IJPT
1735-2657/11/101-44-48
IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

IJPT 10: 44-48, 2011

RIDR

RESEARCH ARTICLE

Potential Drug Interactions in War-Injured Veterans

M. GHARAKHANI, S. RAZEGHI JAHROMI, H. SADEGHIAN, S. FAGHIHZADEH, H. KAZEMI, J. ARABKHERADMAND, P. KOULIVAND, L. BAYAN and A.GORJI

For author affiliations, see end of text.

Received June 6, 2010; Revised September 29, 2010; Accepted October 5, 2010

This paper is available online at *http://ijpt.iums.ac.ir*

ABSTRACT

Drug-drug interaction (DDI) is one of the most important problems in the treatment of patients suffering from different chronic intractable diseases. The war-injured veterans are one of the groups that are prone to chronic refractory diseases. This investigation was conducted on war-injured veterans treated in a multi-disciplinary clinic in Tehran. Using Poisson model, a total of 150 patients was collected from the patients treated in a multidisciplinary clinic during three months. The prescriptions were processed using the Drug Interactions Checker. Drug interactions in these patients were categorized to three levels, i.e. mild, moderate, and severe. Drug interactions were identified in 148 patients with different intensity. Based on FDA classification, the mild, moderate, and severe DDI were observed in 56 (37.3%), 139 (92.7%), and 74 (49.3%) patients, respectively. The total number of drug interactions was 1239 in these patients. The most common type of DDI was observed in the patients who received anti-depression drugs. This study shows that war-injured veterans are a group of patients with high risk of drug interaction. The results indicate the necessity and importance of devising some guidelines to prevent or at least decrease the drug interactions in war-injured veterans with chronic refractory diseases.

Keywords: Drug interaction, Chronic intractable diseases, War-injured patients

A drug interaction is a situation in which a drug affects the activity of another one. Although interactions may exist between drugs and foods or drugs and herbs, drug interaction usually refers to influence of two or more medicaments on each other (drug-drug interactions; DDI). The incidence and severity of DDI are on the rise as more medications are brought to market [1]. DDI may occur out of accidental misuse or due to lack of knowledge about the active ingredients involved in the relevant substances.

DDI is one of the most important problems in the treatment of patients suffering from different chronic intractable diseases [2]. Due to the complexity of diseases and adding the other signs and symptoms to the primary disorder, these patients usually treated with multiple drugs. DDI may result in unwanted side effects, cause toxicity or reduce the efficacy of the interacting drug, and mislead the physicians in diagnosis and therapy by induction of new complications to the existing problems [2-5]. Furthermore, DDI may change the nature of a given drug [6] which means that the observed effect of a drug is not something that would be expected from either drug alone even at high doses [7]. DDI may also lead to a new disease [8], decreased drug tolerability [9], and withdrawal syndrome [10]. DDI can exhibit in a broad range of clinical manifestations such as sudden death [11-13], seizure attacks [14], cardiac arrhythmia [15, 16], malignant hypertension [17], neuroleptic malignant syndrome [18], as well as delirium [19, 20]. In addition, DDI disproportionately increases expenses and impacts patient income [21]. DDI have also important implications for managed care [22].

The war-injured veterans are among the patients with higher risk for different chronic intractable diseases [23]. War-injured veterans are suffering from several different diseases that lead to increase in both number and dosage of drug use. This may enhance DDI in this group of the patients. The aim of this study is to investigate the incidence of DDI in veterans who injured during Iraq-Iran war and treated in a multi-disciplinary clinic.

Table 1. Different types of applied drugs in 150 war-injured veterans treated in a multi-disciplinary clinic in Tehran

Drugs	Number of the patients (%)	Drugs	Number of the patients (%)
Anti-epileptic	133 (88.7)	Antibiotic	5 (3.3)
Anti-depressant	100 (66.7)	Sedative	5 (3.3)
Anti-HTN	51 (34)	Anti-osteoarthritis	4 (2.7)
Anti-psychotic	43 (28.7)	Anti-inflammation	4 (2.7)
Analgesic	35 (26.6)	Anti-histamine	4 (2.7)
Anti-spastic	31 (20.8)	Anti-coagulant	3 (2)
Anti-anxiety	28 (18.7)	Anti-constipation	3 (2)
Anti-acid	18 (12)	Anti-dementia	2 (1.3)
Anti-Angina	14 (9.3)	Immunosuppressive	1 (0.7)
Blood cholesterol. lowering	12 (8)	CNS. stimulant	1 (0.7)
Anti-asthma	8 (5.3)	Mucolytic	1 (0.7)
Blood glucose lowering	7 (4.7)		

MATERIALS AND METHODS

The investigation was conducted on war-injured veterans treated in a multi-disciplinary clinic in Tehran. These veterans were injured during Iraq-Iran war (1980-1988). This multi-disciplinary clinic treats patients with chronic pain, refractory epilepsy, chronic headache, and spinal cord injury. All drugs used by each patient were identified during an interview by a physician. The patients who used the drugs irregularly or at toxic doses were excluded. According to Food and Drug Administration classification (FDA) [24], DDI in our patients was classified as severe, moderate and mild, depending to their severity of clinical significance and cross-over checked manually for the presence of enough published scientific evidence for the identified interacting agents. FDA defines a serious adverse event as one when the patient outcome is one of the following: death, life-threatening, hospitalization, disability, and congenital anomaly [24]. Severe DDI is either well documented and have the potential of being harmful to the patient and have the potential of serious adverse outcome. Moderate interactions are of moderate clinical significance, are less likely than severe interactions to cause harm to the patient, or are less well documented. Mild interactions are of minor clinical significance and are least significant because of limited risk to the patient [25, 26].

In this study, more than 90% of the patients were suffering from DDI. Based on $n = \frac{Z\frac{a^2}{2}p(1-p)}{d^2}$ and with 95% confidence (d: 0.8), it was calculated that 143 patients are needed for this study. Using Poisson model, a total of 150 patients was collected from the patients treated in the clinic during three months. The distribution pattern was tested with homogeneity of variances. The results are presented as mean ± standard deviation.

RESULTS

The patients under investigation consisted of 150 war-injured men. From these patients, 54 were (36%) treated for epilepsy, 41 (27.3%) for headache, 37 (24.7%) for pain, and 18 (12%) for the spinal cord injury. These patients were between 25 to 82 years old (46.6 ± 6.7 years). The number of medicaments used by each person was between 2 to 14 (5.6 ± 2.7 drugs per day). The mean duration of drug use in these patients was 9.2 ± 2.8 years. This group of patients were suffering from multiple medical problems and therefore relying on several medications. The patients received different types of drugs regarding their varied disorders. The most common applied medicaments in these patients were antiepileptic drugs (AEDs). The data revealed that AEDs were administered in 133 (88/7%), antidepressant in 100 (66.7%), anti-hypertension in 50 (33.3%), neuroleptics in 43 (28.7%), analgesics in 35 (26.6%), anti-spastic in 31 (20.8%), and anti-anxiety in 28 (18.7%) patients. Details of different types of consumed drugs are given in Table 1.

DDI was not observed in only two patients. The number of DDI was ranged from 1 to 40 with the mean of 8.26 ± 0.6 in each patient. Based on FDA classification, severe DDI was identified in 74 (49.3%) patients, whereas moderate and mild DDI was observed in 139 (92.7%) and 56 (37.3%) patients, respectively. Each patient was at risk for multiple potential mild to severe DDI with highest rate of moderate DDI. Total number of potential mild, moderate, and severe DDI in these patients was 77, 1050, and 112, respectively. The number of DDI increased with the number of medications prescribed per patient. Details of severe DDI are presented in Table 2.

Severe DDI was identified in 52 patients (58% of total severe DDI) receiving two or more different anti-depression drugs, followed by the combination of anti-depression agents and analgesics (13% of total severe DDI) and the co-application of anti-psychotic and anti-epileptic drugs (8% of total severe DDI). Details of severe DDI occurring in the patients treated with antidepressant in our study are presented in Table 3.

Table 2. The frequency of different types of severe drug-drug interactions (DDI) and the percentage of the total numbers of that in 150 war-injured veterans treated to a multi-disciplinary clinic in Tehran

Type of drugs	Frequency of DDI occurrence	% of total severe DDI
Anti-depression/anti-depression	58	52%
Anti-depression/analgesic	15	13%
Anti-psychotic/anti-epileptic	9	8%
Anti-epileptic/anti-epileptic	8	7%
Anti-depression/Anti-psychotic	4	4%
Antipsychotic/analgesic	3	3%
Anti-hypertension/Anti-hypertension	3	3%
Cholesterol lowering/cholesterol lowering	2	2%
Anti-depressant/anti-anxiety	2	2%
Anti-hypertension/bronchodilatator	2	2%
Analgesic/anti-angina	2	2%
Anti-acid/anticoagulant	1	1%
Anti-biotic/anti-inflammation	1	1%
Antipsychotic/antipsychotic	1	1%
Anti-psychotic/anti-anxiety	1	1%

Table 3. The frequency of total severe drug-drug interactions (DDI) among different types of antidepressant drugs in 150 war-injured veterans treated to a multi-disciplinary clinic in Tehran

Different types of antidepressants	Number of the patients (%)	Different types of antidepressants	Number of the patients (%)
TCA & SSRI	27(46.5)	SSRI & DNRI	3 (5.1)
TCA & SNRI	7 (12)	TCA & SARI	3 (5.1)
TCA & TCA	5 (8.6)	SARI & SSRI	3 (5.1)
TCA & DNRI	4 (6.8)	SSRI & SNRI	2 (3.4)
SNRI & DNRI	2 (3.4)	SARI & SNRI	1 (1.7)
SARI & DNRI	1 (1.7)		

TCA, tricyclic antidepressants; SSRI, selective serotonin reuptake inhibitors; SNRI, serotonin and nor epinephrine reuptake inhibitors; DNRI, dopamine-nor epinephrine reuptake inhibitor; SARI, serotonin antagonist reuptake inhibitors.

DISCUSSION

The present study revealed that nearly all war-injured veterans suffering from intractable diseases and treated in a veteran multi-disciplinary clinic affected by potential DDI. Most potential DDI recognized as moderate type of DDI (the interaction may result in an exacerbation of the patient's condition and require changing in drugs) in more than 90% of patients. However, severe DDI (the interaction may be life-threatening and may require medical interventions to minimize or prevent serious adverse effects) was also observed in more than 30% of these patients during our study, the patients who received antidepressants were at highest risk of DDI. Each patient was at risk for several DDI.

In the United States 25% of ambulatory patients taking two or more drugs were at risk for clinically important DDI [27]. A European study of 1601 ambulatory elderly patients, taking an average of seven different drugs, found that 46.0% were at risk for at least one clinically important potential DDI [28]. The risk of DDI, however, increases by hospitalization. It has been reported that about 40% of hospitalized patients had at least one potential DDI [29].

Some investigations on DDI in patients with chronic diseases revealed a lower rate of DDI occurrence compared to the results of the present study. An investigation conducted on 131 patients showed that the most common used drug was antidepressant and the mean of prescribed drugs was 9.1 per day [30]. Although DDI was observed in 117 individuals, the total number of drug interaction was 121. Another study conducted by Coelho and Brum noted even a lower number of DDI among patients receiving antidepressant, antihypertensive and glucose lowering drugs. The results showed that only 47 DDI was observed among 663 patients [31]. However, other investigations especially those investigated DDI in the war-injured veterans pointed to a much higher occurrence rate of DDI. High rates of both clinically significant and unrecognized DDI were noted at a veteran hospital that had adopted a wide range of computer technologies and personnel strategies designed to improve medication safety. Among 937 veterans, 483 clinically significant DDI were identified, accounting for 52 DDI per 100 admissions and an incidence density of 70 DDI per 1000 patient-days. Nine percent of all DDI result in serious harm [32]. A study included more than 2.7 million veterans who filled prescriptions for medications involved in potential DDI across 128 ambulatory care clinics of the Department of Veterans Affairs medical centers in the United States revealed that the highest DDI exposure rate was 129.2 per 1,000 recipients of monoamine oxidase inhibitors that occurred with combinations of selective serotonin-reuptake inhibitors [33].

It has been shown that DDI increases with patient age as well as with admission to a critical care unit, and with receiving antidepressant drugs. DDI are more frequent observed in men and increases as the number of prescribed drugs increases [1-34]. Drug interactions are more frequent in patients over 60 because they suffer from chronic conditions requiring multi-drug therapy. DDI occurred at much higher rate in war-injured veterans in our study. These patients have many of above mentioned risk factors. They are all men, suffering from chronic intractable diseases, receiving several drugs, and many of them are treated with antidepressant medications. Many of war-injured veterans are suffering from pain, epilepsy, and different mental health problems [35]. This is usually a reason for receiving several drugs from different categories. Regarding to the uncommon diseases which are not seen in other social groups, the war-injured veterans with chronic intractable diseases use various drugs composed of particular ingredients. Systematic investigations on some of these particular ingredients have not been conducted yet. Furthermore, the clinical activities on some of these drugs have not been enough to find out the side effects [24].

In the present study, the most common DDI between different types of drugs was observed by combination use of different types of antidepressants. Several studies pointed to the high occurrence of DDI in the patients receiving antidepressants. In one study in patients registered in two Brazilian hospitals [31], 4.37% of the 663 patients used antidepressants, of which 19 were exposed to 47 interactions due to pharmacokinetic (23.4%), pharmacodynamic synergy (61.7%), and simultaneous pharmacokinetic/pharmacodynamic mechanisms (15.9%). An investigation conducted on the Australian war veterans showed that co-prescribing of drugs with antidepressants occurring in 8% of antidepressant users. Total numbers of 4037 potential interactions were identified in 3818 veterans to whom were dispensed antidepressants [36]. The major limitation of this investigation is the lack of an assessment of DDI consequences. It is unknown how many of these patients were suffering an adverse drug event due to the potential interactions. The results of the present study highlight the ongoing necessity for monitoring and preventing of DDI in war-injured veterans. Many of DDI detected in the present study were considered avoidable because safer alternative therapies were available. Devising some guidelines to prevent, or at least decrease, drug combinations in the war-injured veterans should be considered. The easiest way to reduce the frequency of DDI in these patients is to decrease the number of medicines prescribed. Nevertheless, sometimes it is difficult to reduce the number of drugs prescribed for patients with multiple chronic conditions; therefore, to lower the frequency of potential interactions. It could be necessary to make a careful selection of therapeutic alternatives, and in cases without other options, patients should be continuously monitored to identify adverse events. Furthermore, in order to decrease the side effects of DDI during prescribing new drugs, it is required to consider the biological differences of war-injured veterans occurred due to long-lasting use of several drugs at the same time.

REFERENCES

1. Manzi SF. Shannon M. Drug interactions - A review. Clin Pediat Emerg Med 2005; 6:93-102.
2. Pugh MJ, Vancott AC, Steinman MA, Mortensen EM, Amuan ME, Wang CP, Knoefel JE, Berlowitz DR. Choice of initial antiepileptic drug for older veterans: possible pharmacokinetic drug interactions with existing medications. J Am Geriatr Soc 2010; 58:465-71.
3. Ludgate J, Keating J, O'Dwyer R, Callaghan N. An improvement in cognitive function following polypharmacy reduction in a group of epileptic patients. Acta Neurol Scand 1985; 71:448-52.
4. Preskorn SH. Do you believe in magic? J Pract Psychiatry Behav Health 1997; 3:99-103.
5. Preskorn SH. A message from Titanic. J Pract Psychiatry Behav Health 1998; 4:236–42.
6. Johne A, Schmider J, Brockmöller J, Stadelmann AM, Störmer E, Bauer S, Scholler G, Langheinrich M, Roots I. Decreased plasma levels of amitriptylineand its metabolites on comedication with an extract from St John's wort (Hypericum perforatum). J Clin Psychopharmacol 2002; 22:46-54.
7. Beasley CM Jr, Masica DN, Heiligenstein JH, Wheadon DE, Zerbe RL. Possible monoamine oxidase inhibitor–serotonin uptake inhibitor interaction: fluoxetine clinical data and preclinical findings. J Clin Psychopharmacol 1993; 13:312-20.
8. Malek-Ahmadi P, Allen SA. Paroxetine–molindone interaction [case report]. J Clin Psychiatry 1995; 56:82-3.
9. Ahmed I, Dagincourt PG, Miller LG, Shader RI. Possible interaction between fluoxetine and pimozide causing sinus bradycardia. Can J Psychiatry 1993; 38:62-3.
10. Bertschy G, Baumann PA, Eap CB, Baettig D. Probable metabolic interaction between methadone and fluvoxamine in addict patients. Ther Drug Monit 1994; 16:42-5.
11. Preskorn SH, Baker B. Fatality associated with combined fluoxetine-amitriptyline therapy. JAMA 1997; 277:1682.
12. Ferslew KE, Hagardorn AN, Harlan GC, McCormick WF. A fatal drug interaction between clozapine and fluoxetine. J Forensic Sci 1998; 43:1082-85.
13. Preskorn SH. Fatal drug–drug interactions as a differential consideration in apparent suicides. J Psych Prac 2002; 8:233-38.
14. Spigset O, Hedenmalm K, Dahl ML, Wiholm BE, Dahlqvist R. Seizures and myoclonus associated with antidepressant treatment: assessment of potential risk factors, including CYP2D6 and CYP2C19 polymorphisms, and treatment with CYP2D6 inhibitors. Acta Psychiatr Scand 1997; 96:379-84.
15. Richard IH, Kurlan R, Tanner C, Factor S, Hubble J, Suchowersky O, Waters C. Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. Neurology 1997; 48:1070-7.
16. Robinson RF, Nahata MC, Olshefski RS. Syncope associated with concurrent amitriptyline and fluconazole therapy. Ann Pharmacother 2000; 34:1406-9.
17. Otte W, Birkenhager TK, van den Broek WW. Fatal interaction between tranylcypromine and imipramine. Eur Psychiat 2003; 18:264-5.
18. Preskorn SH. I don't see'em. J Pract Psychiat Behav Health 1997; 3:302–7.
19. Stanford BJ, Stanford SC. Postoperative delirium indicating an adverse drug interaction involving the selective serotonin reuptake inhibitor, paroxetine? J Psychopharmacol 1999; 13:313-17.
20. Reeves RR, Mack JE, Beddingfield JJ. Neurotoxic syndrome associated with risperidone and fluvoxamine. Ann Pharmacother 2002; 36:440-43.

21. Bates DW, Spell N, Cullen DJ, Burdick E, Laird N, Petersen LA, Small SD, Sweitzer BJ, Leape LL. The costs of adverse drug events in hospitalized patients. JAMA 1997; 277:307-11.

22. Preskorn SH. How drug-drug interactions can impact managed care. Am J Manag Care 2004; 10:S186-98.

23. Yu W, Ravelo A, Wagner TH, Phibbs CS, Bhandari A, Chen S, Barnett PG. Prevalence and costs of chronic conditions in the VA health care system. Med Care Res Rev 2003; 60:146S-67S.

24. Preskorn SH, Werder S. Detrimental Antidepressant Drug–Drug Interactions: Are They Clinically Relevant? Neuropsychopharmacol 2006; 31:1605-12.

25. Hansten PD, Horn JR. The top 100 drug interactions: a guide to patient management. Freeland, Washington: H & H Publications 2009.

26. Hansten PD, Horn JR. Drug interactions & updates. 7th ed. Vancouver, Washington: Applied Therapeutics Inc 1992.

27. Costa AJ. Potential drug interactions in an ambulatory geriatric population. Fam Pract 1991; 8:234-6.

28. Bjorkman IK, Fastbom J, Schmidt IK, Bernsten CB. Pharmaceutical Care of the Elderly in Europe Research (PEER) Group. Drug-drug interactions in the elderly. Ann Pharmacother 2002; 36:1675-81.

29. Lindblad CI, Artz MB, Pieper CF, Sloane RJ, Hajjar ER, Ruby CM, Schmader KE, Hanlon JT. Potential drug-disease interactions in frail, hospitalized elderly veterans. Ann Pharmacother 2005; 39:412-17.

30. Markowitz JS, Devine CL. Drug interaction potential of fluoxetine, sertraline, and paroxetine in four state psychiatric hospital populations. Ther Drug Monit 1997; 19:244-5.

31. Coelho PV, Brum CA. Interactions between antidepressant and antihypertensive and glucose lowering drugs among patients in the HIPERDIA program, Coronel Fabriciano, Minas Gerais State, Brazil. Artigo 2009; 25:2229-36.

32. Nebeker JR, Hoffman JM, Weir CR, Bennett CL, Hurdle JF. High rates of adverse drug events in a highly computerized hospital. Arch Intern Med 2005; 165:1111-6.

33. Mahmood M, Malone DC, Skrepnek GH, Abarca J, Armstrong EP, Murphy JE, Grizzle AJ, Ko Y, Woosley RL. Potential drug-drug interactions within Veterans Affairs medical centers. Am J Health Syst Pharm 2007; 64:1500-5.

34. Silkey B, Preskorn SH, Shah R. Complexity of medication use in the Veterans Affairs Healthcare System: Part II. Antidepressant use among younger and older outpatients. J Psych Prac 2005; 11:16-26.

35. Sayer NA, Chiros CE, Sigford B, Scott S, Clothier B, Pickett T, Lew HL. Characteristics and rehabilitation outcomes among patients with blast and other injuries sustained during the Global War on Terror. Arch Phys Med Rehabil 2008; 89:163-70.

36. Roughead EE, McDermott B, Gilbert AL. Antidepressants: prevalence of duplicate therapy and avoidable drug interactions in Australian veterans 2007; 4:366-70.

CURRENT AUTHOR ADDRESSES

M. Gharakhani, Shefa Neuroscience Center, Tehran, Iran.

S. Razeghi Jahromi, Shefa Neuroscience Center, Tehran, Iran.

H. Sadeghian, Shefa Neuroscience Center, Tehran, Iran.

S. Faghihzadeh, Department of Bio-Statistic, Tarbiat Modares University, Tehran, Iran.

H. Kazemi, Shefa Neuroscience Center and, Department of Pediatric, Shahed University, Tehran, Iran.

J. Arabkheradmand, Shefa Neuroscience Center, Tehran, Iran.

P. Koulivand, Shefa Neuroscience Center, Tehran, Iran.

L. Bayana, Shefa Neuroscience Center, Tehran, Iran.

A.Gorji, Shefa Neuroscience Center and, Institut für Physiologie I, Westfälische Wilhelms-Universität Münster, Münster, Germany. E-mail: gorjial@uni-muenster.de (Corresponding author)