

 Ahead of print

Vitamin C, omega-3 and paracetamol pharmacokinetic interactions using saliva specimens as determiners

Ausama Ayob Jaccob  / Zainab Haroon Ahmed / Baan Majid Aljasani

Published Online: 2019-08-06 | DOI: <https://doi.org/10.1515/jcpp-2019-0011>

30,00 € / \$42.00 / £23.00  [GET ACCESS TO FULL TEXT](#)

Abstract

Background

With its low side effects profile and availability as an over-the-counter drug, paracetamol has been utilized extensively worldwide as an antipyretic and analgesic agent for decades. This is associated with the increasing concern over its ease of access and/or unawareness of the consumers to this issue of paracetamol-induced hepatotoxicity. Paracetamol-induced liver injury today is a big problem where most of the researchers are interested in the possible role of the naturally available antioxidants to ameliorate hepatotoxicity through kinetic interference. So the present study was designed to evaluate the effect of vitamin C and omega-3 on the pharmacokinetic property of paracetamol.

Methods

Six young (average age 29) healthy volunteers participated in the study. The study included three consecutive periods, each of which preceded by overnight fasting and separated by 6 day washout periods. The first period involved the ingestion of a single paracetamol dose. The second one included the ingestion of paracetamol and vitamin C concomitantly, and the final period included paracetamol plus omega-3. Saliva samples were collected and prepared for High-performance liquid chromatography analysis.

Results

There was a significant increase in saliva paracetamol level after 30 min of administration when given concomitantly with vitamin C compared with the remaining groups. No significant differences in the paracetamol concentration profile between the subjects for each group were observed at 60, 90, 120 and 150 min in all treated groups.

Conclusion

Concurrent administration of vitamin C with paracetamol increases significantly the C_{max} level (maximum measured concentration) in saliva and increases the extent of absorption and the possibility of drug-drug interaction and risk of side effects.

Keywords: omega-3; paracetamol; pharmacokinetics; saliva; vitamin C

References

- [1] Bannwarth B, Péhourcq F. Pharmacologic basis for using paracetamol: pharmacokinetic and pharmacodynamic issues. *Drugs* 2003;63:5–13.
PubMed Google Scholar
- [2] Nowak JZ, Jozwiak-Bebenista M. Paracetamol phenomenon: unprecedented worldwide popularity vs. toxic effects. *Mil Pharm Med* 2013;4:16.
Google Scholar
- [3] Mazaleuskaya LL, Sangkuhl K, Thorn CF, FitzGerald GA, Altman RB, Klein TE. PharmGKB summary: pathways of acetaminophen metabolism at the therapeutic versus toxic doses. *Pharmacogenet Genomics* 2015;25:416–26.
PubMed CrossRef Web of Science Google Scholar
- [4] Abdel-Dayem MA, Elmarakby AA, Abdel-Aziz AA, Pye C, Said SA, El-Mowafy AM. Valproate-induced liver injury: modulation by the omega-3 fatty acid DHA proposes a novel anticonvulsant regimen. *Drugs R D* 2014;14:85–94.
PubMed CrossRef Google Scholar
- [5] Pingili RB, Pawar AK, Challa SR. Systemic exposure of paracetamol (acetaminophen) was enhanced by quercetin and chrysin co-administration in Wistar rats and in vitro model: risk of liver toxicity. *Drug Dev Ind Pharm* 2015;41:1793–800.
Crossref PubMed Web of Science Google Scholar
- [6] Qinna NA, Shubar MH, Matalka KZ, Al-Jbour N, Ghattas MA, Badwan AA. Glucosamine enhances paracetamol bioavailability by reducing its metabolism. *J Pharm Sci* 2015;104:257–65.
Web of Science CrossRef PubMed Google Scholar
- [7] Qinna NA, Ismail OA, Alhussainy TM, Idkaidek NM, Arafat TA. Evidence of reduced oral bioavailability of paracetamol in rats following multiple ingestions of grapefruit juice. *Eur J Drug Metab Pharmacokinet* 2016;41:187–95.
Crossref PubMed Google Scholar
- [8] Kang D, Shao Y, Zhu Z, Yin X, Shen B, Chen C, et al. Systematically identifying the hepatoprotective ingredients of schisandra lignan extract from pharmacokinetic and pharmacodynamic perspectives. *Phytomedicine* 2019;53:182–92.
Crossref PubMed Web of Science Google Scholar
- [9] Zaidi SM, Banu N. Antioxidant potential of vitamins A, E and C in modulating oxidative stress in rat brain. *Clin Chim Acta* 2004;340:229–33.
Crossref Google Scholar
- [10] Naidu KA. Vitamin C in human health and disease is still a mystery? An overview. *Nutr J* 2003;21:7.
Google Scholar
- [11] Sabiu S, Sunmonu TO, Ajani OA, Ajiboye TO. Combined administration of silymarin and vitamin C stalls acetaminophen-mediated hepatic oxidative insults in Wistar rats. *Rev Bras Farmacogn* 2015;25:29–34.
Crossref Web of Science Google Scholar
- [12] Lee MG, Chiou WL. Mechanism of ascorbic acid enhancement of the bioavailability and diuretic effect of furosemide. *Drug Metab Dispos* 1998;26:401–7.
PubMed Google Scholar
- [13] Nagayama H, Hamamoto M, Ueda M, Nito C, Yamaguchi H, Katayama Y. The effect of ascorbic acid on the pharmacokinetics of levodopa in elderly patients with Parkinson disease. *Clin Neuropharmacol* 2004;27:270–3.
PubMed CrossRef Google Scholar

- [14] Meganathan M, Gopal KM, Sasikala P, Mohan J, Gowdhaman N, Balamurugan K, et al. Evaluation of hepatoprotective effect of omega 3-fatty acid against paracetamol induced liver injury in albino rats. *Global J Pharmacol* 2011;5:50–3.
🔗 Google Scholar
- [15] Serhan CN, Clish CB, Brannon J, Colgan SP, Chiang N, Gronert K. Novel functional sets of lipid-derived mediators with antiinflammatory actions generated from omega-3 fatty acids via cyclooxygenase 2-nonsteroidal antiinflammatory drugs and transcellular processing. *J Exp Med* 2000;192:1197–204.
🔗 PubMed🔗 Crossref🔗 Google Scholar
- [16] Hickman RJ, Neill J. Influence of pH on drug absorption from the gastrointestinal tract. *J Chem Educ* 1997;74:855–6.
🔗 Crossref🔗 Google Scholar
- [17] Divoll M, Greenblatt DJ, Ameer B, Abernethy DR. Effect of food on acetaminophen absorption in young and elderly subjects. *J Clin Pharmacol* 1982;22:571–6.
🔗 Crossref🔗 Google Scholar
- [18] Raffa RB, Pergolizzi JV, Taylor R, Decker JF, Patrick JT. Acetaminophen (paracetamol) oral absorption and clinical influences. *Pain Pract* 2014;14:668–77.
🔗 Web of Science🔗 Crossref🔗 PubMed🔗 Google Scholar
- [19] Da Silva LM, da Silva RC, Maria-Ferreira D, Beltrame OC, da Silva-Santos JE, Werner MF. Vitamin C improves gastroparesis in diabetic rats: effects on gastric contractile responses and oxidative stress. *Dig Dis Sci* 2017;62:2338–47.
🔗 Web of Science🔗 PubMed🔗 Crossref🔗 Google Scholar
- [20] Slosky M, Thompson BJ, Sanchez-Covarrubias L, Zhang Y, Laracuente ML, Vanderah TW, et al. Acetaminophen modulates P-glycoprotein functional expression at the blood-brain barrier by a constitutive androstane receptor-dependent mechanism. *Mol Pharmacol* 2013;84:774–86.
🔗 PubMed🔗 Web of Science🔗 Crossref🔗 Google Scholar
- [21] Ghanem CI, Gomez PC, Arana MC, Perassolo M, Ruiz ML, Villanueva SS, et al. Effect of acetaminophen on expression and activity of rat liver multidrug resistance-associated protein 2 and P-glycoprotein. *Biochem Pharmacol* 2004;68:791–8.
🔗 Crossref🔗 PubMed🔗 Google Scholar
- [22] Novak A, Carpini GD, Ruiz ML, Luquita MG, Rubio MC, Mottino AD, et al. Acetaminophen inhibits intestinal p-glycoprotein transport activity. *J Pharm Sci* 2013;102:3830–7.
🔗 Web of Science🔗 Crossref🔗 PubMed🔗 Google Scholar
- [23] Mark LH, Jeffrey RG, Nicos K, David WG, David AS, Emily AS, et al. Vitamin C antagonizes the cytotoxic effects of antineoplastic drugs. *Cancer Res* 2008;68:8031–8.
🔗 Crossref🔗 Web of Science🔗 PubMed🔗 Google Scholar
- [24] Jaeschke H, McGill MR, Ramachandran A. Oxidant stress, mitochondria, and cell death mechanisms in drug-induced liver injury: lessons learned from acetaminophen hepatotoxicity. *Drug Metab Rev* 2012;44:88–106.
🔗 Crossref🔗 PubMed🔗 Web of Science🔗 Google Scholar
- [25] Ipsen DH, Tveden-Nyborg P, Lykkesfeldt J. Does vitamin C deficiency promote fatty liver disease development? *Nutrients* 2014;6:5473–99.
🔗 Web of Science🔗 PubMed🔗 Crossref🔗 Google Scholar
- [26] Saito Y, Shichiri M, Hamajima T, Ishida N, Mita Y, Nakao S, et al. Enhancement of lipid peroxidation and its amelioration by vitamin E in a subject with mutations in the SBP2 gene. *J Lipid Res* 2015;56:2172–82.
🔗 Crossref🔗 Web of Science🔗 Google Scholar
- [27] González R1, Cruz A, Ferrín G, López-Cillero P, Fernández-Rodríguez R, Briceño J, et al. Nitric oxide mimics transcriptional

and post-translational regulation during α -tocopherol cytoprotection against glycochenodeoxycholate-induced cell death in hepatocytes. *J Hepatol* 2011;55:133–44.

 Crossref  PubMed  Web of Science  Google Scholar

- [28] Houston JB, Levy G. Drug biotransformation interactions in man VI: acetaminophen and ascorbic acid. *J Pharm Sci* 1976;65:1218–21.
 Crossref  PubMed  Web of Science  Google Scholar
- [29] Abdel-Daim M, Abushouk A, Reggi R, Yarla NS, Palmery M, Peluso I. Association of antioxidant nutraceuticals and acetaminophen (paracetamol): friend or foe? *J Food Drug Anal* 2018;26:S78–87.
 Crossref  Web of Science  PubMed  Google Scholar
- [30] Navarro SL, Chen Y, Li L, Li SS, Chang JL, Schwarz Y, et al. UGT1A6 and UGT2B15 polymorphisms and acetaminophen conjugation in response to a randomized, controlled diet of select fruits and vegetables. *Drug Metabol Dispos* 2011;39:1650–7.
 Crossref  Google Scholar
- [31] Jari R, Raf M, Joachim B, Patrick A. Exploring gastric drug absorption in fasted and fed state rats. *Int J Pharm* 2018;548:36–641.
 Web of Science  Google Scholar
- [32] Feng R, Wang Y, Liu C, Yan C, Zhang H, Su H, et al. Acetaminophen-induced liver injury is attenuated in transgenic fat-1 mice endogenously synthesizing long-chain n-3 fatty acids. *Biochem Pharmacol* 2018;154:75–88.
 PubMed  Web of Science  Crossref  Google Scholar
- [33] Speck RF, Lauterburg BH. Fish oil protects mice against acetaminophen hepatotoxicity in vivo. *Hepatology* 1991;13:557–61.
 PubMed  Google Scholar
- [34] de Meijer VE, Kalish BT, Meise JA, Le HD, Puder M. Dietary fish oil aggravates paracetamol-induced liver injury in mice. *J Parenter Enteral Nutr* 2013;37:268–73.
 Crossref  Web of Science  Google Scholar
- [35] Jaeschke H, McGill MR, Williams CD, Ramachandran A. Current issues with acetaminophen hepatotoxicity clinically relevant model to test the efficacy of natural products. *Life Sci* 2011;88:737–45.
 PubMed  Crossref  Web of Science  Google Scholar
- [36] Cone EJ, Jenkins AJ. Saliva drug analysis. In: Wong SH, Sunshine I, editors. *Handbook of analytical therapeutic drug monitoring and toxicology*. Boca Raton, FL: CRC Press, 1997:303–33.
 Google Scholar
- [37] Kneisel S, Auwarter V, Kempf J. Analysis of 30 synthetic cannabinoids in oral fluid using liquid chromatography-electrospray ionization tandem mass spectrometry. *Drug Test Anal* 2013;5:657.
 Crossref  Web of Science  PubMed  Google Scholar
- [38] Langel K, Gjerde H, Favretto D, Lillsunde P, Øiestad EL, Ferrara SD, et al. Comparison of drug concentrations between whole blood and oral fluid. *Drug Test Anal* 2014;6:461.
 PubMed  Web of Science  Google Scholar
- [39] Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm Res* 1995;12:413–20.
 PubMed  Crossref  Google Scholar
- [40] Idkaidek NM. Comparative assessment of saliva and plasma for drug bioavailability and bioequivalence studies in humans. *Saudi Pharm J* 2017;25:671–5.

- [41] Idkaidek N, Arafat T. Saliva vs. plasma bioequivalence of paracetamol in humans: validation of class I drugs of the salivary excretion classification system. *Drug Res (Stuttg)* 2014;64:559–62.
 Crossref  Google Scholar
-

Copyright © 2011–2019 by Walter de Gruyter GmbH

Powered by PubFactory