ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM
Research Article

Drug-Induced Hepatotoxicity

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Received: March 31, 2017; **Published:** April 22, 2017

Abstract

Drug Induced Hepatotoxicity is the most common cause of acute liver failure in developed countries. It represents approximately 10% of cases of acute liver failure worldwide and around the 40 - 50% of all cases of liver injury. The aim of this study is to expose the result about the incidence of drug induced hepatotoxicity obtained from a pharmacovigilance data base and which are the most frequently drugs associated.

Study: To determinate the incidence of Drug induced hepatotoxicity was performed a retrospective study based on a pharmacovigilance data base from an Argentinian tertiary care hospital, Hospital General de Agudos Dr Cosme Argerich, During a five years' period from June 2008 to February 2012.

Results: From a pharmacovigilance base of 2993 Adverse Drug Reactions, we detected 428 events of drug induced hepatotoxicity, 14 of them were severe and two were lethal. The group of drugs most frequently associated were antibiotics, neuropsychiatric drugs and NSAIDs. Males were most frequently affected than women.

Conclusions: Drug induced hepatotoxicity is the most frequently cause of acute liver failure in developed countries and one of the most frequent in developing countries and has been the leading cause of withdrawal of drugs from the market. It's becoming a serious health problem that affects all the actors involved in the health system. The diagnosis and recognition are often difficult so the true incidence of this phenomenon is still unknown. In concordance with the international bibliography the most common association was seems with antibiotics and neuropsychiatric drugs.

Keywords: *Drug Induced Hepatotoxicity; DILI*

Introduction

Drug induced Hepatotoxicity is the most common cause of acute liver failure. It represents approximately 10% of acute liver failure worldwide and around the 40 - 50% of all cases of liver injury [1]. it is estimated that at least 1000 drugs on the market have been implicated in DILI in more than one occasion, and is the most frequent adverse drug event leading to abandonment of otherwise promising new drug during the preclinical or clinical development stage [2].

It remains one of the most challenging disorders because of the particular difficulties for diagnosis and management. Quantitative information about risk and incidence of drug induced hepatotoxicity is relatively scarce [3-5] thereby our interest to make and approach to estimate the real impact of this issue, and to determinate with are the drugs most often involved.

The first step in describing Drug induced hepatotoxicity is to differentiate idiosyncratic (unpredictable) from intrinsic (predictable) toxicity. The most common example of a drug causing predictable hepatotoxicity is acetaminophen. This type of drug injury has a short latency period, is dose related, and is the most common form of drug induced hepatotoxicity observed according to the literature. On the contrary, idiosyncratic DILI is unpredictable, has longer/variable latency, and is less common. Examples of idiosyncratic toxicity include those related to amoxicillin/clavulanate, nonsteroidal anti-inflammatory drugs, and isoniazid.

The second distinction to make is in regard to the pattern of drug injury. DILI can be categorized as hepatic (hepatocellular injury), cholestatic, or mixed on the basis of liver biochemical parameters [6].

Based on biochemical parameters, hepatotoxic reactions are determinate at least by GTP elevation x 3 + FAL > 2 upper limits of normal. BT > 2 upper limits of normal + any alteration of GTP or FAL.

There are describe over the literature risk factors for hepatotoxicity like: inter individual susceptibility, genetics factor, age, sex, metabolic and hormonal factors, consume of alcohol, pharmacology interaction, and doses [7].

Aim

The aim of this study is to expose the result about the incidence of liver injury obtain from the pharmacovigilance data base in hospitalized patients and make an approach of which are the most common association involves.

Material and Methods

It was performed a retrospective study based on a pharmacovigilance data base from an Argentinian general hospital, during a five years' period from June 2008 to February 2012, to determinate the incidence of Drug induced liver injury (DILI). Every service of the hospital was considered and included.

Was applied the Naranjo Score [8] for assessing drug causality in the medical adverse events (Table 1). The scoring is: 9, certain Adverse drug reaction (ADR); 5-8, probable ADR; 1-4, possible ADR; 0, doubtful. We only are considered certain and possible ADR. Also, the events were classified according to seriousness (was considered serious when it was lethal, it compromised life, lead to hospital admission or prolonged it, caused teratogenicity or permanent disability). All this ADR were reported to the Argentinian Regulatory Agency (ANMAT).

Questionnaire	Yes	No	Don't know
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse events appear after the suspected drug was given?	+2	-1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0
Did the adverse reaction appear when the drug was readministered?	+2	-1	0
Are there alternative causes that could have caused the reaction?	-1	+2	0
Did the reaction reappear when a placebo was given?	-1	+1	0
Was the drug detected in any body fluid in toxic concentrations?	+1	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0

Table 1: *Naranjo Algorithm for assessing drug causality in a medical adverse event. The scoring is: 9, certain ADR; 5-8, probable ADR; 1-4, possible ADR; 0, doubtful.*

The liver injury was determinate by biochemical parameters and biopsy if it was needed. The data base was also discriminated in gender and age, trying to find some association with these two risks factor according with the available literature [6-9]. And classified by group of drugs involved in the phenomenon.

Results

During the period while the study was performed were detected 2993 adverse drug reaction, 428 of them were Drug induced hepatotoxicity 14.30% (CI 95%: 14.3 - 15,60) of these ones 14 cases were serious, 3.27% (CI 95%: 1.96 - 5.4), and 3 of them lead to death.

In discordance with the actual bibliography were more frequently affected Male patients, 258 cases 60.20% (CI 95%: 55.57 - 64.68) and females were affected in 169 cases 39.48% (CI 95%: 34.97 - 44.19). The average age was for Males 54.54 (CI 95%: 52.35 - 56.73) and for Females 51.90 (CI 95%: 49.40 - 54.77) without real difference between groups.

Table 2 shows the classes of drugs involved by frequency, Antibiotics were the most common association, causing a total of 253 cases of the total 428 (59%; CI 95 %: 54.39 - 63.67), the second association more frequent was with neuropsychiatric drugs, responsible of 59 cases 13,70% (CI 95%: 10.84 - 17.37), NSAIDs caused 39 cases 9.11% (CI 95%: 6.64 - 12.21) and cardiovascular drugs were involved in others 37 cases 8.64% (CI 95%: 6.34 - 11.69).

Drug or group of drugs involved	Number of cases	Percent	IC 95% +/-
NSAIDs	39	9.11%	1.14
Anesthesics	1	0.23%	0.41
Antihistamines	1	0.23%	0.41
Antimicrobials	253	59.11%	0.41
Cardiovascular	37	8.64%	1.12
Corticosteroids	1	0.23%	0.41
Endocrinological	4	0.93%	0.51
Gastrointestinal	2	0.46%	0.45
Hematologic	5	1.16%	0.54
Neuropsychiatric	59	13.70%	1.35
Others	3	0.70%	0.48
Chemotherapy	10	2.33%	0.66
Unknown	13	3.03%	0.74

Table 2: *Drugs involved in DILI.*

Discussion

Drug induced hepatotoxicity is in the general population a rare adverse drug reaction, but is the most common cause of acute liver failure and has been the leading cause of withdrawal of drugs from the market. It's becoming a serious health problem that affects all the stakeholders involved in the health system, because of the increasing of the morbidity, mortality and the economic impact.

The diagnosis and recognition are often difficult so the true incidence of this phenomenon is still unknown. In concordance with the international bibliography the most frequently related to this toxicity was seems with antibiotics and neuropsychiatric drugs [10-11].

This study provides the most common association drugs involve in liver injury in a base of hospitalized patients, but is still needed additional education about ADRs, enhanced reporting by health care professionals and real world statistics to facilitate an understanding of the true prevalence and incidence of drug hepatotoxicity.

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Volume 2 Issue 5 April 2017