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 associated with healthcare in both human and veterinary medicine, as animals live long lives and receive many medicines to treat their illnesses. Currently, many electronic databases are being used as tools for potential DDI prediction, for example, Micromedex and Drugs.com. The purpose of this study was to examine the different abilities for the identification of potential DDIs in veterinary medicines by Micromedex and Drugs.com.

Results: A list of 140 drugs, mainly used for the treatment of disease in animal hospitals, was complied, but the Micromedex and Drugs.com databases could recognise only 96 of these drugs. After inputting the recognised drug list into the databases, Micromedex showed 429 pairs of potential DDIs, whilst Drugs.com showed 842 pairs of potential DDIs. The analysis comparing results between the two databases showed 139 pairs (12.28%) with the same severity and 993 pairs (87.72%) with different severities. Major mechanisms of contraindicated and major potential DDIs were cytochrome P450 induction-inhibition and QT interval prolongation.

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

Background

Multiple-drug prescriptions for the treatment of diseases and complications usually occurs in humans and animals [1, 2]. One category of adverse drug reactions (ADRs) is defined as drug-drug interactions (DDIs), in which one drug interferes with another. In particular, healthcare providers combine drugs for synergistic action and therapeutic benefit, but toxicity or adverse events may also be possible [3]. DDIs can lead to drug toxicity or decreased therapeutic effect, resulting in increase of morbidity and mortality [4–6]. The degree of severity of DDIs is categorised as follows: contraindicated, major, moderate, minor and none [7, 8]. A serious concern is focusing on the contraindicated and major severities 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: open-access resources and subscription databases [9–11]. In general, patients usually select open-access databases, for example, Drugs.com, to access potential DDI identification. Conversely, healthcare providers prefer using a subscription database to identify potential DDIs, for example, Micromedex. Interestingly, these two databases have different features [12] and show different results in identifying potential DDIs between the prescribed drugs for oral cancer treatment [13]. Also, in veterinary medicine as well as human medicine, multidrug therapy is commonly used for the treatment of animals [14]. However, few studies focus on the competency of databases to detect potential DDIs for the management of complicated diseases in animals, for example, 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 differences in performance of DDI databases for identifying potential DDIs with complicated disease treatments used in animals.

**Results**

From the 96 drugs used in this study, 1132 unduplicated pairs were found by the selected databases as potential DDIs. Micromedex identified 429 pairs of potential DDIs and Drugs.com identified 842 pairs of potential DDIs. Table 1 exhibits the classification of severity for the 429 pairs identified by Micromedex as contraindicated in 18 pairs, major in 206 pairs, moderate in 143 pairs and minor in 62 pairs. Meanwhile, Drugs.com classified 842 pairs of potential DDIs as 165 pairs in major degree, 561 pairs in moderate degree and 116 pairs in minor degree. Fig. 1 demonstrates the documentation rating in each severity degree of potential DDIs identified by Micromedex, for which the summation of excellent and good scientific evidence was 63.87% (274/429).

**Table 1** Collation result of the potential DDIs between the two databases.

| Severity levels  | 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

After comparing all of the potential DDI results analysed by the two databases, 139 pairs (12.28%) showed the same severity, whilst 993 pairs (87.72%) of results showed a difference in severity. From all of the results, contraindications and major DDIs identified by Micromedex and major DDIs reported by Drugs.com were selected for determination of the type of mechanism of each potential DDI report, as shown in Table 2. Among the 86 pairs of significant potential DDIs, 15 pairs were at the contraindication degree reported by Micromedex and classified at the major degree by Drugs.com. The remaining 71 pairs were reported at the major degree by both databases.

**Table 2** The significant drug pairs in potential DDIs examined by the two databases.
| Micromedex | Drugs.com | List of drugs paired | PK-PD | Mechanism details |
|------------|-----------|----------------------|-------|-------------------|
| Contraindication | Major | Major |                   |       |
| 1. Amiodarone—Dronedarone | PD | Additive QT-interval prolongation |
| 1. Amiodarone—Ketoconazole | PK | CYP3A4 inhibition by Ketoconazole |
| 2. Ciprofloxacin—Dronedarone | PK | Additive QT-interval prolongation |
| 3. Cyclosporine—Dronedarone | PK | CYP3A4 inhibition by Cyclosporine |
| 4. Dronedarone—Erythromycin | PD | CYP3A4 inhibition by Erythromycin |
| 5. Dronedarone—Flecainide | PK | Additive QT-interval prolongation |
| 6. Dronedarone—Itraconazole | PK | CYP3A4 inhibition by Itraconazole |
| 7. Dronedarone—Ketoconazole | PD | Additive QT-interval prolongation |
| 8. Dronedarone—Procainamide | PK | CYP3A4 inhibition by Itraconazole |
| 9. Dronedarone—Sotalol | PK | CYP3A4 inhibition by Ketoconazole |
| 10. Felodipine—Itraconazole | PK | CYP3A4 inhibition by Itraconazole |
| 11. Felodipine—Ketoconazole | PK | CYP3A4 inhibition by Ketoconazole |
| 12. Itraconazole—Nisoldipine | PK | CYP induction by Rifampin |
| 13. Ketoconazole—Nisoldipine |   |                     |
| 14. Praziquantel—Rifampin |   |                     |

| Major | Major |                   |       |
|-------|-------|-------------------|-------|
| 1. Amikacin—Furosemide | PD | Additive or synergistic toxicity |
| 2. Aminophylline—Ciprofloxacin | PK | Decreased clearance of Theophylline by Ciprofloxacin |
| 1. Aminophylline—Mexiletine | PK | Decreased hepatic metabolism |
| 2. Amiodarone—Ciprofloxacin | PK | Additive effects on QT interval |
| 3. Amiodarone—Digoxin | PD, PK | P-glycoprotein inhibition by Amiodarone |
| 1. Amiodarone—Erythromycin | PD, PK | Additive effects on QT prolongation, CYP3A4 inhibition by Erythromycin |
| 1. Amiodarone—Flecainide | 1. Amiodarone—Itraconazole | 2. Amiodarone—Procainamide |
|--------------------------|----------------------------|---------------------------|
| PK                      | PD                         | PK                        |

1. Amiodarone—Rifampin
2. Amiodarone—Sotalol
3. Amiodarone—Verapamil
4. Amiodarone—Diltiazem
5. Amlodipine—Rifampin
6. Atenolol—Verapamil

| 1. Atenolol—Diltiazem | 1. Benazepril—Spironolactone | 1. Benazepril—Trimethoprim |
|------------------------|-----------------------------|----------------------------|
| PD                     | PD, PK                       | PD, PK                     |

1. Benazepril—Trimethoprim
2. Carvedilol—Verapamil

1. Carvedilol—Diltiazem

Antiarrhythmic inhibition by Amiodarone, CYP2D6 inhibition by Amiodarone, CYP3A4 inhibition by Itraconazole, Antiarrhythmic inhibition by Amiodarone, CYP induction by Rifampin, Additive effects on refractory potential CYP3A4 inhibition by Verapamil, CYP induction by Diltiazem, Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil, Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem, Increased potassium retention secondary to lowered aldosterone levels, Additive effects of hyperkalemia, Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil, Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem, An additive effect of risk for tendon.
1. Ciprofloxacin—Prednisolone
   - PK
   - Additive effects on the QT interval

2. Ciprofloxacin—Procainamide
   - PK
   - Additive effects on the QT interval

3. Ciprofloxacin—Sotalol
   - PK
   - Decreased clearance of Theophylline

4. Ciprofloxacin—Theophylline
   - PK, PD
   - CYP1A2 inhibition by Ciprofloxacin
   - CYP3A4 inhibition by Itraconazole

1. Cyclosporine—Itraconazole
   - PK
   - Cyclosporine metabolism induction by Rifabutin

2. Cyclosporine—Rifabutin
   - PK
   - Increased Cyclosporine clearance and decreased systemic bioavailability by Rifampin

3. Cyclosporine—Rifampin
   - PD
   - Decreased systemic bioavailability by Rifampin

1. Digoxin—Dronedarone
   - PD
   - P-glycoprotein inhibition by Dronedarone

2. Digoxin—Itraconazole
   - PK
   - Increased Itraconazole metabolism and clearance

1. Enalapril—Spironolactone
   - PD
   - Additive effects of hyperkalemia

2. Enalapril—Trimethoprim
   - PD, PK
   - CYP3A4 inhibition by Erythromycin and Ketoconazole

3. Erythromycin—Ketoconazole
   - PD, PK
   - Additive effects on QT prolongation

1. Erythromycin—Procainamide
   - PD
   - CYP3A-mediated inhibition by Diltiazem

2. Erythromycin—Sotalol
   - PD
   - Additive cardiovascular effects, decreased metabolism of some

3. Erythromycin—Verapamil
   - PD

4. Erythromycin—Diltiazem
   - PD

5. Esmolol—Verapamil
   - PD
1. Esmolol—Diltiazem

1. Flecainide—Procainamide
2. Flecainide—Sotalol
3. Fluticasone—Itraconazole

1. Fluticasone—Ketoconazole

1. Furosemide—Gentamicin
2. Furosemide—Kanamycin
3. Furosemide—Streptomycin
4. Furosemide—Tobramycin
5. Itraconazole—Nifedipine
6. Itraconazole—Rifabutin

1. Itraconazole—Rifampin
2. Itraconazole—Sildenafil
3. Ketoconazole—Procainamide
4. Ketoconazole—Rifabutin

1. Ketoconazole—Rifampin
2. Ketoconazole—Rifapentine

PK beta-blockers by Verapamil
Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem
Additive effects on QT prolongation
PK Additive effects on refractory potential
PK inhibition by Itraconazole
PK CYP3A-mediated inhibition by Itraconazole
PK synergetic toxicity
PK Additive or synergetic toxicity
PK synergistic toxicity
PK Additive or synergistic toxicity
PK CYP3A-mediated inhibition by Itraconazole
PK CYP3A4 induction by Rifabutin,
PK CYP3A4 inhibition by Itraconazole
PD CYP3A-mediated induction by Rifampin
PD, PK CYP3A4 inhibition by Itraconazole
Additive QT-interval prolongation
PD, PK CYP3A-mediated inhibition by Ketoconazole,
PK CYP3A-mediated induction by Rifabutin
PK CYP3A4 induction by Rifampin
PK Additive effects on the QT interval
3. Ketoconazole—Sotalol
4. Metoprolol—Verapamil

1. Metoprolol—Diltiazem
PK
Additive cardiovascular effects, decreased metabolism of some beta-blockers by Verapamil
PD
Additive cardiovascular effects, decreased metabolism of some beta-blockers by Diltiazem

1. Mexiletine—Theophylline
PK
Decreased hepatic metabolism, CYP1A2 inhibition by Mexiletine
PK
CYP3A4 induction by Phenobarbital
PK
CYP3A4 induction by Phenytoin
PK
CYP3A4 induction by Rifabutin
PK
CYP3A4 induction by Rifampin
PK
CYP3A4 induction by Rifapentine

1. Nifedipine—Phenobarbital
PD, PK
Additive effects on refractory potential
Increased potassium retention secondary to lowered aldosterone levels

2. Nifedipine—Phenytoin
PK
CYP3A4 induction by Phenytoin

3. Nifedipine—Rifabutin
PK
CYP3A4 induction by Rifabutin

4. Nifedipine—Rifampin
PK
CYP3A4 induction by Rifampin

5. Nifedipine—Rifapentine
PD, PK
CYP3A4 induction by Rifapentine

6. Procainamide—Sotalol
PD
Additive cardiovascular effects, decreased metabolism of some beta-blockers by Sotalol

7. Ramipril—Spironolactone
PD
Additive cardiovascular effects, decreased metabolism of some beta-blockers by Spironolactone

1. Ramipril—Trimethoprim

2. Salmeterol—Itraconazole

1. Salmeterol—Ketoconazole

1. Sotalol—Verapamil

1. Sotalol—Diltiazem
In terms 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, whilst PD-based DDIs caused QT prolongation and potassium retention. We also found some conflict between the results of the two databases, in which one database reported potential DDIs as major but another one reported them as minor or not DDIs. For the dissimilar results as shown in Table 3, 32 pairs were identified by Micromedex as major DDIs but only minor or not DDIs by Drugs.com. Conversely, 53 pairs were specified as major DDIs by Drugs.com whilst Micromedex identified these as not DDIs.

**Table 3 Different results between the two databases in the identification of the potential DDIs**
| Micromedex | Drugs.com | List of drugs paired |
|------------|-----------|---------------------|
| Major      | Minor     |                     |

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  

| Major | 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                                  |
|--------|----------------------------------------|
| 1.     | Albuterol—Carvedilol                    |
| 2.     | Amikacin—Polymyxin B                   |
| 3.     | Aminophylline—Carvedilol               |
| 4.     | Amiodarone—Furosemide                  |
| 5.     | Amiodarone—Nafcillin                   |
| 6.     | Amiodarone—Phenobarbital               |
| 7.     | Amiodarone—Rifabutin                   |
| 8.     | Amiodarone—Terbutaline                 |
| 9.     | Amlodipine—Rifabutin                   |
| 10.    | Atenolol—Aminophylline                 |
| 11.    | Atenolol—Theophylline                  |
| 12.    | Diltiazem—Flecainide                   |
| 13.    | Diltiazem—Ittraconazole                |
| 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                  |
| 36.    | Phenytoin—Amlodipine                   |
Discussion

The two databases used in our study could recognise animal medicines less frequently than human medicines. This may be because the databases do not include complete information about animal medicines in their DDI databases. However, Drugs.com included a list of veterinary products that covered many animal species and provided useful information, for example, dosage, administration, precautions and adverse reactions. Therefore, veterinary pharmacists should use this drug database for searching for drug information and as a source for reference documents. The potential DDI results from the drug lists were different for the two electronic databases. In this study, the results from Drugs.com exhibited a higher number of potential DDIs than Micromedex by nearly 2.0 times. This result was correlated with Lauren et al., who found that Drugs.com had higher sensitivity than Micromedex for screening DDIs in oral cancer treatment [13]. Suriyapakorn et al. compared the capability of the databases to identify potential DDIs with metabolic syndrome medications and also found that Drugs.com provided more sensitivity than the other database [15]. The reason for the high sensitivity of Drugs.com in identifying DDIs may be caused by using databases from many providers to analyse data that is contained in Micromedex. We compared the result from Micromedex between the drug list used for metabolic syndrome in human and animal diseases in identity contraindicated and major potential DDIs. The drug list for animal disease treatment identified more pairs of contraindicated and major potential DDIs; the reason might be that the drugs used in animals included many drugs related to antiarrhythmic agents, antimicrobials and antihypertensive drugs, which often show a high incidence of potential DDI when
prescribed with other drugs [16–18]. Veterinary pharmacists should realise when prescribing these drug groups to avoid the severe adverse reactions.

The combination of drugs prescribed to treat canine atopic dermatitis were identified as a potential DDIs; for instance, a co-prescription of ketoconazole with cyclosporine has been suggested, which could reduce the therapeutic cost and is convenient to use. This combination appears to provide greater clinical benefits for the treatment than disadvantages. Nevertheless, an excessive number of alerts of potential DDI lacking supporting information could cause wearying to healthcare providers as well as animal owners. Many healthcare providers dislike using drug interaction databases [19] for several reasons, including alert fatigue [20–21], workflow disturbance [22] and believing that there is no clinical significance related to most DDI alerts [23]. Ideally, an applicable drug interaction database should have both high sensitivity in identifying significant interactions and high specificity in excluding insignificant interactions. As a result, healthcare providers should be sure to use more than one DDI reference for reaching the best final answer when identifying potential DDIs [24]. Apart from using several DDI databases, healthcare providers should share their decision-making with animal owners regarding any significant potential DDI pairs, to preclude animals from adverse events and minimise liability.

In multiple-drug prescriptions, drug dosages usually have a relationship with drug interactions. For example, giving high doses of some drugs may cause interactions, but if they are used at lower doses, the possibility of a DDI may decrease. Ideally, the DDI database should be able to overlook an interaction if the given drugs are at doses that will not likely develop into a DDI [25–26], which the two databases in this study were not able to do. Therefore, the input of dosage should be added to databases, so healthcare providers can select the dose of drugs under consideration. Interestingly, Micromedex and Drugs.com provide detailed information differently. Micromedex adds more information on allergy interaction, alcohol interaction, lab interaction, tobacco interaction, pregnancy interaction and lactation interaction; Drugs.com provides more information only on food interactions and presents results into two categories: consumer and professional. The diversity of information from these two databases gives many benefits to increase the confidence of healthcare providers when many health conditions are discussed with their clients.

For determination of the mechanisms of potential DDIs in contraindicated and major severity levels identified by the two databases, PK-based was the main mechanism of DDI, followed by PD-based and PK-PD-based. The PK-based DDI causes a change of drug concentration in plasma or at the targeted organ by altering the absorption, distribution, metabolism and elimination. In this study, CYP enzyme inhibition was the main result of PK-based DDI, which leads to the accumulation of co-administered drugs, for example, ciprofloxacin inhibits CYP1A2 activity and decreases the clearance of theophylline, resulting in fatal adverse drug reaction via drug toxicity. PD-based DDI is caused by one drug interfering with another drug at the target site. The main result of PD-based DDI in our study was QT prolongation, which may lead to irregular heart rhythm and sudden death, for example, co-administration of erythromycin with sotalol may result in an additive QT prolongation. As a result, healthcare providers should truly understand these DDI mechanisms to prescribe multiple drugs properly.
This study has several important limitations. The most important one is that only two drug databases were used for the evaluation, so future studies should include additional databases of both subscription and open-access type, such as Lexicomp and Epocrates Free, respectively. Changing of the drug list was also one of our concerns; each year new drugs were developed whilst old drugs disappeared. The drug list used in this study was gathered in the first quarter of 2020, so it might have changed at any time. The updating frequency of databases for their potential DDI reports might affect the results of the analysis. The potential DDI result produced by the updated version of Micromedex and Drugs.com at different time points might give different outcomes from our study, performed in the first quarter of 2020. Additionally, the two databases have no data on several drugs used in animal hospitals, resulting in incomplete potential DDI analysis. Hence, some differences may occur once all drugs are added into the databases. Finally, 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 [27]. 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

Drug interaction databases showed highly variable performance in assessing the DDIs of veterinary drugs. Open-access resources, such as Drugs.com, could detect more potential DDIs. However, Micromedex, a subscription database, provided more supportive information and special features. The judgement of healthcare providers should be used, with the consent of animal owners, to determine appropriate treatments for animals and avoid potential DDIs by using several databases for the data evaluation.

Materials And Methods

Drug selection

A list of 578 drugs was taken from those used in one animal hospital in Thailand and the VetList database [28], on 9 January 2020. From the total, 140 drugs were selected as frequently prescribed for the treatment of diseases in animal hospitals. Remarkably, Micromedex and Drugs.com could not recognise 44 of these drugs, so those remaining were used for this analysis, as shown in Fig. 2 and Table 4. The unrecognised 44 items were aditroprim, afoxolaner, avoparcin, baquioprim, carprofen, clomocycline, danofloxacin, demethylchlorotetracycline, deracoxyb, difloxacin, enrofloxacin, eprinomectin, fipronil, firocoxib, glutathione, ibafloxacin, imidacloprid, imidapril, ivermectin, levosimendan, limecycline, marbofloxacín, methacycline, methoprene, milbemycin oxime, moxidectin, oclacitinin, orbifloxacin, ormetoprim, pimobendan, pirlimycin, pradofloxacin, rolitetracycline, samylin, spiramycin, sulfadimethoxine, sulfadoxine, sulfamethazine, teicoplanin, tepoxalin, tilmicosin, tulathromycin, tylosin and virginiamycin.

Table 4 List of drugs used for the potential DDIs analysis
| Drug class          | Drug groups          | Drug lists                                      |
|---------------------|----------------------|------------------------------------------------|
| Analgesics          | Nonopioid            | 1.  Meloxicam                                   |
| Anthelminthics      | N/A                  | 1.  Praziquantel                               |
| Antiarrhythmics     | Antiarrhythmic agent class I | 1.  Flecainide  
|                     |                      | 2.  Lidocaine  
|                     |                      | 3.  Mexiletine  
|                     |                      | 4.  Procainamide                               |
| Antiarrhythmic agent class III |                      | 1.  Amiodarone  
|                     |                      | 2.  Dronedarone  
|                     |                      | 3.  Sotalol                                    |
| Antiarrhythmic agent class IV |                | 1.  Diltiazem                                  |
| Beta-blockers       |                      | 1.  Atenolol                                   |
|                     |                      | 2.  Esmolol                                    |
|                     |                      | 3.  Metoprolol                                 |
| Cardiac glycoside   |                      | 1.  Digoxin                                    |
| Antimicrobials      | Aminoglycosides      | 1.  Amikacin                                   |
|                     |                      | 2.  Gentamycin                                 |
|                     |                      | 3.  Kanamycin                                  |
|                     |                      | 4.  Streptomycin                               |
|                     |                      | 5.  Tobramycin                                 |
| Carbapenems         |                      | 1.  Primaxin                                   |
| Cephalosporins      |                      | 1.  Cefamandole                                |
|                     |                      | 2.  Cefotaxime                                 |
|                     |                      | 3.  Cephalexin                                 |
|                     |                      | 4.  Cephalothin                                |
|                     |                      | 5.  Ceftriaxone                                |
| Chloramphenicols    |                      | 1.  Chloramphenicol                            |
| Fluoroquinolones    |                      | 1.  Ciprofloxacin                              |
| Glycopeptides       |                      | 1.  Vancomycin                                 |
| **Lincosamides** | 1. Clindamycin  
2. Lincomycin |
| **Macrolides**   | 1. Erythromycin |
| **Monobactams**  | 1. Aztreonam |
| **Penicillinase resistant penicillins** | 1. Methicillin |
| **Penicillins** | 1. Amoxicillin/Clavulinate  
2. Amoxicillin  
3. Ampicillin  
4. Carbenicillin  
5. Nafcillin  
6. Oxacillin  
7. Penicillin G  
8. Penicillin V |
| **Polymyxins**  | 1. Polymyxin B  
2. Polymyxin E |
| **Rifamycins**  | 1. Rifabutin  
2. Rifampin  
3. Rifapentine |
| **Sulfonamides** | 1. Sulfadiazine  
2. Sulfamethoxazole |
| **Tetracyclines** | 1. Chlortetracycline  
2. Doxycycline  
3. Minocycline  
4. Oxytetracycline |
| **Trimethoprim** | 1. Trimethoprim |

| **Anticonvulsants** | **Barbiturates** | 1. Phenobarbital |
| **Hydantoin** | 1. Phenytoin |
| **Benzodiazepine** | 1. Diazepam |
| Class                        | Subclass                  | Examples                  |
|------------------------------|---------------------------|---------------------------|
| Miscellaneous                |                           |                           |
|                              | 1. Gabapentin              |                           |
|                              | 2. Pregabalin              |                           |
| Antifungal agents            | Azole derivatives         | 1. Itraconazole           |
|                              |                           |                           |
|                              | Imidazole derivatives     | 1. Ketoconazole           |
|                              |                           | 2. Miconazole             |
| Antihistamines               | H₁ receptor antagonists   | 1. Cetirizine             |
|                              |                           | 2. Chlorpheniramine       |
| Antihypertensive drugs       | Angiotensin-converting enzyme inhibitors | 1. Benazepril           |
|                              |                           | 2. Enalapril              |
|                              |                           | 3. Ramipril               |
|                              | Beta-blockers             | 1. Carvedilol             |
|                              | Calcium channel blockers  | 1. Amlodipine             |
|                              |                           | 2. Felodipine             |
|                              |                           | 3. Isradipine             |
|                              |                           | 4. Nifedipine             |
|                              |                           | 5. Nisoldipine            |
|                              |                           | 6. Verapamil              |
|                              |                           | 7. Nicardipine            |
| Antitussives                 | N/A                       | 1. Dextromethorphan       |
| Bronchodilators              | Beta-2 receptor agonists  | 1. Salmeterol             |
|                              |                           | 2. Terbutaline            |
|                              |                           | 3. Ventolin               |
|                              | Phosphodiesterase inhibitors | 1. Aminophylline         |
|                              |                           | 2. Theophylline           |
| Corticosteroids              | Systemics                 | 1. Prednisolone           |
|                              | Topicals                  | 1. Fluticasone            |
| Diuretics                    | Loop diuretics            | 1. Furosemide             |
|                              |                           | 2. Torsemide              |

Potassium-sparing
| Category                  | Subcategory                          | Example               |
|---------------------------|--------------------------------------|-----------------------|
| Hormones                  | Thyroid products                      | 1. Levothyroxine      |
| Herbal products           | N/A                                   | 1. Aloe vera          |
| Immunosuppressants        | Calcineurin Inhibitors                | 1. Cyclosporine       |
| Mucolytic agents          | N/A                                   | 1. Acetylcysteine     |
| Expectorants              | N/A                                   | 1. Guaifenesin        |
| Vasodilating agents       | Phosphodiesterase-5 enzyme inhibitors | 1. Sildenafil          |
| Miscellaneous             | Amino acid supplements                | 1. Methionine         |
|                          | Antioxidants                          | 1. Alpha-lipoic acid  |
|                          | Antiseptics                           | 1. Chlorhexidine      |
|                          | Liver supplements                      | 1. SAM-E (S-adenosylmethionine) |
|                          | Vitamin like substances               | 1. Coenzyme Q10       |

N/A, not available

**Drug interaction databases selection**

The subscription drug interaction database Micromedex (Truven Health Analytics, USA) was selected for the analysis of potential DDI on the basis of local availability through Chulalongkorn University. The open-access drug interaction database Drugs.com (Drugsite Trust, USA) was used because this database is well known and easy to use. The results of DDI from the two databases provided the same information, as follows: severity levels, probable mechanism, clinical management, literature and references. However, Micromedex provided more supportive information about documentation levels and the onset of the interaction.

**DDI categorisation**

For every selected drug queries posed to the databases, the two drug interaction databases categorised potential DDIs with a few different formats and explanations. Micromedex has five severity categories to identify potential DDIs, as follows: contraindicated, major, moderate, minor and unknown. Drugs.com has no category for contraindicated. Interestingly, only Micromedex categorised the documentation level for the detected potential DDIs, at three levels, as follows: excellent – the interaction has been clearly verified...
from controlled studies; good – the interaction is strongly suspected but lacks well-controlled studies; fair – availability of documentation is poor but the interaction is suspected to exist on the basis of pharmacological considerations, or a pharmacologically related drug provides good documentation. All results of the potential DDIs in this study were obtained from searches in the two databases and gathered in January 2020.

**List Of Abbreviations**

ADR: Adverse drug reaction  
CYP: Cytochrome P450  
DDI: Drug-drug interaction  
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**

Each author declares no competing interests.

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**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 revising the manuscript. All authors have read and approved the final version of the manuscript.

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Figures
Figure 1

Result of the potential DDIs in each documentation level of Micromedex
Figure 2

Procedure for drug selection