United Journal of Pharmacology and Therapeutics

Review Article

Different Effects of Acetaminophen between Male and Female

Ciconini L, Carrascoza GG and Perez AC*

Department of Pharmacology, Federal University of Minas Gerais (UFMG), Brazil

Volume 1 Issue 3 - 2018
Received Date: 15 Oct 2018
Accepted Date: 17 Nov 2018
Published Date: 22 Nov 2018

2. Keywords

Acetaminophen; paracetamol; male; female

1. Abstract

Acetaminophen (APAP), also known as Paracetamol, is a common analgesic and antipyretic medication widely prescribed worldwide. Although medical practitioners generally consider it a safer medication with fewer adverse effects than those of other medications, it is responsible for nearly 50% of acute liver failure cases in the USA, and many others side effects such as hypotension and renal impairment. Because of that, on March 26, 2014, the FDA and the pharmaceutical industry took action to protect consumers by formally withdrawing all prescription combination drug products with more than 325 mg acetaminophen from the market.

Furthermore, research has shown that the incidence of some side effects varied between men and women, causing scientists to inquire if there is a difference in the metabolism of the drug and how it could be related to the outcomes on the two groups. The present review aimed to research APAP overdose and metabolism, making possible to group and analyze the distinct effects of the drug on both sexes

3. Introduction

Acetaminophen (N-acetyl-p-aminophenol or APAP) also known as paracetamol is a member of the aniline family of analgesics and despite the introduction of many new analgesics, it is still one of the most widely used analgesic- antipyretic agents [1]. It works by blocking prostaglandin synthesis from arachidonic acid by inhibiting the enzymes cyclooxygenase (COX)-1 and -2 [1], leading to its analgesic and antipyretic effect [2].

For nearly half a century, APAP has been one of the most widely used drugs. It can be found as a single component or combined with other synergic prescribed drugs [3]. While opioids need a prescription, paracetamol is sold over-the-counter.

APAP has well-established efficacy and is recommended as a first-line treatment for mild to moderate acute pain [4]. Although medical practitioners generally consider it a safer medication with fewer adverse effects than those of other drugs, life-threatening hepatic toxicity is a well-recognized adverse complication in patients with large dose ingestion [3]. In the United States, 82000 emergency room visits and 26000 hospitalizations are attributed to acetaminophen overdose annually [5].

The medication undergoes hepatic conjugation by glucuronosyl transferase (20%-46%) and sulfo transferase (20%-46%) into acetaminophen glucuronide and acetaminophen sulfate, respectively. Glucuronidation, sulfation, and subsequent renal excretion normally remove about 85%-90% of a therapeutic dose of acetaminophen [1]. However, after large doses of the medication, these pathways can become saturated and the remainder of the drug is metabolized by the hepatic cytochrome P450 (CYP2E1, CYP1A2, CYP3A4 subfamilies) to the toxic intermediate, N-Acetyl-P-Benzoquinoneimine (NAPQI) [3]. This metabolite can be detoxified by conjugation with glutathione (GSH); however, an excess of NAPQI, after APAP overdose, depletes GSH and binds to cellular proteins leading to cell death [6]. APAP maximum recommended therapeutic daily dose is 4 g for adults. Generally, toxicity results from 7.5 to 10.0 g for an adult dose [3]. APAP has not shown liver injury as its only side effect. Kidney insults and hypotension have also been described. Furthermore, a difference between male and female on acetaminophen toxicity, efficacy, pharmacokinetic and pharmacodynamics has been observed as well. Thereby, this article aims to analyze the heterogeneity of both sexes regarding acetaminophen's metabolism and effects.

***Corresponding Author (s):** *Andrea C Perez, Department of Pharmacology, Federal University of Minas Gerais (UFMG), Brazil, E-mail: acp@icb.ufmg.br*

Citation: Ciconini L, Carrascoza GG and Perez AC, Different Effects of Acetaminophen between Male and Female. United Journal of Pharmacology and Therapeutics. 2018;1(3): 1-5.

4. Methods

The literature search was conducted using articles from the period of 2002 to 2018, in the databases PubMed. The keywords "acetaminophen", "side effects" and "gender" had been used. It was selected 119 articles and the ones that did not compare the effects of acetaminophen in men and woman or that did not have statistical significance ($p<0.05$) were excluded. Additionally, the bibliography of the selected articles have also been checked and used in the review.

5. Results

The present research has found a significant difference ($p<0.05$), between male and female, regarding the aspect of acetaminophen use and its outcomes. The review exhibits that APAP induced acute liver injury and APAP induced acute liver failure incidences are not the same on both sexes. Moreover, a trial using mice demonstrated an increased hepatotoxicity on male mice compared to the opposite sex [6]; however, human studies have gotten different results compared to animals [5].

Relative to pain management, male and female responses varied depending on the origin of the painful stimuli. While female shows a better renal pain management with APAP than male [7], no statistically significant result could be achieved on orthopedics procedures [8].

On the purpose of better understanding this contrast between genders, some studies have used in vitro human cells. An experiment with human hepatocytes displays different responses on female and male organelles when exposed to increasing doses of APAP [9]. However, when using monocytes, no significant difference between the sexes is observed [10].

Pharmacokinetics and pharmacodynamics are also analyzed and compared in this review, contributing to the understanding of the different responses in the usage of APAP by both sexes.

6. Discussion

6.1. Pharmacokinetic and pharmacodynamics

It´s well established that paracetamol is almost exclusively eliminated by conjugation into either paracetamol glucuronide or paracetamol sulfate, while limited amounts are excreted in the urine as unchanged paracetamol or undergo oxidation to result in toxic metabolites (N-Acetyl-P-Benzoquinoneimine, NAPQI).

In a study, made by the Acute Liver Failure Study Group, 98 subjects received two tablets of 500mg acetaminophen each and had plasma samples collected at 1, 2, 3, 4, 5, 6, 8, 10, 12 hours and 4 days after the administration. the Pharmacokinetic of APAP between genders is compared. The research demonstrates that shorter median half-life values are observed for acetaminophen, acetaminophen glucuronide, and acetaminophen sulfate in women compared with men. Lower median plasma metabolite/acetaminophen bio availability is also observed for acetaminophen glucuronide and acetaminophen sulfate in women compared with men [11].

These findings are consistent with gender-related differences in drug and metabolite distribution rather than any effect on drug clearance and/or metabolism. Lower weight-adjusted acetaminophen volume of distribution has been previously reported in women compared with men and is probably a reflection of the relatively poor distribution of acetaminophen (and metabolites) into fatty tissue, which tends to provide a higher proportion of body weight in women than in men [12]. The results may point to a possible correlation between differences in the metabolism and outcomes of acetaminophen use on both sexes.

Another study [13], with 24 subjects, 8 males, 8 females not taking Oral Contraceptive Steroids (OCS) and 8 females taking OCS containing ethinyloestradiol 0.03mg and levonorgestrol 0.15 mg, searched for the influence of sex and use of oral contraceptive steroids on acetaminophen metabolism. The subjects received two tablets of 500 mg paracetamol each and saliva samples were collected prior to and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6 and 8 hours after drug administration. Urine was collected for 24h following the paracetamol dose.

The research demonstrates that paracetamol clearance is 22% higher in males (5.62 mL/min Kg) than in non-OCS females (4.61 mL/min Kg), but half-life is not significantly different. The volumes of distribution for paracetamol are lower in both female groups compared to male, probably due to the greater amount of fat in a woman and the relatively poor distribution of acetaminophen into fatty tissue.

The research also exhibits that metabolic clearance of the glucuronide conjugate is 28 % higher in males, but there are no gender-related differences in the renal clearance of paracetamol or sulfate and glutathione-derived conjugates. Therefore, the result is related to the increased activity of the glucuronidation pathway in males.

Females taking OCS have a clearance 49 % greater than those not taking the drug, and 22 % higher than in men (marginal statistical difference $p=0.06$). Paracetamol half-life is also decreased in the first group. The reason for that is the induction of UDP- glucurony transferase leading to the increase in the clearance of glutathion-derived metabolites in OCS users. In contrast, sulphation enzymes are not inducible, leading to no statistical difference between groups regarding the clearance of their sub-

strates.

Paracetamol is bio transformed in the liver primarily by conjugation with glucuronic acid and sulphate, with a small proportion of the dose being transformed by cytochrome P450 to a toxic intermediate (NAPQI) which is detoxified by conjugation with glutathione. Thereby, the induction of the last pathway could enhance acetaminophen`s toxicity.

The clearance of the glutathione-derived products was significantly greater in OCS users compared to non-pill using females. Therefore, the oxidative metabolism of paracetamol, determined as clearance of the glutathione-derived conjugates, was induced in the OCS users compared to the control female group.

The results presented in the study suggest that OCS may be a relative risk factor in the development of paracetamol-induced hepatotoxicity in females [13].

6.2. Pain management

Acetaminophen can be bought as a single drug, or as part of a combination of drugs. On end-stage disease conditions, the use of opioids is limited by the belief that these drugs have severe side effects including possible addiction. This has led to excessive use of NSAIDs and APAP.

A randomized double-blind clinical trial was conducted in Al-Zahra Hospital affiliated to the Isfahan University of Medical Science (Iran) in 2012. They have studied 124 patients assigned in two groups, one receiving acetaminophen and the other receiving morphine, both for the treatment of renal colic pain. On the APAP group, the assigned patients received 15 mg/kg during 15 minutes and a visual analog scale rating the amount of pain from 0 to 10 was used. Relative to this scale, females have experienced a bit more pain relief than males [7].

Another randomized study that evaluated pain management after major orthopedics surgery did not show the same result as the above study. 101 patients were dived into two groups. The first group was composed of 49 patients receiving 15 minutes intravenous (IV) infusion of 1g of acetaminophen, while the second group, composed of 52 patients, received placebo. Both could have on-demand patient control opioids. The placebo group had time to rescue medication of 48 minutes, while the other group had a time of 3 hours.

However, in the APAP + morphine group, gender did not appear to influence significantly the analgesics efficacy observed with IV APAP [8].

6.3. Toxicity and liver failure

A retrospective population-based study covered all patients that attended the National University Hospital (NUH) in Iceland between January 1st, 2004 and December 31st, 2009 with overdose or liver injury, as identified by the computerized hospital database. In this study, the mean sex-specific annual incidence for all visits involving paracetamol overdose is 38 for females and 12 for males per 100,000 inhabitants. Furthermore, the range of reported ingested paracetamol is 1-45 g. The median paracetamol ingestion is for males 15 g and females 13 g. Despite that, gender proportion developing Acute Liver Failure (ALF) is not significantly different. They have also verified that young females with intentional overdose account for most of the cases of acetaminophen intoxication [14].

A research using data of over 9 million beneficiaries receiving care under the US Military Health System between 2004 and 2008 also shows that paracetamol overdose is more common in females. People aged 15-17 and 18-24 are more likely to have an overdose than those aged 45-64 [15].

Another study [5], using information from the prospective, multicenter Acute Liver Failure Study Group (ALFSG) cohort, aims to evaluate sex differences in the presentation and clinical course of acetaminophen-induced Acute Liver Injury (ALI) and Acute Liver Failure (ALF) and to secondarily compare overall and transplant-free survival by sex. In this study, the scientists demonstrated that women with acetaminophen-induced ALF are more likely to have a psychiatric disease, to be taking psychiatric medications and to have an endocrine disorder. Furthermore, approximately half of patients with acetaminophen-induced ALF have unintentional acetaminophen overdose (53%), whereas 40% are suicide attempts (unknown intentionality in the remaining 7%). Rates of suicide attempt are similar between men and women, but a greater proportion of women have co-ingestions with opioids, benzodiazepines, or diphenhydramine. Regarding complications of ALF, females are more likely to have high-grade Hepatic Encephalopathy (HE) at study entry and during the 7-day follow-up period. Likewise, women are more likely to be intubated in the study and during follow-up. Vasopressor and mannitol use are also greater at study entry in this group.

Additionally, female sex is associated with increased risk of severe HE at both study entry and follow-up. On adjusted analysis, co-ingestions in women confers a nearly 2-fold higher of severe hepatic encephalopathy at both study entry and follow-up. In contrast, there is no significant difference in risk of severe HE in men by co-ingestion history at either study entry or follow-up [5].

6.4. In vitro studies

An experiment has used Male (M), pre-menopausal female (3F), and postmenopausal female (4F) cryopreserved human hepato-

cytes, derived from 12 donors per group to compare the effect of Diclofenac, Chlorpromazine, Verapamil, Acetaminophen, Omeprazole, and Caffeine in those cells. In this study, the scientists observed in vitro differences related to the amount of ATP, nuclear intensity, reactive oxygen species formation, mitochondrial damage, endoplasmic reticulum status, plasma membrane permeability, and accumulation of intracellular calcium in the hepatocytes exposed to those drugs.

6.4.1. ATP: Male (M), pre-menopausal female (3F), and post-menopausal female (4F) pooled primary hepatocytes derived from 12 donors per group were exposed to 8 increasing concentrations of Diclofenac, Chlorpromazine, Acetaminophen, Verapamil, Omeprazole, and Caffeine. A dose-response curve showing a decrease in ATP levels at increasing concentration of drugs was obtained at each of the tested time points. Statistically significant differences between the three groups tested are observed for acetaminophen, only with 5 h treatment, which demonstrates a higher toxicity in 4F and M compared to 3F hepatocytes at this time point.

Nuclear intensity assessment: A dose-dependent increase in nuclear intensity is often associated with nuclear condensation as a result of cell injury. No statistically significant nuclear intensity modifications were obtained comparing M, 3F, and 4F hepatocytes at any of the tested exposure times for Acetaminophen.

6.4.2. Reactive Oxygen Species (ROS) formation: ROS are a natural by-product of the normal oxygen metabolism, but when increased and persistent they may result in significant cell damage known as oxidative stress. In primary hepatocytes treated with acetaminophen for 30 min, ROS accumulated in female cells are slightly significantly lower concentration than in male cells.

6.4.3. Mitochondrial damage: mitochondrial permeability and the loss of mitochondrial membrane potential with subsequent release of pro-apoptotic proteins from the inner membrane space into the cytosol and decreased ATP production are hallmarks of cell death. Mitochondrial damage was induced at lower concentrations in postmenopausal females (4F) compared to pre-menopausal females (3F) and males (M) after exposition to acetaminophen during 4 hours.

6.4.4. Endoplasmic reticulum (ER): ER-stress induces dilatation of ER-membranes and other alterations in ER-appearance. The study measured ER morphological changes. Dose-response curves for ER intensity shows that male hepatocytes exposed for 5h with Acetaminophen are significantly more sensitive to ER modification than pre- and post-menopausal female cells. (ER morphology does not necessarily correlate with ER stress; it is a coping mechanism that does not always indicate stress).

6.4.5. Plasma membrane permeability: After 4h, Acetaminophen-treated male hepatocytes membrane disruption was induced at lower concentration compared to pre-and post-menopausal female cells.

6.4.6 Accumulation of intracellular calcium: Loss of calcium homeostasis with increased intracellular calcium level results from failure of energy-dependent Ca^{++}/Mg^{++} ATPase pump and it is also related to increased membrane permeability and cell-mediated death. Calcium accumulation was measured in treated primary hepatocytes; the value obtained for acetaminophen do not have any statistically significant differences between the three groups of cells tested [9].

This study aimed to elucidate cell-based sex differences in response to toxicants and the molecular pathways affected. However, some difficulties have occurred in the study. For example, the three groups of human hepatocytes were exposed for a maximum of 6 hours due to the limited life-span of the cells in suspension, preventing longer exposes of hepatocytes to the drugs. Another research, trying to overcome this problem, used monocytes (MH) instead of hepatocytes, because these leucocytes have a lifespan of about 4 weeks in vitro.

The article acquired human peripheral monocytes from healthy volunteers. MH cells were compared to hepatocytes from the same donors showing activities of various hepatocyte enzymes, such as DPP4, LDH, gamma-GT, and ALT. They also exhibit activities of the CYP450 enzymes 3A4, 2C9 and 1A2, in a similar pattern to the hepatocytes. To study drug hepatotoxicity, the cells were treated with APAP and diclofenac. To test CYP2E1, which has a role in the toxicity of paracetamol and metabolism of alcohol; cells were pre-treated for 48h with ethanol. The results indicate that ethanol pre-treatment increases APAP toxicity. This finding is in parallel to the clinically relevant aggravation of APAP-induced liver damage by ethanol consumption [10].

7. Conclusion

There are marked sex-based differences in the epidemiology, clinical manifestations, as well as pharmacodynamics, pharmacokinetics, and adverse drug effects. For many years, females have been under-represented in basic researches and clinical trials due to male´s constant hormone levels [9]. This creates an uncertainty about whether study results could be generalized to male and female. Likewise, the use of acetaminophen may not have the same outcomes on both sexes. In this study, it is observed different rates of APAP metabolism as well as the volume of distribution between males and females. Moreover, the use of OCS has also modified those aspects and may be related to increased toxicity. It´s well known that the use of OCS is widespread and could be related to the fact that hepatotoxicity is more

common and severe in women.

Furthermore, the intake of other pain medications with APAP is more frequent in woman. Despite greater co-ingestion use, female sex remains independently associated with severe hepatic encephalopathy. This suggests that factors beyond their greater pain pills co-ingestion are also important. Facing this variability in drug response, in-vitro studies have demonstrated special importance in better understanding the many biochemical pathways of the drug on both sexes. It has shown contrasts regarding mitochondrial damage, ROS formation, and endoplasmic reticulum appearance. Those findings reflect that molecular patterns are not the same on both sexes, and could influence in the response to APAP use. However, due to limitations in the hepatocytes short lifespan and monocytes particularities, there is still a need for further in-vitro studies to draw better conclusions. Finally, there is a need for more researches regarding the different aspects of sex particularities, not only with APAP use but also with other drugs. This may lead to a more particular medical approach and avoidance of undesirable effects.

References

1. Aminoshariae A, Khan A. Acetaminophen: Old Drug, New Issues. J Endod. 2015;41(5):588-93.

2. Prescott LF. Paracetamol: past, present and future. Am J Ther. 2000;7(2):143-7.

3. Chen YG, Lin CL, Dai MS, Chang PY, Chen JH, Huang TC, et al. Risk of Acute Kidney Injury and Long-Term Outcome in Patients With Acetaminophen Intoxication. A Nationwide Population-Based Retrospective Cohort Study. Medicine (Baltimore). 2015;94(46):e2040.

4. Håkonsen H, Hedenrud T. A population-based study of risk perceptions of paracetamol use among Swedes-with a special focus on young adults. Pharmacoepidemiol Drug Saf. 2017;26(8):992-7.

5. Rubin JB, Hameed B, Gottfried M, Lee WM, Sarkar M, Acute Liver Failure Study Group. Acetaminophen-induced Acute Liver Failure Is More Common and More Severe in Women. Clin Gastroenterol Hepatol. 2018;16(6):936-46.

6. Du K, Williams CD, Mcgill MR, Jaeschke H. Lower susceptibility of female mice to acetaminophen hepatotoxicity: Role of mitochondrial glutathione, oxidant stress and c-jun N-terminal kinase. Toxicol Appl Pharmacol. 2014;281(1):58-66.

7. Azizkhani R, Pourafzali SM, Baloochestani E, Masoumi B. Comparing the analgesic effect of intravenous acetaminophen and morphine on patients with renal colic pain referring to the emergency department: A randomized controlled trial. J Res Med Sci. 2013;18(9):772-6.

8. Sinatra RS, Jahr JS, Reynolds L, Groudine SB, Royal MA, Breitmeyer JB, et al. Intravenous Acetaminophen for Pain after Major Orthopedic Surgery: An Expanded Analysis. Pain Pract. 2012;12(5):357-65.

9. Mennecozzi M, Landesmann B, Palosaari T, Harris G, Whelan M. Sex Differences in Liver Toxicity-Do Female and Male Human Primary Hepatocytes React Differently to Toxicants in Vitro? PLoS One. 2015;10(4):e0122786.

10. Benesic A, Rahm NL, Ernst S, Gerbes AL. Human monocyte-derived cells with individual hepatocyte characteristics: a novel tool for personalized in vitro studies. Lab Invest. 2012;92(6):926-36.

11. Court MH, Zhu Z, Masse G, Duan SX, James LP, Harmatz JS, et al. Race, Gender, and Genetic Polymorphism Contribute to Variability in Acetaminophen Pharmacokinetics, Metabolism, and Protein-Adduct Concentrations in Healthy African-American and European-American Volunteers. J Pharmacol Exp Ther. 2017;362(3):431-40.

12. Abernethy DR, Divoll M, Greenblatt DJ, and Ameer B. Obesity, sex, and acetaminophen disposition. Clin Pharmacol Ther. 1982;31(6):783-90.

13. Miners J, Attwood J, Birkett D. Influence of sex and oral contraceptive steroids on paracetamol metabolism. Br J Clin Pharmacol. 1983;16(5):503-9.

14. Kjartansdottir I, Bergmann OM, Arnadottir RS, Björnsson ES. Paracetamol intoxications: a retrospective population-based study in Iceland. Scand J Gastroenterol. 2012;47(11):1344-52.

15. Taylor LG, Xie S, Meyer TE, Coster TS. Acetaminophen overdose in the Military Health System. Pharmacoepidemiol Drug Saf. 2012;21(4):375-83.