Comparing Potential Drug-Drug Interactions in Veterinary Medications Using Two Electronic Databases

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Abstract

Background: One of the most common global health issues in humans and animals is drug-drug interactions (DDIs). This issue increases the risks of health care in both human and veterinary medicine, as animals live long lives and receive many medicines to treat their illnesses. Currently, many electronic databases are using as a tool for potential DDI prediction, e.g., Micromedex and Drugs.com. The purpose of this study was to compare the ability of Micromedex and Drugs.com to detect potential DDIs in veterinary medicines.

Results: There were 140 drugs, mainly used for the treatment of disease in animal hospitals, but the Micromedex and Drugs.com databases unidentified 44 items, therefore only 96 items were used in this study. The analysis detected 1,132 potential DDI pairs from the two databases. Micromedex identified 429 pairs of potential DDIs, while Drugs.com identified 842 pairs of potential DDIs. The same severity of the potential DDIs occurred between the two databases for 139 pairs (12.28%) and a different severity was found for 993 pairs (87.72%).

Conclusion: Although Micromedex had a lower sensitivity to find out potential DDIs than Drugs.com, Micromedex provided more informative documentation. Veterinary pharmacists should evaluate potential DDIs from different databases and communicate with both the veterinarian and animal owners to ensure an appropriate drug prescription.

Background

Currently, the treatment of disease and complications are usually related to multiple drug use [1, 2]. One category of adverse drug reactions (ADRs) is defined as drug-drug interactions (DDIs), where one drug interferes with another. Particularly, health care providers expect synergistic action and therapeutic benefit from drug combinations, but toxicity or adverse events may also be possible [3]. DDIs can lead to drug toxicity or decreased therapeutic effect, resulted in increased of morbidity and mortality [4–6]. The severity of DDIs can be divided into five degrees: contraindicated, major, moderate, minor, and none [7, 8]. A serious concern is focusing on the contraindicated and major degrees when dispensing drugs to patients as well as animals. Recently, attention has shifted to developing online databases for detecting potential DDIs. Online DDI databases have two major types: free online resources and copyrighted databases [9–11]. In general, patients usually use a free online database, for example, Drugs.com to access potential DDI identification. Conversely, health care providers usually identify potential DDIs by using a copyrighted database, for example, Micromedex. Interestingly, these two databases have different features [12] and show different results in detecting potential DDIs between the prescriptions of oral oncolytic [13]. Also, in veterinary medicine, multidrug therapy as well as human medicine is commonly used for the treatment of animals [14]. However, there are no studies regarding the ability of databases to identify potential DDIs for the treatment of complicated diseases in animals, e.g., cardiovascular diseases, urinary diseases, metabolic diseases, skin diseases and cancers. These diseases require multiple drug use and might result in DDIs in sick animals. This study aimed to investigate the different

abilities of the two electronic databases about identifying potential DDIs with complicated disease medications used in animals. The result of this study could stimulate awareness of different information sources from various databases, and lead to appropriate communication between health care providers and animal owners.

Results

From 96 items used in this study, 1,132 pairs of potential DDIs were found by the two databases. Micromedex identified 429 pairs of potential DDIs and Drugs.com identified 842 pairs of potential DDIs. The classification of severity for the 429 pairs identified by Micromedex was contraindicated in 18 pairs, major 206 pairs, moderate in 143 pairs, and minor 62 pairs. Drugs.com identified major potential DDIs of 165 pairs, moderate of 561 pairs, and minor of 116 pairs (Table 2). Among the 429 pairs of potential DDIs identified by Micromedex, DDIs with excellent or good scientific documentation rating (63.87%) and stratifying the severity of DDIs according to the documentation rating are reported in Table 3.

Table 2
Comparison of the potential DDIs characterized by
Micromedex and Drugs.com

Severity	Micromedex n (%)	Drugs.com n (%)
Contraindicated	18 (4.20)	N/A
Major	206 (48.02)	165 (19.59)
Moderate	143 (33.33)	561 (66.63)
Minor	62 (14.45)	116 (13.78)
Total	429 (100.00)	842 (100.00)
N/A, not available		

Table 3
Documentation of potential DDIs categorized by Micromedex

Severity	Excellent n (%)	Good n (%)	Fair n (%)
Contraindicated	3 (16.67)	3 (16.67)	12 (66.66)
Major	18 (8.74)	100 (48.54)	88 (42.72)
Moderate	7 (4.89)	87 (60.84)	49 (34.27)
Minor	0 (0.00)	56 (90.32)	6 (9.68)
Total	28 (6.53)	246 (57.34)	155 (36.13)

From the reports of the potential DDIs, the same severity was found by the two databases for 139 pairs (12.28%), while 993 pairs (87.72%) of reports showed a different severity when comparing the two databases. Of these severity reports, contraindications and major DDIs reported by Micromedex and major DDIs reported by Drugs.com were selected for the determination of the type of mechanism of each potential DDI report, as shown in Table 4. Among the 86 pairs of significant potential DDIs, 15 pairs were at the contraindication level reported by Micromedex and classified at the major level by Drugs.com. The remaining 71 pairs were reported at the major level by the two databases. For the determination of mechanism, 51% (44/86) were pharmacokinetics (PK) based, 34% (29/86) were pharmacodynamics (PD) based, and 15% (13/86) were PK/PD based. The majority of PK based DDIs involved cytochrome P450 (CYP) induction and inhibition, while PD based DDIs were QT prolongation and potassium retention. We also found some conflict in potential DDI reports from the two databases in which one database reported potential DDIs as major but another one reported it as minor or not a DDI. For these differing severity reports, major DDIs of 32 pairs reported by Micromedex were identified as only minor or not a DDI by Drugs.com. On the contrary, Drugs.com reported major DDIs for 53 pairs, although Micromedex identified these as not DDIs (Table 5).

Table 4
The significant severity in potential DDIs examined by Micromedex and Drugs.com

Micromedex	Drugs.com	DDIs paired lists	PK/PD	Mechanism details
Contraindication	Major	1. Amiodarone—Dronedarone	PD	Additive QT-interval prolongation
			PK	CYP3A4 inhibition by Ketoconazole
		2. Amiodarone—Ketoconazole	PD	Additive QT-interval prolongation
			PK	CYP3A4 inhibition by Cyclosporine
		3. Ciprofloxacin—Dronedarone	PK	CYP3A4 inhibition by Erythromycin
			PD	Additive QT-interval prolongation
		4. Cyclosporine—Dronedarone	PK	CYP3A4 inhibition by Itraconazole
			PK	CYP3A4 inhibition by Ketoconazole
		5. Dronedarone—Erythromycin	PD	Additive QT-interval prolongation
			PD	Additive QT-interval prolongation
		6. Dronedarone—Flecainide	PK	CYP3A4 inhibition by Itraconazole
			PK	CYP3A4 inhibition by Ketoconazole
		7. Dronedarone—Itraconazole	PK	CYP3A4 inhibition by Itraconazole
			PK	CYP3A4 inhibition by Ketoconazole
		8. Dronedarone—Ketoconazole	PK	CYP induction by Rifampin
		9. Dronedarone—Procainamide		
		10. Dronedarone—Sotalol		
		11. Felodipine—Itraconazole		
		12. Felodipine—Ketoconazole		
		13. Itraconazole—Nisoldipine		
		14. Ketoconazole—Nisoldipine		

Micromedex	Drugs.com	DDIs paired lists	PK/PD	Mechanism details
		15. Praziquantel—Rifampin		
Major	Major	1. Amikacin—Furosemide	PD	Additive or synergistic toxicity
			PK	Decreased clearance of Theophylline by Ciprofloxacin
		2. Aminophylline—Ciprofloxacin	PK	Decreased hepatic metabolism
			PD	Additive effects on QT interval
		3. Aminophylline—Mexiletine	PK	P-glycoprotein inhibition by Amiodarone
			PD, PK	
		4. Amiodarone—Ciprofloxacin	PD, PK	Additive effects on QT prolongation, CYP3A4 inhibition by Erythromycin
		5. Amiodarone—Digoxin	PK	Antiarrhythmic inhibition by Amiodarone, CYP2D6 inhibition by Amiodarone
			PD	
		6. Amiodarone—Erythromycin	PK	CYP3A4 inhibition by Itraconazole
		7. Amiodarone—Flecainide	PD	Antiarrhythmic inhibition by Amiodarone
			PK	
		8. Amiodarone—Itraconazole	PK	CYP induction by Rifampin
		9. Amiodarone—	PK	Additive effects on refractory potential
		Procainamide	PD, PK	CYP3A4 inhibition by Verapamil
			PD, PK	CYP3A4 inhibition by Diltiazem
		10. Amiodarone—Rifampin	PD	CYP induction by Rifampin
			PD	Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil
		11. Amiodarone—Sotalol	PD, PK	Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem
			PD, PK	
		12. Amiodarone—Verapamil	PD	Increased potassium retention secondary to lowered aldosterone levels
		13. Amiodarone—Diltiazem	PD	Additive effects of hyperkalemia
		14. Amlodipine—Rifampin	PK	Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil
			PK	
		15. Atenolol—Verapamil	PK	Additive cardiovascular effects, decreased metabolism of some beta-
			PK, PD	

Micromedex	Drugs.com	DDIs paired lists	PK/PD	blockers by Diltiazem Mechanism details
			PK	An additive effect of risk for tendon rupture
		16. Atenolol— Diltiazem	PD	Additive effects on the QT interval
		17. Benazepril — Spironolactone	PD PK	Additive effects on the QT interval
		18. Benazepril —Trimethoprim	PK PD	Decreased clearance of Theophylline, CYP1A2 inhibition by Ciprofloxacin
		19. Carvedilol —Verapamil	PD PK	CYP3A4 inhibition by Itraconazole
		20. Carvedilol —Diltiazem	PK PD, PK	Cyclosporine metabolism induction by Rifabutin
		21. Ciprofloxacin— Prednisolone	PD, PK PD	Increased Cyclosporine clearance and decreased systemic bioavailability by Rifampin
		22. Ciprofloxacin— Procainamide	PD PK	P-glycoprotein inhibition by Dronedarone
		23. Ciprofloxacin— Sotalol	PD PK	Digoxin metabolism and clearance inhibition by Itraconazole
		24. Ciprofloxacin— Theophylline	PD PD	Increased potassium retention secondary to lowered aldosterone levels
		25. Cyclosporine— Itraconazole	PD PK	Additive effects of hyperkalemia
		26. Cyclosporine— Rifabutin	PK PK	CYP3A4 inhibition by Erythromycin and Ketoconazole
		27. Cyclosporine— Rifampin	PK PD	CYP3A4 inhibition by Erythromycin
		28. Digoxin— Dronedarone	PK PK	CYP3A-mediated inhibition by Diltiazem
		29. Digoxin— Itraconazole	PK PK	Additive cardiovascular effects, decreased metabolism of some beta- blockers by Verapamil
		30. Enalapril— Spironolactone	PD PD	Additive cardiovascular effects, decreased metabolism of some beta- blockers by Diltiazem
		31. Enalapril— Trimethoprim	PD, PK PD, PK	Additive effects on QT prolongation
				Additive effects on refractory potential
				CYP3A-mediated inhibition by Itraconazole

Micromedex	Drugs.com	DDIs paired lists	PK/PD	CYP3A-mediated inhibition by Ketoconazole Mechanism details
		32. Erythromycin—Ketoconazole	PK	Additive or synergistic toxicity
			PK	Additive or synergistic toxicity
		33. Erythromycin—Procainamide	PK	Additive or synergistic toxicity
			PK	Additive or synergistic toxicity
		34. Erythromycin—Sotalol	PD	CYP3A4 inhibition by Itraconazole
			PD	CYP3A4 induction by Rifabutin, CYP3A4 inhibition by Itraconazole
		35. Erythromycin—Verapamil	PD	CYP3A-mediated induction by Rifampin
			PK	
		36. Erythromycin—Diltiazem	PK	CYP3A4 inhibition by Itraconazole
			PD, PK	Additive QT-interval prolongation
		37. Esmolol—Verapamil	PD, PK	CYP3A-mediated inhibition by Ketoconazole, CYP3A-mediated induction by Rifabutin
		38. Esmolol—Diltiazem	PD	CYP3A-mediated induction by Rifampin
		39. Flecainide—Procainamide		CYP3A4 induction by Rifapentine
				Additive effects on the QT interval
		40. Flecainide—Sotalol		Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil
		41. Fluticasone—Itraconazole		Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem
		42. Fluticasone—Ketoconazole		Decreased hepatic metabolism, CYP1A2 inhibition by Mexiletine
		43. Furosemide—Gentamicin		CYP3A4 induction by Phenobarbital
				CYP3A4 induction by Phenytoin
		44. Furosemide—Kanamycin		CYP3A4 induction by Rifabutin
				CYP3A4 induction by Rifampin
		45. Furosemide—Streptomycin		CYP3A4 induction by Rifapentine
				Additive effects on refractory potential
		46. Furosemide—Tobramycin		Increased potassium retention secondary to lowered aldosterone levels

Micromedex	Drugs.com	DDIs paired lists	PK/PD	Additive effects of hyperkalemia Mechanism details
		47. Itraconazole—Nifedipine		CYP3A-mediated inhibition by Itraconazole
		48. Itraconazole—Rifabutin		CYP3A-mediated inhibition by Ketoconazole
		49. Itraconazole—Rifampin		Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil
		50. Itraconazole—Sildenafil		Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem
		51. Ketoconazole—Procainamide		Additive effects of hyperkalemia
		52. Ketoconazole—Rifabutin		
		53. Ketoconazole—Rifampin		
		54. Ketoconazole—Rifapentine		
		55. Ketoconazole—Sotalol		
		56. Metoprolol—Verapamil		
		57. Metoprolol—Diltiazem		
		58. Mexiletine—Theophylline		
		59. Nifedipine—Phenobarbital		
		60. Nifedipine—Phenytoin		
		61. Nifedipine—Rifabutin		

Micromedex	Drugs.com	DDIs paired lists	PK/PD	Mechanism details
		62. Nifedipine —Rifampin		
		63. Nifedipine —Rifapentine		
		64. Procainamide —Sotalol		
		65. Ramipril— Spironolactone		
		66. Ramipril— Trimethoprim		
		67. Salmeterol —Itraconazole		
		68. Salmeterol — Ketoconazole		
		69. Sotalol— Verapamil		
		70. Sotalol— Diltiazem		
		71. Spironolactone —Trimethoprim		

Table 5
The difference in the severity of potential DDIs examined by Micromedex and Drugs.com

Micromedex	Drugs.com	DDIs paired lists
Major	Minor	<ol style="list-style-type: none"> 1. Amiodarone—Sulfamethoxazole 2. Digoxin—Gentamicin 3. Digoxin—Spironolactone 4. Digoxin—Trimethoprim 5. Erythromycin—Sulfamethoxazole 6. Flecainide—Trimethoprim 7. Lidocaine—Phenytoin 8. Procainamide—Sulfamethoxazole 9. Sotalol—Sulfamethoxazole

Micromedex	Drugs.com	DDIs paired lists
Major	None	<ol style="list-style-type: none"> 1. Amiodarone—Trimethoprim 2. Amlodipine—Digoxin 3. Amoxicillin—Chlortetracycline 4. Amoxicillin/Clavulinate—Chlortetracycline 5. Ampicillin—Chlortetracycline 6. Chlortetracycline—Methicillin 7. Chlortetracycline—Nafcillin 8. Chlortetracycline—Oxacillin 9. Chlortetracycline—Penicillin G 10. Chlortetracycline—Penicillin V 11. Digoxin—Felodipine 12. Digoxin—Isradipine 13. Digoxin—Meloxicam 14. Digoxin—Nicardipine 15. Erythromycin—Trimethoprim 16. Flecainide—Lidocaine 17. Flecainide—Trimethoprim 18. Isradipine—Procainamide 19. Isradipine—Sulfamethoxazole 20. Isradipine—Trimethoprim 21. Itraconazole—Sotalol 22. Mexiletine—Sotalol 23. Sotalol—Trimethoprim
None	Major	<ol style="list-style-type: none"> 1. Albuterol—Carvedilol 2. Amikacin—Polymyxin B 3. Aminophylline—Carvedilol 4. Amiodarone—Furosemide 5. Amiodarone—Nafcillin 6. Amiodarone—Phenobarbital

Micromedex	Drugs.com	DDIs paired lists
		7. Amiodarone—Rifabutin 8. Amiodarone—Terbutaline 9. Amlodipine—Rifabutin 10. Atenolol—Aminophylline 11. Atenolol—Theophylline 12. Diltiazem—Flecainide 13. Diltiazem—Itraconazole 14. Diltiazem—Rifabutin 15. Erythromycin—Itraconazole 16. Erythromycin—Sildenafil 17. Esmolol—Aminophylline 18. Felodipine—Rifabutin 19. Gentamicin—Polymyxin B 20. Isradipine—Phenobarbital 21. Isradipine—Rifabutin 22. Itraconazole—Amlodipine 23. Itraconazole—Isradipine 24. Itraconazole—Nicardipine 25. Itraconazole—Rifapentine 26. Kanamycin—Polymyxin B 27. Metoprolol—Aminophylline 28. Metoprolol—Theophylline 29. Nicardipine—Phenobarbital 30. Nicardipine—Rifabutin 31. Phenobarbital—Amlodipine 32. Phenobarbital—Nisoldipine 33. Phenytoin—Felodipine 34. Phenytoin—Isradipine 35. Phenytoin—Nicardipine

Micromedex	Drugs.com	DDIs paired lists
		36. Phenytoin—Amlodipine
		37. Procainamide—Terbutaline
		38. Rifabutin—Nisoldipine
		39. Rifampin—Cefamandole
		40. Rifampin—Felodipine
		41. Rifampin—Nicardipine
		42. Salmeterol—Carvedilol
		43. Sotalol—Albuterol
		44. Sotalol—Aminophylline
		45. Sotalol—Salmeterol
		46. Sotalol—Terbutaline
		47. Streptomycin—Polymyxin B
		48. Terbutaline—Carvedilol
		49. Theophylline—Carvedilol
		50. Theophylline—Esmolol
		51. Theophylline—Sotalol
		52. Tobramycin—Polymyxin B
		53. Verapamil—Itraconazole

Discussion

The potential DDI reports from the drug lists were different between the two electronic databases. Drugs.com reported more potential DDIs than Micromedex by approximately 2.0-fold. This result was correlated with the findings of Lauren et al., who found that the performance of screening DDIs in oral oncolytics detected by Drugs.com had higher sensitivity than Micromedex [13]. Suriyapakorn et al. also mentioned that Drugs.com was more sensitive to identifying potential DDIs with metabolic syndrome medications than Micromedex [16]. The reason for this phenomenon may be explained by the fact that Drugs.com has a larger database which is contributed to by four suppliers, including Micromedex. Some reports of potential DDIs are a combination of drugs used in the routine treatment of canine atopic dermatitis; for example, a co-administration of ketoconazole with cyclosporine has been recommended, which could decrease the therapeutic cost and convenient use. The potential DDIs of these two drugs seem to have positive clinical outcomes rather than negative adverse events. However, a large number of potential DDI alerts with limited documentation might lead to data alert fatigue in both health care

providers and animal owners. Many health care providers are dissatisfied with drug interaction databases [17] for reasons including alert fatigue [18–19], workflow disruption [20], and feeling that most DDI alerts are unnecessary or clinically irrelevant [21]. Ideally, an applicable drug interaction database should have both high sensitivity in detecting clinically relevant interactions and high specificity in ignoring clinically unimportant and irrelevant interactions. As a result, health care providers should not assume that only one database can provide the final answer in defining potential DDIs. Health care providers are recommended to use more than one DDI reference [22] as well as shared decision-making with animal owners for any significant potential DDI pairs to preclude animals from adverse events and minimise liability.

Many drug interactions are related to the dose of drugs that are prescribed together. For example, some drugs may have interactions at high doses, but if they are used at lower doses, they will have a lower possibility of a DDI. An ideal DDI database should be able to ignore an interaction if the drugs are given at doses that will not likely develop into a DDI [23–24]. Between the two databases, none of them had this ability. Therefore, the input of dosage should be added to databases, so health care providers can select the dose of suspected drugs. Interestingly, Micromedex and Drugs.com provide detailed information differently. Micromedex adds more information on alcohol interaction, tobacco interaction, pregnancy interaction, and lactation interaction, while Drugs.com presents results into two categories: consumer and professional. The diversity of additional information from these two databases gives many benefits to increase the confidence of health care providers when many health conditions are related to their patients.

This study has several important limitations. The important one is that only two drug databases were used for the evaluation, so future studies should include additional databases for both copyrighted and free online databases such as Lexicomp and Epocrates Free, respectively. It is also important to consider dynamic changes in the drug list in this study, via the introduction of new drugs and the removal of old drugs from time to time. This study set a cut-off for the drug list in early 2020, so the current drug list in late 2020 might have undergone some changes. The updating frequency of databases for their potential DDI reports might affect the results of the analysis. The current version of Micromedex and Drugs.com in late 2020 might report potential DDIs with different results from our study performed in early 2020. Besides, the two databases have no data on several drugs used in animal hospitals, resulting in incomplete potential DDI analysis. Therefore, there may be a greater (or lesser) discrepancy impact between the databases if all drugs were included. Also, the results of all probable mechanisms of action in our study referred to humans, which might differ from animals due to dissimilar physiology and drug metabolising enzyme systems [25]. Therefore, more study of potential DDIs in animals is recommended to improve medical care and decrease the possibility of DDIs as a result of multidrug therapy in animals.

Conclusions

In conclusion, drug interaction databases showed highly variable performance in assessing the DDIs of veterinary drugs. The Drugs.com database had a higher sensitivity to identified potential DDIs, but

Micromedex provided more informative documentation. The judgment of the health care provider's should be used with the consent of animal owners to determine appropriate treatments for animals.

Materials And Methods

Drug selection

This descriptive study included a list of medicines from one animal hospital in Thailand and VetList [15] that was taken on 9th January 2020. From 578 items in total, 140 drugs were frequently prescribed for the treatment of the diseases in animal hospitals. Remarkably, 44 drugs were not found in the Micromedex and Drugs.com databases, so only 96 items were included in the study (Fig. 1 and Table 1). The unrecognised 44 items were including aditroprim, afoxolaner, avoparcin, baquiloprim, carprofen, clomocycline, danofloxacin, demethylchlortetracycline, deracoxib, difloxacin, enrofloxacin, eprinomectin, fipronil, firocoxib, glutathione, ibafloxacin, imidacloprid, imidapril, ivermectin, levosimendan, limecycline, marbofloxacin, methacycline, methoprene, milbemycin oxime, moxidectin, oclacitinib, orbifloxacin, ormetoprim, pimobendan, pirlimycin, pradofloxacin, rolitetracycline, samylin, spiramycin, sulfadimethoxine, sulfadoxine, sulfamethazine, teicoplanin, tepoxalin, tilmicosin, tulathromycin, tylosin, and virginiamycin.

Table 1
Drug lists for the examination of potential DDIs

Drug class	Drug groups	Drug lists
Analgesics	Nonopioid	1. Meloxicam
Anthelmintics	N/A	2. Praziquantel
Antiarrhythmics	Antiarrhythmic agent class I	3. Flecainide 4. Lidocaine 5. Mexiletine 6. Procainamide
	Antiarrhythmic agent class III	7. Amiodarone 8. Dronedarone 9. Sotalol
	Antiarrhythmic agent class IV	10. Diltiazem
	Beta-blockers	11. Atenolol 12. Esmolol 13. Metoprolol
	Cardiac glycoside	14. Digoxin
	Aminoglycosides	15. Amikacin 16. Gentamycin 17. Kanamycin 18. Streptomycin 19. Tobramycin
	Carbapenems	20. Primaxin
Antimicrobials	Cephalosporins	21. Cefamandole 22. Cefotaxime 23. Cephalexin 24. Cephalothin 25. Ceftriaxone
	Chloramphenicols	26. Chloramphenicol
	Fluoroquinolones	27. Ciprofloxacin

Drug class	Drug groups	Drug lists
	Glycopeptides	28. Vancomycin
	Lincosamides	29. Clindamycin
		30. Lincomycin
	Macrolides	31. Erythromycin
	Monobactams	32. Aztreonam
	Penicillinase resistant penicillins	33. Methicillin
	Penicillins	34. Amoxicillin/Clavulinate
		35. Amoxicillin
		36. Ampicillin
		37. Carbenicillin
		38. Nafcillin
		39. Oxacillin
		40. Penicillin G
		41. Penicillin V
	Polymyxins	42. Polymyxin B
		43. Polymyxin E
	Rifamycins	44. Rifabutin
		45. Rifampin
		46. Rifapentine
Anticonvulsants	Sulfonamides	47. Sulfadiazine
		48. Sulfamethoxazole
	Tetracyclines	49. Chlortetracycline
		50. Doxycycline
		51. Minocycline
		52. Oxytetracycline
	Trimethoprim	53. Trimethoprim
	Barbiturates	54. Phenobarbital
	Hydantoin	55. Phenytoin

Drug class	Drug groups	Drug lists
	Benzodiazepine	56. Diazepam
	Miscellaneous	57. Gabapentin 58. Pregabalin
Antifungal agents	Azole derivatives	59. Itraconazole
	Imidazole derivatives	60. Ketoconazole 61. Miconazole
Antihistamines	H ₁ receptor antagonists	62. Cetirizine
		63. Chlorpheniramine
Antihypertensive drugs	Angiotensin-converting enzyme inhibitors	64. Benazepril 65. Enalapril 66. Ramipril
		67. Carvedilol
		68. Amlodipine 69. Felodipine 70. Isradipine 71. Nifedipine 72. Nisoldipine 73. Verapamil 74. Nicardipine
Antitussives	N/A	75. Dextromethorphan
Bronchodilators	Beta-2 receptor agonists	76. Salmeterol 77. Terbutaline 78. Ventolin
		79. Aminophylline 80. Theophylline
Corticosteroids	Systemics	81. Prednisolone
	Topicals	82. Fluticasone

Drug class	Drug groups	Drug lists
Diuretics	Loop diuretics	83. Furosemide 84. Torsemide
	Potassium-sparing	85. Spironolactone
Hormones	Thyroid products	86. Levothyroxine
Herbal products	N/A	87. Aloe vera
Immunosuppressants	Calcineurin Inhibitors	88. Cyclosporine
Mucolytic agents	N/A	89. Acetylcysteine
Expectorants	N/A	90. Guaifenesin
Vasodilating agents	Phosphodiesterase-5 enzyme inhibitors	91. Sildenafil
Miscellaneous	Amino acid supplements	92. Methionine
	Antioxidants	93. Alpha-lipoic acid
	Antiseptics	94. Chlorhexidine
	Liver supplements	95. SAM-E (S-adenosylmethionine)
	Vitamin like substances	96. Coenzyme Q10
N/A, not available		

Databases

IBM Micromedex Web application access was used in this study; it is a copyrighted database of IBM Corp., USA. The official registration and operations were conducted for academic purposes under the license from Chulalongkorn University. The DDI reports of the Micromedex database consisted of severity levels, documentation, onset, probable mechanism, management, literature, and references. The Drug Interactions Checker is a free online database provided by Drugs.com. This database is powered by four independent leading medical-information suppliers: Wolters Kluwer Health, American Society of Health-system Pharmacists, Cerner Multum, and Micromedex from Truven Health. The DDI reports of Drugs.com consisted of severity levels, management, probable mechanism, literature, and references.

Identification of DDIs

All the selected drugs were inputted into the databases for potential DDI detection by using the generic name. All potential DDIs were recorded to determine the sensitivity and specificity of the reports.

Micromedex has classified the severity of the potential DDIs into five levels of seriousness: contraindicated, major, moderate, minor, and unknown. Meanwhile, Drugs.com classified the potential DDIs into four groups: major, moderate, minor, and unknown. Only Micromedex classified the documentation of the outcomes as excellent, good, fair, and unknown; however, Drugs.com did not document these outcomes. The meaning of each documentation is as follows: excellent is indicated as controlled studies that have clearly established the existence of the interaction, good is defined as strongly suggesting the interaction exists but well-controlled studies are lacking, and fair is identified as poor available documentation but pharmacologic considerations lead clinicians to suspect the interaction exists; or, the documentation is good for a pharmacologically similar drug. For both Micromedex and Drugs.com reported the onset of the potential DDIs but in a different way. Micromedex reported this as one topic, while Drugs.com included the onset in the DDI monograph. All potential DDI reports were collected from the databases in January 2020.

List Of Abbreviations

ADRs
Adverse drug reactions
CYPs
Cytochrome P450s
DDIs
Drug-drug interactions
PD
Pharmacodynamics
PK
Pharmacokinetics

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Additional material

Not applicable.

Availability of data and materials

All data are presented in the manuscript.

Competing interests

All authors declare no competing interests.

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No funding was obtained for this study.

Authors' contributions

TB collected, analysed, and interpreted the data and drafted the manuscript. PK contributed to study design, data analysis, and revising the manuscript. AK contributed to study design, data analysis, and revised the manuscript. All authors have read and approved the final version of the manuscript.

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Figures

Figure 1

Diagram of the study.