Liver Injury by Drugs Metabolized via Cytochrome P450

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Abstract: Idiosyncratic drug induced liver injury (iDILI) is a rare pathological condition in predisposed individuals, whereby the immune system likely plays a major contributory role for initiation and perpetuation of the liver injury. The initiation of an immune response requires the activation of the innate immune system to the adaptive immune system through antigen presenting cells by molecules such as danger-associated molecular pattern molecules (DAMPs). Poorly understood is the role of cytochrome P450 (CYP) in triggering and perpetuating iDILI. For example, among 36 drugs implicated in iDILI assessed for causality by RUCAM, 22/36 drugs (61.1%) are metabolized via CYP, suggesting that reactive oxygen species (ROS) generated during the catalytic CYP cycle are involved in triggering the liver injury by these drugs. In this context, ROS could modify hepatic RNA, which after activation could code for proteins functioning as antigens and activating the innate immune system to the adaptive immune system. Characterized by immunological features including CYP antibody generation, liver injury by halothane is a perfect example for iDILI caused by a drug metabolized by CYP. Further clinical studies are needed to verify or dismiss this proposal.

Keywords: Cytochrome P450, CYP isoforms, DILI, Drug induced liver injury, Roussel Uclaf Causality Assessment Method, RUCAM.

1. INTRODUCTION

A recent scientometric investigation highlighted the knowledge mapping of idiosyncratic drug induced liver injury (iDILI) throughout the world with details on the most quoted publications and scientists most engaged in research [1]. There is considerable interest in diagnostic aspects of iDILI with focus on RUCAM (Roussel Uclaf Causality Assessment Method) to assess causality [2-7] and mechanistic steps leading to iDILI [8,9]. The idiosyncratic nature makes mechanistic studies on iDILI very difficult. Nevertheless, the involvement of the adaptive immune system is likely in some patients with iDILI associated with specific HLA (Human Leucocyte Antigen) genotypes [8]. In general, it is believed that the initiation of an immune response requires activation of antigen presenting cells by molecules such as danger-associated molecular pattern molecules (DAMPs). Poorly understood is the role of cytochrome P450 (CYP) in triggering and perpetuating iDILI [9].

In the present report the role of CYP and its isoforms was investigated in cases of RUCAM based DILI caused by various drugs, analyzing whether drugs implicated in idiosyncratic DILI are metabolized by hepatic microsomal CYP or hepatic nonCYP enzymes.

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2. LITERATURE SEARCH AND SOURCE

The PubMed database was searched for articles by using the following key terms: idiosyncratic drug induced liver injury (DILI); drugs; cytochrome P450 (CYP): CYP isoforms. These terms were used alone or in combination. Limited to the English language, publications from each search terms were analyzed for suitability of this review article. Publications were complemented from the large private archive of the authors. The final compilation consisted of original papers, consensus reports, and review articles with the most relevant publications included in the reference list of this review.

3. DRUG METABOLISM VIA HEPATIC MICROSOMAL CYTOCHROME P450

Many drugs are preferentially metabolized by hepatic microsomal CYP and its isoforms [10-13], whereas the role of nonCYP pathways seems to be smaller [14]. Drug metabolism via CYP requires as reducing equivalent NADPH + H^+ [10,15], which is converted to NADP+ through the NADPH CYP reductase in its oxidized form that becomes reduced (Figure **1**). The reduced form of NADPH CYP reductase in turn converts the oxidized CYP to its reduced form, which has a broad substrate specificity and binds not only endogenous substrates but also exogenous substrates such as drugs, ethanol, carcinogens, procarcinogens, and aliphatic halogenated hydrocarbons such as carbon

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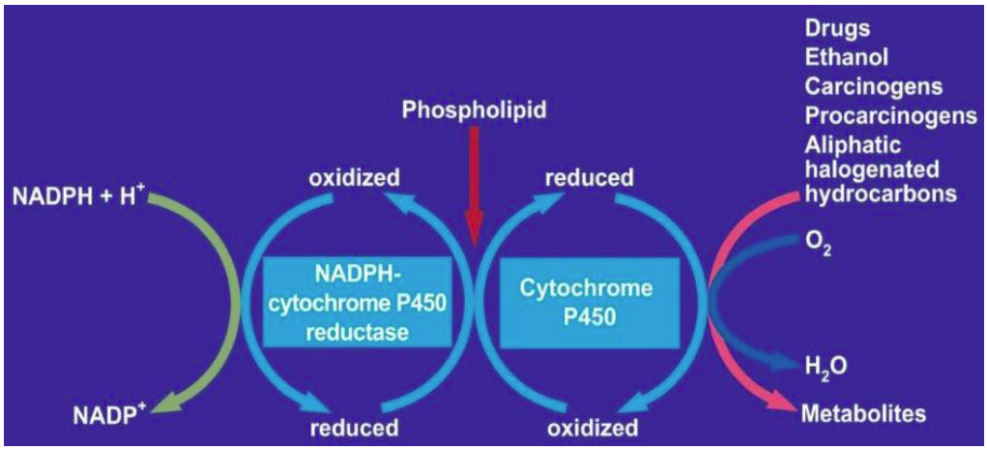

Figure 1: Metabolism of drugs and other exogenous compounds via cytochrome P450 and the NADPH cytochrome P450 reductase

tetrachloride (Figure **1**) [10,16,17]. Drug metabolism at the site of CYP can be inhibited by other substrates competing at the same site of CYP or be increased if CYP is upregulated by inducers. Finally, CYP consists of various isoforms with differences in substrate specificities [10]. Interactions of drugs with CYP and its isoforms are therefore rather complex and difficult to be anticipated in humans.

Whenever a drug enters the catalytic CYP cycle as a substrate to be oxidized, it first must bind to CYP (Figure **2**) [18]. Electrons provided by NADPH + H^+ through the NADPH CYP reductase (Figure **1**) and introduction of molecular oxygen lead to the oxidized form of CYP, which becomes oxidized again after splitting off the oxidized drug. CYP is then again free for the next drug to be oxidized. Under normal conditions, this enzymatic process proceeds smoothly, but occasionally reactive oxygen species (ROS) are generated due to incomplete split of oxygen leading to liver injury [14].

4. INVOLVEMENT OF CYP IN DILI BY SELECTED DRUGS

In order to analyze the involvement of CYP in iDILI, the first step was to choose drugs implicated in iDILI assessed for causality by the original RUCAM [19,20] and the updated RUCAM [21]. For this purpose, 48 drugs were selected in the LiverTox database and classified as the most commonly drugs implicated in iDILI based on the high number of published reports, certainly a disputable approach [22]. Upon reassessment it turned out that for only 36/48 drugs RUCAM based DILI cases were found in the literature [22]. Among the 36 drugs with iDILI cases verified for causality by RUCAM, for at least 22 drugs (61.1%), clinical or experimental evidence exists that the

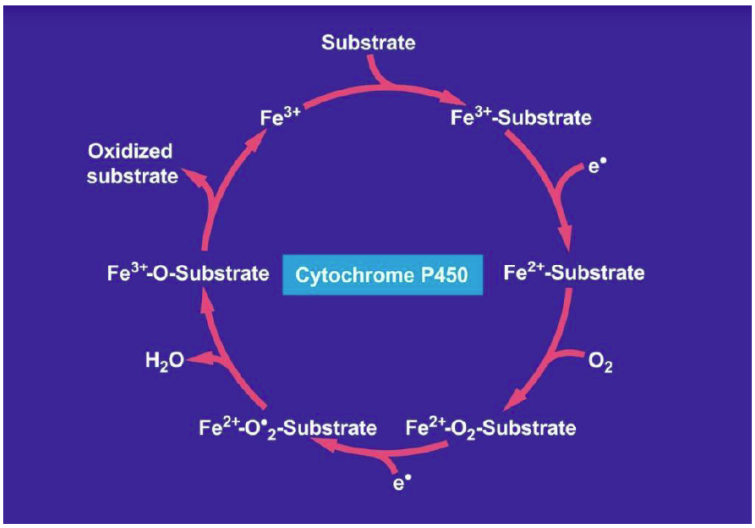

Figure 2: Catalytic cytochrome P450 cycle metabolizing drugs and other exogenous substrates

Table 1: Ranking of drugs causing DILI with causality assessment cases by RUCAM. Modified from a previous publication [9,22]. Listed are the top ranking 48 drugs causing DILI with verified causality using RUCAM. Abbreviations: CYP, Cytochrome P450; DILI, Drug induced liver injury: NA, not available

Drug	RUCAM based DILI cases (n)	Metabolized by CYP isoform	References
1. Amoxicillin-clavulanate	333	-	Hautekeete [23]
2. Flucloxacilllin	130	CYP 3A4	Dekker [24]
3. Atorvastatin	50	CYP3A4/5	Zanger [25]
4. Disulfiram	48	CYP 2E1	Hopley [26]
5. Diclofenac	46	CYP2C8	Zanger [25]
6. Simvastatin	41	CYP3A4/5	Fatunde [27]
7. Carbamazepine	38	CYP3A4/5	Zanger [25]
8. Ibuprofen	37	CYP 2C8/9	Hopley [26]
9. Erythromycin	27	CYP 3A4	Hopley [26]
10. Anabolic steroids	26	CYP2C19	Yamazaki [28]
11. Phenytoin	22	CYP 2C9	Hopley [26]
12. Sulfamethoxazole/Trimethoprim	21	CYP 2C9	Hopley [26]
13. Isoniazid	19	CYP 2E1	Hopley [26]
14. Ticlopidine	19	CYP 2C19	Hopley [26]
15. Azathioprine/6-Mercaptopurine	17	-	Johansson [29]
16. Contraceptives	17	CYP3A4	Scott [30]
17. Flutamide	17	CYP1A2	Zanger [25]
18. Halothane	15	CYP2E1	Zanger [25]
19. Nimesulide	13	CYP 2C9	Yu [31]
20. Valproate	13	CYP 2C9	Kiang [32]
21. Chlorpromazine	11	CYP 2D6	Hopley [26]
22. Nitrofurantoin	11	-	Wang [33]
23. Methotrexate	8	-	Donehower [34]
24. Rifampicin	7	-	Acocella [35]
25. Sulfazalazine	7	-	Das [36]
26. Pyrazinamide	6	-	Shih [37]
27. Natriumaurothiolate	5	-	Björnsson[38]
28. Sulindac	5	CYP 1A2	Brunell [39]
29. Amiodarone	4	CYP 3A4	Hopley [26]
30. Interferon beta	3	-	Bertz [40]
31. Propylthiouracil	2	CYP/NA	Heidari [41]
32. Allopurinol	1	-	Turnheim [42]
33. Hydralazine	1	-	Talseth [43]
34. Infliximab	1	-	LiverTox [44]
35. Interferon alpha/ Peginterferon	1	-	Okuno [45]
36. Ketaconazole	1	-	Kim [46]
37. Busulfan	0	-	Myers [47]
38. Dantrolene	0	-	Amano [48]
39. Didanosine	0	-	Andrade [49]
40. Efavirenz	0	CYP 2B6	Desta [50]
41. Floxuridine	0	-	Landowski [51]
42. Methyldopa	0	CYP/NA	Dybing [52]
43. Minocycline	0	-	Nelis [53]
44. Telithromycin	0	CYP 3A4	Shi [54]
45. Nevirapine	0	CYP 3A4	Erickson [55]
46. Quinidine	0	CYP 3A4	Nielsen [56]
47. Sulfonamides	0	CYP/NA	Back [57]
48. Thioguanine	0	-	Choughule [58]

metabolism proceeds via various CYP isoforms, whereas for the remaining 14 drugs (38.9%) CYP was not implicated in their metabolism (Table **1**) [23-58]. These results show that iDILI is caused mainly by drugs that are substrates of CYP, whereas a smaller proportion of drugs cause iDILI without being substrates of CYP. Therefore, metabolism via CYP is not obligatory for a drug causing iDILI.

5. DISCUSSION

Drugs might cause iDILI whether they are substrates of CYP or not, but the proportion of drugs metabolized by CYP is greater (Table **1**). As a result, pathogenetic principles may differ among iDILI cases, depending on the involvement of CYP in the metabolism of the drug incriminated in the liver injury. However, the pathogenetic principles that could explain differences in liver injury pattern and clinical features remain to be established. The large iDILI group caused by drugs metabolized by CYP requires further attention, because during drug metabolism via the NADPH and oxygen depended process, ROS is generated via the catalytic CYP cycle. ROS can injure the liver [59]. Clearly, iDILI is a rare disease in predisposed individuals, whereby the immune system likely plays a major role for initiation and perpetuation of the liver injury [8,9]. The initiation of an immune response requires the activation of the innate immune system to the adaptive immune system through antigen presenting cells by molecules such as danger-associated molecular pattern molecules (DAMPs) [8,9]. Poorly understood is the role of CYP in triggering and perpetuating iDILI. Among 36 drugs implicated in iDILI assessed for causality by RUCAM, 22/36 drugs (61.1%) are metabolized via CYP, suggesting that radicals generated during the catalytic CYP cycle are involved in triggering the liver injury by these drugs. ROS could modify hepatic RNA, which after activation causes the production of proteins functioning as antigens and activating the innate immune system to the adaptive immune system. Characterized by immunological features including antibody generation, liver injury by halothane could be a perfect example for iDILI caused by a drug metabolized by CYP [60]. Further clinical and perhaps experimental studies are needed to verify or dismiss this hypothesis.

6. CONCLUSION

Based on iDILI cases assessed for causality using RUCAM, two groups ermerged, one caused by drugs that are metabolized by CYP and another one with drugs that are metabolized through nonCYP pathways. Drugs undergoing CYP dependent metabolism may cause iDILI through the generation of ROS, which inturn could modify hepatic RNA, which after activation causes the production of proteins functioning as antigens and activating the innate immune system to the adaptive immune system. Characterized by immunological features including antibody generation, liver injury by halothane could be a perfect example for iDILI caused by a drug metabolized by CYP. Further studies are needed to verify or dismiss this proposal.

AUTHOR CONTRIBUTION

RT and GD conceptualized the outline of the manuscript. RT wrote the first draft, which was edited by GD who added major points to current issues. Both authors agree on the final text to be submitted.

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CONFLICTS OF INTEREST

The authors have no conflict of interest to declare with respect to this invited review article.

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