Profile Of Hepatotoxicity In Current Toxicology Practice In Egypt

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Citation

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Abstract

BACKGROUND: The clinical review aimed to determine the characteristics and clinical profile of poison induced liver injury in the current clinical toxicology practice in Poison Control Center, Ain Shams University Hospitals.
METHODS: During the period between July 1st 2009 and 30th of June 2010, patients were clinically assessed and reviewed for liver tests. All known hepatotoxins were included in the review whether liver injury resulted or not.
RESULTS: Phosphides and organophosphate were the commonest causes of hepatotoxicity. Frequency of liver toxicity was significantly higher in paraphenylenediamine, methanol and lead poisoning. Concomitant renal insufficiency was significantly more common in shock. Shock was significantly more frequent in patients who had liver impairment than in patients with normal liver function.Mortality patients in the liver impairment group, manifested significantly higher frequency of metabolic and respiratory acidosis than in survivors. Death was significantly correlated with liver impairment and in renal insufficiency only in shock states.
CONCLUSION: Antidotes protected against toxic hepatitis. Serious fulminant hepatitis with or without shock were the most serious outcome of phosphides intoxication. Mortality was correlated to liver or renal impairment only in shock states. Factors carrying bad prognosis include shock, renal insufficiency, metabolic and respiratory acidosis as concomitant clinical features. Recovery from toxic hepatitis was the rule in 97 out of 124 patients (78.2%)

INTRODUCTION

Acute poisoning with hepatotoxic drugs and poisons are a major common cause of liver injury. The commonest poisons involved in the daily toxicology practice in Poison Control center Ain Shams University include acetaminophen, iron, phosphorus and phosphide. Other less common toxins include alcohol, organophosphates insecticides, PPD (Paraphenylenediamine), phenytoin and other antiepileptic.

Although drug-related hepatotoxicity is uncommon its true incidence is difficult to determine. Larrey [1] reported the incidence for many drugs, as between 1 in 10,000 and 1 in 100,000 patients. The numbers may be much higher, because of underreporting, difficulties in detection or diagnosis, and incomplete observation of persons exposed [2].

This review aims to outline the profile of hepatotoxicity in Egypt in acute setting, describe the different presentations and define the prognostic factors

METHODS

All cases received in Poison Control Center Ain Shams University were retrospectively reviewed by multiple reviewers for hepatotoxicity and for drugs known to induce toxic liver injury in the period between 1st of July 2009 until 30th of June 2010 are as well included in the review.

The severity of liver cell damage is assessed by serial measurement of serum total bilirubin, albumin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and prothrombin time [3, 4]. Drug-related hepatotoxicity has been considered when typical symptoms occur in conjunction with biochemical evidence of liver injury. Rising transaminases from normal values on admission (day 1), over the following 2 – 3 days of poisoning event as well as regression on recovery from poisoning were recorded. Other associated laboratory findings included decrease of serum albumin and prolongation of prothrombin time (or its international normalized ratio INR) [2]. Liver toxicity was correlated to the offending agent by confirmed screening for phosphides, iron, valproate, carbamazepine, theophylline, CO, methanol or acetaminophen toxic blood levels, and erythrocyte and plasma cholinesterase levels suggestive of organophosphate poisoning.

Cases with positive chronic liver diseases, or acute viral

etiology were excluded from this review.
Frequency of hepatotoxicity was statistically calculated using Chi square. Complications and clinical outcome were statistically analyzed using correlation coefficient.

RESULTS

Hepatotoxic reactions ranging from mild to severe with hepatic encephalopathy occurred in 124 out of 16774 patients received in one year in the poison control center Ain Shams University with a frequency of 7.4 cases per thousand patients.
Hepatotoxicity was caused by ethyl alcohol in only 3 cases with a frequency of 1.16%, and in 5 cases of methanol (frequency of 22.7%), 3 of which developed renal insufficiency and died. Carbon monoxide was responsible for 7 cases of liver impairment 3 of whom died, without evident correlation to hemodynamic derangement.
Phosphide caused liver impairment in 25 patients (frequency of 3.68%). Among the deaths, two out of 3 patients were in shock while only one had normal blood pressure ($X^2 = 897.3$ – $P < 0.001$). Tramadol was responsible for elevation of liver enzymes in 6 out of 460 patients two of whom died.
Organophosphates were incriminated in 22 out of 1608 intoxicated patients. Liver impairment in the form of elevated transaminases and alkaline phosphatase persisted during the course of the intoxication for a period ranging between 3 to 6 days and regressed gradually thereafter without any sign of liver dysfunction. Deaths frequency significantly increased in relation to hypotension ($X^2 = 66.6$ – $P<0.001$) and shock ($X^2 = 41.08$ – $P<0.001$), rather than to the degree of liver transaminase rise.
Acetaminophen poisoning caused liver impairment in 7 out of 376 patients. In two out of 7 patients an undue delay in receiving N-acetyl cysteine was recorded and in one patient, history of regular alcohol intake was responsible for liver impairment. In all cases with hepatotoxicity, transaminases, alkaline phosphatase and mild bilirubin rise were evident.
The frequency of liver injury secondary to paraphenylenediamine (PPD) is significantly higher than all other drugs. Lead and methanol follow in frequency.
Hepatotoxic reactions secondary to acetaminophen (frequency of 1.86%), alcohol (frequency of 1.16%) carbamazepine (frequency of 1.92%) and valproate (frequency of 4.65%) are significantly less frequent than PPD or methanol. Theophylline was the least frequent among the hepatotoxic drugs (Table 1)

Table 1

Responsible hepatotoxic drugs and poisons and the frequency of hepatotoxic occurrence

	Nº of cases with	Total Nº of cases	Frequency		Nº of cases with	Total Nº of cases	Frequency
Acetaminophen	7	376	1.86%	Methanol	5	22	22.7%
Alcohol	3	258	1.16%	Neuroleptic	4	368	1.08%
Benzodiazepine	2	435	0.46%	NMS	1	3	33.3%
Botulism	1	4	25%	Opiate	2	41	4.87%
B-Blockers	1	272	0.36%	Organophosphorus	22	1608	1.36%
Carbamate	1	218	0.46%	Phosphide	25	679	3.68%
Calcium Channel Blocker	2	58	3.44%	PPD	7	10	70%
Carbamazepine	5	359	1.92%	Snake	3	113	2.65%
CO	7	223	3.13%	Theophylline	1	656	0.15%
Cyanamide	1	5	20%	Tramadol	6	460	1.3%
Digoxin	2	89	2.24%	Unknown Poison*	4	1153	0.34%
Food Poisoning	2	2066	0.1%	Valproate	2	43	4.65%
Kerosene	2	597	0.33%	Unknown sting**	1	49	2.04%
Lead	5	31	16.1%	Total	124	16774	0.7%

*Unknown poisons are poisons not identified by our usual toxicology screen and history-ignored by patients and / or relatives
**Unknown stings are likely scorpion, spider, or wasp sting
Total number received in the whole year is 16774 including hepatotoxic poisons (represented in the table above) and poisons non affecting the liver (not included in the table)

Table 2

Renal, hemodynamic complications and mortality of patients with hepatotoxicity

	Nº of patients with hepatotoxicity	Nº of patients with live & renal functions	Nº of Deaths in patien with hepatotoxicity
Hypertension	**4**	**1**	**1**
Unknown poison	1	1	1
Organophosphorus	1		
Tramadol	2		
Hypotension	**26**	**3**	**8**
B-Blockers	1		
Carbamazepine	2		
CO	2		1
Digoxin	1		
Cyanamide	1		1
Kerosene	2	1	
Methanol	3	1	1
Neuroleptic	1		
Organophosphorus	5	1	2
Paracetamol	2		
PPD(paraphenylenediamine)	2		
Theophylline	1		1
Tramadol	2		1
Unknown sting	1		1
Normal	**74**	**12**	**3**
Alcohol	3		
Benzo	1		
Botulism	1		
Carbamazepine	3		
CO	3	1	1

	Nº of patients with hepatotoxicity	Nº of patients with liver & renal	Nº of Deaths in patients with hepatotoxicity
Digoxin	1		
Food Poisoning	2		
Lead	5	1	
Neuroleptic	2	1	
NMS	1	1	
Opiate	2	1	
Organophosphorus	9	1	
Paracetamol	5		
Phosphide	22	1	1
PPD	4	2	
Snake, viper	3	1	
Tramadol	2	1	1
Unknown Poison	3	1	
Valproate	2		
Shock	**20**	**13**	**15**
Benzodiazepine	1	1	1
Carbamates	1		1
CO	2	1	1
Methanol	2	2	2
Neuroleptic	1	1	1
Organophosphorus	7	5	5
Phosphide	3	1	2
Calcium Channel Blocker	2	1	1
PPD	1	1	1
TOTAL	**124**	**29**	**27**

Shock and hypotension accounted for 23 out of 27 mortality patients (85%) with hepatotoxicity while it accounted for ten out of 23 mortality cases (43%) with normal liver function (Table 3). Concomitant renal insufficiency was significantly more frequent in cases of shock (Table 1). Shock was significantly more frequent in patients who had liver impairment than in patients with normal liver function (Table 4).Mortality patients in the liver impairment group, manifested significantly higher frequency of metabolic and

respiratory acidosis than in survivors (Table 5), Death frequency was significantly higher with liver impairment where it accounted for 27 out of 124 patients (21.7%) while it was 1.9% of patients (23 out of 1209) with normal liver function. Death frequency was significantly higher in patients having liver dysfunction compared to patients with normal liver function (Tables 6). In general no correlation existed between hepatotoxicity and death (r = 0.195), however in shock states death was significantly correlated to renal insufficiency (r = 0.951) and to liver impairment (r = 0.966).

Table 3

Influence of hemodynamic changes on frequency of concomitant renal insufficiency in patients with toxic hepatitis

	Hepatotoxicity	Concomitant renal Insufficiency	
Normal hemodynamic status	74 (59.7%)	12 (41.4%)	Chi-Square = 37.355 P <0.001 Highly significant
Hypertension	4 (3.2%)	1 (3.4%)	
Hypotension	26 (20.9%)	3 (10.3%)	
Shock	20 (16.2%)	13 (44.9%)	
Total	124 (100%)	29 (100%)	

Table 4

Possible causation of shock and changes of hemodynamic status to LFTs impairment in Deaths

	Normal LFTs	Impaired LFTs	Chi squared = 137.129 P < 0.0001 Extremely statistically significant.
Shock	6 (26.1%)	15 (55.5%)	
Hypotension	4 (17.4%)	8 (29.6%)	
Hypertension	3 (13%)	1 (3.7%)	
Normal BP	10 (43.5%)	3 (11.2%)	
Total	23 (100%)	27 (100%)	

Mortality in the whole series was 73 out of 16774 cases or 4.3 cases per 1000 (0.43%) while mortality among patients suffering liver injury in the form of impaired functions or elevated transaminases = 27 out of 124 patients (21.7%).

Table 5

Mortality in relation to ABG changes in patients with impaired liver function and or evidence of liver injury

MORTALITY ABG finding	Death	Survival	Total
Not performed	3	21	24
ABG Tested	24	76	100
ABG Changes			
Normal	2 (8, 34%)	26 (34, 22%)	28
Hypoxemia	5 (20.81%)	15 (19.73%)	20
Metabolic Acidosis	11 (45.84%)	19 (25%)	30
Respiratory Acidosis	4 (16.67%)	5 (6.57%)	9
Respiratory Alkalosis	2 (8.34%)	11 (14.48%)	13
Grand Total	27	97	124

Chi squared equals 55.134 with 4 degrees of freedom.
The two-tailed P < 0.0001 (extremely statistically significant)

Table 6

Chi-Square test of the frequency of mortality cases with hepatotoxicity in relation to the mortality frequency of total number of intoxication

	Total number of cases (%)	N° of cases with hepatotoxicity (%)	Chi square = 26.727 with 1 degrees of freedom P value < 0.0001 Extremely statistically significant.
Survival	16701 (99.565%)	97 (78.23%)	
Death	73 (0.435%)	27 (21.77%)	

Discussion

Hepatotoxic reactions ranging from mild to severe with hepatic encephalopathy occurred with a frequency of 7.4 cases per thousand patients. A similar frequency was recorded in several centers [5,6]

Although some incidence describe toxic hepatitis due to chronic drugs intake, responsible for a total of 2.3% [5] and as much as 10% of all hepatitis [6] yet the incidence of acute liver injury caused by drug overdose as represented in our review is as low as 0.7% of all acute poisoning patients, highlighting the more common hepatotoxic reaction to chronic drug intake. Serious liver injury can be precipitated with higher frequency following acute poisoning by phosphides, paraphenylenediamine (PPD), organophosphates, methanol or carbon monoxide (CO) poisoning

Phosphorus and Phosphides intoxication

Yellow phosphorus was at a time commercialized under the name of Al Mohlek (Phosphorus mixed with a fatty substance in a paste and dispensed in collapsible squeezable tubes) was withdrawn as it was responsible for suicidal attempts in adolescents. The picture of fulminant hepatitis with hepatic encephalopathy was almost always fatal in all patients.

Metal phosphides account for large percentage of poisoning in Poison Control Center reaching 4.5% of the total number of patients in certain years. Zinc phosphide and less commonly but more seriously aluminum phosphides, manifest a non-uniform clinical intoxication. They accounted for 679 out of 16774 (4%) patients received in the year of the review. Serious intoxication was described in 25 out of the 679 patients (3.68%) ending fatally in 3 of them. Shock represented a bad prognostic factor especially when preceded by severe metabolic acidosis. Zinc phosphide is much less toxic than the aluminium salt or the old-used phosphorus paste both of which readily release phosphine gas. Toxic hepatitis is more frequent with yellow phosphorus that possesses higher lethality in the first day with refractory shock, severe metabolic acidosis and non-cardiogenic pulmonary edema or later with rapidly progressing fulminant hepatitis and hepatic encephalopathy within three to five

days.

Refractory myocardial depression from aluminum phosphide toxicity [7] is not uncommon and was considered a poison of very high mortality (two out of the three deaths). Upon exposure to moisture, it liberates phosphine gas, which is absorbed rapidly by inhalation or through the cutaneous routes [8]

On the opposite zinc phosphide requires humidity and acidic medium to release phosphine radicle. The picture is less dramatic than yellow phosphorus or aluminum phosphide intoxication with an onset that may be delayed to several hours. Some patients were asymptomatic, despite gradually developing metabolic acidosis. The picture is, however, highly variable with an acute rapidly progressive shock, atrial and less commonly ventricular tachyarrhythmia, acute pulmonary edema and cardiopulmonary arrest within few hours in some patients, while others manifest a more delayed onset with mild to moderate metabolic acidosis culminating in acute hepatitis with abdominal pain, vomiting, heart burn and rise of liver transaminase. Jaundice appears at an early stage. Bilirubin is greatly elevated, whereas prothrombin concentration value falls with the start of acute liver cell failure. Signs of increasing liver insufficiency and uremia are manifestations of unfavorable prognosis. While all patients with shock demonstrate severe metabolic acidosis, many asymptomatic or mildly symptomatic cases exhibit severe metabolic acidosis without hemodynamic compromise presenting simply with fatigue and hyperventilation. Patients surviving the early phases of shock and acidosis may still risk later severe hepatotoxicity, often ending in encephalopathy within 3 to 7 days and eventually death.

Acute non cardiogenic pulmonary edema (NCPE) is usually associated by myocardial depression and shock. In our opinion the fumes generated from the phosphides, are greatly responsible for NCPE. Other causes include the strong arrhythmogenic potential of phosphide radicals and the intrinsic myocardial depression. This dramatic picture with rapid onset multi-organ failure has been repeatedly described [9]

The criteria carrying the worst prognosis include the occurrence of metabolic acidosis [10], shock, myocardial damage [8], and acute pulmonary edema in the first few hours, and severe prolongation of prothrombin time and other signs of hepatic encephalopathy on the second day and thereafter. In our opinion the metabolic acidosis severity is the most confident early index pointing to prognosis.

Treatment has always been supportive. Gastric lavage revealed fumes of phosphine gas. It is a common practice to perform gastric lavage with sodium bicarbonate in cases of zinc phosphide ingestion to avoid the conversion of zinc phosphide to phosphine gas by the effect of stomach hydrochloric acid. However, bicarbonate value has not been confirmed. Cathartic was used to reduce phosphorus absorption but its usefulness has not been demonstrated. The absence of a specific antidote results in very high mortality and the key to treatment lies in rapid decontamination and institution of resuscitative measures [11].

Iron poisoning: Mild hepatic dysfunction resulted from the ingestion of iron in 52 cases either because the iron level was lower than 350 µg /dl or because a rapid treatment with desferrioxamine was instituted with higher iron blood levels. Actually with the rapid management with desferrioxamine throughout this year, no iron poisoning cases demonstrated signs of toxic hepatitis as followed for five days for liver transaminases, alkaline phosphatase and bilirubin. In our experience no fatality has been documented following iron poisoning over 28 years of practice.

Although both iron and phosphorus intoxication provoke hepatocellular zone 1 necrosis [4], they greatly differ in the severity of the clinical picture and prognosis.

Acetaminophen (Paracetamol) Poisoning was documented in 376 out of 16774 patients. Most of patients had nausea and vomiting. 7% of patients were slightly disoriented and confused. Around 45% of patients were admitted in ICU for significant symptoms (vomiting and dehydration) and 2% had rising transaminases. None developed clinical signs of hepatotoxicity with an acetaminophen level below the lower line of Rumack nomogram. None developed renal insufficiency and no mortality was recorded. All patients received IV N-acetyl cysteine (NAC) guided by the 48 hours IV protocol. In three patients presenting with a significant delay (the longest delay being 24 h) the transaminases jumped to several thousand reaching 4900 IU/L. All other cases responded to NAC given within the first 8 hours. In few cases the transaminases rose to overestimated values compared to the modest rise of paracetamol blood level. This was explained by the chronic administration of other hepatotoxic drugs as chronic carbamazepine or valproate treatment or chronic alcoholism in all these few cases.

Other Hepatotoxins

Paraphenylenediamine (PPD). Hepatitis usually complicates paraphenylenediamine toxicity. In 7 out of 10 cases (70%), liver impairment was documented, representing the highest incidence of hepatotoxicity in our series. Other toxic features include methemoglobinemia, gastritis, hoarseness of voice,

cardiotoxicity, convulsions, coma and sudden death. The major early challenge to life is asphyxia and renal failure requiring hemodialysis at later stages [12, 13]. In our series liver transaminases elevation and hyperbilirubinemia usually did not significantly correlate with muscle enzyme elevation and appear two to three days after CPK enzyme rise. However, toxic hepatitis is likely to occur with significant rise of CPK and rhabdomyolysis.

Valproate

An asymptomatic modest rise in serum transaminases was evident in two of our patients subsiding in one week. Such described elevations subside on withdrawing the drug or reducing the dose, in about 11% of patients receiving valproate [4].

Ischemic hepatitis

This term is defined as marked and rapid elevation of serum transaminases in the setting of an acute fall in cardiac output. Hypoxic hepatitis or shock liver is alternative definitions [14]. It is believed to be the consequences of multi-organ injury an outcome depends on the severity of liver impairment and the etiology and severity of the pathogenesis of the intoxication [15]. Zone 3 necrosis, without inflammation, results. Clinical evidence of hepatic failure is absent. It may be associated with renal impairment and hyperglycemia. Serum bilirubin and alkaline phosphatase values increase slightly, but serum transaminases and lactic dehydrogenase values rise rapidly and strikingly. Values return speedily towards recovery in less than 1 week. Mortality is high (58.6%) and depends on the underlying cause and not the liver injury [4]. The pathophysiology of ischemic hepatitis is believed to be the result of a reduction in systemic blood flow as typically occurs in shock [13]. In our series 20 out of 124 patients developing signs of hepatitis were shocked. These patients developed acute circulatory failure, or severe hypoxemia secondary to respiratory failure. A strong correlation existed between cases of shock, increased frequency of renal insufficiency and mortality. Acute organophosphate poisoning and carbon monoxide were responsible for hypoxic hepatitis. In addition, pulmonary edema and acute respiratory distress, progressive hypoxemia, decreased pulmonary compliance and increased P(A-a)O2 and Qs/QT occurred after injury [16] and were actually documented in our patients suffering respiratory acidosis and hypoxemia.

Organophosphates insecticides are considered in our series to be the foremost cause after phosphide, producing toxic liver injury viewing the large number of patients affected by organophosphates poisoning. Among 1608 patients received with organophosphates poisoning, 22 developed signs of hepatotoxicity. However, toxic hepatitis is not the major health concern in these patients compared to the serious associated cholinergic crisis and close impact on the respiratory and hemodynamic functions from which all mortality were attributed. Toxic hepatitis manifested by increase of ALT, AST and alkaline phosphatase on the second or third day of poisoning rarely exceed 500 IU/L and usually regress to normal reference range within 7 to 10 days Acute circulatory failure and shock resulted from methanol poisoning known to produce intracellular hypoxia by the effect of formic acid. Although toxic hepatitis in 5 and concomitant renal insufficiency in 3 cases were evident, yet fatality was attributed to systemic derangement due to severe acidosis, ischemic encephalopathy, myocardial ischemia and shock.

Carbon Monoxide, the silent killer is responsible for 223 accidents all of which resulted in serious poisoning. Blood carboxyhemoglobin level ranged between 15 and 48 %, however, these values were underestimated viewing the rapid elimination of CO on patient exposure to fresh air during transportation to hospital. Seven out of 223 cases developed toxic hepatitis evident with mild to moderate transaminases enzymes elevation on the third to fourth day post exposure. In all these cases with hepatic involvement, patients had impaired neurological signs evident by CT brain as well as ECG ischemic signs. Concomitant renal insufficiency was evident in 3 cases unrelated to hemodynamic dysfunction. Ischemic hepatitis is considered in the pathogenesis of toxic hepatitis secondary to carbon monoxide viewing the multi-organ involvement. Carboxyhemoglobin blood level did not predict development of neurological involvement or ischemic hepatitis

Viper bite was responsible for significant hepatocellular reactions in 3 cases that were attributed to impaired liver blood perfusion due to associated coagulopathy.

CONCLUSIONS

It was evident that hepatotoxicity in acute overdose differs to a great extent from the hepatotoxic reaction related to prolonged treatment. While ethyl alcohol, acetaminophen, iron, carbamazepine and valproate did not produce significant hepatotoxicity; other poisons were extremely hazardous as phosphides, paraphenylenediamine, methanol, carbon monoxide and organophosphates especially in acute poisoning settings. Antidotes, given in proper time and proper doses avoided the hazardous toxic reactions of the liver to acetaminophen and iron. However, antidotes given in the context of poisoning by other drugs and toxins as

organophosphates and methanol did not protect the patients from hazardous liver reactions. The most important and sensitive index for the evolution of the hepatotoxic reaction in acute poisoning is the prothrombin time. Except for phosphides and yellow phosphorus, mortality from these cases was related to other systemic toxic reactions rather than to the effects on the liver. Hypoxemia, respiratory acidosis, metabolic acidosis, shock and renal insufficiency were bad prognostic factors in most deaths. Hepatotoxicity was part of multi systemic involvement in acute severe poisoning and had a non-significant role in the mortality except for phosphorus intoxicated patients who developed liver cell failure in the context of fulminant hepatitis.

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