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Drug Interactions Involving the Cytochrome P450 Enzymes: Analysis of Common Combinations of Antibiotics and Pain Relieving Drugs

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Abstract

Objective: For clinicians it is challenging to oversee complex drug interactions of multi-drug administration. Rheumatoid arthritis (RA) patients are frequently under long-term medication with multiple anti-inflammatory and pain-relieving drugs, which are mainly metabolized by the Cytochrome P450 enzymes (CYPs). Additionally, treatment of co-morbidities, such as inflammatory periodontal disease (PD) may have to involve further drug administration. The aim of this investigation was to analyze drug interactions in the therapy of RA and PD and to provide a resource for health professionals to easily check interactions and avoid potential side effects.

Methods: Information on drug administration in the therapy of RA and PD and expression data of human tissues regarding CYPs was gathered and/or analyzed from scientific literature and web resources. A literature compilation was developed and CYP interaction tables were generated.

Results: Side effects, such as enzyme overload or enzyme induction and inhibition may occur in the therapy of RA and PD. To overcome these problems, a web-interface was developed to optimize drug cocktails. The compilation provides manually curated information on the metabolism of 1,500 drugs including 100,000 PubMed references, covering a variety of co-morbidities. Moreover, based on the WHO classification system for drugs (ATC-codes), the knowledge base offers drug alternatives, avoiding CYP-related problems. The web-interface is publicly available: http://bioinformatics.charite.de/perio

Conclusions: After a detailed drug anamnesis, health professionals should use a web-interface to check drug interactions involving CYP metabolism, which may circumvent adverse side effects and optimize interdisciplinary drug therapy.

Introduction

Rheumatoid arthritis (RA) is the most frequent inflammatory joint disease affecting more than 50 million people worldwide [1]. RA patients are frequently treated with pain relieving and anti-inflammatory drugs (NSAIDs). Furthermore, corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) and biologics are administered depending on RA severity and progression [2]. In 2008, a world-wide group of rheumatologists developed a set of recommendations for the RA treatment, which is updated at regular intervals [3]. The recommendations are target-based on evidence and expert opinion. The primary treatment aim is the clinical disease remission. Also, the individual drug therapy is at least adjusted every three months, which requires frequent drug anamnesis and adaptation by health professionals besides rheumatologists.

The RA etiology is unclear, however next to genetic and environmental factors such as age, gender, HLA genotype and smoking, bacterial infections seem to play an important role [4]. It is proposed that RA results from a failure of the immune response attacking an unknown antigen such as hidden viral or bacterial infections, also diseases preceding RA may cause a failure immune response to viral or bacterial antigens [5].

Periodontal disease (PD) is a bacterial infection affecting the periodontium, which can cause increasing degradation of tooth-supporting soft- and hard tissues, ultimately resulting in tooth loss [6]. Gram-negative anaerobic bacteria, organized as a structured biofilm on the tooth surface are the primary cause involved in the initiation and the progression of PD [7]. The best described periodontal pathogens are *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythensis* and *Porphyromonas gingivalis* (*P. gingivalis*) [8]. *P. gingivalis*, one of the major periodontal pathogens, is able to invade endothelial cells and human chondrocytes [9]. It is the only known bacterium expressing the peptidylargininde iminase (PAD) enzyme, which is responsible for the post-translation and conversion of arginine to citrulline [5]. Citrulline modifications lead to the production of anti-CCP antibodies, which are found most frequently in RA patients [10]. Furthermore, aggressive periodontitis, affecting young individuals, is characterized by severe periodontal attachment loss and bone destruction. In comparison to adult periodontitis, aggressive periodontitis shows a more rapid disease onset and a faster progression. It was shown that a combination of mechanical and antibiotic treatment effectively provides favorable clinical results on periodontal and systemic health in generalized aggressive periodontitis patients [11]. In general, the selection of the antibiotic is adapted to the spectrum of bacteria (Table 2).

Increasing evidence shows that patients with RA have an increased prevalence of periodontal attachment loss compared to healthy

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individuals [12]. Evidence from epidemiological studies suggests a bi-directional association [13]. In both the diseases, dysregulated immune responses seem the crucial factor facilitating tissue degradation and loss of function [14]. Intervention studies indicate causal relationship by showing that periodontal therapy has beneficial systemic effects on RA disease activity [15]. PD and PA are prevalent chronic inflammatory diseases associated with significant morbidity and mortality and therefore immense impact upon the economy, health and quality of life. RA and PD are associated with increased mortality due to a number of co-morbidities. Both are chronic inflammatory diseases associated with soft and hard tissue damage, a dysregulation of immune response and common genetic and lifestyle factors influencing the diseases [16].

A number of cross-sectional studies reported an increased incidence of PD in RA patients [17] and a higher prevalence for RA in patients suffering from PD. An increased risk for systemic diseases such as cardiovascular disorders, diabetes and osteoporosis was described for both diseases [18]. Therefore, next to the drug-therapy of RA and PD additional drugs may have to be administered for the treatment of the co-morbidities. Therefore, further undesired drug-drug interactions may be admitted by health professionals treating RA patients.

Drug metabolism is a complex biochemical network, which consists of many different parts and reactions in the human organism. Some drugs are excreted in urine and feces without passing any metabolic modifications in the liver. However, most of the systemic drugs have a multi-step metabolism (typically oxidation and conjugation). The oxidation reactions are mainly catalyzed by the Cytochrome P450 enzymes (CYPs) family of CYP enzymes [19], which belong to the family of monooxygenases has been the focus of pharmaceutical research for decades. CYPs catalyze a large amount of chemical reactions, such as alcohol oxidations, dehydrogenation and isomerizations. It is a difficult task of medical science and daily clinical practice to find effective and safe combinations of drugs that do not affect each other's metabolic pathways. If this is not taken into account, severe adverse effects including death occur. The Human Genome Project discovered 57 human CYPs [20]. Due to many polymorphisms and inducability, the biological activities of the CYPs vary noticeable among humans, which is an important issue for researchers as well as clinicians. Knowledge of the level and the catalytic activity of the specific CYP as well as the effect on drug metabolism could and should lead to personalized drug dosages to optimize the therapeutic effect and minimize harmful side effects. If a drug induces a specific CYP, which is also active in another drug's metabolism, the dosage of the first drug should be increased to achieve the same therapeutic effect [21]. In case of a CYP inhibition, the dosage can be reduced, which lowers side effects.

Due to multi-drug administration, adverse side effects, such as deadly acute renal failure (31) are discussed intensely in pharmaceutical research [22].

Frequently occurring problems, which we address here, are firstly adverse side effects because of enzyme overload and secondly, ineffective therapy because of enzyme induction or inhibition. Therefore, drug interactions in the therapy of RA and PD were analyzed in the present study.

Materials and Methods

Textmining

Information on drug metabolism is spread over 100,000 articles in PubMed. To collect relevant articles a specific search tool was developed. Abstracts of PubMed database were automatically filtered for relevant articles using specific keywords. Medical subject headings (MeSH) represent the National Library of Medicine's vocabulary thesaurus and were used for disease definitions and synonyms. The abstracts were screened for WHO-drugs and their synonyms, as well as a set of human CYPs with synonyms and the papers found in PubMed were manually processed. Each drug was attributed to those CYPs that are involved in drug metabolism as a substrate, an inhibitor or an inducer.

Treatment schemes

Information on drug administration in the therapy of RA and PD was collected from scientific literature. Additionally, for RA, international recommendations [23] and for PD different national guidelines [24] could be taken into account. Web resources provided further information on drug metabolism, e.g. Nelsons Homepage [25], Flockharts Interaction table [26], University of Maryland's Drug Checker, PubChem [27], Protein Data Bank [28] and FDA-files.

Drug classification

The recommendations of the WHO Expert Committee for updating the WHO Model List of Essential Medicines are updated annually [29]. In 2004, a list of all items, according to their 5-level Anatomical Therapeutic Chemical (ATC) classification code was published. The ATC-code classifies drugs into different groups according to anatomic site of action, therapeutical effect and chemical structure. The therapeutic subgroup, which is determined by the second level, was used to find drug alternatives.

Expression data

Affymetrics data were used to compare the CYP mRNA expression of human body tissues. The series of datasets taken from GEO (Gene expression Omnibus, http://www.ncbi.nlm.nih.gov/geo/) were generated from ten donors and represent normal human bodies (Series GSE3526, [30]). It contains seven different tissues, oral, pharyngeal, esophageal and intestinal mucosa, as well as skeletal tissue and bone. All probe sets related to Cytochromes were normalized and condensed to 40 types of CYPs. To assess differences in expression, a heat-map was built with Genesis [31].

Database and web-server

Two CYP interaction tables were generated for the therapy of RA and PD. Numerous problems, such as enzyme overload or enzyme induction and inhibition could occur in the combined therapy of RA and PD. Some of these drug-drug interactions are rather unnecessary because the choice of another antibiotic could already circumvent the problem. In the present study, a web-interface for clinicians to check drug-drug interactions was generated to overcome CYP based problems. The database provides information on drug metabolism including PubMed references. Based on the WHO classification system (ATC), the database provides drug alternatives.

The present database is designed as a relational database on a MySQL server. For chemical functionality, the MyChem package is included, which aims to provide a complete set of functions for handling chemical data within MySQL. The website is built with PHP and javascript and the web access is enabled via Apache Webserver 2.2.

Results

The results of the present literature analysis are summarized in tables 1 and 2, respectively. Table 1 show that especially CYPs 2C8,

Drug	NSAIDs	DMARDs	Opioids	Steroids	Substrate	Inhibitor	Inducer
Aspirine	X				2C8, 2C9		2C19
Diclofenac	X				2C8, 2C9, 2C19, 3A4,	2C8, 2C9, 3A4	
Ibuprofen	X				2C8, 2C9, 2C19	2C9	
Indometacine	X				2C9, 2C19	2C9, 2C19	
Ketoprofen	X					2C9, 2C10	
Metamizol	X						2B6, 3A4
Naproxen	X				1A2, 2C8, 2C9		
Oxaprozin	X				2C9		
Paracetamol	X				1A1, 1A2, 2A6, 2C8, 2C9, 2D6, 2E1, 3A4	3A4	2D6, 2E1, 3A4/5
Phenylbutazon	X				2C9		3A4
Piroxicam	X				2C9	2C9	
Betamethasone				X	19A	3A4	19A
Hydrocortisone				X	3A4	3A4	2C8, 3A4
Prednisone				X	3A4	3A4	1A1, 1A2, 3A4
Codeine			X		2D6, 3A4	2D6	
Fentanyl			X		3A4	3A4	
Morphin			X		2C8, 3A4		
Tramadol			X		2B6, 2D6, 3A4	2D6, 3A4	
Chloroquine		X			1A1, 2C8, 2D6, 3A4	2D6	
Cyclosporine		X			3A4	2C19, 2D6, 3A4	
Hydochloroquine		X				2D6	
Leflunomide		X			2C8, 2C9	2C8, 2C9	

Additional administration of antibiotics in the therapy of PD could influence the metabolism of the other drugs administered for RA therapy. Potent antibiotic agents against periodontal bacterial pathogens are listed in Table

Table 1: Drugs in the therapy of RA with CYP metabolism. Involved CYPs are ordered in mode of action (substrate, inhibitor, inducer) and references are given in supplementary material.

	Bacteria					
	Aa	Tf	Pg	Substrate	Inhibitor	Inducer
Amoxicillin	+	+	++	2C19		
Ciprofloxacine	+				1A2, 3A4	2E1
Clindamycine		++		3A4	3A4	
Doxycycline		+			3A4	
Metronidazole	++		+	2C9, 3A4	2C9, 3A4	
Tetracycline	+	+			3A4	

Table 2: Effectiveness and CYP metabolism of antibiotic agents used in the therapy of PD. References given in parentheses. "Aa" means Aggregatibacter actinomycetemcomitans, "Tf" Tannerella forsythensis and "Pg" Porphyromonas gingivalis. +: 10-fold increased, ++: 10^2-fold increased concentration of antibiotic in gingival fluid, expressed in multiples of in-vitro measured minimal inhibitory concentration [32].

2C9, 2C19, 2D6 and 3A4 are involved in the metabolism of the analyzed drugs used for treatment of RA and PD [32].

Expression data

The built heat-map lists seven tissues involved in RA and PD and the expression of several CYPs therein (Figure 1). Expression ranges from -2.24-fold lower to 2.24-fold higher values. The CYP expression in target tissues has not been taken into account so far, but is an interesting issue because it is a major factor for the effective retention period. For example, CYP 3A7, which was formerly known as fetal enzyme, was recently shown to be upregulated in the bone [32]. This means that the function of the CYP 3A family is significantly increased, which leads to shorter duration of action of drugs like Paracetamol, Diclofenac, Prednisone, Fentanyl etc.

Discussion

In an aging society with increasing morbidities and co-morbidities drug interactions have to be realized and or prevented by health professionals. One of the most difficult tasks of the decision making process is to find combinations of drugs that do not affect each other's metabolic pathways. Despite the large amount of information on CYPs, optimizing multiple drug prescriptions using CYP metabolism is still complicated [33]. Drug-drug interactions are complex and information on drug metabolism is spread over 100,000 articles in PubMed, which may be overwhelming and not possible to handle by the clinician. Information on CYP-structures [34], binding sites [35], interactions and different genotypes [36] must be combined to allow reducing side effects and to determine correct dosages of medicine undesired side effects when prescribing more than one drug [37]. To overcome this problem a tool for medical and dental clinicians was generated to identify and examine drug-drug interactions online. The SuperCYP database [38] contains information on 1,170 drugs with more than 3,800 interactions including scientific references. This comprehensive resource is freely available at http://bioinformatics.charite.de/perio and is also usable on smartphones and tablet-PCs and could be used as basis for personalized medicine.

Evidence of an association between RA and PD, two of the most common inflammatory diseases in human, is increasing [39].

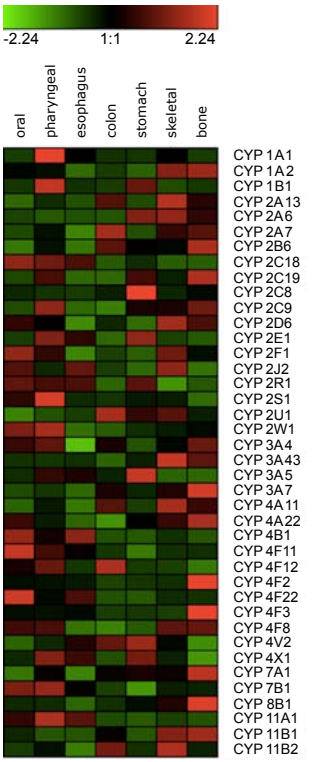

Figure 1: Heat-map of target tissues in RA and PD and the expression of several CYPs therin. Expression ranges from -2.24-fold lower (green rectangles) to 2.24-fold higher values (red recatangles).

In addition, both diseases are associated with systemic chronic inflammatory co-morbidities such as cardiovascular disease. Based on the fact that the medication of pain relieving and disease-modifying drugs can hardly be modified, it is primarily the dentist's task to choose an antimicrobial agent for adjunctive periodontal treatment that is on the one hand most effective in its antibacterial efficacy and on the other hand does not negatively affect the therapy and its side effects in RA patients.

The present data on CYP metabolism suggests two key problems of drug-drug interactions in the treatment of PD in RA patients, discussed below (Tables 3 and 4). First, Aspirine, a commonly used NSAID in the therapy of RA, is metabolized by CYP 2C8 and 2C9 and induces 2C19, which is also the substrate of Amoxicillin, a ß-lactam antiobiotic drug often prescribed as antimicrobial therapy adjunctive to mechanical debridement in oral infections such as aggressive periodontitis. Due to induction of CYP 2C19 and inactivation of Amoxicillin may be possible. Therefore, a replacement by another group of antibiotic agent, such as Ciprofloxacine, which is also effective against periodontal pathogens, would be less harmful with respect to CYP metabolism, and therefore could easily bypass this problem (Table 3).

The table shows drug interactions of the NSAID, Aspirine, with antimicrobial drugs, Amoxicilline (red line because of the conflict regarding CYP 2C19 [orange cells]) and Ciprofloxacine. Ciprofloxacine avoids the CYP 2C19 conflict (green). "S" means substrate, "Ind" means inducer and "Inh" means inhibitor. Suggestions like that are automatically generated by the Web-Server using the classification and metabolic information stored on the server for the drug-cocktail entered by the user.

In addition, in the therapy of RA, NSAIDs and DMARDs are often combined with each other and drug-drug interactions often occur. If an antibiotic agent with the same metabolic pathway is administered, side effects because of enzyme overload are possible and could be avoided by choosing agents with different metabolic pathways. The NSAID, Oxaprozine, and the Leflunomide, a DMARD, share the same metabolic pathway via CYP 2C9. Additionally, Leflulomide inhibits CYP 2C8 and 2C9. Administration of Amoxicilline in combination with the antimicrobial drug, Metronidazol, which uses the same metabolic pathway as Oxaprozine and Leflulomide and inhibits the CYP, as well, could lead to adverse side effects because of enzyme overload. Clindamycine, which is also potent against periodontal pathogens, might be a good alternative (Table 4) [40,41].

Advances in genetic research have enabled genotyping and analysis of individual data on expression of target genes and metabolic enzymes. Such expression data in target tissues should be considered in selection of drugs.

	Drug	1A2	2C8	2C9	2C19	3A4
Aspirine	NSAID		S	S	Ind	
Amoxicilline	Antibiotic agent				S	
Ciprofloxacine	Antibiotic agent	Inh				Inh

Table 3: Ineffective therapy because of enzyme induction or inhibition.

	Drug	2C8	2C9	2C19	3A4
Oxaprozine	NSAID		S		
Leflunomide	DMARD	S, Inh	S, Inh		
Metronidazol	Antibiotic agent	Inh	S, Inh		S, Inh
Amoxicilline	Antibiotic agent			S	
Clindamycine	Antibiotic agent				S, Inh

Table 4: Potentially adverse side effects because of enzyme overload.

The Web-Server presented in this study provides a user-friendly platform enabling medical and dental health professionals to optimize drug choice and combinations regarding the degree of CYP capacity utilization. With respect to increasing evidence of associations between oral and systemic chronic inflammatory diseases, such as PD and RA, knowledge about drug interactions become crucial to optimize health care.

Conflict of interest

There is no actual or potential conflict of interest.

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Authorship Contributions

Participated in research design: Preissner, Kuzman, Pischon

Performed data analysis: Preisser, Kuzman

Wrote manuscrcript: Preissner, Pischon

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