

Review of updates on the prevalence and epidemiology of Acetaminophen poisoning in the United States and the United Kingdom

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Abstract

Paracetamol was licensed for assumedly safe worldwide usage in 1955 and is debatably the most common form of pain relief, headache palliative and hyperthermia medication used in both pediatric and adult populations in the Americas. Acetaminophen as it is commonly referred to in the United States is a component of very numerous treatment protocols for a wide range of ailments worldwide. Its patency permits has given rise to newer names in various countries using such names as paracetamol and panda. Although fatal and nonfatal liver based injuries, (some microscopic and others macroscopic) have been reported since 1966 due to overdose medications (usually self inflicted) due to self medications. Despite these problems, it's a reasonably safe drug when taken within its therapeutic dose range. Paracetamol poisoning is portrayed as a foremost causative factor in the emergence of acute liver damage in the Americas. It is note worthy that certain factors tend to favor the emergence of paracetamol induced liver damage like chronic use of alcohols, certain enzyme inducing drugs, and associated liver parenchymal diseases even under the circumstances of a normal therapeutic usage of the drug- paracetamol / acetaminophen. Certain questions beg for answers. Are there new findings from decades of pharmacovigilance? Is there a possibility of genetic mutations observed? Is paracetamol still steadfastly safe as portrayed in pregnancy as has been documented since 1966? These are some questions seeking updates.

Keywords: *Hepatic failure; drug poisoning; pharmacovigilance; epidemiology; prevalence; hyper medication*

Introduction

Acetaminophen is an analgesic and an antipyretic drug. It has ubiquitous applications and is readily available worldwide with no less greater potential for toxic effects as compared to other common pain relief medications like ibuprofen and aspirin ^{[1][3a]} but review of updates show it indeed has a much higher potential for events of hyper medication. According to Larson et al ^[2] it is said to be the commonest direct etiologic agent in cases of acute hepatic failure in the United States and the United Kingdom. In England and Wales an estimate of over 40,000 cases of acetaminophen poisoning occurred from 1989 to 1990, (mortality of over 0.39%) ^[3b]. It is estimated that average of 175 deaths and 16 to 19 liver transplants occur as a result of poisoning each year in England and Wales.(See fig.1.) Acetaminophen overdose results in more visits to emergency units in the US than overdose of any other pharmacological substance, over 50,000 emergency room visits, 2,100 hospitalizations, and over 452 deaths due to acute liver failure per year. ^{[4][5]}. A study of reported cases of acute liver failure in the USA noted that acetaminophen was the culprit in over 40% of all cases in adults, and over 23% of cases in under fives age groups. As at May 18, 2016, it is stated that acetaminophen poisoning has overtaken viral hepatitis as the leading cause of acute liver failure in the United States. (emedicine.medscape.com/article/820200-overview)

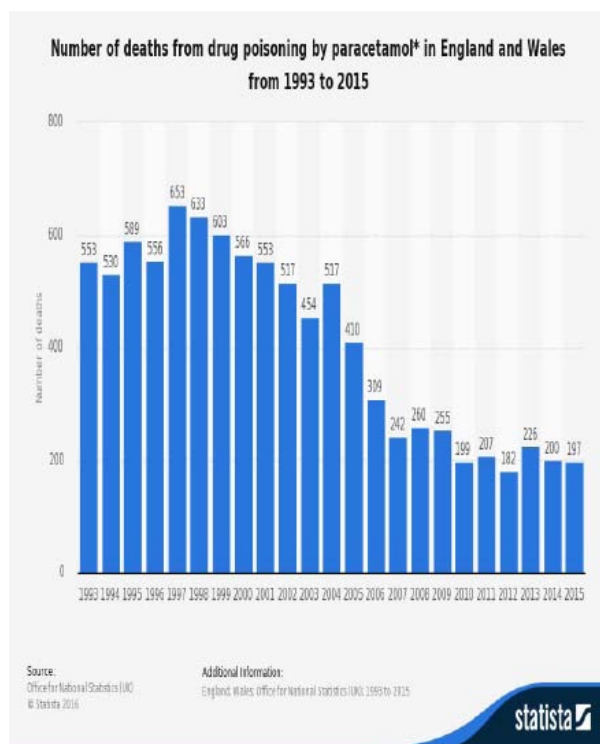


Fig.1

Hyper dosages and suicide

Paracetamol is one of the leading self prescribed drugs in cases of voluntary hyper medications.^{[5][6]} In the UK, paracetamol is the most common culprit in hyper dosage, responsible for more than 40% of oral intake of poisons admissions to the hospital and associated with an approximated over one hundred and fifty deaths per year.<http://bestpractice.bmj.com/best-practice/monograph/337/resources/references>). However, the incidence of poisoning in the US was above seventy thousand acetaminophen-related cases documented at the American Association of Poison Control Centers in 2006, with cases of young females out weighing all other gender or age based demarcations. There were approximately over 950 cases of severe paracetamol toxicity and over 97 cases of paracetamol-related deaths. (See fig.2&3). The drug was also implicated as a drug of choice in voluntary self harm schemes amongst teenagers in the most developed economies of the world.

In a majority of developing countries, like Nigeria, the incidence of paracetamol poisoning rarely approximates that of the United States or United Kingdom rather it seems toxicities due to Tramadol and other narcotic agents hold sway amongst the teenage group 14 – 18years. Paracetamol overdose can result from paracetamol-only preparations but also from special combinations of paracetamol with other drugs like the popular combifen and cafégot brands in Nigeria. These paracetamol-containing preparations can be either prescription medication or non-prescription preparations. Over 49 million people are said to use paracetamol or paracetamol-combination products each 7day period in the USA.

There is documentation of the presentation of stages of clinical debility over hours in any case of acetaminophen poisoning. Within the first twenty four hours of ingestion, the victim will experience excessive sweating (diaphoresis), nausea and vomiting. There may be an ironical improvement of symptoms over the following forty eight hours but with the development of right upper quadrant pain. As from the 72nd hour to the 96th hour post ingestion without medical intervention, liver functions begin to fail and gastrointestinal problems may ensure. However, from 4th day up to 2weeks post ingestion, patient's liver problems may resolve in over 70% of all victims. The Rumack-Matthew normogram is a device for assessing probability of hepatotoxicity in acute overdose. (See fig.3.)

Self prescription

Other important factors in the etiology of over dose of acetaminophen are homemade-prescribed regimen for all nature of pains, emergency department patients overuse of non-prescription pain killers, dental pain patients, the use of combination regimen duplicated in various products which may contain and provide increased quantities of acetaminophen unwittingly can lead to unintended overdose, and of course the vascular crisis of sickle cell anemia.

There are an increasing number of research reports of therapeutic paracetamol poisoning relating to the use of intravenous paracetamol in both the adult and pediatric age groups.^{[7][8][9]} Acetaminophen is available in both fast-release and long duration-release forms. The therapeutic dose is 10 to 15 milligram per kilogram per dose in children less than five years and 325 to 1000 milligram per dose in adults, given 4-6 times a day, with a maximum recommended daily dose of 80 milligram per kilogram in children or 4 gram in adults.

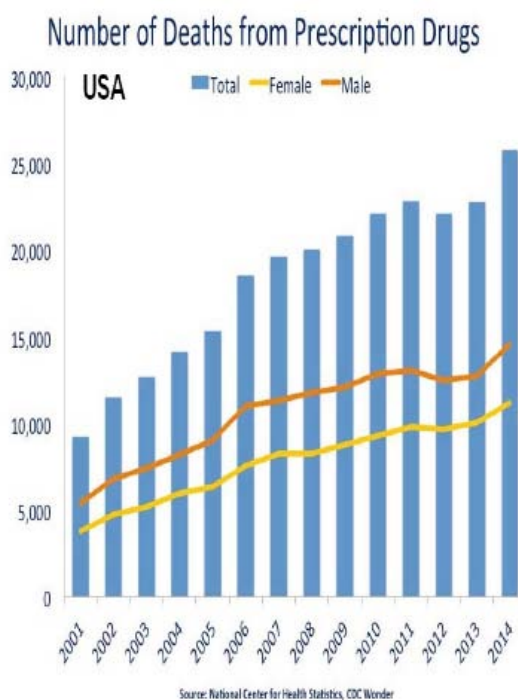


Fig.2.

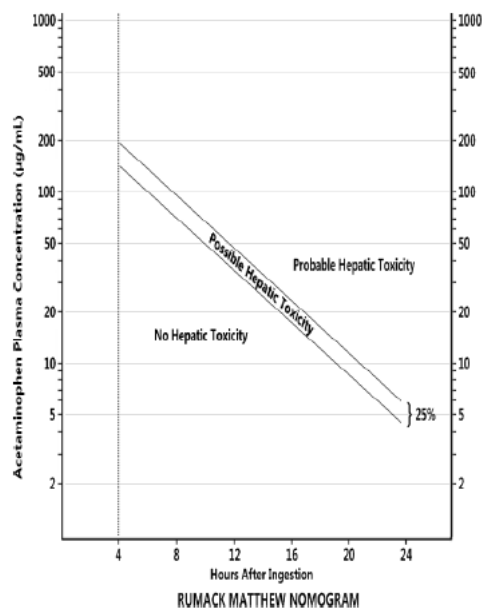


Fig.3*

*(Adapted from Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; 55(6):871–876.)

Pharmacogenetics

Baseline glutathione levels are an important consideration in determining pharmacogenetics which definitely varies per person. It is important to note that toxicity is less likely to result from a single dose of less than 150 mg/kg in a child or 7.5 to 10 g for an adult. However it is more likely to occur with single ingestions greater than 250 mg/kg or those greater than 12 g over a 24-hour period. Noteworthy is the fact that 97% of all patients who ingest doses in excess of 350 milligram per kilogram develop severe liver toxicity unless appropriately treated. Acetaminophen exhibits 100% complete absorption from the intestines. Peak serum concentrations occur between 30th minute and the 120th minute post oral ingestion of therapeutic regime.

Factors causing delays in attainment of peak serum concentrations include co-ingestion of anti-cholinergic, co-use of morphine, codeines, tramadol and also the use of long duration release forms of the drug. Elimination half-lives range from 60minutes to 240 minutes for all paracetamol preparations, but elimination phase may be delayed in onset for extended-release preparations due to nature of its formulations. Longer half-lives greater than 240 minutes have been observed in patients with liver failure. The casualty rate from acetaminophen overdose worsens 48 hours after ingestion, reaches a peak on day 4, and then eases off. The zenith indicator of worsening prognosis is the presence of acidemia. A mortality rate of over 92 % without liver transplant was reported in patients whose *pHs* was less than 7.30. Other indicators of poor prognosis are renal failure, liver encephalopathy, prothrombin time elevation, blood lactic acid elevation and low *factor V* level.^{[10][11][12][13][14][15][16].}

Suarez-Kurtz et al^[17] published an article in 2014 proving that ethnicity played a major role in determining adverse effects to acetaminophen. Ward et al., 2001^[18] carried out a research linking degree of adverse reactions or toxicities to certain nutritional deficiencies.

Pharmacovigilance

By August 2013, the United States FDA had issued a warning on the reporting of a skin dyscrasia directly linked to the drug acetaminophen as discovered by ongoing pharmacovigilance protocols. This was a side effect originally confined to allergies to non steroidal anti-inflammatory agents. FDA issues a safety alert to the public on 1st august 2013. By 14th January, 2014, FDA directed all doctors and pharmacists to desist from prescribing acetaminophen or any combined therapy of more than three hundred and twenty five milligrams of the drug. Major

manufacturers of acetaminophen products with dosages more than 325mg acetaminophen have stopped marketing same in the United States by 28th of March, 2014. Latest reviews as at 1st September 2015 has questioned the safety on continued use of acetaminophen as a routine pain medication during pregnancy. Source (www.fda.gov).

Legislative interventions.

Keith Hawton et al^[19] published (2013) in the British medical journal assessing the long term effect of a legislation by the UK parliament seeking a reduction in size of paracetamol packs as an intervention to curb the rising incidence of paracetamol poisoning. The law was passed in September 1998. The research stated that there was 43% reduction in deaths associated with acetaminophen poisoning in over 11years post introduction of the legislation in the United Kingdom. (See fig.3).

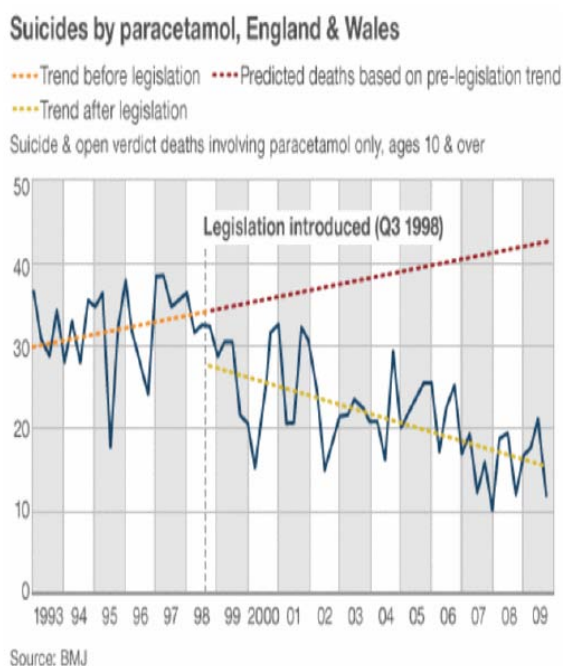


Fig.4

Methods

The research method was a Meta-analysis type, collating and analyzing data from online scientific data bases, abstract guides and references, content analysis, published articles, medical textbooks and research materials from Universities.

Results and conclusions

The issue of acetaminophen poisoning is an ever present challenge in our world. As long as acetaminophen remains an over the counter medication around the world, the prevalence rates of its toxicity will remain alarmingly high. The pharmacovigilance protocols in the United States had received updates in emergence of new adverse effects of the drug and had issued an alert to its healthcare professionals. The United Kingdom issued a legislation which seemed to have a tremendous positive effect on the prevalence of the drug poisoning over a period of 11 years. The continual surveillance of Acetaminophen in the United States and the United Kingdom is commendable and should be emulated by the under developed countries as a standard practice. The research regarding safety of paracetamol in pregnancy is still ongoing although FDA of the United States had issued a query on September, 2015 regarding the matter.

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