



Webscout:

Drug-induced injuries —a growing concern by health authorities

by Joelyn Flauaus

The world population is continuously growing older because of an increased life expectancy and is thus using more and more drugs, whether prescription or over-the-counter drugs. Therefore, chances of drug-induced injuries are rising.

Over the years, a number of postmarketing labelling changes or drug withdrawals from the market due to postmarketing discoveries have occurred. Even the best planned and carefully designed clinical studies have limitations. To detect all potential adverse drug reactions, you need quite a large number of subjects exposed to the drug and the number of subjects participating in the clinical studies might not be large enough to detect especially rare adverse drug reactions. To minimise the risk of postmarketing discoveries such as unrecognised adverse drug reactions, certain risk factors, e.g. laboratory or ECG abnormalities, are subject of increased regulatory review.

The most frequent cause of safety-related withdrawal of medications (e.g. bromfenac, troglitazone) from the market and for FDA non-approval is the drug-induced liver injury (DILI). Different degrees of liver enzyme elevations after drug intake can result in hepatotoxicity, which can be fatal due to the irreversible damage to the liver. Since animal models cannot always predict human toxicity, drug-induced hepatotoxicity is often detected after market approval. In the United States, DILI is contributing to more than 50% of acute liver failure cases (data from WM Lee and colleagues from the Acute Liver Failure Study Group).

The second leading cause for withdrawing approved drugs from the market is QT interval prolongation, which can be measured during electrocardiogram (ECG). Some non-cardiovascular drugs (e.g. terfenadine) have the potential to delay cardiac repolarisation and to induce potentially fatal ventricular tachyarrhythmias such as Torsades de Pointes.

Drug toxicity is also a common cause of acute or chronic kidney injury and can be minimised or prevented by vigilance and early treatment. NSAIDs, aminoglycosides, and calcineurin inhibitors are for example some drugs that are known to induce kidney dysfunction. Most events are reversible, with kidney function returning to normal when the drug is discontinued.

Consequently, the pharmaceutical industry has a strong interest to identify drugs bearing the risk of causing adverse drug reactions as early as possible in order to improve the drug development programme. I have put together a selection of websites providing you with more insights about certain drug-induced injuries and their impact.

Drug-induced liver injury:

<http://www.fda.gov/Cder/guidance/7507dft.pdf>

Draft Guidance for Industry—drug-induced liver injury (Premarketing Clinical Evaluation): this guidance outlines

how laboratory measurements that signal the potential for DILI can be obtained and evaluated and introduces an approach to identify drugs that are likely to cause significant hepatotoxicity (Hy's law).

Drug-induced QT/QTc interval prolongation:

<http://www.fda.gov/CDER/GUIDANCE/6922fnl.pdf>

Guidance for Industry E14—Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: this guidance provides background information on the impact of QT prolongation and describes methods to assess the potential of a drug to delay cardiac repolarisation.

Drug-induced kidney injury:

<http://www.ifcc.org/PDF/20010908.pdf>

This article [1] of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) provides an overview on drug-induced kidney injuries. Several mechanisms of drug-induced renal dysfunction including hemodynamic and intrinsic kidney injuries and intrarenal obstruction are described.

Data on drug approvals, safety-based withdrawals and boxed warnings are also publicly available on the internet, as follows:

USA

Recalls, Market Withdrawals and Safety Alerts:

<http://www.fda.gov/opacom/7alerts.html>

Black Box Warning information:

<http://formularyproductions.com/blackbox>

List of drugs on the market that have a warning that appears on the package insert indicating they carry a significant risk of serious or even life-threatening adverse effects. These drugs are listed by their generic names.

Europe

EMA Marketing Authorisation (MA) Withdrawals and Suspensions—Medicinal Products for Human Use:

<http://www.emea.europa.eu/htms/human/withdraw/withdraw.htm>

EMA Human Medicines—Product Safety Announcements:

<http://www.emea.europa.eu/htms/human/drugalert/drugalert.htm>

If you find a website that should be mentioned in the next issue, or if you have any other comments or suggestions, please email me at: Joelyn.Flauaus@sanofi-aventis.com.

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Reference:

1. Drug-Induced Kidney Injury - eJIFCC 20/01 2009 <http://www.ifcc.org>