Toxic Acute Liver Failure

Essay

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

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Usama Mohamed Rabea Moustafa

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List of Abbreviations

AASLD	:	American association for the study of liver disease
ABC	:	Adenosine triphosphate- binding cassette
ALF	:	Acute liver failure
ALP	:	Alkaline phosphatase
ALT	:	Alanine aminotransferase
ARDS	:	Acute respiratory distress syndrome
AST	:	Aspartate aminotransferase
ATP	:	Adenosine triphosphate
BAL	:	Bioartificial liver
BSEP	:	Bile-salt export protein
CBF	:	Cerebral blood flow
CCP	:	Cerbral perfusion pressure
CHM	:	Chinese herbal medicines
CYP	:	Cytochrome p450
DILI	:	Drug-induced liver injury
HAART	:	Highly active antiretroviral therapy
HAV	:	Hepatitis A virus
HBc IgM	:	Hepatitis B core immunoglobulin M
HBs Ag	:	Hepatitis B Surface antigen
HCV	:	Hepatitis C virus
HDS	:	Herbal and dietary supplements

HEV	:	Hepatitis E virus
HIV	:	Human immune-deficiency virus
HLA	:	Human leukocyte antigens
HSV	:	Herpes simplex virus
ICH	:	Intracranial hypertension
ICP	:	Intracranial pressure
ICU	:	Intensive care unit
INR	:	International normalized ratio
KCH	:	King's college hospital
MDR	:	Multi-durg resistant protein
MELD	:	Model for end stage liver disease
UDP	:	Uridinediphosphate
UGT	:	Uridinediphosphate-Glucuronyltrasferases
ULN	:	Upper limit normal
VZV	:	Varicella zoster virus

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Introduction

Acute liver failure (ALF) is an uncommon but dramatic clinical syndrome characterized by sudden and massive hepatic necrosis that results in jaundice, coagulopathy [international normalized ratio (INR) $\geq$ 1.5], and hepatic encephalopathy (any degree of altered mentation) in the absence of pre-existing liver disease ***(Lee, 2012)***.

The most prominent causes include drug-induced liver injury, viral hepatitis, autoimmune liver disease and shock or hypoperfusion. Many cases have no identifiable cause ***(Hiramatsu et al., 2008).***

The most common drugs implicated in acute drug-induced liver injury (DILI) are acetaminophen followed by antibiotics ***(Galan et al., 2005).***

Hepatotoxicity associated with herbal and dietary supplements (HDS) use may be missed, there are no accurate estimates of the frequency of hepatotoxicity attributable to HDS as patients often do not report the use of herbal products to their clinicians, and self-medicate with large amounts ***(American Botanical Council, 2009).***

The initial clinical features of ALF may be nonspecific and may include anorexia, fatigue, abdominal pain and fever. As the metabolic and detoxification function of liver becomes impaired, the signs of ALF emerge, including jaundice, encephalopathy, coagulopathy, haemodynamic instability, acute lung injury/acute respiratory distress syndrome (ARDS), renal failure, sepsis, and metabolic disturbance ***(World, 2013).***

Cerebral edema leading to intracranial hypertension (ICH) is one of the major causes of morbidity and mortality in patients with ALF. The pathogenesis of cerebral edema and ICH in ALF appears to be multifactorial. Ammonia is converted in the astrocytes to osmotically active glutamine, producing osmotic cerebral edema ***(Bjerring et al., 2009).***

The management of ALF challenges the best skills because of its rapid progression and frequently poor outcomes. Early identification of the etiology & specific treatment ALF is crucial to improve the outcome. Extrahepatic organ failure should be well managed with advanced intensive care management. Better-targeted use of liver transplantation techniques becomes important to save the patients who fail to recover spontaneously. A better understanding of the pathophysiology of ALF will probably lead to further improvement in survival rates ***(Yan et al., 2012).***

Aim of the work

The aim of this review is to highlight the aetiology and pathophysiological aspects of toxic acute liver failure and to provide recommendations for the management of this potentially dangerous condition.

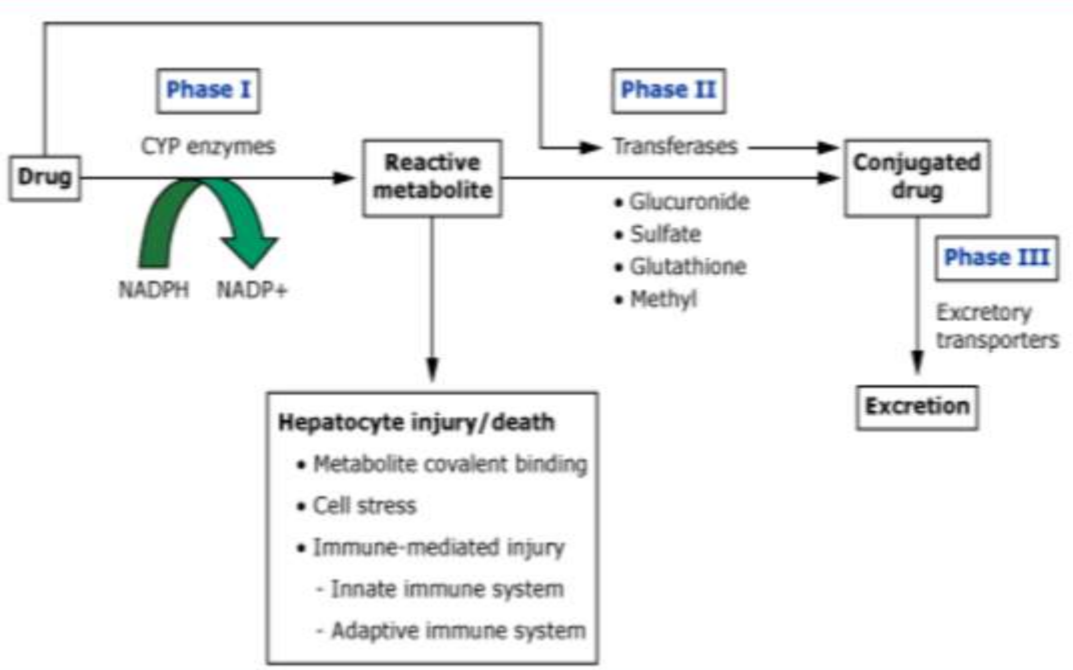
Aetiology and pathophysiological considerations of toxic acute liver failure

Role of the liver in drug metabolism

The liver is responsible for the selective uptake, concentration, metabolism, and excretion of the majority of drugs and toxins that are introduced into the body. While some parent drugs can directly cause hepatotoxicity, it is generally the metabolites of these compounds that lead to drug-induced liver injury (DILI). These compounds are processed by a variety of soluble and membrane-bound enzymes, especially those related to the hepatocyte endoplasmic reticulum. Each drug has its specific enzyme disposal pathway(s) of biotransformation involving one or more of these enzyme systems ***(Park et al., 2005)***.

Genetic variation in drug metabolism is increasingly being recognized as a factor in the development of DILI. Environmental factors (eg, alcohol use) may also alter the processing of drugs and toxins. The majority of drugs absorbed from the gastrointestinal tract are lipophilic and water-insoluble. They are rendered water-soluble via hepatic metabolism and thus, more easily excreted in the bile or renally filtered. Exogenous products are hepatically metabolized predominantly through two mechanisms: phase I and phase II reactions (fig.1) ***(Park et al., 2005)***.

<u>Fig. (1)</u> Hepatic drug metabolism. According to: ***(Park et al., 2005)***.



The subsequent products are then excreted via excretory transporters on either the canalicular or sinusoidal membranes (phase III reactions) ***(Gunawan and Kaplowitz, 2007)***.

Phase I reactions: Phase I reactions transform lipophilic molecules into more polar, hydrophilic molecules via oxidation, reduction, or hydrolysis. These reactions are catalyzed by the membrane-bound cytochrome P450 superfamily of mixed function oxidases (CYP) ***(Werck-Reichhart and Feyereisen, 2000).***

Approximately 60 genes coding for CYP proteins have been identified in humans. These enzymes are organized into families (eg, CYP2) and subfamilies (eg, CYP2E1). The vast majority of these enzymes are located on the cytoplasmic side of the membrane of the endoplasmic reticulum (microsomal-type) or the mitochondria (mitochondrial type). The microsomal-type is responsible for phase I drug metabolism ***(Danielson, 2002)***.

Hepatic metabolism of exogenous drugs and toxins is performed mainly by the CYP1, CYP2, and CYP3 families, with a smaller contribution from CYP4. The remaining families are often highly specific for the metabolism of endogenous compounds and are not inducible by exogenous compounds. The most important drug metabolizing member is CYP3A4, which comprises approximately 60 percent of all hepatic cytochromes and catalyzes the biotransformation of over 50 percent of commonly used drugs. Free radicals and toxic electrophilic compounds can be produced during this process ***(Danielson, 2002)***.

CYP activity: Cytochrome activity varies considerably depending in part upon the concentration of the enzymes and the degree of induction by exogenous factors (Table 1) ***(Hansten and Horn, 2014).***

Table (1): Cytochrome P450 inhibitors and inducers. According to: ***(Hansten and Horn, 2014).***

Strong inhibitors	Moderate inhibitors	Strong inducers	Moderate or weak inducers
– Atazanavir	– Abiraterone	– Carbamazepine	– Aprepitant
– Boceprevir	– Amiodarone	– Dexamethasone	– Armodafinil
– Chloramphenicol	– Aprepitant	– Enzalutamide	– Artemether
– Clarithromycin	– Bicalutamide	– Fosphenytoin	– Bexarotene
– Cobicistat and cobicistat containing coformulations	– Cimetidine	– Mitotane	– Calcitriol
– Conivaptan	– Ciprofloxacin	– Nafcillin	– Clobazam
– Delavirdine	– Clotrimazole	– Nevirapine	– Dabrafenib
– Fosamprenavir	– Crizotinib	– Oxcarbazepine	– Desvenlafaxine
– Idelalisib	– Cyclosporine	– Pentobarbital	– Dicloxacillin
– Indinavir	– Desipramine	– Phenobarbital	– Eslicarbazepine
– Itraconazole	– Diltiazem	– Phenytoin	– Estrogens
– Ketoconazole	– Danazol	– Primidone	– Etravirine
– Lopinavir	– Dronedarone	– Rifabutin	– Exemestane
– Nicardipine	– Erythromycin	– Rifampin (rifampicin)	– Flucloxacillin
– Posaconazole	– Fluconazole	– Rifapentine	– Griseofulvin
– Ritonavir and ritonavir containing coformulations	– Haloperidol		– Hydrocortisone
– Saquinavir	– Metronidazole		– Medroxyprogesterone
– Telaprevir	– Miconazole		– Modafinil
– Telithromycin	– Mifepristone		– Paclitaxel
– Voriconazol	– Norfloxacin		– Pioglitazone
	– Quinupristin-dalfopristin		– Prednisone
	– Tetracycline		– Ritonavir
	– Verapamil		– Terbinafine