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Hepatotoxic Effect of Acetaminophen (Paracetamol): Mini Review

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ABSTRACT

Hepatotoxicity produced by chemicals and drugs may be similar to any kind of physically happening hepatic disease. When the drug is consumed constantly, yet after the progress of symptoms the cruelty of liver injury is increased to a high degree. Paracetamol is a known antipyretic and an analgesic which produces hepatic necrosis in high doses. Higher doses of paracetamol and N-acetyl-p-benzoquineimine can alkylate and increases the levels of Bilirubin, SGOT, SGPT and ALP. It is secure in therapeutic doses but can produce harmful effects on liver that leads to its damage in male, rodents at high doses. Liver injury caused by drugs is one of the most widespread factors. The management of liver disorders by a particular and uncomplicated drug is still a fascinating problem. Therefore, it is necessary to discover the alternative drugs for managing the inflammatory processes to substitute the currently used chemical drugs of doubtful effectiveness and security.

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Hepatic drug metabolism

Chemical substances and drugs which come into body via any route (oral, parental and inhalational etc) are chiefly metabolized by the liver. CYP-450 and Cytochrome reductase enzymes of hepatocytes are mostly concerned with metabolism of drug. Drugs and chemicals becomes water soluble by the action of these enzymes. As a result, they can simply excrete. The excretion of drugs may involve many steps. The most essential is conjugation process. Cellular substances are conjugate with drugs eliminated through the cells by energy and they also excreted both in urine or bile. If the liver did not metabolize the drugs and chemicals which results in their gathering and as ultimately boost hepatotoxicity in persons [1], [2].

Drug induced liver injury

There are of two types of drugs which have effects on the liver. Direct, indirect, high and low incidence correspondingly. Drugs such as paracetamol can produce direct injury and typically require few days to cause direct injury. The lethal effects of indirect toxicity are symptomless usually occurs from 8 weeks to 1 year. These possessions target the biochemistry of liver cells. It causes hepatitis and ultimately cell death. These act upon the mitochondria, nucleus, and endoplasmic reticulum (ER), cytoskeleton and microtubules. They indirectly affect cell organelles by activating and inhibiting kinases, process of transcription and synthesis of protein. Which result in high intracellular pressure which leads to cell death by apoptosis or cell necrosis [3-5].

Liver injury/hepatotoxicity

Hepatotoxicity produced by chemicals and drugs may be similar to any kind of physically happening hepatic disease. When the drug is consumed constantly, yet after the progress of symptoms the cruelty of liver injury is increased to a high degree. Inorganic compounds like arsenic, phosphorus, iron and copper generate liver injury. Whereas the organic agents like Pyrrolizidine alkaloids, mycotoxins and bacterial toxins are physically present phytotoxins. Synthetic organic compounds which are used as therapeutic agents are also incorporated as liver toxic agents. Additionally, exposure to environmental, occupational or domestic contact of any hepatotoxic compound may cause hepatotoxicity [3].

There are two major types of drug reactions which influence the liver.

Direct/Predictable

When a medicine and its constituents are directly lethal to the liver or it slows down the immunity of the host. Hepatotoxicity produced by them is dose reliant and the undesirable effects happen in many persons.

Indirect/Unpredictable/Idiosyncratic

When a drug or its constituents act indirectly and produce allergic reaction in the host. In this group the individuals do not have hepatotoxic consequences in a habitual way and these effects are not dose dependent. For example: Acetaminophen. Hepatotoxins generate changes in the liver, which differ from gentle to harsh necrosis and death. Gentle changes can be checked by biochemical evaluation of serum in which transaminase are mainly elevated. Two main types of pathological changes are produced by hepatotoxic agents.

Acute liver disease

It is categorized as fatty changes in liver, necrosis of liver cells, Cholestasis, vascular disease or granulomatous response

Chronic liver disease

It is categorized by liver cell fibrosis, cirrhotic changes and the neoplasm [6].

Classification of different drug reactions has been shown in following table.

Paracetamol and Hepatotoxicity

Paracetamol was introduced for the first time in 19th century in Germany [7]. Paracetamol is a commonly used as an antipyretic drug, which is secure in therapeutic doses but can produce harmful effects on liver that leads to its damage in male, rodents at high doses. Though, high dose of paracetamol is known to be liver toxic and nephrotoxic in experimental animals and men[8].

At minor concentrations, 80% of orally taken paracetamol is excreted mostly as sulphate and glucuronide complexes prior to its oxidation and only 5% is oxidized by hepatic cytochrome P450 (CYP2E1) to an extremely reactive and noxious electrophile which is N-acetyl-p-benzoquinoneimine (NAPQI). The paracetamol is used as a tool to induce liver injury in

experimental animals [9]. This toxic compound causes peroxidative removal in adipose tissue which results in fatty infiltration of the liver cells. Serum bilirubin imitates the depth of jaundice and elevated transaminase and alkaline phosphatase are the clear signals of cellular outflow and loss of efficient integrity of cell membrane [10].

Upon paracetamol overdose the glucuronidation and sulfation routes become inundated and as a result, paracetamol is ever more metabolized into NAPQI. Semiquinone radical, single-electron diminution metabolite of NAPQI intervene is the reason for the cytotoxic property of NAPQI. Then these semiquinone radicals merge directly with cellular macromolecules to produce toxicity or on the other hand, the radical can be re-oxidized to their novel quinones by giving one electron to molecular oxygen in aerobic conditions. This donation of one electron then produces reduced oxygen radical species and hydroxyl radical. These semiquinone and oxygen radicals are accountable for cytotoxic possessions observed with quinones. Yet elevated doses of paracetamol NAPQI could alkylate and oxidize the intracellular GSH and protein thiol, which causes the reduction of liver GSH pool. This intermediate reacts with former nucleophilic centres of essential molecules in hepatocytes which lead to hepatic injury [11].

Paracetamol liver injury is mainly caused by N-acetyl-p-benzoquinoneimine (NAPQI), which produces oxidative stress and depletion in glutathione. Main cause of paracetamol toxicity is the development of poisonous metabolites when its fraction is metabolized in cytochrome P-450. Introduction of cytochrome or reduction of liver glutathione is a precondition of paracetamol induced liver injury [12]. Paracetamol has been used as an appliance to provoke hepatic injury in trial animals [9]. Moreover, paracetamol directly reduces cellular proliferation, bring oxidative anxiety which results in lipid peroxidation, and deplete ATP levels and modify Ca++ homeostasis. These all changes are supposed potentially lethal to cell. In hepatotoxicity, the transportation role of liver cells becomes disturbed, which causes plasma membrane outflow, in this manner it causes the leakage of enzymes which leads to their elevated serum level. The liver damage caused by overdose of paracetamol was authenticated by high levels of biochemical parameters such as ALP, SGPT, SGOT, serum bilirubin (both total and direct), total cholesterol and serum triglycerides. Hepatocytes hold a range of metabolic actions and have a host of enzymes. SGPT, SGOT are found in high concentration in the cytoplasm and SGPT mainly in mitochondria. The eminent manners of SGPT, SGOT in paracetamol induce hepatotoxicity in serum is suggestive of cellular outflow

and loss of efficient reliability of cell membrane in liver. SGPT is the most excellent parameter as compared to SGOT to validate the liver harm, while SGOT also found in kidney and heart muscles. Due to nephrotoxic activity of paracetamol, it damages the cells of kidney and liberates SGOT to serum. In paracetamol hepatotoxicity, the intensity of SGOT is greater than SGPT [13].

Paracetamol is excreted chiefly as sulphate and glucuronide. Just 5% of paracetamol is changed into N-acetyl-p- benzoquinoneimine. Upon administration of lethal doses of paracetamol, the sulfation and glucuronidation routes become saturated and therefore, elevated levels of paracetamol molecules are tarnished to extremely reactive N-acetyl-p-benzoquinoneimine (NAPQI) through cytochrome-450 enzymes. A semiquinone radical which is achieved by loss of one electron of NAPQI can binds to large molecules of cellular covering and increases the lipid peroxidation which results in the tissue harm. Elevated dosage of paracetamol as well as NAPQI could alkylate and oxidize protein thiol and intracellular glutathione which causes the depletion of liver GSH pool afterward leads to amplified lipid peroxidation and hepatic damage [14].

This poisonous chemical caused peroxidative deprivation in adipose tissue which results in fatty permeation of liver cells. Serum bilirubin indicates the intensity of jaundice and the boost levels of transaminases and alkaline phosphatase are the clear sign of cellular outflow and loss of functional ability of cell membrane. PCM causes hepatic injury by the action of its poisonous metabolite, N-acetyl-p-benzoquinone-imine, which is produced by the action of cytochrome P-450. This NAPQI reacts with reduced glutathione (GSH) to give non-toxic 3-GS-yl-paracetamol. Reduction of GSH causes the lasting quinone to attach to cellular macromolecules which causes the cell death. Frequent studies disclose that ‘PCM’ toxicity activates the macrophages. Kupffer cells are located in the liver and they have phagocytic property. On establishment, Kupffer cells liberate a number of signalling molecules, together with hydrolytic enzymes, eicosanoids (local hormones like leukotrienes, prostaglandins, thromboxanes and prostacyclins) superoxide and nitric oxide. Kupffer cells may perhaps also discharge many inflammatory cytokines [15-16].

When paracetamol is given at toxic doses it can obstruct the glutathione synthesis. This leads to lack of glutathione. When this deficit is up to 30% of normal then hazardous effects may happen in the liver. When glutathione altitude is decreased and is not present in an adequate

amount to bind with NAPQI, additional free metabolite of paracetamol binds to protein in cell which is profound macromolecules and it results in liver injury [17], [18].

CONCLUSION

The liver is the prime internal glandular organ of the body. It performs countless functions of the body as compared to other organs. Whole blood supply of human passes through its various times in a day. It has an important responsibility in the human metabolism. Liver diseases are one of the core causes of death in man and animals in the world. Liver injury caused by drugs is one of the most widespread factors. The management of liver disorders by a particular and uncomplicated drug is still a fascinating problem. Therefore it is necessary to discover the alternative drugs for managing the inflammatory processes to substitute the currently used chemical drugs of doubtful effectiveness and security.

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