Using genomics to help predict drug interactions

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Abstract

This article proposes using genomic information to help tailor the output of a drug interaction program for a patient. This paper focuses on a particular CYP450 enzyme to illustrate adding genomic information to an existing drug interaction database. The data are formatted as an Extensible Markup Language (XML) document. The additional interaction information based on genomics for a patient is added to an XML document using XML tags. The suggestion is to combine specifics about a patient's genome with genomic information in the drug interactions database to increase the accuracy and details of a drug interaction program.

1. Introduction and overview

Adverse drug interactions present a problem for doctors prescribing medication. This problem is becoming more difficult because the volume of documented interactions is increasing. The interactions table in The Medical Letter Handbook of Adverse Drug Interactions increased from 294 pages in the 1997 edition [1] to 503 pages in the 2003 edition [2]. The ability of informatics to help warn clinicians of adverse drug interactions was mentioned as part of the grave problem of adverse drug events presented in a study published in JAMA. This study suggested a 6.5 rate of adverse drug events per 100 nonobstetrical hospital admissions [3]. The study concluded that adverse drug events were common and often preventable. Another study of hospital medical errors, To Err is Human, stated that medication errors now occur frequently in hospitals, yet many hospitals are not making use of known systems to improve safety [4]. The cost of these adverse drug events from errors, that are preventable, is probably in the billions of dollars. Adverse drug interactions are part of the overall problem of adverse drug events. The study mentioned that the use of informatics was a way to help combat the problem of medication errors.

Currently there are many drug interaction programs and handbooks to help warn clinicians of adverse drug interactions. Three well known sources for drug interaction information include Facts and Comparisons [5] whose product Drug Interaction Facts, features drug–drug and drug–food interaction information in a quick electronic format, First Data Bank whose product Evaluations of Drug Interactions (EDI) is a comprehensive source of drug–drug interaction information [6], and The Medical Letter database of adverse drug interactions [7]. This paper uses as its example and source of drug interaction information The Medical Letter database because it is easy to manipulate and readily available to the author.

This database lists interactions under groupings of drug–drug pairs. It is available as a printed book, or in electronic form as a set of data files accessible through PDA, personal computer, and web-based programs. The programs read a list of drugs, normally a patient drug list, then search the database for adverse drug interactions. The output is not tailored to the patient, except by the program's patient drug list.
2. Proposed use of bioinformatics

Adverse drug interactions may be more accurately reported if contextual information other than simply a medication list is available about a patient. Such contextual information includes the patient’s basic profile, medical condition, and genetic makeup. This paper addresses the relationship between drug interactions and genetic information about the patient. By tailoring a patient’s adverse drug interaction report to the patient’s known genetic makeup, a more accurate picture of possible interactions between a patient’s medications may be provided to health care professionals.

This paper exemplifies the influence of genetic information on drug interactions, and discusses the way in which the dependency of drug interactions on genetic variations can be modeled in an XML data document.

This paper proposes reducing drug interactions by tailoring the presentation of drug interaction information based on genetic differences that affect drug metabolism and interactions. According to a physician, a clinical imperative for Pharmacogenetics is to tailor a patient’s treatment by individual characteristics such as genetic makeup. The physician states the evidence of tailoring the treatment to the patient is meager in pharmacology [8]. This paper suggests that incorporating the knowledge of the patient’s genetic differences into an adverse drug interaction database would be a significant step toward providing personalized drug interaction results that would improve the adverse drug interaction reporting. The drug interaction data would be presented in a tagged XML document and would be extended with another XML document containing genetic data.

3. Genetic effects on drug interactions

The cytochrome P450 (or CYP450) enzyme system is a major metabolic pathway for drugs and other substances. Knowledge of the substrates, inhibitors, and inducers of the CYP450 system and how one drug affects another drug’s performance via this system can assist in the prediction of serious adverse drug interactions [9]. A few of the enzymes in this system participate in the metabolism of most drugs [10].

These genetic variations can contribute to individual variability in drug response and safety, including drug interactions. There are 480 references to the CYP450 enzyme in the database of 2822 adverse effects [11]. The CYP450 enzymes take part in the metabolism of many drugs. Many drug-drug interactions can be explained by competition for these enzymes or effects on these enzymes. The effects on a CYP450 enzyme may be to inhibit the enzyme, that is, reduce its activity, or to induce the enzyme, that is, increase its activity [12]. For example, quinidine inhibits the CYP2D6 isoenzyme, that is, reduces its activity. CYP2D6 metabolizes β-blockers, such as metoprolol [13]. Adding metoprolol to a patient’s regimen that includes quinidine can result in a drug interaction, in particular, metoprolol toxicity due to this decreased metabolic activity [14].

There are genetic differences other than those associated with the CYP450 family that affect drug interactions. For example, there are genetic differences with the P-glycoprotein transporter that have been shown to affect drug interactions in different individuals [15]. There are also other enzymes that affect drug metabolism, such as those involved in glucuronidation, that vary in function due to genetic variation and may have an affect on interactions.

This paper focuses on a particular CYP450 enzyme to illustrate its proposal to add genomic information to the database. It focuses on an enzyme in the CYP2C19 isoenzyme subfamily. This subfamily metabolizes several drugs that are involved in significant drug interactions [16].

4. CYP2C19 effect on interactions

CYP2C19 is a genetically determined enzyme, S-mephentoin 4'-hydroxylase. Its phenotypes include poor metabolism and excessive metabolism. It metabolizes drugs such as diazepam. When another drug is a substrate for this enzyme, an inhibitor, or inducer of this enzyme, an interaction may occur [17]. For example, fluvoxamine is an inhibitor of CYP2C19 that reduces its activity, and affects the disposition of diazepam, which is metabolized by CYP2C19, causing a drug interaction.

There are various genotypes of CYP2C19. These genetic variations determine whether CYP2C19 acts as a poor metabolizer or an excessive metabolizer [17]. These different phenotypes can affect a drug’s metabolism or interactions between drugs that affect CYP2C19 or that are affected by CYP2C19.

A table of the various genotypes of CYP2C19 and resulting enzyme activity is available at http://www.imm.ki.se/CYPalleles. The detection of the mutations causing allele variants can predict the phenotype.

5. Examples of interactions affected by CYP2C19 genotypes

There are several examples of interactions involving the CYP2C19 enzyme mentioned in The Medical Letter database of adverse drug interactions. Two examples follow.
5.1. Example 1: Monoamine oxidase inhibitors with omeprazole

From the drug interaction program:

**DRUG LIST IS**
MAO inhibitors (Monoamine oxidase inhibitors)  
Omeprazole

**INTERACTION FOR:**
MAO inhibitors (Monoamine oxidase inhibitors)  
Omeprazole

**Effect 1:**  
Possible moclobemide toxicity (decreased metabolism; CYP2C19)

**Reference citation:**  

**Comment/Recommendation:**  
Based on study in healthy subjects; monitor clinical status

In this case, a study showed that the effect of omeprazole on moclobemide was different with regard to the genetic polymorphism of CYP2C19. Patients with genotypes that indicated extensive metabolism greatly inhibited the elimination of moclobemide, but this was not the case in patients whose genotypes indicated poor metabolizers [19]. In this study, the interaction between the two drugs is significantly different depending on the genotype of CYP2C19.

5.2. Example 2: Lansoprazole with Theophyllines

**DRUG LIST IS**
Lansoprazole  
Theophyllines

**INTERACTION FOR:**
Lansoprazole  
Theophyllines

**Effect 1:**  
Possible decreased theophylline effect in some patients (increased metabolism)

**Reference citation:**  


**Comment/Recommendation:**  
Effect small; clinical significance probably minimal; no interaction found in healthy subjects given intravenous theophylline; no interaction found in healthy subjects given oral theophylline

In this interaction, between lansoprazole and theophyllines, a study showed that groups with different CYP2C19 genotypes for poor metabolizers or extensive metabolizers showed significant differences in the pharmacokinetics of lansoprazole. However, the usual doses of lansoprazole had no clinically significant influence on theophylline clearance. That is, the genotype for poor metabolizers had no clinically significant interaction compared to the genotype for extensive metabolizers [20].

We can see from these examples that the different genotypes for CYP2C19 can result in significant differences in metabolism. In one, there was a significant difference in the interaction depending on genotypes. In the other, there was not a clinically significant difference in the interaction because different metabolic pathways compensated for the CYP3C19 poor metabolizer variant.

6. Modifying the database of adverse drug interactions with genotype information

This section will discuss the format of the adverse drug interaction data, XML technology and why XML was chosen to represent the drug interactions data, adding additional information for drug interactions based on genetic differences, gathering genomic data for patients, and offer a hypothetical example of using genomic information in a drug interaction program.

6.1. Description of the adverse drug interactions database

The available drug interaction source database, available to researchers and others, is easily modified to other formats. The source format for Example 1 above is

```
drug1:Monoamine oxidase inhibitors  
drug2:Omeprazole  
effect:  
Possible moclobemide toxicity (decreased metabolism; CYP2C19)  
references:  
K-S Yu et al., Effect of omeprazole on the pharmacokinetics of moclobemide accord-
```
6.2. What is XML and why use it to represent our data?

One definition of XML is that it is a family of technologies that can do everything from formatting documents to filtering data [21]. XML is a syntax and grammatical system for constructing markup languages. The Medical Letter has a research XML document for describing drug interactions for possible use in an Electronic Medical Record (EMR). In the adverse drug interaction XML document tags are defined following the XML syntax rules.

An XML representation for the Monoamine oxidase inhibitors and Omeprazole presented above follows. This is one of many interactions enclosed in <interaction> tags. This XML document was created from the source data above by using various text-processing tools such as a stream editor or Perl. Since the source document was well delimited with keywords such as “drug1:”, “drug2:”, “effect:”, “references:”, “comment:”, and parentheses to mark mechanism of interactions, the process of translating the source document to the XML document was fairly straightforward.

```xml
<xml version="1.0"?>
<Medical_Letter_Drug_Interaction>
<interation>
<pair drug>Monoamine oxidase inhibitors</pair>
</inter_drug>
</interaction>
<adverse_effect>
Possible moclobemide toxicity
</adverse_effect>
<mechanism_of_interaction>
decreased metabolism; CYP2C19</mechanism_of_interaction>
</adverse_effect>
</references>
</references>
</interaction>
</Medical_Letter_Drug_Interaction>
```

6.3. Adding genomic data for the drug interactions data

Although this paper’s emphasis is the effects of CYP2C19 variations on drug interactions, other factors can affect drug interactions. A patient’s age, nutrition, environment such as pollution, disease state, and infectious diseases affect a patient’s response to drugs and can have an affect on drug interactions [22]. Therefore, the proposal to add genotype information to an XML document will be to add it to part of a general section of patient specific information. The XML heading for this will be <Patient_Variables>, which will contain the genotype information.

The representation of the CYP genotype information can follow the current nomenclature. In CYP2C19 the ’2’ specifies enzyme family (there are 14 known families in humans), the ’C’ designates the sub-family (42 known in humans), and the ’19’ indicates the specific enzyme. Pairs of asterisks with numbers can follow the specific enzyme as in CYP2C19*1/*2. The *1/*2 designates the “allele pattern.” We can have two numbers here since we have two copies of every gene. The number 1, is the most common form of the gene, and a number 2 or greater indicates a variant [22].

Using this nomenclature in our XML document we can define an XML tag for all patient specific information under <Patient_Variables>. Within the <Patient_Variables> section we can have the tag <gene> with an allele attribute. This allele attribute would have the allele information, e.g., <gene allele="CYP2C19*1/*1">. Under <gene> we could have a <drug_interactions> tag that would contain specific information relating the allele for <gene> to the drug interaction.

The source of the drug interaction with genomics information would be a content editor who would write and input the information after a review of the scientific literature. This would be a significant task.

6.4. Getting the genotype or phenotype information for a patient data record

Another step in this process would be to get the genotype information for the patient and relate it to our data of known genomic effects on drug interactions mentioned in the previous section. It is possible to perform tests to determine genotype or phenotype behavior for the CYP enzymes, including CYP2C19. For example, one way to determine genotypes for CYP2C19 is to use polymerase chain reaction analysis. By searching for
two mutations common for the phenotype of “poor metabolism” a determination can be made whether the patient is a poor metabolizer or excessive metabolizer [19]. In the future, mapping a patient’s genome may someday be both possible [23] and affordable [24] although some patients may be wary to get their genome and give it to a health care provider [25]. Nevertheless, with our continued understanding of genetic polymorphism and development of gene chip technology, it is quite feasible for individuals to be genotyped with respect to the enzymes of interest [26]. A major pharmaceutical company has already announced a gene test to predict how a person will react to many prescribed medicines. The test runs on a gene chip capable of detecting many gene variations [27,28]. Some have even suggested that patients could carry a “smart card” of patient medical information containing the enzyme genetic information [26]. So, in the future, getting the patient genomic data for use in an electronic medical record should be possible.

6.5. Relating the patient data genomic information to the drug interaction genomic information

A system that would make use of the genomic information for a patient’s drug interactions would have to associate the genomic data for the patient (Section 6.4), the data for a particular drug interaction (Section 6.3), and the patient’s drug list. One could complete this by transferring the information to a database system or using XML parsers.

6.6. A hypothetical example for adding genomic information

The interaction between Lansoprazole and Tacrolimus as an XML document is:

```xml
<?xml version="1.0"?>
<Medical_Letter_Drug_Interactions>
  <interaction>
    <inter_drug>Lansoprazole</inter_drug>
    <inter_drug>Tacrolimus</inter_drug>
    <adverse_effect>Single case report (2002) in patient with reduced CYP2C19 activity; causal relationship not established; monitor tacrolimus concentrations and clinical status; neither rabeprazole nor famotidine appeared to affect tacrolimus</adverse_effect>
  </interaction>
  <gene allele="CYP2C19*1/*2">Increased interaction risk, see interactions comment and references</gene>
</Medical_Letter_Drug_Interactions>
```

The only case report for this interaction occurred with a patient who had a CYP2C19 gene mutation. The clinicians noticed a significantly high level of tacrolimus and suspected an interaction between lansoprazole and tacrolimus. The clinicians used a polymerase chain reaction analysis test to determine that the patient had heterozygous mutation at exon 5 of CYP2C19. The nomenclature for this is CYP2C19*1/*2. The *1 represents the common allele, the *2 represents the mutation. With the hypothesis that the mutant allele is more likely to cause an interaction than the non-mutant allele we could add XML code to the database. Since this information is meant to tailor the presentation of the interactions for a particular patient, we could include our information within <Patient_Variables> tags. Since we want to include genomic information, we introduce a <gene> tag with an attribute indicating the genetic allele. Then we introduce an interaction tag, signifying that this gene could influence the interaction between the drugs mentioned signified with attribute tags drug1 and drug2. The document data for this interaction could be “increased interaction risk, see comment and references,” referring to the comment in the program’s or handbook’s interaction regarding the case report from 2002.

```xml
<?xml version="1.0"?>
<Patient_Variables xmlns:xsi="http://www.w3.org/2000/10/XMLSchema-instance" xsi:noNamespaceSchemaLocation="C:\Documents and Settings\Don Gardner\Desktop\paper\gene_emr.xsd">
  <gene allele="CYP2C19*1/*2">Increased interaction risk, see interactions comment and references</gene>
</Patient_Variables>
```
Since this interaction has not been documented here without the mutation, after further study it may be determined that the interaction does not occur unless there is a mutation. In that case, we could add more information nested under <Patient_Variables> as shown above in the document under <gene allele = CYP2C19*1/*1>.

An advantage to XML is that schema can be written to describe and validate an XML document. A schema that validated for the above XML document is:

```xml
<?xml version = “1.0”?>
<!– edited with XMLSPY v2004 rel. 3 U (http://www.xmlspy.com) by Don Gardner (The Medical Letter) –>
  <xsd:element name = “Patient_Variables” type = “PVtype”/>
  <xsd:complexType name = “PVtype”>
    <xsd:sequence>
      <xsd:element name = “gene” type = “gene-type” maxOccurs = “unbounded”/>
    </xsd:sequence>
  </xsd:complexType>
  <xsd:complexType name = “genetype”>
    <xsd:sequence>
      <xsd:element name = “drug_interaction” type = “DItype”/>
    </xsd:sequence>
    <xsd:attribute name = “allele” type = “xsd:string” use = “required”/>
  </xsd:complexType>
  <xsd:complexType name = “DItype”>
    <xsd:sequence>
      <xsd:element name = “inter_drug” type = “xsd:string” minOccurs = “2” maxOccurs = “2”/>
      <xsd:element name = “effect_modification” type = “xsd:string”/>
    </xsd:sequence>
  </xsd:complexType>
</xsd:schema>
```

This schema states that we have a section of Patient Variables. The element defined is a “gene” element and there could be others. The gene element has an attribute indicating an allele. Under the gene element is a “drug interaction” element, and there could be other elements defined. The “drug interaction” element contains a comment that is the possible modification of the drug interaction due to the presence of the allele.

Given this added information to the database, the next time the adverse drug interaction program is run for a patient receiving both lansoprazole and tacrolimus the program could be enhanced to check the CYP genome information about the patient. If the information exists, the presentation of the interaction could be modified with the added text that relate to the text of the drug interaction.

In the case study represented here, the patient’s genome was not checked with the polymerase chain reaction analysis test until after the clinicians suspected a problem with the CYP2C19 enzyme due to high concentrations of tacrolimus. For future patients, knowing the genome before administration of both lansoprazole and tacrolimus would help. Given that most of the time, the CYP2C19 genome state is not known, the advice from the database is to “monitor tacrolimus concentrations and clinical status.” However, if the CYP2C19 allele were known and were part of the patient record, then that information with the added information in the database could tailor the interaction output for the patient. The allele state could be known by a previous test, or perhaps in the future, a patient’s genome could be known and part of the patient’s record. Then the drug interaction program would have the added task of noting that the allele state of CYP2C19 affects the interactions and would check the patient’s genome before continuing.

7. Modification of drug interaction program using the database with genomic information

An example of an interactions report with genomic information added to the program’s details is:

**Interactions Report**

**March 05, 2004 (01:27 PM)**

**DRUG LIST IS**

**Lansoprazole**

**Tacrolimus**

**INTERACTION FOR:**

**Lansoprazole**

**Tacrolimus**

**Effect 1:**
Possible increased tacrolimus toxicity (mechanism not established)

**Reference citation:**
M Homma et al., Effects of lansoprazole and rabeprazol on tacrolimus blood concentration: case of a renal transplant recipient with CYP2C19 gene mutation. Transplantation, 73:303, 2002;
Comment/Recommendation:

Single case report (2002) in patient with reduced CYP2C19 activity; causal relationship not established; monitor tacrolimus concentrations and clinical status; neither rabeprazole nor famotidine appeared to affect tacrolimus; a small retrospective study found no effect of proton pump inhibitors on tacrolimus, but few details were given [18].

Patient Specific Addition—Genomics data The patient record indicates the presence of a CYP2C19*1/*2 allele. Our genomics data for drug interactions suggests increased interaction risk, see interactions comment and references.

Note: This patient specific addition was pasted from the XML document to demonstrate adding information based on genomic data.

It should be noted that the CYP2C19 enzyme is one of many in the P450 enzyme system that affect not only drug interactions but drug administration in general. Also, genomic information as part of the adverse drug interaction database is one of many patient specific variables that could be included in the database to make it possible to give more patient specific output.

8. Limitations and future of the current approach

This paper is meant to give an example of how genomic data could fairly easily be represented for use with an existing product and database. This may lead to new scientific methods, but that is an item for future work. The current approach uses XML documents to manage genomic, patient, and drug interaction information. To do the necessary comparisons and relations (e.g., comparing a patient’s genome from a patient record to the XML document of patient variables <Patient_Variables> with genomic information) would require transferring the XML document information to a database system or using an application program interface (API) so that program applications communicate with an XML parser.

Future research would include investigations into standardizing the allele information and the drug interaction information, uploading the XML documents to database systems, developing interfaces within an electronic medical record (EMR), and the use of XML parsers.

9. Conclusion–summary

This paper used an established database of drug interactions and searched for instances that might benefit from additional genomic information. It used an example of Cytochrome P450 isoenzymes that participate in the metabolism of many drugs. There are genetic variations in the metabolism of these drugs and this paper shows how one could include differences in drug interactions related to genetic differences as part of an XML document. Furthermore, it suggests that with this information in an XML document, with patient information, and additional logic to a drug interaction program, one could tailor the output of a drug interaction program for the genetic specifics of the patient. The result will be a decision support tool that utilizes pharmacogenomic knowledge linked to patient data, which will hopefully improve medication management, reduce the incidence of adverse drug interactions, and reduce toxicity in patients.

References


[23] MSNBC news report, October 2, 2002 and numerous news sources.


