CHARACTERIZATION AND CLASSIFICATION OF ADVERSE DRUG INTERACTIONS

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Drug interactions which may cause harmful events are important for our health and new drug development. In the previous work, we extracted the drug interaction data from Japanese drug package inserts and generated the drug interaction network. The network contains a large number of drugs densely connected to each other, where drug targets and drug-metabolizing enzymes were shared in the drug interactions. In this study, we further analyzed the obtained drug interaction network by merging drugs into drug categories based on the Anatomical Therapeutic Chemical (ATC) classification. The merged data of drug interactions indicated drug properties that are related to drug interaction mechanisms or symptoms. We investigated the relationships between the drug groups and drug interaction mechanisms or symptoms.

Keywords: drug interactions; ATC classification system; KEGG.

1. Introduction

Combined use of multiple drugs may cause adverse events. Drug interactions can lead to an increase or a decrease of the drug effects or cause other serious reactions. For example, coadministration of a drug metabolized by Cytochrome P450 3A4 (CYP3A4) and the drug inhibiting CYP3A4, such as cyclosporine and clarithromycin, respectively, results in delayed clearance and elevated blood levels of the former drug, which increases and prolongs both the therapeutic and adverse effects [1]. Known information about potential risks of drug interactions is described in drug package inserts, which are documents attached with prescription medications to provide additional information about the drugs. The package insert information of Japanese marketed pharmaceutical products is provided by the Japan Pharmaceutical Information Center (JAPIC) database (http://database.japic.or.jp/nw/index), which is integrated with the KEGG DRUG database [2] to provide the GenomeNet pharmaceutical products database (http://www.genome.jp/kusuri/). Each JAPIC entry has its unique identifier (JAPIC ID) representing the package insert document of each marketed drug, which includes reported adverse drug interaction information. Adverse drug interactions are described with concrete names of compounds or names of drug classes. Interaction mechanisms and symptoms are classified according to the types of risks, contraindications or cautions

for coadministration. On the contrary, the identifiers of the KEGG DRUG entries (D numbers) are associated with chemical compounds included in marketed drugs. In order to understand adverse drug interactions at the molecular perspective, we combined the compounds (D numbers) with the package inserts (JAPIC IDs) from many marketed products having the same main ingredients. In the previous work, we generated the drug interaction network with the extracted package insert information, and found the network including a number of drugs densely connected to each other, where drug targets and drug-metabolizing enzymes were shared with drug interactions [3]. The aim of this study is to characterize and classify drug interactions in order to suggest risks of potential drug interactions. We used the Anatomical Therapeutic Chemical (ATC) Classification System, which is controlled by the WHO Collaborating Centre for Drug Statistics Methodology, in order to merge the drugs having similar chemical or pharmacological properties to obtain the generic interpretation of the drug interaction network. Obtained data of drug groups, drug targets and drug-metabolizing enzymes were used to determine characteristics of drug interactions. Then we investigated the relationship between interaction characteristics and interaction mechanisms or symptoms.

2. Method

2.1. *Datasets*

All drug interaction data were collected from the JAPIC database, containing the package insert data of 14,104 marketed drugs in Japan (as of June 2009) including the information on generic and trade names, physicochemical and pharmacokinetic properties, drug-metabolizing enzymes, and drug interactions. The drug interaction data is categorized as contraindications or cautions for coadministration, and is described using drug names or drug class names, interaction mechanisms and symptoms. The KEGG DRUG database (http://www.genome.jp/kegg/drug/) contains 8,912 approved drugs in either the U.S. or Japan as of July 2009. Each KEGG DRUG entry contains a D number (accession number), generic and trade names, molecular formula, chemical structure, target information, activity information, the ATC classification, and therapeutic category linked to the KEGG BRITE database (http://www.genome.jp/kegg/brite.html). The KEGG BRITE database is an ontology database and was used to retrieve information on functional hierarchies of drug targets, drug-metabolizing enzymes and compounds. We used the DrugBank database [4] to obtain more information on drug targets and drug-metabolizing enzymes.

2.2. *Drug groups based on the ATC classification*

We used the Anatomical Therapeutic Chemical (ATC) Classification System to group drugs. The ATC code, the identifier of the drug classification, consists of five different levels based to the organ or system on which the drugs act and/or the therapeutic and chemical characteristics. The first level represents anatomical main group, and consists of

one letter (*e.g.*, "A" for alimentary tract and metabolism, "B" for blood and blood forming organs and "C" for cardiovascular system). The second and third levels represent therapeutic and pharmacological subgroups, respectively (*e.g.*, "C03" and "C03C" for diuretics and high-ceiling diuretics, respectively). The fourth and fifth levels indicate chemical subgroup and chemical substance, respectively (*e.g.*, "C03CA" and "C03CA01" sulfonamides and furosemide, respectively). In this study, the last three levels, *i.e.*, the third, fourth and fifth levels, were used to group drugs. For example, a drug erythromycin (D number: D00140) is classified into the ATC code "J01FA01" meaning a drug group "erythromycin", including eleven compounds such as erythromycin ethylsuccinate (D01361), erythromycin lactobionate (D02009) and erythromycin propionate (D02525). The fourth and the third levels of the code, J01FA and J01F, are defined as "macrolides" and "macrolides, lincosamides and streptogramins", respectively, and more compounds are included in those categories. Drugs with known drug interactions were grouped based on the ATC classification at each of those levels. There are cases where some D numbers share ATC codes (*e.g.*, clindamycin phosphate D01073 and clindamycin hydrochloride D02132 share three redundant codes "D10AF01", "G01AA10" and "J01FF01", all of which means "clindamycin"), which were manually merged into one drug group "clindamycin". The KEGG BRITE database was used to retrieve definitions of the drug groups. The drug groups were used to investigate the relationships with interaction mechanisms or symptoms at each ATC classification level.

2.3. *Drug interaction network*

Names of drugs or drug classes that interact with the other drugs were extracted from the drug interaction information in each JAPIC entry, and were replaced by the corresponding JAPIC IDs. The first type of drug interaction network was generated by representing marketed drugs (JAPIC IDs) as nodes and the interactions as edges. We progressively generated drug interaction networks at the different resolutions by merging the nodes according to different levels of the classification, *i.e.*, the JAPIC IDs, the D numbers and the drug groups at different ATC classification levels.

3. Results

We obtained 832 drug targets that were classified in 307 groups according to the definition in the KEGG BRITE database. The drug targets were associated with 926 drugs, among which 212 drugs were reported to act on biogenic amine (*e.g.*, adrenaline, dopamine, histamine, serotonin and acetylcholine) receptors. Table 1 lists major drug targets, definition of drug groups including drugs act on the targets and total number of the drugs.

Table 1. Drug targets and related drug groups

Drug target	Definition of drug group	# of drugs
Adrenaline receptors	Antipsychotics, Beta blocking agents	90

Cys4 zinc finger factors	Corticosteroids	74
Dopamine receptors	Antipsychotics, Dopaminergic agents	56
Histamine receptors	Antihistamines, Antipsychotics	54
Serotonin receptors	Antipsychotics, Antimigraine preparations	49
Oxidoreductases [EC:1.14.14.-]	Macrolides, Antifungals	44
Acetylcholine receptors	Antipsychotics, Anticholinergic agents	36

We searched the drug groups related to the drug-metabolizing enzymes. Table 2 shows examples of the drug group in which most drugs are metabolized by the same enzyme. For example, the drug group of glucocorticoids includes 30 drugs of which 29 are metabolized by the CYP3A4. Definition of the drug groups were retrieved from the KEGG BRITE database. We obtained 63 drug groups related to CYP3A, 34 drug groups to CYP2D6 and 14 drug groups to CYP1A2.

Table 2. Drug groups related to drug-metabolizing enzymes.

Drug-metabolizing enzyme	Definition of drug group	# of drugs
CYP3A4	Glucocorticoids	29 (of 30)
	Dihydropyridine Derivatives	10 (of 11)
	Protein kinase inhibitors	7 (of 7)
	Protease inhibitors	7 (of 7)
CYP2D6	Antidepressants	12 (of 15)
	Phenothiazines with piperazine structure	8 (of 9)
	Phenothiazines with aliphatic side-chain	5 (of 5)
CYP1A2	Natural and semisynthetic estrogens	5 (of 6)

We obtained drug interaction networks with different IDs and groups including JAPIC IDs, D numbers and the drug groups. Table 3 shows the number of edges and nodes in each drug interaction network.

Table 3. Number of nodes and edges in the drug interaction networks.

IDs / drug groups	# of edge	# of node
JAPIC ID	2201571	9227
D number	72611	2153
ATC at fifth level	37847	1617
ATC at fourth level	13637	539
ATC at third level	7067	211

The obtained data of drug targets and drug-metabolizing enzymes was attached to the drug interactions. Figure 1 shows examples of the drug interaction networks. Nodes represent D numbers (Fig. 1A) or drug groups at different ATC classification levels (Fig. 1B, C and D). Edges represent interactions between the nodes, and colored edges indicate the interactions by inhibition of CYPs (red edges) and additive effect or antagonism of biogenic amine receptors (green edges). Network size was reduced dependent on the level of drug groups based on the ATC classification, which helped to extract characteristics of the drug groups and interactions.

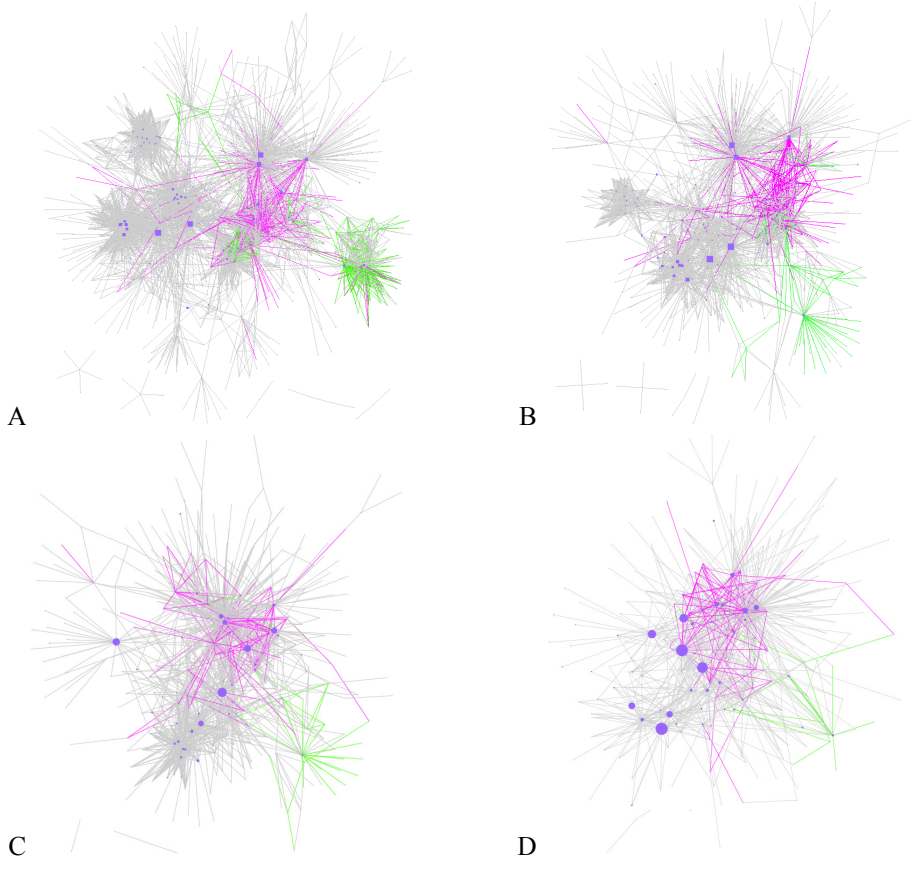

Figure 1. Drug interaction networks of contraindications for coadministration. In each network, nodes indicate as follows. A: D numbers. B: drug groups of "chemical substance" at fifth level of the ATC classification. C: drug groups of "chemical subgroup" at fourth level of the ATC classification. D: drug groups of "pharmacological subgroup" at third level of the ATC classification. Node size reflects number of interactions involved. Edges represent drug interactions between the two nodes. Green edges represent interactions which result from additive effects on the same biogenic amine receptor and red edges represent interactions caused by inhibiting CYP enzymes. The data used to generate these networks is limited to the interactions which were reported as contraindications for coadministration in order to decrease the nodes and edges in the networks.

In the interaction networks with the drug groups (Fig. 1B, C and D), nodes and edges shows drug properties and interaction characteristics. We searched interactions between the drug properties and interaction characteristics including interaction mechanisms and symptoms from the drug interaction networks at the third and fourth levels of the ATC classification. Figure 2 illustrates the extracted characteristic interactions in those networks. Large nodes and thick edges represent the obtained interactions including relationships between drug properties and interaction mechanisms or symptoms reported in the package insert information. In the network at the third level (Fig. 2A), we obtained 564 interactions between corticosteroids and adrenergics, 235 interactions between corticosteroids and insulins, 64 interactions of muscle relaxants with aminoglycosides or

lincosamides and 67 interactions between beta-blocking agents and analgesics or antipyretics. At the fourth level (Fig. 2B), we obtained 92 interactions of fluoroquinolones or tetracyclines with calcium compounds, 55 interactions between angiotensin II antagonists and angiotensin-converting enzymes (ACE) inhibitors, 26 interactions between aminoglycosides and platinum compounds and 12 interactions between digoxin and angiotensin II antagonists.

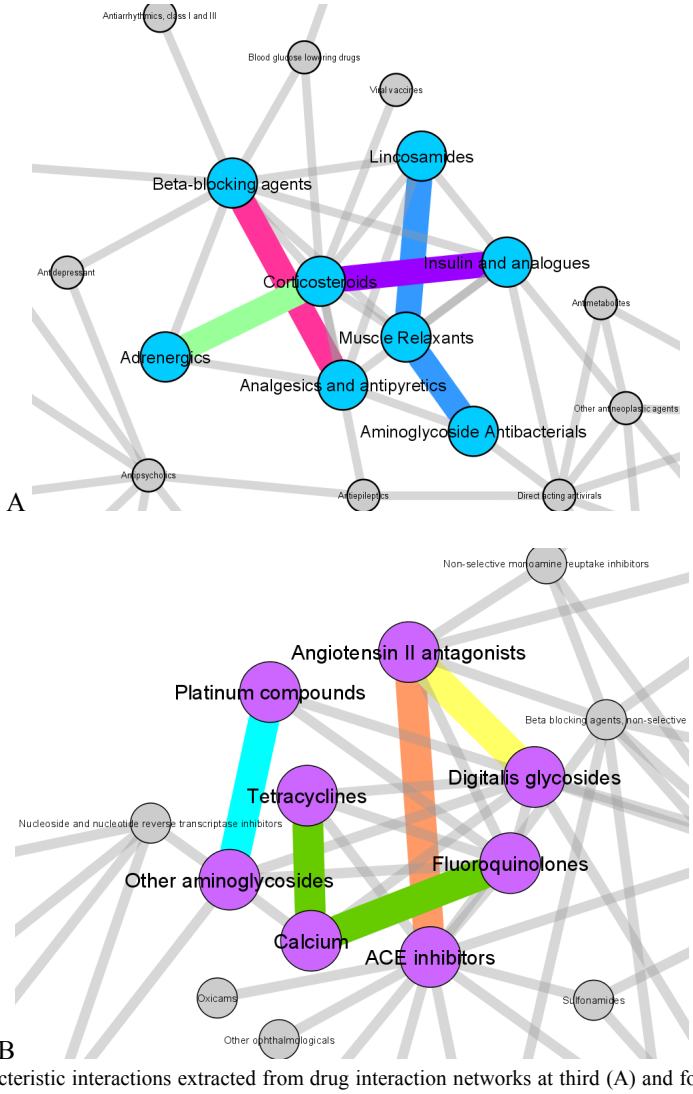

Figure 2. Characteristic interactions extracted from drug interaction networks at third (A) and fourth (B) levels of the ATC classification. The drug groups are illustrated as nodes with their definitions. Edges represent drug interactions between the drug groups. Large nodes and thick edges indicate the extracted interactions in which the drug properties related to the interaction mechanisms or symptoms. (A) The light green edge represents the interaction between corticosteroids and adrenergics. The purple edge indicates interaction between corticosteroids and insulins. Two blue edges show interactions of muscle relaxants with aminoglycosides or lincosamides. The red edge represents the interaction between beta-blocking agents and analgesics and

antipyretics. (B) Two green edges indicate interactions by administration of fluoroquinolones or tetracyclines with calcium compounds. The orange edge indicates the interaction between angiotensin II antagonists and angiotensin-converting enzymes. The light blue edge represents the interaction between aminoglycosides and platinum compounds. The yellow edge shows the interaction of digoxin with angiotensin II antagonists.

4. Discussion

We merged drugs into the drug groups according to the ATC classification to reduce data size and emphasize the relationships between drug properties and interaction characteristics including mechanisms and symptoms. Information on drug targets and drug-metabolizing enzymes indicate characteristics of the drug groups. We can use the drug target data to extract interactions between drugs acting on the same target, which lead to additive effects or antagonisms of the drug target. The drug-metabolizing enzyme data can also be used to search interactions related to the drug-metabolizing enzymes. The obtained data of drug groups related to CYPs indicate that an adverse drug interaction is caused by a combined use of the drug groups metabolized by a CYP and the drug groups that inhibit the same CYP.

We collected drug group pairs in which interaction mechanisms or symptoms are related to definitions of the drug groups manually. The interaction mechanisms and the symptoms were retrieved from drug package inserts and literature. The drugs in the adrenergic agent group acts to decrease serum potassium levels and the corticosteroid group enhances the action [5], which results in the increased effect of reduction in serum potassium level. The corticosteroids also decrease insulin sensitivity [6, 7], hence combined use of corticosteroids and insulin and analogues can cause decreased the insulin sensitivity and decreased antihyperglycemic effects. Non-steroidal anti-Inflammatory drugs (NSAIDs) are reported to inhibit prostaglandin synthesis [8-10]. That can cause elevated blood pressure and reduce the effect of antihypertensive drugs including beta-blocking agents [11]. Absorption of fluoroquinolones [12] and tetracyclines [13] are decreased by chelating effects with calcium compounds. ACE inhibitors [14] and angiotensin II antagonists [15, 16] lead to decreased blood pressure by different mechanisms. Thus the combined use of them results in increased antihypertensive effects. Aminoglycoside antibacterials [17-19] and lincosamides [20, 21] induce neuromuscular blockade, which leads to increased muscle relaxant effects. Both of aminoglycosides and platinum compounds can cause nephrotoxicity [22, 23] and thus coadmnistration of them increases the risk of the renal damage. Administration of digitalis glycosides with angiotensin II antagonists is reported to elevate serum digoxin level however the mechanism is unclear.

The interaction between ACE inhibitors and angiotensin II antagonists (Fig. 2B) is caused by their antihypertensive effects, however the two drugs act on different drug targets (ACE and AT1 receptors). In the KEGG PATHWAY database (http://www.genome.jp/kegg/pathway.html), the two drug targets are included in the same “renin-angiotensin system” pathway map (hsa04614). The map illustrates pathways of the angiotensin production from angiotensinogen and the action of angiotensin and includes related genes such as membrane metalloendopeptidase, neurolysin and chymase. Chymase converts angiotensin I to angiotensin II [24] as ACE, and drugs inhibiting chymase may cause the drug interactions with ACE inhibitors or angiotensin II antagonists, which enhance antihypertensive effects. In another instance, interactions between drugs acting on biogenic amine receptors and calcium channel blockers cause

increased effects of antihypertensive, and the drug targets are illustrated in calcium signaling pathway (hsa04020). Hence, pathway information can help to search more characteristic interaction patterns with drug target data.

We searched characteristic drug interaction patterns from the networks. The extracted interaction patterns can be a clue to estimate unreported drug interactions and drugs interact with new pharmaceutical products.

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