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Review on Tolerability of Paracetamol

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ABSTRACT:-

Excellent tolerance to the therapeutic doses of paracetamol (acetaminophen) is a major factor in the widespread use of the drug. A major problem with paracetamol use is its hepatotoxicity after overdose. Hepatotoxicity has also been reported after treatment doses, but critical analysis shows that many patients with suspected toxic side effects have been overdosed. Importantly, future research suggests that doses of paracetamol dosage are an unlikely cause of hepatotoxicity in patients who drink moderate to moderate severity. Controlled clinical trials have found that paracetamol(acetaminophen) is very well tolerated by gastrointestinal tract. Although variable results have been obtained in case-control studies, most studies have not shown any change or a slight increase in the risk of related piercing, ulcer, or bleeding in the upper abdomen. However, the link between paracetamol use and gastrointestinal toxicity, as well as chronic kidney disease and respiratory disease, is more likely to indicate bias in other control control studies. In particular, such bias may be due to the high tolerance seen of paracetamol in these diseases. Simultaneous use of paracetamol in these diseases means that it leads to a significant relationship between paracetamol and the disease. Despite the paracetamol metabolism in active chemicals, the reaction to hypersensitivity is very small, although urticaria occurs in patients from time to time. Paracetamol appears to be well tolerated during pregnancy although future studies are needed.

INTRODUCTION:-

Paracetamol is a very well-tolerated drug in medical treatment (i.e. up to 4 g / day in adults) and this excellent tolerance is a key factor in its widespread use. The purpose of this review is to evaluate the adverse reactions to paracetamol therapeutic doses. In particular, we examined the conclusions of recent reviews about these reactions and commented on the clinical significance and actual occurrence of these adverse reactions.

Hepatotoxicity after paracetamol is also known and a major problem with the use of this drug. In contrast, hepatotoxicity after treatment doses appears to be very rare. Although many case histories have been interpreted as suggesting that paracetamol therapeutic doses may cause hepatoxicity, recent critical reviews suggest that hepatotoxicity from paracetamol therapeutic drugs is less common than commonly believed. Expected controlled studies often show the safety of paracetamol therapeutic doses in the liver and intestines, although less toxicity may occur in the respiratory tract. In contrast, adverse gastrointestinal reactions have been shown in epidemiological studies. The evaluation of these different outcomes and conclusions is an important aspect of the current review.

Analysis of the epidemiological studies of paracetamol shows that a few studies have biases that may make the conclusions drawn do not apply to the occurrence of adverse reactions. Some bias is confused by reference. In the case of paracetamol, this confusion may occur when paracetamol is preferred by individuals or consumers over NSAIDs due to the perceived safety of paracetamol in relation to a particular organ system (e.g. intestinal tract). This type of bias, although well-recognized, is difficult to eradicate when the full history of the patient is unknown to investigators, as is often the case.

Identificationof Studies:-

Appropriate studies and review papers reviewed extensively on the Medline website (1975-January 2005), using keywords' acetaminophen 'or' paracetamol ', as well as' side effects',' side effects', 'tolerance', ' gastro. intestines', 'stomach', 'liver', 'liver', 'glutathione', 'metabolism', 'renal', 'kidney', 'sodium', 'pregnancy', 'asthma', 'hypersensitivity', 'prosta gland' in ',' cancer 'or' dose '. References to the most recent review (2000 – January 2005) and research papers are also used to identify relevant papers.

Metabolism of Paracetamol (Acetaminophen) Relevant to its Toxicity :-

Much of the paracetamol metabolism is mediated by the formation of glucuronic acid and sulfate conjugates (Fig. 1). These two conjugates make up about 80% of paracetamol elimination. In addition, a small amount is issued unchanged. None of these processes are associated with toxicity, with the exception of occasional thrombocytopenia that may be due to paracetamol sulfate. In contrast, it is well known that the oxidative metabolism of paracetamol can lead to hepatotoxicity. The cytochrome P450 (CYP) system in the liver produces the production of the active N-acetyl- p-benzoquinone (NAPQI), as discussed in section 4, is the cause of the centrilobular hepatotoxicity factor paracetamol overdose. Active NAPQI combines with its glutathione paracetamol-glutathione conjugate. A large portion of this compound is converted to cysteine conjugate and then to N-acetyl conjugate, which is excreted in urine.

CYP2E1 is a CYP enzyme that releases paracetamol. This conclusion is mainly due to the fact that disulfiram, with its active metabolite diethyldithiocarbamate, is a selective inhibitor of CYP2E1 and reduces the excretion of NAPQI metabolites by about 70% Paracetamol is also added to NAPQI via myeloxidases several, 6] and the activity of COX-1 peroxidase. [7,8] Free radical forms are also produced by these peroxidases leading to the final production of paracetamol dimer and other paracetamol polymers.

The main function of myeloperoxidase is to promote the formation of hypochlorous acid, an important bactericidal product of neutrophils and monocytes. By acting as a substrate for myeloperoxidase, paracetamol reduces the production of hypochlorous acid. However, a decrease in the formation of hypochlorous acid after paracetamol therapeutic doses appears to be insufficient to produce significant antibacterial activity in these cells.

The conversion of paracetamol into active metabolites by myeloperoxidase raises the question of whether toxicity may be produced by this enzyme. The metabolism of several drugs, such as propylthiouracil and clozapine, oxidase in neutrophils and monocytes is associated with the development of agranulocytosis and sys with my eloper sometimes causing agranulocytosis sometimes lupus. There are also claims that patients paracetamol, although conclusive evidence is still lacking. In addition, given its extensive use and rare reports of possible interactions between granulocytosis and paracetamol intake, any cause of agranulocytosis with paracetamol should be very rare. The production of active metabolites using the activity of Cox -1is peroxides and note 0f .it was previously thought that COX-2 metabolites paracetamol is similar to C0X 1. although cox 1 is the enzymes known only as cyclooxygenase , both have dual function, namely the functions of cyclo-oxygenase and peroxidase. The metabolism of paracetamol by the peroxidase activities of these enzymes may be closely related to its mechanism of action. In addition, overproduction of active metabolites of paracetamol using COX enzymes may cause cellular toxicity in the kidney medulla.

It should be emphasized that the level of in vivoit should be emphasized that the activity level of vivothe peroxidase for COX isoenzymes is unknown. It is widely thought that CYP2E1 is a major source of NAPQI, but the contribution of peroxidase in vivo has not been determined. The dimer and other polymers are produced by selective peroxidase but, to our knowledge, their urine output has not been tested. At this stage, the clinical significance of the oxidative metabolism of paracetamol by peroxidase in active metabolites is unknown, but it should be borne in mind in any consideration of paracetamol toxicity.

Hepatotoxicity of paracetamol:-

Paracetamol overdose leading to liver damage and encephalopathy occurs more slowly in children than in adults, 25 but it can be dangerous.26,27 Since liver transplantation is an acceptable treatment for this condition it is important to identify those children who may need it early. This is a preliminary retrospective study to assess predictable risk factors in children with significant paracetamol hepatotoxicity and to consider whether the standard KCH condition of adult supplementation list following paracetamol overdose works in children.

This study reviewed a 10-year experience from a single major pediatric liver unit. Most of the patients were young women taking paracetamol overdose by mistake following an unexpected action, 11,18,28 and some younger children had experienced a recurring overdose. the dose 4 hours after drinking suggests who should receive antidote, 21 and the dose or dose does not predict the severity of hepatotoxicity. We did not find a correlation between the average imported dose (348 v 285 mg / kg) and severity of liver disease. This confirms previous studies that did not show significant differences in paracetamol intake among children with abnormally developed children (345 mg / kg) compared with normal liver function (236 mg / kg) 19 and those who were mild (390 mg / kg) or hepatotoxicity heavy (324 mg / kg) .28 The ingested dose may not be a useful parameter to assess severe hepatotoxicity, not only because the dose when presented may be difficult to quantify, but also because of the potential for multiple and / or concomitant doses. to clean. Although the average paracetamol level was high(61%) patients, were low or undiagnosed in 39% had a direct history of paracetamol overdose with significant hepatotoxicity. This may be due to late delivery in the hospital or too little food. A similar low dose was reported in a small series of young children with complete liver failure following prodromal illness.20 Rumack Matthews and program are useful in identifying paracetamol levels that require treatment in the first 24 hours but do not differentiate between children who become more serious later. or significant hepatotoxicity.

This study noted that delayed delivery (24 v 44 hours) in hospital after overdose was a risk factor for severe hepatocellular injury and the need for OLT, as well as increased mortality. This confirms the results of previous studies that showed that initiating treatment delays was an important risk factor in the development of encephalopathy. In addition, younger years may also predict severe hepatotoxicity. Although children under the age of 7 are more likely to be exposed to the dangerous paracetamol, patients under the age of 7 developed hepatotoxicity following repeated doses. Three are listed for liver transplantation; 2/6 died despite OLT and 1/6 died awaiting implantation. Although these children had similar hepatic toxicity in adolescents, they were not included in the risk analysis, due to age-related cytochrome P-450 activity differences.Hepatic transaminase levels were significantly increased in both groups following paracetamol overdose, but they did not differentiate between groups. Jaundice was not a clinically significant feature, although serum bilirubin was significantly higher in group II ($p = 0.01$). Miles et al18 and Alonso et al20 noted a distinct clinical pattern with slightly elevated bilirubin levels and extremely high transaminase levels. This is probably due to differences in speed and duration of hepatocyte injury and variability in hepatic net regeneration.

Labelling and Packaging :-

Several studies have discussed cases of hepatic toxicity associated with high doses of paracetamol, with many suggesting that the main cause is paracetamol overdose (Roumie& Griffin, 2004; Graudins&Gazarian, 2006; Wilson et al, 2010; King et al , 2011; Bond et al, 2012). In 2008, it was reported that paracetamol was the single most commonly used drug in excess of a dose that led to hospitalization in Australia (Daly et al, 2008). In some cases the overdose is intentional, resulting in suicide attempts, but in about 2/3 of the cases (King et al, 2011), the overdose and subsequent liver damage occur for a variety of reasons including: Observational safety due to OTC condition being treated not realizing the potential for liver damage A long-term supratherapeutic dose, which includes paracetamol administration with a combination of products (headache pills, osteoarthritis pills, cold and flu medications) is taken until the pain subsides. This is especially troubling when it is reported that 50% of patients get the best of the best relief at 650 mg, 65% at 975 mg and 75% at 1300 mg (recommended dose of 1-2 tablets 500 mg, with a maximum daily dose of 8 tablets (4000 mg)).

It was often acknowledged that there is a need to educate the public about the dangers of OTC analgesics, especially those containing paracetamol (Roumie& Griffin, 2004; Bond et al, 2012; Wilson et al., 2012). It was suggested by Roumie and Griffin (2004) that this may be achieved with appropriate advice from health professionals and appropriate labeling of small public literacy levels. Suggestions for alternative modes of knowledge to improve comprehension and awareness included extensive printing, clear identification of the active ingredient, simple instructions and exposure to risk images (Roumie& Griffin, 2004). It was also suggested that with the high prevalence of paracetamol use in stores, a consumer-focused approach to the development of icons and messages in order to improve awareness and safe use of paracetamol may benefit consumers. In addition, partnerships between healthcare researchers, industry and government should be formed to find better ways to improve product labeling and educate the public about the meaning of the symptoms and the importance of safe use of these drugs.

In a study examining the use of OTC analgesic and comprehension in older adults, Roumie and Griffin (2004) found that more than 60% of people were unable to identify an effective ingredient to relieve their pain. A similar study was conducted in adolescent research, which also highlighted a lack of understanding about OTC analgesics, and discussed the risk of failure to associate an active ingredient with a brand name and subsequent unintended potential for overuse (Wilson et al., 2010). In a study by King et al (2011) that attempted to formulate a consumer-focused paracetamol label, it was suggested that the cause of unintentional overdose may be the result of misunderstanding of drug labeling or failure to see the effects of overdose. maximum daily dose. Research has highlighted the poor recognition of paracetamol-containing products, the brand name recognition has an active ingredient and its effects when there is a large number of paracetamol-containing products available (King et al, 2011).

The Acute Liver Failure Study Study Group compiled data (1998-2005) of more than 500 paracetamol-related cases of severe liver failure that show that the number has increased significantly since 1998. Half of the charges were self-inflicted and the other half were not intentional. The data showed that most patients with unintentional alcohol abuse repeated the label limits of a 4-gram package and that this group generally (62%) used opiate-paracetamol combinations. In addition, 38% had taken more than one paracetamol-containing agent at a time. Improving education and labeling may help reduce the use of many preparations and perhaps make people more aware that paracetamol can cause serious liver damage (Lee 2007).

Gaps in the knowledge and understanding of caregivers of young children about paracetamol and its safety may result in misuse and unintentional harm (Graudins&Gazarian, 2006). Identified reasons for the abuse of paracetamol in children include lack of awareness: Appropriate indicators The chances of poisoning if a person is overdose or due to continuous control of supratherapeutic doses The availability of a wide range of strengths and ingredients and age appropriate for children These factors highlight the need for information directed at consumers to help understand and raise awareness of caregivers handling these medications (Graudins&Gazarian, 2006).

Although ibuprofen overdose can sometimes lead to serious toxicity with rare adverse events, the risk of life-threatening symptoms due to ibuprofen overdose is considered low (Hall et al, 1988; McElwee et al, 1990). However, ibuprofen can sometimes lead to more serious toxins such as metabolic acidosis, kidney failure and / or kidney failure requiring prolonged dialysis. It has been reported that there is also a lack of awareness of the active ingredient in ibuprofen products by consumers where ibuprofen is contraindicated, hence the potential for adverse events after the use of these products (Roumie& Griffin, 2004). When considering a warning design, compliance with consumer-focused labels, the study identified a number of factors to consider (Wogalter et al 2002; Laughery, 2006). These factors include: Intelligence - prominence or alertnessNouns - including the name of the signal to get attention, risk identification, description of results and meaning (location within product instructions) and how to improve the usability of designs by considering internal user characteristics (e.g. beliefs, risk perceptions, pressure). Testing methods were also developed that can be used to measure the effectiveness of warnings such as the extent to which warnings are passed on to recipients and the extent to which they encourage or influence compliance.

Gastrointestinal tolerability:-

Excellent tolerance to the therapeutic doses of paracetamol (acetaminophen) is a major factor in the widespread use of the drug. A major problem with paracetamol use is its hepatotoxicity after overdose. Hepatotoxicity has also been reported after treatment doses, but critical analysis shows that many patients with suspected toxic side effects have been overdosed. Importantly, future research suggests that doses of paracetamol dosage are an unlikely cause of hepatotoxicity in patients who drink moderate to moderate severity. Controlled clinical trials have found that paracetamol(acetaminophen) is very well tolerated by gastrointestinal tract. Although variable results have been obtained in case-control studies, most studies have not shown any change or a slight increase in the risk of related piercing, ulcer, or bleeding in the upper abdomen. However, the link between paracetamol use and gastrointestinal toxicity, as well as chronic kidney disease and respiratory disease, is more likely to indicate bias in other control control studies. In particular, such bias may be due to the high tolerance seen of paracetamol in these diseases. Simultaneous use of paracetamol in these diseases means that it leads to a significant relationship between paracetamol and the disease. Despite the paracetamol metabolism in active chemicals, the reaction to hypersensitivity is very small, although urticariaoccurs in patients from time to time. Paracetamol appears to be well tolerated during pregnancy although future studies are needed.

Renal tolerability:-

Paracetamol (also known as acetaminophen) causes serious and chronic renal failure. Although the mechanisms leading to liver damage have been extensively studied, the mechanisms of paracetamol-induced cellular protoxicity are not well defined. Paracetamol caused cell death with apoptosis factors in urine proximal tubular epithelial cells. While paracetamol increased the expression of Fas receptor Fas in the cell region, the Fas pathway was not involved in the apoptosis induced by paracetamol of the stem cells. The mitochondrial method did not work during apoptosis induced by paracetamol; there was no depletion of mitochondrial energy or the release of apopogenic traits such as cytochrome- C or Smac / DIABLO. However, paracetamol induced apoptosis is a caspase-dependent process that involves the activation of caspase 9 and caspase-3 in the absence of cytosolic cytochrome c or Smac / DIABLO. The authors also found stress induction of the endoplasmic reticulum (ER), characterized by GADD153 upregulation and translocation to the nucleus, as well as caspase- 12 cleavage. Interestingly, after treatment with murine tubular cells with paracetamol and calpain inhibitors, the production of caspase-12 cleavage was still evident, and calpain inhibitors were unable to protect the tubular cells from paropetosis induced by paracetamol. The results suggest that induction of apoptosis may be less than the nephrotoxic potential of paracetamol and identify ER pressure as a targeted therapeutic target in nephrotoxicity.

Paracetamol, also known as acetaminophen, is widely used as a pain reliever and antipyretic. Overdose of paracetamol can lead to potentially fatal liver and kidney failure in humans and animals being tested and in severe cases to death. Paracetamol is a phenacetin metabolite .Phenacetin was considered one of the protoxic painkillers and has now been withdrawn from the market in many countries. The chronic nephrotoxic effect of paracetamol therapeutic dose is suggested by a case-control study. These findings have led to the recommendation that paracetamol be used only in limited doses and for limited periods. Research on the biologic basis of paracetamol and protoxicity was recently promoted by the National Kidney Foundation Ad Hoc Committee.

Tissue cell loss is a characteristic feature of both acute renal failure and chronic disease and is manifested when cell death is more than mitosis. Apoptosis is an active form of cell death that provides an opportunity for medical intervention. Paracetamol has been shown to improve hepatocyte apoptosis. However, the mechanism of kidney cell death during paracetamol nephrotoxicity and the mechanisms involved are unclear. Indeed, there is evidence that the molecular basis of nephrotoxicity may differ from hepatotoxicity, as N-acetyl-cysteine protects from the latter, but has been shown to be immune to nephrotoxicity.Fas belong to the family of tumor necrosis factor receptor proteins and play an important role in the normal development and homeostasis of T cells. However, improper or excessive Fas-mediated apoptosis has contributed to many pathologic conditions. In the case of hepatotoxicity, the expression Fas rises in the liver of paracetamol-treated animals. The severity of liver damage is reduced by oligonucleotide-mediated suppression of Fas expression, indicating the role of Fas in paracetamol toxicity in the liver. Deadly intracellular proteins comprising caspases, a family of 14 proteases widely expressed in a variety of tissues and cell types, play an important role in promoting apoptosis.Studies in human liver cells have shown that the apoptosis induced by paracetamol depends on caspase and that mitochondria are a major component.

Caspase-12 is localized directly on the cytoplasmic side of the endoplasmic reticulum (ER) and connects ER stress to the cascade activation of the caspase. Because caspase-12 is expressed at higher kidney levels and especially in renal tubular epithelial cells, cells affected during paracetamol and protoxicity, we examined the role of caspase-12 and ER stress in renal tubular epithelial cell death after treatment. -paracetamol.Although the mechanisms leading to liver damage have been extensively studied (14,15,17UU), there is almost no data on paracetamol-induced cellular processes and protoxicity. We have now investigated the ability of paracetamol to induce apoptosis of enlarged epithelial epithelial cells and the involvement of Fas receptor Fas, ER stress, and caspases in this process.

Hemostasis:-

Early changes in coagulation were found in patients following paracetamol overdose. Low levels of clotting factor II, V and VII were present within 24 hours of overdose. Since factor II levels are associated with plasma fibrinogen values during this period, they may be consumed by intravascular coagulation process, although this has not been supported by the presence of elevated titers of fibrin degradation products. The duration of prothrombin duration was greater than 2-2 in 30 hours of heavy drinking in all patients who eventually died, while it was lower than that in those who developed only moderate liver damage. Administration of fresh frozen plasma to patients has been shown to significantly reduce the duration of prothrombin duration, which was significantly lower than three days after the overuse of the group receiving fresh frozen plasma. However, coagulation disorders were short-lived, and prothrombin duration had returned to normal within a week of overdose in control patients, and administration of fresh frozen plasma did not reduce morbidity or mortality in treatment. patients.

Hypersensetivity reaction of paracetamol:-

Paracetamol is a common antipyretic / analgesic and is part of many over-the-counter medications and preparations. Hypersensitivity reactions to paracetamol appear to increase, but there are few data to spread. The mechanism is not well understood. We identified clinical features of 32 patients suspected of being paracetamol-resistant, investigating the root cause of the existing drug and non-steroidal anti-inflammatory drug.

CONCLUSION :-

A major problem arising from the widespread use of paracetamol is the ability to overuse it to cause hepatotoxicity due to drug metabolism in active compounds. Many cases of hepatotoxicity have been reported to be associated with paracetamol therapeutic doses, but critical analysis suggests that many of these conditions are caused by drug overdose. The dose of paracetamol, especially in children and adolescents, should be carefully controlled

to prevent hepatotoxicity. Physicians, nurses, and pharmacists should stress to patients the need to take the right dose of paracetamol, although the discussion of the dangers of drug overdose in the media should be avoided due to the risk of increasing suicide rates due to drug overdose. Adequate labeling based on critical literature analysis is also important.

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