was evidence of over-dispersion in the Poisson regression model. Data management and statistical analysis were performed using Python and RStudios.

2.4. Ethical considerations

The study was approved by relevant institutional review board (Ref. No 21/0825/IRB). Very minimal risk determination was based on non-interventional nature of the study. Subjects' privacy and confidentiality were assured through de-identification, and all data were kept in a secure place within the data source premises.

3. Results

We included 17,455 PPIs prescriptions for a total of 10,086 unique patients with a median age of 53 years (IQR 66–36) and 49.6% (n = 5002) of patients were males. The most commonly prescribed PPIs was pantoprazole (n = 13,883, 79.5%) followed by esomeprazole (n = 3,553, 20.4%) (Table 1).

During the study period, a total of 1,826 potential drug-drug interactions were identified; 1,138 before the recall date with a median of 102.5 potential DDIs per month, whereas after the recall date we identified 688 potential DDIs (median = 115.5) (Table 2). The most common potential DDIs with PPIs were warfarin (n = 896, 49.1%), clopidogrel (n = 281, 15.39%), and escitalopram (n = 185, 10.13%).

The monthly median number of potential DDIs has increased after pantoprazole recall by 13%. Also, we identified a level change in the prevalence of potential DDI occurring immediately after the recall date (Fig. 2). This increase in the level was also present after adjusting for seasonality, but followed by a gradual decrease over time (Fig. 3). The rate ratio of potential DDIs after the recall date was 1.28 (95%CI, 0.85–1.93; p-value 0.24) times more than before the recall date. After adjusting for seasonality, the rate of potential DDIs was 69% higher after the recall in comparison to the baseline (1.69; 95%CI, 0.75–1.91; p-value 0.09).

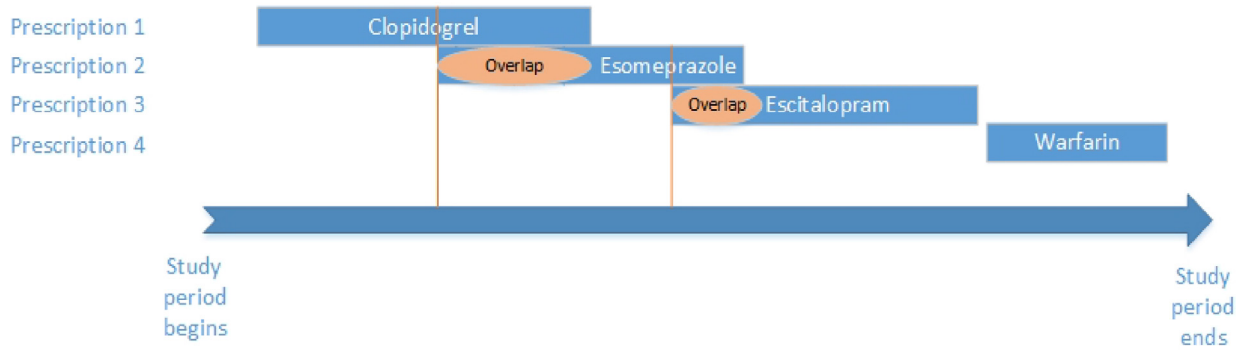

Fig. 1. Illustration of concomitant use definition.

Table 1
Patients' demographics and PPIs use during the study period (2020–2021).

Categories	Subcategories	n	%
Patients' demographics (n = 10,086)			
Age	Median (IQR)	53 (66–36)	
	18–29	1410	14
	30–44	2443	24.2
	45–59	2462	24.4
	60–74	2495	24.7
	> 74	1276	12.7
Gender			
	Male	5002	49.6
	Female	5083	50.4
PPIs use (n = 17,455)			
PPI prescriptions			
	Pantoprazole	13,883	79.5
	Omeprazole	18	0.1
	Esomeprazole	3,553	20.4
	Lansoprazole	1	0.005
Duration of PPIs prescriptions			
	< 21 days	2,772	15.9
	21	14,444	82.7
	> 21	239	1.4

PPIs: proton-pump inhibitors, IQR: interquartile range.

4. Discussion

Treatment plan changes might create challenges for healthcare professionals and patients, especially those using multiple medications. In this study, we provide a case study on possible impact of drug recalls on patients' safety by assessing the treatment switching-related potential drug-drug interactions, as we show an immediate increase in potential DDIs prevalence occurring after pantoprazole recall. Our hypothesis expected an increase in the number of DDIs six months after the recall date as those recalled pantoprazole products were the only available pantoprazole products in the study setting. Therefore, physicians prescribed other types of PPIs including esomeprazole and omeprazole after the recall, which have a higher number of interacting drugs compared with pantoprazole (Table S1 in the appendix). Pantoprazole as it lacks inhibition of CYP2C19 preferred to be prescribed among some patients and studies have found that pantoprazole has fairly fewer drug-drug interactions compared with other PPIs (H et al., 2006; L, 2009).

Drug recalls can contribute to a reduction in the availability of recalled drugs. This can possibly inadvertently increase the health risks for patients, with the limited availability of comparable drugs with the same safety profile as recalled products. A study assessed the impact of two periods of recall of paracetamol products in Australia found an increase in poisoning with alternative analgesics after the recall due to reduced availability of paracetamol (Balit et al., 2002). This study's findings show a sudden increase in pDDIs after the recall, which is likely to the limited pharmacological options with comparable safety profiles. Interestingly, potential DDIs prevalence gradually decrease over the study period, we hypothesized this decrease might be due to the choice of different treatment modalities, avoidance of PPIs use concomitantly with interacting drugs or instructing patients to fill their pantoprazole prescriptions from pharmacies offering products unaffected by the recall.

In 2018, several valsartan-containing pharmaceuticals have been recalled from 22 countries. Studies have documented an increase in emergency department and outpatient visits for hypertension following valsartan recall (Jackevicius et al., 2020; McAlister and Youngson, 2020). Moreover, switching to other angiotensin receptor blockers or alternative antihypertensives was associated with disruption in patients' treatment plan and may have compromised treatment outcomes including effectiveness, safety, or tolerability (Blier et al., 2019; Farrukh et al., 2019; Fenna et al., 2021; Jackevicius et al., 2020; McAlister and Youngson, 2020). Such disruptions or occurrences of harms may have been mitigated by several steps. For example, in our case study, including more than one bioequivalent product in the hospital formulary may largely reduce possibility of treatment disruptions. Furthermore, case-by-case discussion about benefits and potential harms that the recall may be associated with, would help in developing a strategy that minimize the harm in terms of safety and access. We think such discussion should involve all stakeholders affected by the recall including regulators, vendors, pharmacy and therapeutic committee, and healthcare professionals.

Table 2
Potential DDIs associated with PPIs use before and after the recall date.

Period	Variable	n (months)	Mean	SD	Median	IQR	Min	Max
Before recall	Frequency	12	94.8	33.0	102.5	52.5	55	155
	Rate	12	27.9	7.3	26.5	8.7	17.5	43.1
After recall	Frequency	6	114.7	27.5	115.5	32	72	148
	Rate	6	40.43	8.4	41.9	9.7	26.8	49.2

DDIs: drug-drug interactions; IQR: interquartile range; Max: maximum; Min: minimum; PPIs: proton-pump inhibitors; SD: standard deviation;

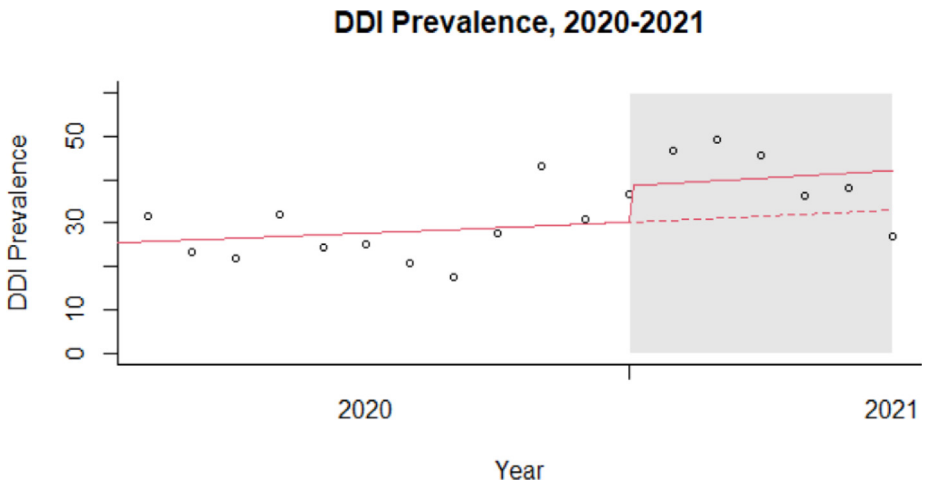

Fig. 2. Prevalence of potential DDIs associated with PPIs use throughout the study period. Fig. 2. Interrupted time series of fitted values of DDIs. Level change observed. Solid line: fitted values of DDIs. Dashed line: predicted values of DDIs DDIs: drug-drug interactions; PPIs: proton-pump inhibitors.

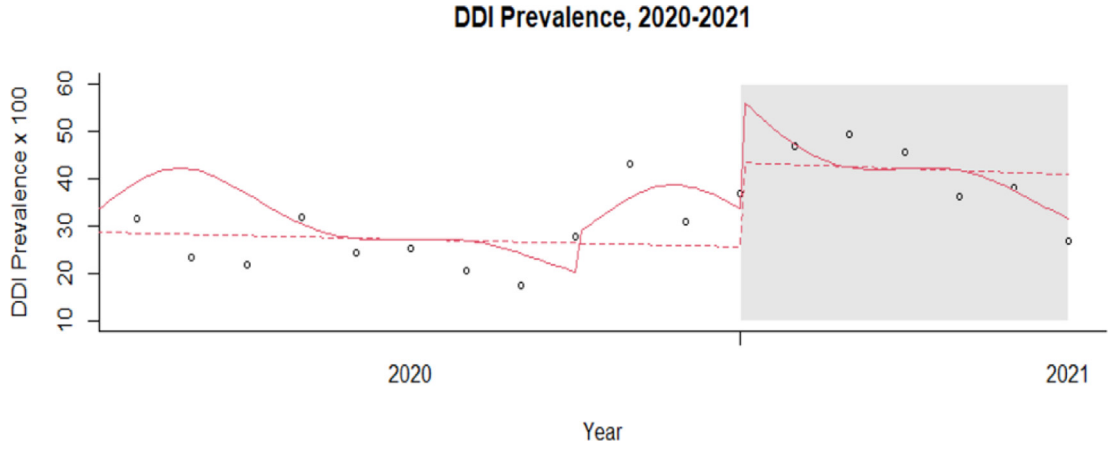

Fig. 3. Prevalence of potential DDIs associated with PPIs use throughout the study period after adjusting for seasonality Fig. 3. Interrupted time series of seasonally adjusted values of DDIs. An increase level followed by a gradual decrease was observed Solid line: trend of DDIs after adjusting for seasonality. Dashed line: trend before adjusting for seasonality. DDIs: drug-drug interactions; PPIs: proton-pump inhibitors.

This study has some limitations. For example, we assessed the impact of recall on patients' safety using potential DDIs, as a surrogate endpoint rather than outcome of DDIs. However, endpoints, such as potential DDIs, are commonly used in research as part of the causal pathway to clinical outcomes. The study used preexisting data, which is prone to some limitations, such as incomplete or missing data about prescription duration. However, we speculate this would have negligible impact on the study internal validity, as the number of excluded prescription was low (10 records). The short duration of follow-up time (6 months after the recall) and small number DDIs might have affected the study power and potentially leading to type II error, but changes in the sample size was not feasible as we included all available prescriptions.

5. Conclusion

Pantoprazole recall was associated with inadvertent effects on patients' treatment plan, as it was associated with a transient increase in the risk of potential drug interactions. While issuing a recall lies within the responsibility of regulatory agencies, executing the recall process involves multiple stakeholders, and they may consider potential direct and indirect effects on patients during planning the recall phase. Future research could assess the communication of these recalls to patients and others impacted by the recall in terms of comprehension, accuracy, adequacy, and usefulness.

6. Authors' contributions

AMA: proposal and manuscript writing, and data acquisition and analysis. WAA and MAA: data acquisition and supervision. AAA: proposal and manuscript writing, data analysis, and supervision. All authors have made substantial contributions to editing the manuscript.

7. Ethics approval and consent to participate

The study was approved by King Khalid University Hospital (KKUH) institutional review board (Ref. No 21/0825/IRB). Very minimal risk as no intervention is involved in the study design. Subjects' privacy and confidentiality were assured, no identifiers were collected.

8. Disclaimer

The views expressed in this paper are those of the author(s) and do not necessarily reflect those of the SFDA or its stakeholders.

Guaranteeing the accuracy and the validity of the study results is a sole responsibility of the research team.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2023.04.011.

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