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Paracetamol: Its Efficacy, Advantages & Disadvantages

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ABSTRACT

Paracetamol comprises a unique role in adults as well as children because it is a first choice for the treatment of fever as well as pain. It must be used in the recommended dosage. Fever along with mind pain relieved by paracetamol. Paracetamol is quite effective to moderate pain in combination with another drug. It has few side effects also which might be tolerable but sometimes leads to serious adverse reactions that may even cause death. Paracetamol provides an addition significant effects to the opiates. This paper summarizes the efficacy, the mechanism of action, the methods of the production of Paracetamol, the medical uses, the advantages and disadvantages of Paracetamol. Acetaminophen which is commonly known as Paracetamol is a well growing non-prescription analgesic and antipyretic drug all over to world from infants to elders. The future developments of Paracetamol normally comprise newer formulation for achieving long term administrations. There is need for the development of more intravenous paracetamol availability and its marketing in the future. Future advances might be making it possible for preventing the damage to liver and kidneys in patients because of the inappropriate dosage. In future there are new findings must be there in this area for the best clinical use.

Keywords: Action, Analgesic, Dosage, Drug, Figure, Paracetamol, Pain, Production

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INTRODUCTION

Paracetamol is a very operative analgesic specifically when it is administered. It is very useful for a wide range to clinical condition. The action mechanism of paracetamol is well explained and comprises huge pain related pathways. The clinical significance of paracetamol might exert some effect on every organ system. Paracetamol is synthesized by Morse in the year 1878 and implemented for the medicinal use in the year 1883. It is now commonly using drug all over the world. Paracetamol is called as Acetaminophen, also which is a medication that treats fever and a kind of pain. It is suitable for almost all ages. Paracetamol has a vital part in the multimodal analgesic and it gives excellent security profiles except in case of over dosage with some of the drug's interactions. Rectal & oral administration gives analgesia in between 40 minutes having an effect of approximately 1 hour.

The mechanism of action of paracetamol is much surprising. After 100 of years and even more the action mechanisms of paracetamol remain determined. There are number of mechanisms of paracetamol that includes the effects on the production of prostaglandin, opioid, on serotonergic, NO (nitric oxide) and some cannabinoid pathway. There is action mechanism of Prostaglandin Inhibition given below in [Figure 1].

Inhibition of Prostaglandin

Paracetamol is both antipyretic and an analgesic. It is acting from the inhibition to COX (cyclooxygenases) which mediates the productions of prostaglandin, as of NSAIDs (called as Non-Steroid Anti Inflammation of Drugs). It

demonstrated for not reducing inflammation of tissues. There are various enzymes which are responsible for action metabolism of the arachidonic acids to both thromboxane and prostaglandins that mainly referred as cyclooxygenases that more suitably called as prostaglandins H2 synthetases' and comprises 2 active sites: POX (peroxidase site) & the COX site. The transmission of arachidonic acids towards prostanoids is two-staged process that needs activity on COX site for producing first unstable intermediates hydro peroxide that further converts to the prostaglandin hydrogen by POX site. The activity of enzymes on the COX site depends on the oxidized forms where this interferes indirectly by reducing co-substrates to POX site. The level of the arachidonic acids gets lower in case of intact cell; paracetamol becomes potent inhibitor to synthesis of prostaglandins by blockage of physiologic regeneration of the POX site. In the case of broken cell, the hydrogen peroxide concentration becomes high and the synthesis of prostaglandins becomes inhibited very weakly.

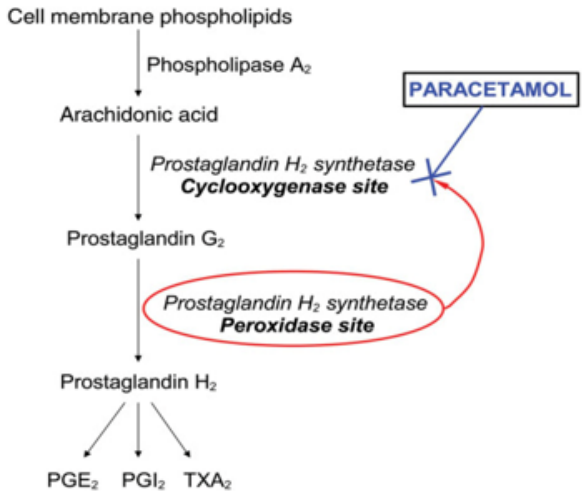

Figure 1: Illustrating the Mechanism of Action of Paracetamol by Inhibition of Prostaglandin [1].

Activation of pathway Serotoninergic

This is a portion of descending system of pain that originates into nuclei of brainstem, cortex & hypothalamus which interacts by pain afferent into dorsal horns. The receptor of Serotonin which is present all over the CNS (Central Nervous System) that involves various functions like- mood, consciousness, memory & vomiting & the nausea, which mediates by HT3 subtype of receptor. It is broadly accepted the serotonergic pathway's activation have an important role in the mechanism of the paracetamol that demonstrate anti-nociceptive effect of it that is inhibited from the administration of subtype of receptor's antagonists, by using antiemetic drug that taken together along with paracetamol in these perioperative periods.

Enhancement of Endocannabinoid

There is an enzyme which is found in the CNS in presence of the fatty acids amide hydrolases (FAAH), Paracetamol gets conjugated by arachidonic acids for forming some active metabolites which is (AM404) N-arachidonoylphenolamine (Figure 2). This AM404 inhibit the up taking of endocannabinoid anandamides by synaptic cleft that increases the cannabinoid's receptor activations over post synaptic membranes. This may explain experience of the tranquility, relaxation & euphoria that is reported by large number of users who are analgesia independent. The center production of the AM404 accounts for the effect of antipyretic of the Paracetamol, referred to prostaglandin production inhibition in brain without any peripheral action.

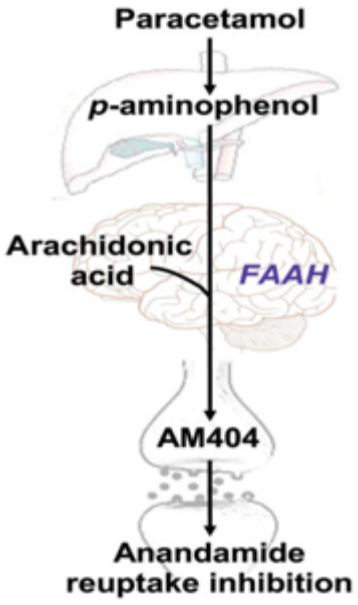

Figure 2: Illustrating the Action Mechanism of Enhancement of Endocannabinoid [1].

There are various methods for the production of the Paracetamol and they are: Classic method (Figure 3) and the Celanese's synthesis (Figure 4).

Classic method: This is the method for Paracetamol's production that involves first step acetylation that ends with the step of acetic anhydride. There is acetylation to 4-aminophenol along with acetic anhydride. The 4-aminophenol's preparation is different. One of the methods is the phenol's nitration along with nitric acid that afford 4-nitrophenol that gets reduced towards 4-aminophenol from the hydrogenation on Raney's nickel. Other method includes reduction of nitrobenzene electrolytically that directly gives 4-aminophenol.

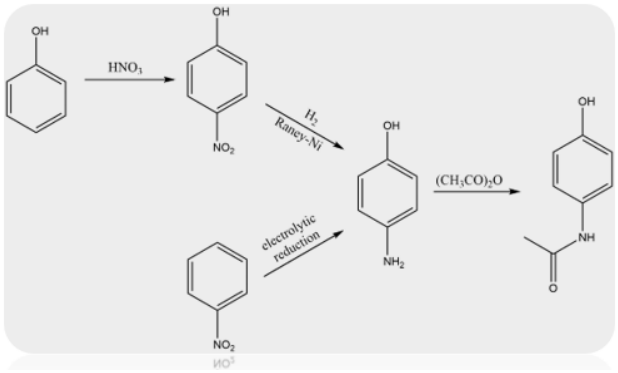

Figure 3: Illustrating the Paracetamol's production by the Classical method [2].

Synthesis of Celanese: There is an alternatively developed industrial synthesis over the Celanese that directly involves phenol's acylation along with acetic anhydride's during hydrogen fluoride (HF) presence that have resulting ketone towards ketoxime along with hydroxylamine along with catalyzed acid Beckmann rearrangement. The 4-Aminophenol is obtained to hydrolysis of amides of Paracetamol. The reaction determines urine sample's Paracetamol: after the hydrochloric acid's hydrolysis, the reaction of 4-aminophenol reaction with solution of ammonia along with the derivative of phenol (Salicylic acids) that forms an indophenol's dye during the air's oxidization.

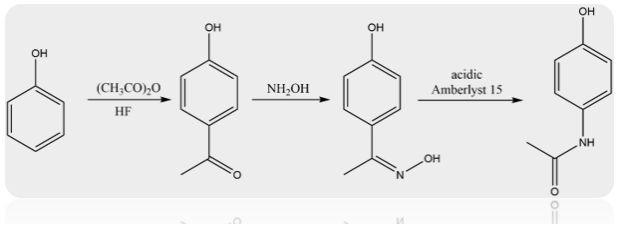

Figure 4: Illustrating the Production of Paracetamol by the Celanese Synthesis [2].

LITERATURE REVIEW

Paracetamol which is also called APAP (acetaminophenol) which is chemically known as N-acetyl's-p-aminophenol's broadly used as antipyretic and analgesic. It is characterized as mildly analgesic. Paracetamol is used in management of pain like: post-surgery or cancer pain when in combination with opioid analgesic. It is also used in the treatment of inflammatory pain. Laurie Prescott[3] studied the future prospects of paracetamol and found out that it is much needed the better dose form for the rectal administrations. And there is need of more production and marketing of the intravenous paracetamol all over the world in the coming future. He also found that in future, recent advancements must prevent the damages to kidneys or livers by the inappropriate dosage of the paracetamol. There is novel possible therapeutic application to paracetamol that includes the usage as antioxidant for preventing cardiovascular & atherosclerosis diseases from inhibiting lower density protein oxidation for preventing the cataracts formulations. Stephen P. Clissold [4] studied the synthesis of Phenacetin & Paracetamol which is followed by various divergent pathway in regard for popularity to mind antipyretic or analgesic drug. Phenacetin & Paracetamol are most effective against mild analgesic which is suitable in the treatment of pain. paracetamol being a therapeutic dose is much tolerated and produced less side effects as compared to aspirin.

Graham Garry et al. [5] studied the action mechanism of the Paracetamol. He found out that it is comprised as a weaker inhibitor for the prostaglandin synthesis. The analgesic effects of paracetamol found to be central & because of the serotonergic pathway, the sites of primary actions are the prostaglandin synthesis. The paracetamol's action is not yet clear at molecular level. Espinosa Bosch et al. [6] studied the paracetamol determination and its historic evolution. They have studied the utility of various technique to quantify the contents of Paracetamol in the formulation of pharmaceutical & the biological sample. There are much of the analytical methods that have proposed the paracetamol's determination. Garry G. Graham et al. [7] studied the tolerance of the Paracetamol. He found out that the consequent usage of the paracetamol in diseases stated the association among paracetamol & the diseases. Instead of the paracetamol's metabolism with reactive compound and hypersensitivity reaction becomes rare, also urticarial occurred among occasional patient. It is well tolerated in pregnancy. Jozwiak Bebenista & Nowak JZ [8] studied the safety concerns and the application of the Paracetamol. Paracetamol is among most popular and commonly suing antipyretic and analgesic drug all over the world which is available even without prescription. Paracetamol is a choice drug in the patients which can't get treated by non-steroid anti-inflammatory drug like patient with bronchial asthma, ulcer disease, salicylate sensitive patient, hemophilia, breastfeeding or pregnant women. This also recommends as first line of treatment of osteoarthritis which is associated with pain. It is a common tolerable drug that produced less side effects by gastrointestinal tracts that steady rise the number of cases that are registered of liver toxicity all around the world. John A. H. Forrest et al. [9] studied the clinical pharmacokinetic of the Paracetamol. They found out that paracetamol is metabolized in the liver. A small fraction of drugs transferred towards high reacting alkylate metabolite that inactivates by reducing glutathione & gets excreted into the urine as mercapturic acid and cysteine acids conjugates. Large dosage of the paracetamol results in acute liver necrosis which results in depletion to glutathione & binding excess reacting metabolite towards vital cell constituent.

DISCUSSION

The efficacy of the Paracetamol defines the equivalent standards of doses of various non-steroid anti-inflammatory drug which includes diclofenac, parecoxib, ibuprofen and many more along very few adverse effects. This comprises several surgical procedures and another chronic & acute pain sources like headache &

musculoskeletal pain that also includes migraine & tension related headache. This must be considered having useful opioid-spare effects, opioid consumption reduction if not borne universally by statistically significant clinical study. The invariability of regular paracetamol reduced pain score & vomiting & nausea & the improvement of patient's satisfaction. This is very useful first line of drugs & work synergically whenever combined to number of another agent that includes codeine, caffeine, tramadol, & ibuprofen that improves analgesic efficacies having minimize side effect of agents.

Also, the action of Paracetamol is faster as compared to oral. There is significantly no difference in the all over efficacy in between routes which is measured by utilizing pain score around 1 hour after the patient's administration in patient that have third molar extraction. In active and healthy individual who have gastric emptying, that undergo day casing surgeries and the readily results might not have extrapolated towards another group of patients. The interaction of drugs with Paracetamol (Figure 5) might occur & caution warranty in the co-administrations. The concomitant in taking of an enzyme which induces substances like: phenytoin, carbamazepine & barbiturates and the chronic alcoholic access as well might increases production of the paracetamol's toxicity risk by an enzyme's inhibitor. The concomitant usage of the Paracetamol along with oral anti-coagulant might leads for slighter variation in the INR value. The increasing monitor for INR must conducted while period for the concomitant usage to 1 week after the discontinuation of Paracetamol's treatment as well.

The MHRA called as Medicine & Healthcare Product Regulatory Agencies license the Paracetamol dosage which is similar to all the administration routes in adult around the 50 kilograms with maximum for 4 hours among every administration. Instead of the higher lipid solubility & less binding of proteins, weightage adjusting dose regimes never have endorsed. The data of pharmacokinetics for Paracetamol to single load of dosage of around 2 grams which has been followed by 4 to 6 hours to 1 gram of dosage & this whole is found out in all the clinical practices to latest years.

Drug Interactions with Paracetamol	Paracetamol absorption is increased by substances that increases gastric emptying (metoclopramide)
	Paracetamol absorption is decreased by substances that decreases gastric emptying (anticholinergic agents, opioids)
	Cholestyramine (ion-exchange resin) reduces the absorption of paracetamol if given within 1 hour of paracetamol
	Caution with concomitant intake of enzymes-inducing substances such as: carbamazepine, phenytoin, barbiturates, isoniazid that may increase the risk of paracetamol toxicity
	Probenecid causes an almost two-fold reduction in clearance of paracetamol by inhibiting its conjugation with glucuronic acid. A reduction of the paracetamol dose should be considered for concomitant treatment with probenecid.
	Salicylamide (analgesic & antipyretic) may prolong the elimination half life of paracetamol.
	Concomitant use of paracetamol (4g per day for at least 4 days) with oral anticoagulants may lead to slight variations of INR values.
	Paracetamol may also increase chloramphenicol concentration.

Figure 5: Illustrating the Interactions of the different Drugs along with Paracetamol.

There are various medical uses of Paracetamol (Figure 6) and is most commonly used medicines all around. Some of the uses of Paracetamol in medical purposes are as follows. Such as: in fever, in menstrual period pain, in toothache, in lower back pain, in headache, in cold/flu, in osteoarthritis and many more.

Fever

Paracetamol is the most commonly used in case of reducing fever. There is wide research onto the antipyretic property of the Paracetamol mainly in adult. Paracetamol in common cold might relieves from running nose & not from the cough, sore throat and many such symptoms. Paracetamol decreases the temperature of the body only to 0.2 to 0.3C. Paracetamol has not any benefit in dengue fever treatment & is accompanied to higher elevation rate for the enzymes of liver.

Pain

It is helpful in the relief to mild towards moderate pain like: muscle ache, headache, toothache, arthritis pain and the pains that are due to the sprains, flu, dysmenorrhea and cold. The treatment of acute milded towards the moderate pain, because of the evidence regarding chronic pain treatment is insufficient.

Musculoskeleton pain

There are many benefits of paracetamol in the skeletal conditions like: backache, osteoarthritis some are uncertain. This appeared for providing very small and not much clinically benefits in the osteoarthritis. The effective size in the clinical trial for paracetamol is small that is mostly ineffective for many of the individuals. Paracetamol is for episodic & short-term use for ones that don't tolerate NSAIDs. Those people who are taking it regularly needs to monitored the toxicity of liver. It is not effective for lower back pain. There is no evaluated use in the clinical trials for radicular & chronic pain.

Headache

Paracetamol have remarking effect to Migraine. The combination of caffeine/ paracetamol/aspirin have large effectiveness and use as first line of treatment to migraine. It has superiority to sumatriptan & ibuprofen.

Dental & post-surgery pain

The dental surgery pain provides action model to analgesic on acute pain. To relieving that pain, paracetamol becomes inferred to ibuprofen. There is promising combination of paracetamol & non-steroid anti-inflammatory drug or the diclofenac that controls pain bitterly than taken alone. Meta-analysis to common post-surgical of pain that includes surgery and another dental shows the codeine/ paracetamol's combination which is much effective than if paracetamol is taken alone. This significantly provides pain relieve to around

53% participants whereas placebo is effective to 7% only [10].

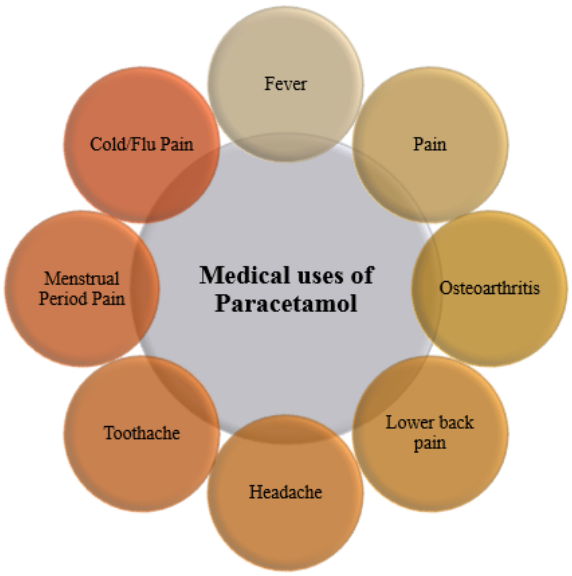

Figure 6: Illustrating the various Medical Uses of the Paracetamol.

There are many of the advantages (Figure 7) & disadvantages (Figure 8) of the Paracetamol. The various advantages include: Paracetamol doesn't produce the toxicity of end-organ that is generally seen in the cardiovascular & kidney and gastrointestinal tract, it lacks central nervous system & opioid relating side effect. It is a lower technology invention like the administration of oral paracetamol, that uses appropriately which have the potentiality for reducing the unnecessary pain. It's an analgesic which might be a choice to every adult patient to whom NSAID & salicylate are contraindicate. It is advantageous to the children having febrile viral illness to whom disprin becomes contraindicated because of the risk to Reye Syndromes that is the brain's swelling which leads to death & even coma. Paracetamol is antipyretic that it reduces fever. It is very secure if correct dosage is taken that not upsets the stomach and may cause the bleeding. It is much suited for children. It is much safe to gastric irritations, bleeding & ulcerations. It can be suitably used to all of the age groups from infant up to elder. It has not any metabolic and acid bases disturbance and effects. It is safe to presence to another disease too.

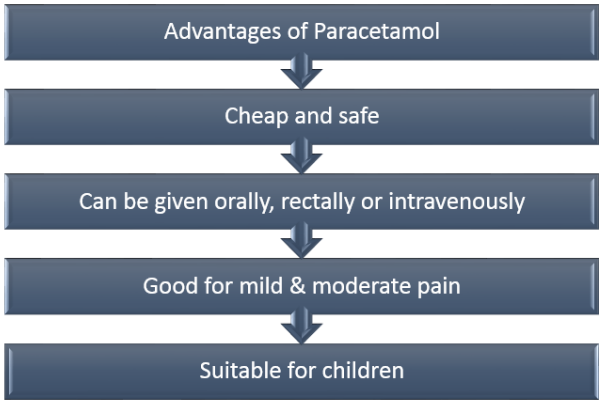

Figure 7: Illustrating various advantages in the uptake of Paracetamol.

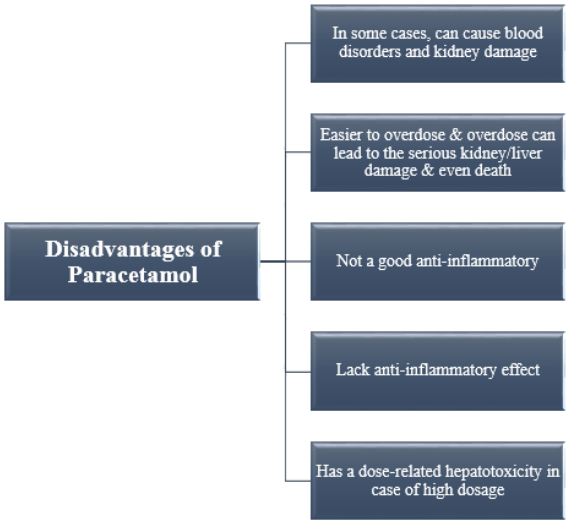

Figure 8: Illustrating various disadvantages and adverse effects of Paracetamol.

Paracetamol has many disadvantages also. It lacks of anti-inflammatory effect. Paracetamol used as a single drug. The analgesic potentiality of Paracetamol is less as of NSAID. It has fewer analgesic effects. It proves toxic if high dosage taken. Its over dosage leads serious damage to liver or kidney and may cause death. It can even cause blood disorder. Paracetamol has no or very less effective to different level of prostaglandin. It isn't much effective in case treatment for dysmenorrhea.

CONCLUSION

Paracetamol has no doubt antipyretic & analgesic effects. Its preparation and research have determined more new uses in a randomized and prospective controlled study. Before the administration of anesthesia induction, paracetamol is largely effective for ketamine to prevent remifentanil inducing hyperalgesia along with an advantage of reducing time for extubating & anesthesia recovery. The addition of paracetamol in lidocaine injection during the regional anesthesia overall improves the quality of block. The consensus on Paracetamol's action is center mediated, an analgesia benefit confers by

the addition at peripheral sequestered pooling of drugs in a well manner. The mechanism of action of the Paracetamol for the production is done by basically of two of the methods. One is the prostaglandin's inhibition and other is the Endocannabinoid's enhancements. These two basically involves in the production mechanism for the action of paracetamol.

The production of paracetamol is done by two of the methods. One is the classical method of production that have involvement of acetylation to acetic anhydride at last step. In this, nitrobenzene gets reducing to electrolytical producing 4-aminophenol. And the other method of production is the Celanese synthesis which is alternatively synthesis of industrial compounds that helps in production of paracetamol following by the catalyzation of acid by Beckmann's rearrangements. There are interactions of drugs with paracetamol that helps in altering the properties of the paracetamol. Paracetamol is a common medicine all over and is suitable for all age groups. It has various medical uses like in the treatment of fever, pain, cold or flu etc. it has advantages as well as adverse effects also. It is much cheap and safe to use. Over dosage must be avoided and proves fatal. It can be taken intravenously, orally and rectally too. It is suitable for mild to moderate pain. Paracetamol have many of the disadvantages also. It can lead to serious kidney and liver damage when taken over dosage of it. It has toxicity related to intake of dosage hypersensitivity and lacks many of the anti-inflammatory properties.

Acetaminophen which is commonly called as Paracetamol is a leading non-prescribed antipyretic analgesic drug. The future developments include novel formulation for achieving rapidly absorption to the faster onset of the actions & the prolong absorption which extends duration of an action to regularly long-term administration. The future development includes novel formulation for achieving the rapid absorptions to the fast on set to actions that extends duration for the action to long-term administrations. There is requirement of enhanced dosage form that is needed for the recital's administrations. The presence of intravenous paracetamol is only in the fewer countries, presently. It must be marketed broadly in the future.

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