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Prevalence of potentially hazardous drug interactions amongst Australian veterans

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Up to 21% of adverse drug event related hospital admissions are due to drug interactions. Clinical significance of drug interactions varies.
- Studies which only identified drug interactions of potentially major clinical significance found lower prevalence, of between 2 and 16%.
- Prevalence of drug interactions defined 'potentially hazardous' has had limited study, with no publications identified for the Australian population.

WHAT THIS STUDY ADDS

- In the study population of 287 074, 1.5% of subjects were dispensed potentially hazardous interacting drug pairs.
- However, limited to populations on specific medicines, it was found that for patients dispensed verapamil, methotrexate, amiodarone, lithium, warfarin, cyclosporin and itraconazole, potentially hazardous interactions occurred at a rate greater than 5%.
- These patients should be the focus of medication review programmes to avoid potentially serious adverse drug events.

BACKGROUND

Up to 21% of adverse drug event-related hospital admissions are due to drug interactions. Clinical significance of drug interactions varies, and drug interactions defined 'potentially hazardous' are more likely to contribute to morbidity and mortality.

AIM

The aim of this study was to assess the prevalence of potentially hazardous drug interactions in an elderly Australian veteran population.

METHODS

This study assessed the prevalence of potentially hazardous drug interactions, where hazardous was defined in three or more international drug interaction references, using Repatriation Pharmaceutical Benefits Scheme pharmacy claims data. Analysis was limited to patients who received regular concurrent dispensings of potentially hazardous interacting medicines.

RESULTS

Of the 287 074 subjects included in the study, 1.5% were dispensed potentially hazardous interacting drug pairs. For patients dispensed cyclosporin, concomitant use of a statin was common (47%); as was statin use with those dispensed itraconazole (31%). Of those dispensed methotrexate, 24% also received a non-steroidal anti-inflammatory drug; of those on lithium, 18% also received an ACE inhibitor or angiotensin 2 receptor blocker; of those on warfarin, 7.2% and 5.9% were co-dispensed an non-steroidal anti-inflammatory drugs or antiplatelets respectively; for those on verapamil, 5.3% were co-dispensed a beta-blocker, while for those on amiodarone 6.2% were co-dispensed digoxin.

CONCLUSIONS

Overall prevalence of potentially serious drug interactions appears to be low in the Australian veteran population. However, patients taking cyclosporine, itraconazole, methotrexate, lithium, warfarin, verapamil and amiodarone appear to be most at risk and their medicine use should be regularly reviewed to prevent potentially hazardous drug interactions.

Introduction

In 2005 nearly 100 000 hospital separations in Australia were associated with adverse drug events (ADEs), representing 1.3% of all hospital admissions [1]. It has been estimated that 43% of ADEs are potentially preventable [2], and ADEs precipitated by drug interactions fall into this category. International studies have estimated that between 1% and 21% of ADE related hospital admissions are due to drug interactions [3, 4]. An Australian study of 8215 general practice encounters found that 10.6% of patients had an ADE in the preceding 6 months, and 2% of these ADEs were due to drug interactions [5]. Another Australian study involving case note review of 1000 patients at high risk of medication problems found that 3% of potential medication-related problems were due to drug interactions [6]. Studies involving case note reviews or interviews amongst hospitalized patients and those presenting at emergency departments have estimated the prevalence of potential drug interactions is between 31% and 68% [7–10].

Studies which only identified drug interactions of potentially major clinical significance found lower prevalence. An American study which used prescription claims data to identify the prevalence of 25 potentially major drug interactions found 2.2% of nearly 3 million subjects were dispensed interacting drug pairs [11]. A study using data from a Swedish prescription claims database found the prevalence of potentially serious interactions amongst the elderly was 5% [12]. An Italian study estimated the prevalence of potentially severe drug interactions to be 16% [13]. Although several Australian studies have estimated the prevalence of potential drug interactions in small cohorts [7, 8], we located no studies which focused on the prevalence of potentially hazardous drug interactions across the wider Australian population. The aim of this study was to assess the prevalence of potentially hazardous drug interactions in the Australian veteran population.

Methods

Data for this study were sourced from the Department of Veterans' Affairs (DVA) pharmacy claims database. The DVA pharmacy claims database contains details of all medicines dispensed to veterans for which the DVA pays a subsidy. The DVA treatment population is comprised mainly of Australian defence force veterans and their eligible dependants, including spouses, widows or widowers and children. Over two thirds of the DVA treatment population have served in the Australian defence force, with 89% of those who served being male [14]. Reflecting this, in 2009 59% of the overall DVA treatment population were male and over 70% were aged 70 years or over [15]. The DVA pharmacy data file contains over 100 million records for a treatment population of 310 000 veterans. The DVA also maintain a client file, which includes data on patient gender and date of birth.

Drug interactions included in the study were identified from four international drug information resources: Vidal [16], British National Formulary [17], Drug Interaction Facts [18] and Drug-Reax [19]. Interactions of potentially major clinical significance were selected using the following criteria: interactions listed as contra-indicated or 'to avoid' in Vidal, interactions highlighted as hazardous in the British National Formulary, interactions with a significance rating of 1 (most severe) and severity of outcome listed as major in Drug Interaction Facts, and interactions with a severity of outcome listed as major in Drug-Reax. A list of drug interactions was established where the interaction was identified using these criteria in at least three of the publications. We excluded interactions for products that could not be identified in the DVA pharmacy dataset, for example, St John's Wort, alcohol, orange juice and grapefruit juice. We also excluded interactions for products not routinely used by the veteran population (for example oral contraceptives) and products not subsidized on the Pharmaceutical Benefits Scheme or Repatriation Pharmaceutical Benefits Scheme. Products with a recommended dosage schedule shorter than 3 weeks, for example antibiotics, were excluded. The final list of 52 drug interactions considered for analysis is presented in Table 1.

Analysis of the DVA pharmacy claims database was undertaken to determine the prevalence of interactions listed in Table 1. Analysis was limited to patients who received regular concurrent dispensings of potentially hazardous interacting medicines. This was defined as patients who received one or more dispensing of each of the interacting medicines in the 3 months from June–August 2005, and also received at least one dispensing of each of the same interacting medicines in the 3 months from September–November 2005. Prevalence of co-dispensing of potentially hazardous interacting drug pairs was determined using the number of people regularly dispensed the first drug in the pair as the denominator. All analyses were undertaken using SAS, V9.1 (SAS institute, Cary, North Carolina, USA).

Results

Between 1 June and 30 November 2005 287 074 veterans received at least one dispensing of a prescription medicine. The average age was 78.1 years (standard deviation (SD) 10.8), with 55% male and 45% female. On average, veterans were dispensed nine different pharmaceutical products (SD 6) in the 6 month period, and 26.5 prescriptions (SD 21).

In the 6 month study period, 4211 veterans (1.5%) were identified with at least one potentially hazardous drug interaction. The average age was 80.4 years (SD 7), with

Table 1

Serious drug interactions as identified by at least three drug interaction sources

Interactions considered to be serious by all four references:
Allopurinol and azathioprine
Allopurinol and mercaptopurine
Amiloride and potassium salts
Amiodarone and quinidine
Amiodarone and thioridazine
Cyclosporin and orlistat
Imipramine and clonidine
Itraconazole and pimozide
Lithium and haloperidol
Methotrexate and aspirin
Pravastatin and gemfibrozil
Sildenafil, tadalafil, vardenafil and nitrates
Spironolactone and amiloride
Spironolactone and potassium salts
Triptan and ergot alkaloids
Triptan and monoamine oxidase inhibitors
Verapamil and β-adrenoceptor blockers
Interactions considered to be serious by three references:
Amiloride and ACE inhibitors
Amiloride and tacrolimus
Amiodarone and chlorpromazine
Amiodarone and digoxin
Amiodarone and disopyramide
Amiodarone and haloperidol
Amiodarone and phenothiazines
Amiodarone and sotalol
Atenolol and clonidine
Captopril and potassium salts
Carbamazepine and dextropropoxyphene
Cyclosporin and statins
Diclofenac and heparin
Digoxin and quinidine
Fluoxetine and moclobemide
Fluoxetine and selegiline
Imipramine and entacapone
Imipramine and moclobemide
Itraconazole and quinidine
Itraconazole and simvastatin or atorvastatin
Itraconazole and tacrolimus or sirolimus
Lithium and ACE inhibitor or AIIRB
Llithium and frusemide
Lithium and hydrochlorothiazide
Lithium and phenothiazines
Methotrexate and NSAIDs
Spironolactone and ACE inhibitors
Spironolactone and lithium
Spironolactone and tacrolimus or sirolimus
Tramadol and monoamine oxidase inhibitors
Triptan and methysergide
Triptan and SSRIs
Warfarin and anti-platelet medicines
Warfarin and NSAIDs
Warfarin and miconazole (or other imidazoles)

61% male and 39% female. On average, veterans who were dispensed at least one interacting pair were dispensed 16 different pharmaceutical products (SD 7.6) in the 6 month period and 53 prescriptions (SD 26).

The highest prevalence of interacting drug pairs dispensed was cyclosporin and statins, occurring in 47% of the 32 patients dispensed cyclosporin (Table 2). Co-dispensing of itraconazole and statins was also prevalent; occurring in 31% of the 16 patients dispensed itraconazole. Twenty-four percent of patients dispensed methotrexate also received a non-steroidal anti-inflammatory drug (NSAID) and 18% of those dispensed lithium also received an angiotensin converting enzyme (ACE) inhibitor or angiotensin II receptor blocker. For those dispensed warfarin, co-dispensing with NSAIDs or antiplatelets had prevalence of 7.2% and 5.9%, respectively. For those on verapamil, co-dispensing with β-adrenoceptor blockers was 5.3%. For those dispensed amiodarone co-dispensing with digoxin was 6.2%, while for those dispensed triptans, co-dispensing with selective serotonin re-uptake inhibitors (SSRIs) was 12.6% (Table 2). Prevalence of co-dispensing of other interacting drug pairs was low. Of the 52 drug interactions studied, 32 had a prevalence of less than 1% (Table 2).

Discussion

This is the largest Australian study to assess the prevalence of potentially serious drug interactions; with 1.5% of the patients dispensed potentially hazardous drug interactions. Although some potentially serious interactions were prevalent, for example statin use in the itraconazole population (31%) and in the cyclosporin treated population (47%); use of itraconazole and cyclosporin is not common, and they are usually administered under specialist care, meaning that few patients were exposed to potential adverse events from these drug combinations.

Of more concern were the potentially hazardous interactions likely to occur in the general practice (primary health care) setting. For example, co-dispensing of warfarin with NSAIDs or antiplatelets had a prevalence of 7.2% and 5.9%, respectively, in the veteran population. Extrapolation of these results to the overall elderly Australian population (aged 65 years and over) of 2.9 million [20], where it is estimated that 6 out of every 1000 people use warfarin daily [21], suggests that up to 1280 Australians could be dispensed warfarin and NSAIDs concurrently and 1050 could be dispensed warfarin and antiplatelet drugs concurrently. Similar extrapolations suggest that up to 715 Australians could receive concurrent verapamil + β-adrenoceptor blocker (with 4.6 per 1000 Australians using verapamil daily [21]), 600 could receive concurrent lithium + angiotensin converting enzyme inhibitor or angiotensin II receptor blocker (with 1.1 per 1000 Australians using lithium daily [21]), and up to 250 Australians

Table 2
Prevalence of interactions

Group (number of veterans dispensed medicine during follow-up)	Interacting drug(s):	Patients dispensed interacting drug pair (%)
Warfarin (*n* = 19 049)	NSAIDs	1373 (7.2%)
	Anti-platelet medicines	1124 (5.9%)
	Miconazole (or other imidazoles)	0
Allopurinol (*n* = 11 981)	Mercaptopurine	0
	Azathioprine	3 (0.0%)
Amiloride (*n* = 360)	Potassium salts	10 (2.8%)
	ACE inhibitors	3 (0.8%)
	Tacrolimus	0
Amiodarone (*n* = 4875)	Thioridazine	0
	Quinidine	0
	Chlorpromazine	2 (0.0%)
	Disopyramide	0
	Haloperidol	17 (0.3%)
	Phenothiazines	113 (2.3%)
	Sotalol	11 (0.2%)
	Digoxin	300 (6.2%)
Verapamil (*n* = 7705)	β-adrenoceptor blockers	412 (5.3%)
Cyclosporin (*n* = 32)	Orlistat	0
	Statins	15 (46.9%)
Spironolactone (*n* = 3308)	Amiloride	2 (0.1%)
	Potassium salts	135 (4.1%)
	ACE inhibitors	61 (1.8%)
	Lithium	4 (0.1%)
	Tacrolimus/sirolimus	0
Methotrexate (*n* = 783)	Aspirin	88 (11.2%)
	NSAIDs	188 (24.0%)
Sildenafil, tadalafil, vardenafil (*n* = 2563)	Nitrates	22 (0.9%)
Atenolol (*n* = 22 956)	Clonidine	30 (0.1%)
Carbamazepine (*n* = 1128)	Dextropropoxyphene	8 (0.7%)
Imipramine (*n* = 1086)	Clonidine	0
	Entacapone	0
	Moclobemide	3 (0.3%)
Itraconazole (*n* = 16)	Pimozide	0
	Simvastatin/atorvastatin	5 (31.3%)
	Tacrolimus/sirolimus	0
	Quinidine	0
Lithium (*n* = 278)	Haloperidol	2 (0.7%)
	ACE inhibitor or AIIRB	49 (17.6%)
	Furosemide	12 (4.3%)
	Hydrochlorothiazide	0
	Phenothiazines	9 (3.2%)
Tramadol (*n* = 6433)	Monoamine oxidase inhibitors	0
Pravastatin (*n* = 12 827)	Gemfibrozil	52 (0.4%)
Triptans (*n* = 175)	Ergot alkaloids	3 (1.7%)
	Monoamine oxidase inhibitors	2 (1.1%)
	Methysergide	5 (2.9%)
	SSRIs	22 (12.6%)
Captopril (*n* = 22 956)	Potassium salts	413 (1.8%)
Diclofenac (*n* = 4881)	Heparin	8 (0.2%)
Digoxin (*n* = 8992)	Quinidine	14 (0.2%)
Fluoxetine (*n* = 2368)	Moclobemide	0
	Selegiline	0

could receive concurrent amiodarone + digoxin (with 1.4 per 1000 Australians using amiodarone daily [21]).

Veterans dispensed potentially hazardous interacting drug pairs tended to use more medicines and had more prescriptions dispensed than other veterans. Prior studies have also noted that the likelihood of being dispensed interacting drug pairs increases with number of medicines prescribed [10, 12, 13, 22]. Although the likelihood of receiving a prescription at a doctor visit is similar for veterans and the wider Australian population of similar age, veterans tend to have more doctor visits and therefore receive more prescriptions than other Australians [23]. On average, veterans in the 70–79 year age group receive three more prescriptions each year compared with other Australians of the same age (42 *vs.* 39 prescriptions, $P < 0.05$), with male veterans receiving more prescriptions (46 *vs.* 37) and female veterans receiving fewer (37 *vs.* 40) [23]. There is no evidence, however, to suggest that veterans receive more unique prescription medicines than other Australians of similar age and our results are likely to be applicable to other elderly Australians.

The major limitation of our study is that we did not assess harm associated with these potentially hazardous interactions. ADEs contribute to substantial morbidity and mortality within the Australian population [5, 24, 25]. The Quality in Australian Health Care study found that in 1992 16.6% of hospital admissions were associated with an adverse event, including 31% of the 262 admissions coded under the diagnostic category 'Injuries, poisonings and toxic effects of drugs' [24]. A Western Australian study of hospital admissions associated with ADEs between 1981 and 2002 found that the rate of ADEs increased more than five-fold over the 20 year study period [25]. The extent of ADEs due to drug interactions was not reported in these studies. However a study conducted between 2003 and 2004 found that 2% of ADEs were due to drug interactions, with a prevalence of 0.2% in the cohort [5]. The prevalence of potential interactions in our study was higher at 1.5%, probably because potentially hazardous interactions do not necessarily result in ADEs for all patients. Our overall prevalence was similar to that of potentially serious drug interactions found in American and Swedish studies (2.2% and 5%, respectively) [11, 12]. A strength of our study is that we limited the potentially hazardous interactions to those that were identified as serious or hazardous in at least three internationally recognized reference texts.

Our study is likely to have underestimated the prevalence of potentially hazardous interactions because interactions were only identified where there were at least two dispensings of each medicine, thus concomitant use could be considered definite. Instances of one dispensing were excluded as it could not be determined if use was truly concomitant. However, this means we will have omitted those who experienced an ADE due to the interaction within the first 2–3 weeks of treatment and thus were never dispensed the subsequent prescription. This also

means we will have omitted potential interactions involving single courses of treatment, for example antibiotics. Prior studies have noted that interactions involving antibiotics have a prevalence of between 3 and 10% [11, 26].

In addition, we will have missed interactions where medicines can be purchased over the counter, for example warfarin and NSAIDs or aspirin. Of the patients dispensed methotrexate, 24% and 11% were co-dispensed NSAIDs and aspirin, respectively. Toxicity from this potential interaction is less likely when low doses of methotrexate (less than 20 mg per week) are used in combination with an NSAID, and when low doses of aspirin are used in combination with methotrexate [27]. Another limitation of our study is that doses of prescribed medicines are not available on the DVA database, so the extent to which dosage may have had an impact on toxicity cannot be determined. Also, we could not determine the extent to which interacting drug pairs were intentionally dispensed by pharmacists, or the frequency with which interacting drug pairs were dispensed undetected by the pharmacist. In Australia, pharmacists only have access to the dispensing history for medicines dispensed in the present pharmacy. If the second medicine in an interacting pair was dispensed elsewhere the interaction could not have been detected by the pharmacist at the time of dispensing.

In conclusion, only 1.5% of the 287 074 subjects included in the study were dispensed potentially hazardous interacting medicines. However, limited to populations on specific medicines, it was found that for patients dispensed verapamil, methotrexate, amiodarone, lithium, warfarin, cyclosporin and itraconazole, potentially hazardous interactions occurred at a rate greater than 5%. These patients should be the focus of medication review programmes to avoid potentially serious adverse drug events.

Competing interests

There are no competing interests to declare.

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