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PHARMACOVIGILANCE

Safety data and withdrawal of hepatotoxic drugs

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Summary
Background and aim. — The occurrence of drug induced liver injury (DILI) is the most common reason of post-marketing withdrawals. DILI in humans is difficult to predict using in vitro cytotoxicity screening and animal studies. A review of hepatotoxicity data was performed with the aim of identifying relevant factors that could have predicted the occurrence of serious DILI.
Methods. — The drugs withdrawn from the market due to hepatotoxicity in Europe and/or in USA either by marketing authorization holders or by Regulatory agencies from 1997 to 2016 were selected. The liver safety data and the withdrawal decisions were identified from a search within the European medicine agency (EMA) website, the Food and drug administration (FDA) orange book and PubMed®.
Results. — From 1997 to 2016, eight drugs were withdrawn from the market for hepatotoxicity reason: tolcapone, troglitazone, trovafloxacin, bromfenac, nefazodone, ximelagatran, lumiracoxib and sitaxentan. The safety data suggest that while liver test abnormalities have been detected during clinical trials, other relevant factors leading to the discontinuation of these drugs have been identified: lack of predictability of animal models, inappropriate liver function test, non-compliance with drug treatment, less attention paid to rare adverse drug reactions, unpredictable occurrence and irreversible outcome of liver toxicity.
Conclusion. — Several relevant factors may contribute to an inadequate risk management leading to the discontinuation of the drugs. Preclinical safety data are not sufficient to allow early prediction of DILI in humans and post-marketing safety monitoring and signal detection still should be used to identify potential serious cases of DILI. However, it seems that changes in Pharmacovigilance legislation with a closer management of drug safety may have contributed to the improvement of the risk minimization.

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Abbreviations

5-HT	5-hydroxytryptamine
ALF	acute liver failure
ALT	alanine transaminase
BSEP	bile salt export pump
COMT	catechol-O-methyl transferase
COX	cyclooxygenase
DILI	drug-induced liver injury
EMA	European medicines agency
FDA	Food and drug administration
GSH	glutathione
HLA	human leukocyte antigen
LFT	liver function test
MHC	major histocompatibility complex
NSAID	non-steroidal anti-inflammatory drugs
PPAR	peroxisome proliferator-activated receptors
REMS	risk evaluation and mitigation strategies
RNA	ribonucleic acid
RMP	risk management plan
ULN	upper limit of normal
UK	United Kingdom
USA	United States of America

Background

The regulatory authorities as Food and drug administration (FDA) and European medicine agency (EMA) review the evidence on drug safety concern from preclinical trials, clinical trials, spontaneous case reports and randomized controlled trial. An opinion is given on whether the marketing authorisations of medicinal products containing that particular drug should be maintained, changed or withdrawn [1]. In vitro hepatotoxicity assays during early drug development allows screening a large set of marketed drugs that produce liver toxicity by multiple mechanisms for the purpose of assessing their correlation with human toxicity [2]. Although in vitro cytotoxicity assays have a low sensitivity thus making a low concordance with human liver toxicity, they have been widely used in preclinical testing because a small quantity of drug is required [3]. Liver injury at extremely high doses in animal models does not necessarily predict problems in humans [4]. Moreover, no universally animal model has been accepted and approved by regulatory agencies because drugs that induce predictable and dose-related injury are often discovered and rejected in preclinical testing. Therefore, there is limited data for a systematic assessment of the predictive value of such findings for drug induced liver injury (DILI) in humans. DILI is defined as a liver injury caused by various medications, herbs, or other xenobiotics, leading to abnormalities in liver tests or liver dysfunction with the reasonable exclusion of other etiologies [5]. The role of animal studies in predicting DILI in humans remains questionable [6,7]. Most of drugs that induce liver injury in humans have not shown hepatotoxicity in animal studies: A study showed that 43% of clinical toxicities were not predicted from animal studies [8]. Concordance between pre-clinical studies and clinical trials was seen in 63% of non-rodent studies, primarily the dog, and in 43% of rodent studies, primarily the rat. The average rate of concordance between liver toxicity and animals remains at about 55% [9]. One study revealed that in 67% cases in which toxicity during clinical trials led to the termination of drug development, these incidences were not predicted by animal studies [10]. Few published analyses of comparative animal-human toxicity data on drugs were done, probably because of the perceived confidential nature of such data. The false negatives in animal studies can be explained by the lack of predisposing factors as underlying diseases and by the animal species differences concerning bioavailability and metabolism [11]. Several investigators have therefore proposed the use of humanized animals. Recent advances in preclinical testing strategies have improved our ability to identify drugs with risk for DILI [12]. The construction of predictive models benefits from an integration of chemical structure, cellular end points, toxicogenomics data and data from multiple sources. However, the limited power of DILI prediction is mostly attributed to the complex nature of DILI, a poor understanding of mechanisms, a scarcity of human hepatotoxicity data and insufficient bioinformatics capabilities [13].

Therefore, a review of hepatotoxicity data was performed with the aim of identifying relevant factors that could have predicted the occurrence of serious DILI. This study could contribute to better define the occurrence of this adverse effect [14].

Methods

The drugs withdrawn from the market due to hepatotoxicity from 1997 to 2016 in Europe and/or in United States of America (USA) either by marketing authorization holders or by drug agencies have been selected. The study period allows a 20-year follow-up on the safety of drugs product. The liver safety data and the withdrawal decision were identified from a search within the EMA website, the FDA orange book and PubMed® only among these 2 regions of the world. The date of withdrawal was defined by the time where the drug was removal for hepatotoxicity reason by the manufacturer authorization holder or by the national health authority (FDA or EMA). The conditions of occurrence of liver injury were described for each drug withdrawn and an analysis of liver safety concern was provided during the entire life cycle of the drugs and was presented in Tables 1 and 2 [15–23].

Results

In the European union and in USA, eight drugs were withdrawn for liver toxicity reasons from 1997 to 2016: Tolcapone, troglitazone, trovafloxacin, bromfenac, nefazodone, ximelagatran, lumiracoxib and sitaxentan [24].

Tolcapone is a reversible inhibitor of the enzyme catechol-O-methyl (COMT) transferase marketed in Europe and in US in 1997 for the treatment of Parkinson's disease in combination with levodopa. In the preclinical studies, no evidence of serious hepatic dysfunction was recognized. In phase 3 of clinical trials, the incidence of serum alanine transaminase (ALT) elevations was approximately 1% greater than placebo with the 100 mg dose and approximately 3% greater than placebo with the 200 mg dose. For this reason,

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