Saudi Pharmaceutical Journal 27 (2019) 717–723

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Effect of an educational intervention on the number potential drug-drug interactions

Aigul Z. Mussina [a,*], Gaziza A. Smagulova [b], Galina V. Veklenko [c], Bibigul B. Tleumagambetova [d], Nazgul A. Seitmaganbetova [e], Aigul A. Zhaubatyrova [f], Lazzat M. Zhamaliyeva [g]

[a] Department of Propedeutics of Internal Diseases and Clinical Pharmacology, West Kazakhstan Marat Ospanov State Medical University, Abulhair Khan Avenue, 21-1-30, Aktobe 030020, Kazakhstan
[b] Department of Propedeutics of Internal Diseases and Clinical Pharmacology, West Kazakhstan Marat Ospanov State Medical University, Alia Moldagulova Avenue, 47-84, Aktobe 030000, Kazakhstan
[c] Department of Propedeutics of Internal Diseases and Clinical Pharmacology, West Kazakhstan Marat Ospanov State Medical University, Eset Batyr Street, 109-1-8, Aktobe 030000, Kazakhstan
[d] Department of Propedeutics of Internal Diseases and Clinical Pharmacology, West Kazakhstan Marat Ospanov State Medical University, Almaty District, Residential Massif Kargaly, 2 Mikroroyon, 16v – 230, Aktobe 030000, Kazakhstan
[e] Department of Propedeutics of Internal Diseases and Clinical Pharmacology, West Kazakhstan Marat Ospanov State Medical University, 131g Bokenbay Batyr Street – 126, Aktobe 030000, Kazakhstan
[f] Department of Propedeutics of Internal Diseases and Clinical Pharmacology, West Kazakhstan Marat Ospanov State Medical University, Novatorov lane 1, Aktobe 030012, Kazakhstan
[g] Center for Family Medicine and Primary Care Research, West Kazakhstan Marat Ospanov State Medical University, Alia Moldagulova Avenue, 11B – 120, Aktobe 030019, Kazakhstan

ARTICLE INFO

Article history:
Received 29 November 2018
Accepted 6 April 2019
Available online 8 April 2019

Keywords:
Pharmacotherapy
Drug-drug interaction
Education
Cardiology

ABSTRACT

Background: The objective of this study was to evaluate effect of an Educational intervention on the number Potential Drug-Drug Interactions in the Emergency Hospital.
Methods: The prevalence and structure of Major Drug-Drug Interactions at Emergency care Hospitals of Aktobe, Uralsk, Atyrau cities (Kazakhstan) were studied (pharmacoepidemiological, cross-sectional study). Educational interventions were developed and implemented to improve pharmacotherapy in the Cardiology Department of the Aktobe Emergency Hospital, followed by an assessment of their effect.
Results: The effect of educational interventions was revealed, which led to a significant decrease in the indicators of drug interactions of the Major Drug-Drug Interactions by 18.2% (OR: 0.45; 95% CI, 0.25-to-0.82) in the cardiological patients of the Emergency Care Hospital of Aktobe city compared to the Regional Cardiology Center of Uralsk.
Conclusion: The implementation of educational pharmacotherapy programs decreased the number of clinically significant drug interactions in the Cardiology Department of Emergency Hospitals.

1. Introduction

Drug interaction is an important medical issue as it can reduce or facilitate the effect of drugs and cause side effects in patients receiving multiple drug therapy (Murtaza et al., 2016).

Some adverse drug interactions had fatal consequences and caused the withdrawal of popular medications from the market (Kraft and Waldman, 2001; Wienkers and Heath, 2005).

In clinical practice, there is an important gap between what is theoretically known about DDIs and appropriate management of patients, especially in the elderly who do usually require polypharmacy for co-morbidities (Raschi et al., 2015).

On one hand, the number of prescribed drugs is a recognized independent risk factor for serious adverse drug reactions (ADRs) in the elderly (Saedder et al., 2015; Davies and O'Mahony, 2015), a vulnerable population with age-related changes in

* Corresponding author at: Department of Propedeutics of Internal Diseases and Clinical Pharmacology, West Kazakhstan Marat Ospanov State Medical University, Maresyev str., 68, 030019 Aktobe, Kazakhstan.
E-mail addresses: bacocha@mail.ru (A.Z. Mussina), gvictor63@mail.ru (G.V. Veklenko), honey_biba@mail.ru (B.B. Tleumagambetova), guldana-gulsezim@yandex.ru (N.A. Seitmaganbetova), aigul_zhaubatyrova@mail.ru (A.A. Zhaubatyrova), lzhamalieva@mail.ru (L.M. Zhamaliyeva).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2019.04.007
1319-0164/

pharmacokinetic and pharmacodynamic parameters, concomitant comorbidities and organ impairments, which increase the risk of hospitalization and mortality (Magro et al., 2012). On the other hand, only a fraction of DDIs (that are preventable according to the drug mechanism of action) are clinically important (i.e. they require therapy adaptation and/or they can result in ADRs), and only a minority can be actually avoided by safely removing the potential precipitant agent. In addition, the clinician's perception of the clinical relevance of DDIs is not fully appreciated, thus underestimating relevant risk when multiple drugs are co-administered (van Roon et al., 2005; Ko et al., 2008).

Most of the evidence about fatal ADRs caused by DDIs comes from case reports or case series (Magee et al., 2010; Moling et al., 2009; Madadi et al., 2010).

The high prevalence of DDI in large-scale European epidemiological studies (Zheng et al., 2018; Oertle, 2012) necessitates a more responsible conduct of pharmacotherapy by clinicians to prevent their adverse effects.

The scientific publications describe works that confirm the efficiency of the use of trainings for physicians on the need to monitor patients when prescribing clinically significant interactions. The research group of Italian scientists evaluated influence of the educational campaign for general practitioners on the number of clinically significant interactions of drugs in elderly patients with polypharmacy. They obtained a reduction in the majority of common Drug Interactions, in particular, associated with non-steroidal anti-inflammatory drugs, and a reduction in polypharmacy in prescriptions (Malone et al., 2013). The opposite result was obtained from clinical pharmacists in the USA, the study of which did not demonstrate a positive effect on reduction of the level of potential hazardous DDI prescription (Di Giorgio et al., 2016). "Republican Center for Health Development" of the Ministry of Healthof the Republic of Kazakhstan ("RCHD") informs the following: According to paragraph 3 of Article 33 of the Code, health care providers are guided by clinical protocols when providing medical assistance (Clinical diagnosis and treatment protocols Ministry of Health and Social Development of the Republik of Kazakhstan). RCHD of the Ministry of Healthcare of the Republic of Kazakhstan recommends to use the online resource Drug Interactions (FDA). In most countries of the world, researchers used it to analyze drug interactions in ongoing therapy in hospital patients and in primary outpatient practice. Attempts to clarify the DDI issues made scientists develop complex measures (Roblek et al., 2016; Gülçebi İdriz Oğlu et al., 2016), including educational interventions among doctors, pharmacists, creation of algorythms for use of significant DDI, development of reference books (Strain et al., 2001; Wang et al., 2015).

Studies show that doctors' knowledge of the potentially significant DDI they prescribe is usually poor in such a serious issue of clinical pharmacology as potentially dangerous drug interactions (Astrand et al., 2006). These results are supported by other studies (Ko et al., 2008) and underscore the need to develop systems that warn clinicians on the prescription of clinically adverse interactions.

The lack of data on the study of the state of pharmacotherapy in the Republic of Kazakhstan, especially in the issues of drug interactions in emergency medical care hospitals, the lack of data on the effect of educational interventions on these indicators, was the reason for such research.

1.1. Aim of the study

The aim of this research was to study the prevalence and structure of potentially dangerous major grade DDI using the automated electronic resource Drug Interaction (FDA) and to evaluate the effect of educational interventions on the state of pharmacotherapy in the Emergency Hospital.

Ethical approval

The research work was approved by the bioethical committee of the West Kazakhstan Marat Ospanov State Medical University (MoM No. 15 dated 24.11.2016). Informed consent was not required because the review of retrospective Drug-Drug Interactions alert logs and prescriptions did not involve individually identifiable data of any sort.

2. Methods

2.1. Study design

The study was conducted in two stages: the first stage (pharmacoepidemiological cross-sectional study) is a retrospective analysis of the pharmacotherapy of patient records in Emergency Hospitals in the West Kazakhstan from 01.01.2014 to 31.12.2014. The prevalence and structure of Major DDI at Emergency Care Hospitals of Aktobe, Uralsk, Atyrau cities were studied.

Major DDI were identified using Drug Interaction Checker source (FDA). The prevalence of Major DDI and their structure were studied.

Data on age and field of patients, diagnoses, complications, duration of stay in the hospital, prescribed drugs was gathered.

All drugs were classified under the international anatomical-therapeutic classification. In case of combination drugs containing a combination of active substances, each of substances was treated separately.

The following was calculated: percentage of patients with DDIs; percentage of patients with at least one DDI; the number of combinations involving Major.

The DDI structure is described by the most frequent particular drug combinations.

2.2. Stage 1 (systematic random selection study)

Selection of stage 1 was formed by systematic random selection (each 3rd case history from the general list of patients of the Departments).

Inclusion criteria: stay in the hospital for more than 24 h, prescription of more than 2 drugs, age from 18 years-old.

Exclusion criteria: stay in the intensive care department for more than 3 days, patient 'age younger than 18, interactions with acetylsalicylic acid (Aspirin Cardio, Cardiomagnyl, Thrombo ass) in a dose that has antiaggregant effect (325 mg) were not considered. Acetylsalicylic acid in online checkers creates DDI of all 3 grades with most of cardiological drugs, producing dominant effect on the DDI structure, masks other drug interactions, and therefore we decided to exclude the drug from the list of interacting drugs.

2.3. Stage 2 (controlled study)

A set of educational measures to promote pharmacotherapy in the Cardiology Departments of the Emergency Care Hospitals of Aktobe city was developed and introduced at the second stage, after which the effect of these interventions was assessed.

The complex of educational interventions developed in 2015 included: (1) a local clinical guideline for the prevention of adverse clinical outcomes of potentially dangerous drug interactions in the cardiac practice; (2) a training program for doctors, named "Monitoring potentially dangerous drug interactions in cardiac practice"; (3) algorithms for the prevention of the clinical outcomes of potentially dangerous drug interactions.

In both Hospitals, identical groups of drugs were used (angiotensin-converting enzyme inhibitors, beta-blockers, aldos-

terone blockers, anticoagulants, antiaggregants, proton-pump inhibitor, etc.). The drug form of both Hospitals was formed from similar International Names (INN) groups. This allowed us to compare the results of prevalence trends and the structure of potentially dangerous medicinal products after educational interventions.

In 2016, training seminars were held on the prevention of adverse effects of potentially DDI in the Cardiology Department of the Emergency Hospital of Aktobe.

Educational activities in the hospital of emergency medical care in Aktobe:

Block 1: Educational introductory reports for the Aktobe Emergency Hospital on the following topics:

1. Polyparmacy – definitions, concepts
2. Adverse reactions
3. Drug Interactions

2 blocks of educational seminars were held separately for the doctors of the interventional cardiology of the emergency hospital, informing the doctors with leaflet algorithms, introducing a local clinical protocol "Algorithms for preventing adverse clinical consequences of potentially dangerous drug interactions into cardiological practice"

Themes of the workshops 2:

1. Clinically significant drug interactions.

Drug interactions that increase the risk of hyperkalemia. Action algorithm

2. Clinically significant drug interactions.

Drug interactions that increase the risk of hemorrhagic complications. Algorithm action.

3. Clinically significant drug interactions. Drug interactions with the risk of alleviating/reducing the effect of co-prescribed medication. Algorithm action.
4. Clinically significant drug interactions. Drug interactions that increase the risk of heart rhythm disorders. Algorithm action.

2.4. Statistical analysis

All statistical analyses were performed using the Statistical 10 software. The study population was described with percent for categorical variables and with average, standard deviation (SD), medians, range and interquartile interval for continuous variables. Confidence interval (95% CI) was calculated for all category variables 95%. The normality of the variables distribution was verified using the Kolmogorov-Smirnov test. The relationship between continuous variables was established with the Pearson correlation. A P-value below 0.05 was considered significant.

To compare the mean values in two selections (Stage 2), the t-Student or Mann-Whitney test was used for the quantitative variables depending on distribution.

3. Results

3.1. Stage 1

Table 1 shows the quantitative distribution of the analyzed patient records.

We found that Major DDI, revealed retrospectively with the Drug Interaction automated system, occurred in all four Departments and were mainly due to the prescription of cardiovascular drugs.

Table 1
Number of patient records analyzed at stage 1 of the research.

Number of records of in-patients	Aktobe city	Uralsk city	Atyrau city	Total
Cardiology	250	250	230	730
Neurology	250	250	250	750
Therapy	250	100	105	455
Surgery	223	240	139	605
Total	973	840	724	2537

Wherein, Major DDI made 53.8% in the Cardiology Departments significantly higher than in other Departments (neurology: 18%, therapy – 11.9%, surgery – 2.7%, $P < 0.05$).

The most common Major DDI were combinations of spironolactone with angiotensin converting enzyme (ACE) inhibitors and potassium chloride, enoxaparin and fondaparinux with clopidogrel, ACE inhibitors with potassium chloride.

Among all the DDI, the risk of hyperkalemia was the highest with a 35.1% (95% CI 31.6–38.6), followed the hemorrhagic syndrome with 27.1% (95% CI 23.9–30.5). Significantly fewer cases of DDI were found with the risk of fatal arrhythmia (4.9%; 95% CI 3.5–6.7) and the risk of decreasing the clopidogrel effect (4.1%; 95% CI 2.7–5.8). The toxicity of digoxin increased in the 2% of patients (95% CI 1.3–3.5).

3.2. Stage 2

3.2.1. Condition of pharmacotherapy of the regional Cardiology center of Uralsk city

In 2017, a repeated analysis of Cardiology Department patient records of Aktobe (72) and Uralsk (70, the comparison group) was conducted to evaluate educational interventions.

Groups of cardiac patients in the city of Uralsk and the city of Aktobe were comparable in age, main and concomitant clinical diagnoses, complications (Table 2).

In 2017, in total, 12 types of potentially dangerous combinations of drugs were revealed, which were administered 50 times of the regional cardiology center of Uralsk city.

Potentially dangerous DDI occurred in 29 patients – 51.4% (95% CI 49.8–53.8). One patient could have from 1 to 6 Major-combinations. At least 1 Major DDI occurred in 19 patients (27.1%), more than 1 in 10 patients (14.3%).

Table 2
Records Characteristics of patient records analyzed at stage 2 of the research.

	Uralsk city	Aktobe city
N	70	72
Age of patients	from 31 to 91 years	from 30 to 90 years
The average age	62.3 (11.3)	62.4 (13.6)
Men	60%	62.5%
Women	40%	37,5%
The duration of stay in the hospital	from 4 to 14 days	from 6 to 18 days
Clinical diagnosis		
Myocardial infarction	64.3% (95%CI 51.9–75.4)	62.8% (95%CI 50.3–73.6)
Stable angina pectoris	4.3% (95%CI 0.9–12)	6.2% (95%CI 2.3–15.5)
Arterial hypertension	15.7% (95%CI 8.1–26.4)	17.2% (95%CI 8.9–27.3)
Cardiac rhythm disturbance	5.7% (95%CI 1.6–13.9)	5.2 (95%CI 1.5–13.6)
Cardiomyopathy	10% (95%CI 4.1–19.5)	8.6% (95%CI 3.1–17.3)

The most common were combinations of potassium chloride with ACE inhibitors, spironolactone with ACE inhibitors, spironolactone with potassium chloride. The dose of spironolactone was 50 mg, herewith there was no laboratory control over the potassium level in case of the relevant combinations in all the medical records.

Also amiodarone + warfarin DDI was present with a risk of hemorrhagic syndrome, and in this case it is recommended to twice reduce the dose of an indirect warfarin anticoagulant.

Amiodarone + ciprofloxacin DDI was revealed, which involves the risk of arrhythmia, this combination should be avoided.

Conspicuous is that such Major DDI with the risk of hemorrhagic syndrome as warfarin + clopidogrel, fondaparinux + clopidogrel, enoxaparin + fondaparinux, was accompanied by constant laboratory monitoring of hemostasis system (coagulation, prothrombin index, activated partial thromboplastin time, international normalized attitude) every 3–5 days in pharmacotherapy of patients.

Almost all patients received the following combinations of drugs: clopidogrel + pantoprazole, which indicates that the doctors of Uralsk city followed proposed protocols for treatment of coronary heart disease, The list of additional drugs recommends proton pump inhibitor – pantoprazole, but not omeprazole). Coadministration with proton pump inhibitors (omeprazole) may reduce the cardioprotective effects of clopidogrel (Juurlink et al., 2009).

3.2.2. Condition of pharmacotherapy of cardiology department of the Emergency Care Hospital of Aktobe city

In 2017 of the Emergency Care Hospital of Aktobe city in total, 10 types of potentially dangerous combinations of drugs were revealed, which were administered 43 times.

Potentially dangerous DDI occurred in 22 patients – 42.2% (95% CI 40.2–45.3). One patient could have from 1 to 6 Major-combinations. At least 1 Major DDI occurred in 10 patients (13.9%), more than 1 in 12 patients (16.7%).

The most common were combinations of potassium chloride with angiotensin converting enzyme (ACE) inhibitors, spironolactone with ACE inhibitors, spironolactone with potassium chloride. The dose of spironolactone was 25 mg, herewith there was no laboratory control over the potassium level in case of the relevant combinations in 20 patients. Potassium in blood was determined, glomerular filtration rate by the Cockcroft-Gold formula was calculated for the remaining 20 patients with DDI, dangerous in terms of hyperkalemia before prescription of these drugs combinations. And the dose of spironolactone was corrected by a decrease to 25 mg per day depending on the level of potassium in the blood. The emergency care hospital of Aktobe city submitted request for spironolactone in a dose of 25 mg in advance to implement the developed algorithms for monitoring the undesirable consequences of potentially dangerous DDI.

DDI with the risk of hemorrhagic syndrome were fully monitored for bleeding. Almost all patients were monitored for hemostatic system. Only in 3 cases, when warfarin + enoxaparin, clopidogrel + fondaparinux, enoxaparin + warfarin were administered together laboratory parameters were not monitored.

In case of amiodarone + warfarin DDI, the dose of warfarin was reduced, which is a positive point.

DDI with the risk of arrhythmia was prescribed 1 time. The dose of digoxin was corrected by twice decrease in 1 patient with administered DDI dangerous in terms of arrhythmia (amiodarone + digoxin).

As for clopidogrel + pantoprazole DDI, which was administered to 10 patients, its administration was recommended by acute coronary syndrome treatment of 2016, and additionally with the algorithm we developed. Request for pantoprazole in a dose of 20 and 40 mg was also submitted for its implementation.

Table 3 shows the doctors' commitment to monitoring Major drugs interactions, according to the developed and introduced algorithms for the prevention of adverse clinical consequences of potentially dangerous drugs interactions.

When comparing the results by such an indicator as potentially hazardous DDI at Uralsk Cardiological center we observed its statistically insignificant decline by from 52.8% in 2014 to 51.4%, i.e. by 1.4% in 2017 due to decrease in prescritption of such DDI as clopidogrel + omeprazole, due to monitoring of the hemostatic system against the background of DDI with the risk of hemorrhagic syndrome, due to the correction of the dose of digoxin with a certain combination with warfarin.

Conspicuous is the lack of control over possible signs of hyperkalemia in case of DDI with the risk of hyperkalemia. Although the treatment section of chronic heart failure treatment protocol clearly indicates these recommendations. There is no doctors' concern about this risk among doctors.

In Aktobe, a significant decrease in drug interaction was observed (OR 0.235, 95% CI 0.13–0.42).

Table 3 shows the most common Major drug combinations indicating also possible consequences for a patient.

When comparing the results of Major DDI in the Emergency Care Hospital of Aktobe city, a conspicuous decrease was observed. In fact, Major DDI significantly decreases from 60.4% of 2014 to 42.2% of 2017, (−18.2%, $P < 0.05$). As shown in Fig. 1 the conducted educational interventions led to a decrease in the level of Major DDI in the Cardiology of Aktobe (OR: 0.45; 95% CI 0.247–0.82). In Uralsk, there was any decrease in drug interactions (OR 0.9, 95% CI 0.5–1.6).

4. Discussion

We studied the effect of educational interventions on the state of pharmacotherapy in the Emergency Hospital of West Kazakhstan.

Our pharmacoepidemiological study revealed very high level of Major DDI in the Cardiology Departments, significantly exceeding the levels found in the developed countries of the world. Our findings were significantly higher than those from the cardio-resuscitative Departments of the United States, where only the 20.5% of drug interactions are potentially dangerous when using an online checker Lexi-Interact and Micromedex interaction (Smithburger et al., 2012). Our data are comparable with those of Jamaica researchers, where the prevalence of potentially dangerous drug interactions in the University Medical Clinic was the 49.8%, when using an online checker Drug Interactions Checker database of Drugs.com (Kennedy-Dixon et al., 2015).

Since researchers use different online checkers to identify drug interactions with different levels of evidence, it is difficult to compare the results objectively.

It is of note that the prevalence of drug interactions found in the present study was comparable to literature. In one of the multidisciplinary Hospitals in Russia, Drug Interaction (FDA) revealed a 59.5% of potentially DDI in the Cardiology Department (Sychev

Table 3
Risks of Major DDIs in the departments of cardiology in Aktobe, %.

Possible consequences	2014	2017	p
	% of patients		
Risk of hyperkalemia	28.1	19.1	<0,01
Risk of hemorrhagic syndrome	19.1	11.3	<0,01
Risk of fatal arrhythmia	2.9	1.2	<0,01
Risk of clopidogrel effect decrease	2.1	1.4	<0,01
Risk of toxicity of digoxin	1	0.4	<0,01

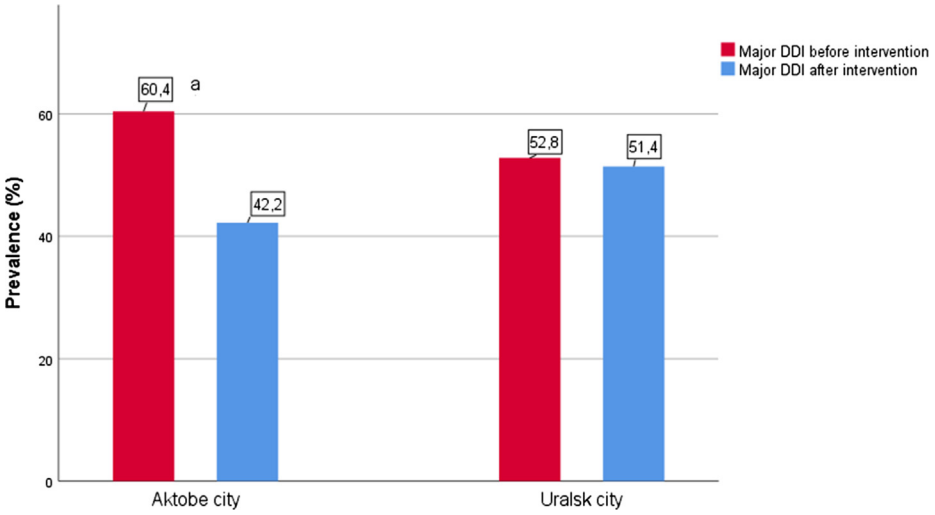

Fig. 1. The Trend of Major Drug-Drug Interactions after interventions in Aktobe city in 2017 (before and after) and in Uralsk city (without educational intervention). [a] – Difference between Major DDI in 2014 and 2017 in Aktobe city ($P < 0.05$).

et al., 2016). Potentially widespread dangerous drug associations are those between spironolactone and perindopril; clopidogrel and omeprazole; amlodipine and simvastatin.

According to literary data, conducted abroad, we see different effects. The use of INTERCheck(®) was associated with a significant reduction in potentially inappropriate medications (PIMs) and new-onset potentially severe DDI. Computerized Prescription Support System (CPSSs) combining different prescribing quality measures should be considered as an important strategy for optimizing medication prescription for elderly patients (Ghibelli et al., 2013).

Study O'Sulliva et al. indicated that drug-related problems are prevalent in older Irish hospitalized inpatients and that a specially developed structured pharmacist review of medication intervention supported by a computerized decision support systems can improve both the appropriateness and accuracy of medication regimens of older hospitalized inpatients (O'Sullivan et al., 2014).

This e-learning educational program had no clear effect on the quality of drug prescription and clinical outcomes in hospitalized elderly patients. Given the high prevalence of PIMs and potential DDI recorded in the frame of this study, other approaches should be developed in order to improve the quality of drug prescription in this population (Franchi et al., 2016).

A national education program aimed at general practitionerss was successful in improving prescribing for hypertension. Lessons learned will be applied in evaluation of future National dispensing programs and are also applicable to analysis of other interventions aimed at influencing prescribing behavior (Horn et al., 2007).

Literature data on measures to improve pharmacotherapy and the results of the study have led us to develop and implement educational interventions (Ko et al., 2008).

The identified problems prompted us to improve the state of pharmacotherapy by developing algorithms for the prevention of hazardous drugs. Specifically, the complex of educational interventions was developed for cardiologists, because the most often Major DDI were encountered in the appointment of combinations of cardiovascular drugs. As a result, it was registered a significant decrease in the number of Major DDI at the Emergency care Hospital of Aktobe city. In 2014, doctors prescribed combinations of drugs with the risk of hyperkalemia and hemorrhagic complications, or with risk of arrhythmia, without monitoring the condition of patients. In 2017, after informing about the prevention of adverse clinical outcomes of DDI, doctors completely excluded contraindicated DDI, by monitoring the functions of patients' bodies and adjusting doses of drugs administered together.

Thus, our study demonstrated the effect of doctors training and involvement of administrative resources to support changes in drug list with regard to the frequencies of DDI at the Emergency Care Hospital of Aktobe city as compared to Uralsk city (OR 0.45, 95% CI 0.25–0.82).

The doctors' adherence to follow the algorithms for the prevention of Major DDI was provided by the ability of medical personnel to check the presence of Major drug interactions in the Drug Interaction (FDA) online checker using cell phones, computers, which was introduced as a tool for DDI evaluation. Also, the positive point was the availability of printed prevention algorithms placed on the desks of staff rooms.

The latest Cochrane review concluded that 'It is unclear whether interventions to improve appropriate polypharmacy, such as pharmaceutical care, resulted in clinically significant improvement' (Patterson et al., 2014). Our study deserves attention, especially considering that not all DDI can be avoided. Depending on the underlying clinical conditions, many drugs are intentionally prescribed by doctors at the same time, since it is assumed that the expected benefit exceeds the theoretical risk of DDI. These potentially interacting prescriptions are justified by adequate risk minimization measures, such as clinical and laboratory monitoring.

The main tool in our study was Drug Interactions. Check of DDI confirmed the well-known need to create a Kazakhstani database on clinically identified drug interactions. This requires further, more extensive pharmacoepidemiological studies.

Enhancing providers' knowledge of pharmacotherapy can help reduce the rate of prescribing potentially interacting medications. This is due to the fact that the main mechanism of interaction is revealed. Providing an algorithm of actions for certain drugs helps the doctor to monitor the patient's condition (clinic, laboratory control).

It would be interesting to study the survival of doctors' knowledge 1 year after the provision of educational interventions.

4.1. Limitations

Limitation of this study is the retrospective design and the lack of analysis of inpatient records with lethal outcome. Therefore, we plan future researches not only to assess drugs interactions, but

also to reveal problems associated with their use, which can be manifested clinically or in laboratory.

The negative point of our study was that no questioning of doctors was conducted on the subject of knowledge on drug interactions.

5. Conclusion

We revealed that among the Departments of Emergency Hospitals in Western Kazakhstan, Major DDI were most often found in the Cardiology Departments. The most common Major DDI were combinations of cardiovascular drugs leading to hyperkalemia and hemorrhagic syndrome. Dangerous combinations of drugs were: spironolactone, angiotensin-converting enzyme inhibitors, enoxaparinum natrium, natrii fondaparinuxum, clopidogrel, potassium chloride and angiotensin II receptor blockers.

The implementation of educational pharmacotherapy programs decreased the number of Major DDI in the Cardiology department of Emergency Hospitals.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The research work was approved by the bioethical committee of the West Kazakhstan Marat Ospanov State Medical University (MoM No. 15 dated 24.11.2016).

Disclosure

The authors have no potential conflicts of interest to disclose.

Author contributions

Conceptualization: L.M. Zhamaliyeva, G.A. Smagulova. Data curation: L.M. Zhamalyieva, G.A. Smagulova. Formal analysis: G. V. Veklenko, A.A. Zhaubatyrova. Investigation: A.Z. Mussina, G.V. Veklenko, B.B. Tleumagambetova, N.A. Seitmaganbetova. Validation: A.Z. Mussina. Writing – original draft: A.Z. Mussina. Writing – review & editing: G.A. Smagulova, L.M. Zhamaliyeva.

Acknowledgements

We express our gratitude to the administration of the WKSMU University for the opportunity to conduct the study, as well as the Aktobe Emergency Hospital and the Hospitals of the cities of Western Kazakhstan for their assistance in providing data for this study.

We thank Dr. Maria Grazia Palmerini, University of L'Aquila (Italy), for the critical revision of the manuscript.

References

Murtaza, G., Khan, M.Y., Azhar, S., Khan, S.A., Khan, T.M., 2016. Assessment of potential drug-drug interactions and its associated factors in the hospitalized cardiac patients. Saudi Pharm J. 24 (2), 220–225. https://doi.org/10.1016/j.jsps.2015.03.009.

Kraft, W.K., Waldman, S.A., 2001. Manufacturer's drug interaction and postmarketing adverse event data: what are appropriate uses? Drug Saf. 24, 637–643.

Wienkers, L.C., Heath, T.G., 2005. Predicting in vivo drug interactions from in vitro drug discovery data. Nat. Rev. Drug Discov. 4, 825–833.

Raschi, E., Piccinni, C., Signoretta, V., Lionello, L., Bonezzi, S., Delfino, M., Di Candia, L., Di Castri, L., Pieraccini, F., Carati, D., Poluzzi, E., De Ponti, F., 2015. Clinically important drug-drug interactions in poly-treated elderly outpatients: a campaign to improve appropriateness in general practice: Clinically important drug-drug interactions in poly-treated elderly patients. Br. J. Clin. Pharmacol. 80 (6), 1411–1420. https://doi.org/10.1111/bcp.12754.

Saedder, E.A., Lisby, M., Nielsen, L.P., Bonnerup, D.K., Brock, B., 2015. Number of drugs most frequently found to be independent risk factor for serious adverse reactions: a systematic literature review. Br. J. Clin. Pharmacol. 80, 808–817.

Davies, E.A., O'Mahony, M.S., 2015. Adverse drug reactions in special populations – the elderly. Br. J. Clin. Pharmacol. 80, 796–807.

Magro, L., Moretti, U., Leone, R., 2012. Epidemiology and characteristics of adverse drug reactions caused by drug-drug interactions. Expert Opin. Drug Saf. 11, 83–94.

van Roon, E.N., Flikweert, S., le Comte, M., Langendijk, P.N., Kwee-Zuiderwijk, W.J., Smits, P., Brouwers, J.R., 2005. Clinical relevance of drug-drug interactions: a structured assessment procedure. Drug Saf. 28, 1131–1139.

Ko, Y., Malone, D.C., Skrepnek, G.H., Armstrong, E.P., Murphy, J.E., Abarca, J., Rehfeld, R.A., Reel, S.J., Woosley, R.L., 2008a. Prescribers' knowledge of and sources of information for potential drug-drug interactions: a postal survey of US prescribers. Drug Saf. 31, 525–536.

Magee, C.N., Medani, S.A., Leavey, S.F., Conlon, P.J., Clarkson, M.R., 2010. Severe rhabdomyolysis as a consequence of the interaction of fusidic acid and atorvastatin. Am. J. Kidney Dis. 56, e11–e15.

Moling, O., Rimenti, G., Pristerà, R., Vedovelli, C., Pagani, L., Spoladore, G., Mian, P., 2009. Fatal lactic acidosis precipitated by nifedipine in a patient treated with disulfiram and antiretrovirals. Drug Metab Lett. 3 (3), 176–180. PubMed PMID: 19702547.

Madadi, P., Hildebrandt, D., Gong, I.Y., Schwarz, U.I., Ciszkowski, C., Ross, C.J., Sistonen, J., Carleton, B.C., Hayden, M.R., Lauwers, A.E., Koren, G., 2010. Fatal hydrocodone overdose in a child: pharmacogenetics and drug interactions. Pediatrics 126 (4), e986–e989. https://doi.org/10.1542/peds.2009-1907.

Zheng, W.Y., Richardson, L.C., Li, L., Day, R.O., Westbrook, J.I., Baysari, M.T., 2018. Drug-drug interactions and their harmful effects in hospitalised patients: a systematic review and meta-analysis. Eur. J. Clin. Pharmacol. 74 (1), 15–27. https://doi.org/10.1007/s00228-017-2357-5.

Oertle, M., 2012. Frequency and nature of drug-drug interactions in a Swiss primary and secondary acute care hospital. Swiss Med. Wkly. https://doi.org/10.4414/smw.2012.13522.

Malone, D.C., Liberman, J.N., Sun, D., 2013. Effect of an educational outreach program on prescribing potential drug-drug interactions. J. Manag. Care Pharm. 19 (7), 549–557. PubMed PMID: 23964616.

Di Giorgio, C., Provenzani, A., Polidori, P., 2016. Potentially inappropriate drug prescribing in elderly hospitalized patients: an analysis and comparison of explicit criteria. Int. J. Clin. Pharm. 38 (2), 462–468. https://doi.org/10.1007/s11096-016-0284-7. PubMed PMID: 26984238.

Clinical Diagnosis and Treatment Protocols. Ministry of Health of the Republic of Kazakhstan, 2018. Available from: <https://medelement.com/page/klinicheskie_protokolyi> (accessed 14 November 2018).

Roblek, T., Deticek, A., Leskovar, B., Suskovic, S., Horvat, M., Belic, A., Mrhar, A., Lainscak, M., 2016. Clinical-pharmacist intervention reduces clinically relevant drug-drug interactions in patients with heart failure: a randomized, double-blind, controlled trial. Int J. Cardiol. 203, 647–652. https://doi.org/10.1016/j.ijcard.2015.10.206. PubMed PMID: 26580349.

Gülçebi İdriz Oğlu, M., Küçükibrahimoğlu, E., Karaalp, A., Sarikaya, Ö., Demirkapu, M., Onat, F., Gören, M.Z., 2016. Potential drug-drug interactions in a medical intensive care unit of a university hospital. Turk. J. Med. Sci. 46 (3), 812–819. https://doi.org/10.3906/sag-1504-147. PubMed PMID: 27513261.

Strain, J.J., Caliendo, G., Alexis, J.D., Karim, A., Loigman, M., LoweIII, R.S., 2001. Cardiac drug and psychotropic drug interactions: significance and recommendations. Heart Dis. 3 (4), 248–262. Review. PubMed PMID: 11975802.

Wang, Z.Y., Chen, M., Zhu, L.L., Yu, L.S., Zeng, S., Xiang, M.X., Zhou, Q., 2015. Pharmacokinetic drug interactions with clopidogrel: updated review and risk management in combination therapy. Ther. Clin. Risk Manag. 11, 449–467. https://doi.org/10.2147/TCRM.S80437. eCollection 2015. Review. PubMed PMID: 25848291; PubMed Central PMCID: PMC4373598.

Astrand, B., Astrand, E., Antonov, K., Petersson, G., 2006. Detection of potential drug interactions – a model for a national pharmacy register. Eur. J. Clin. Pharmacol. 62 (9), 749–756. PubMed PMID: 16896788.

Juurlink, D.N., Gomes, T., Ko, D.T., Szmitko, P.E., Austin, P.C., Tu, J.V., Henry, D.A., Kopp, A., Mamdani, M.M., 2009. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. Can. Med. Assoc. J. 180 (7), 713–718. https://doi.org/10.1503/cmaj.082001.

Ko, Y., Malone, D.C., D'Agostino, J.V., Skrepnek, G.H., Armstrong, E.P., Brown, M., Woosley, R.L., 2008b. Potential determinants of prescribers' drug-drug interaction knowledge. Res. Social Adm. Pharm. 4, 355–366.

Smithburger, P.L., Kane-Gill, S.L., Seybert, A.L., 2012. Drug-drug interactions in the medical intensive care unit: an assessment of frequency, severity and the medications involved. Int. J. Pharm. Pract. 20 (6), 402–408. https://doi.org/10.1111/j.2042-7174.2012.00221.x. PubMed PMID: 23134100.

Kennedy-Dixon, T.G., Gossell-Williams, M., Hall, J., Anglin-Brown, B., 2015. The prevalence of major potential drug-drug interactions at a University health centre pharmacy in Jamaica. Pharm. Pract. (Granada) 13 (4), 601. doi: 10.18549.

Sychev, D.A., Otdelenov, V.A., Krasnova, N.M., Ilyina, E.S., 2016. Polypragmasy: a clinical pharmacologist's view. Ter. Arkh. 88 (12), 94–102. https://doi.org/10.17116/terarkh2016881294-102. Russian. PubMed PMID: 28139567.

Ghibelli, S., Marengoni, A., Djade, C.D., Nobili, A., Tettamanti, M., Franchi, C., Caccia, S., Giovarruscio, F., Remuzzi, A., Pasina, L., 2013. Prevention of inappropriate prescribing in hospitalized older patients using a computerized prescription support system (INTERcheck(®)). Drugs Aging 30 (10), 821–828. https://doi.org/10.1007/s40266-013-0109-5. PubMed PMID: 23943248.

O'Sullivan, D., O'Mahony, D., O'Connor, M.N., Gallagher, P., Cullinan, S., O'Sullivan, R., Gallagher, J., Eustace, J., Byrne, S., 2014. The impact of a structured pharmacist intervention on the appropriateness of prescribing in older hospitalized patients. Drugs Aging 31 (6), 471–481. https://doi.org/10.1007/s40266-014-0172-6. PubMed PMID: 24797285.

Franchi, C., Tettamanti, M., Djade, C.D., Pasina, L., Mannucci, P.M., Onder, G., Gussoni, G., Manfellotto, D., Bonassi, S., Salerno, F., Nobili, A., ELICADHE Investigators, 2016. E-learning in order to improve drug prescription for hospitalized older patients: a cluster-randomized controlled study. Br. J. Clin. Pharmacol. 82 (1), 53–63. https://doi.org/10.1111/bcp.12922. PubMed PMID: 26922904;PubMed Central PMCID: PMC4917810.

Horn, F.E., Mandryk, J.A., Mackson, J.M., Wutzke, S.E., Weekes, L.M., Hyndman, R.J., 2007. Measurement of changes in antihypertensive drug utilisation following primary care educational interventions. Pharmacoepidemiol. Drug Saf. 16 (3), 297–308. PubMed PMID: 16634120.

Patterson, S.M., Cadogan, C.A., Kerse, N., Cardwell, C.R., Bradley, M.C., Ryan, C., Hughes, C., 2014. Interventions to improve the appropriate use of polypharmacy for older people. Cochrane Database Syst. Rev. 2014 (10). CD008165.