Original Article

Gender Variations in Pharmacokinetics of Paracetamol in Hausa/Fulani Ethnic group in Northwest Nigeria – A Two-stage Approach

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Abstract

Background: Paracetamol is one of the most commonly used drugs worldwide and has been linked to drug-related liver damage, even when taken at recommended doses. Ingesting the upper limit of recommended doses of the drug produced a doubling of mortality when compared to not taking the drug. Acetaminophen ingestion has been implicated in the development of angioedema, the exasperation of asthma, and urticaria in patients with aspirin intolerance. **Aim:** This study aimed at assessing gender variations in the pharmacokinetics of paracetamol in Hausa/Fulani, the most populous ethnic group in Nigeria and determines a possibility of toxicity in the group. **Methods:** It was an exploratory study involving twenty participants selected by criterion sampling who satisfied inclusion criteria. They were fasted 11-h preceding acetaminophen administration to 3 h after administration. A single dose of acetaminophen, 1 g orally with 300 ml of distilled water, was administered at 8 A. M. Blood was obtained before the administration and 15, 30, and 45 min, and 1, 2, 3, 4, 5, and 6 h after the administration. Acetaminophen plasma concentrations were determined by validated reverse-phase high-performance liquid chromatography Food and Drug Administration guidelines. **Results:** Six out of 19 (31.6%) participants have higher than maximum therapeutic plasma concentration (>20 μg/ml). Pharmacokinetics parameters were higher in males except for clearance and volume of distribution. **Conclusion:** Clearance from the plasma tends to be more for females than their male counterparts. A good proportion of Hausa/Fulani is prone to acetaminophen toxicity at a therapeutic dose.

Keywords: *Gender, Hausa/Fulani, paracetamol, pharmacokinetics*

Introduction

Paracetamol has been recognized as the most commonly used drug globally, consumed by billions of people across different ages and ethnic groups for both chronic and acute pains.[1] It is the World Health Organization's first step of the analgesic ladder for the treatment of cancer and is also prescribed in osteoarthritis and low back pain.[2] It is responsible for 46% of all acute liver failures in the United States and 40%–70% in the United Kingdom and Europe, respectively.[3] Paracetamol at the recommended dose can no longer be regarded as safe as previously believed.[4]

Inter-ethnic variations in drug response are a well-recognized phenomenon.[5] For a drug consumed by billions of people worldwide, the toxicity of a minute proportion translates into millions of people being affected. During the clinical trial phase of drug development, the test drug is administered without necessarily considering ethnicity and when successfully released into the markets, it is consumed by individuals from diverse ethnic backgrounds on a one-dose-fits-all basis.[6] Personalized medicine is, therefore, premised on administering the right drug at the right dose, to the right patient thereby minimizing adverse drug reactions and enhancing patients' compliance and cost-effectiveness.[7,8] It is, however, very expensive and maybe impossible in developing economies. Focusing therapy based on an ethnic group may be less cumbersome, less expensive, and practical.[9] The relationship between individual participant's demographics and variation in pharmacokinetics can be harnessed toward individualized therapy.[10]

A two-stage approach is employed in pharmacometrics to determine pharmacokinetic parameters in a group of individuals using mean

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estimates.[11] This study aimed at evaluating gender variations in the pharmacokinetics of paracetamol in Hausa/Fulani, the most populous ethnic group in Nigeria and determines a possibility of toxicity in the group. In a previous similar study involving a Yoruba ethnic group, out of 8 participants, 3 were found to have higher than the therapeutically acceptable concentration of paracetamol in their plasma after taking a therapeutic dose.[12] This calls for concern considering the rampant use of paracetamol as the counter drug and its role in hepatotoxicity. So far, to the best of our knowledge, no similar study has been carried in the studied population previously.

Materials and Methods

Design, description of study population

It was an exploratory study in one population. Twenty participants resident in Sokoto from Hausa/Fulani extractions were enrolled through their expressed consents verified by one of the researchers.

Eligibility, exclusion criteria

Only healthy participants as established by physical examination, vital signs measurements, and routine laboratory assessments performed before administration of acetaminophen were enrolled. All volunteers who drink alcohol, smoke tobacco, or suspected of hypersensitivity to acetaminophen were excluded. Other criteria were taking any prescription or herbal medicines within 2 weeks before the study or any over-the-counter medication within 1 week before the study. Similarly, all pregnant, lactating females and children were excluded.[13,14]

Sample size, sampling techniques

Sample was calculated using $n = \{Z_1\text{-}\alpha\sqrt{[P_O\ (1\text{-}P_O)]} + Z_1\text{-}\beta\sqrt{[P_a\ (1\text{-}P_a)}\}^2 \div (P_o\text{-}P_a)^2$.[15] where n = estimated sample size.

Z_1 = standard normal deviation, which is 1.96 at α=0.05, and 0.84 at 80% statistical power.

P_O = Test value of population proportion under the null hypothesis. P_a = anticipated the value of the population proportion. The sample size was calculated based on a conservative estimate of intrasubject multiplicative coefficients of variation (CV) of up to 30% in acetaminophen. Pharmacokinetics between tribes, with alpha = 0.05 and a power of at least 80%. This allows rejection of the respective null hypothesis.[16]

$P_O = 0.30$, $P_a = 0.5$, $\alpha = 0.05$, $\beta = 1–0.05 = 0.95$

The participants were selected by the criterion sampling technique. Only those who satisfied the inclusion criteria were chosen.

Ethical consideration

The study was carried out according to the Declaration of Helsinki. All participants read and signed a study-specific informed consent form before participating in the study and participation was voluntary. The study protocol, investigators, study site, informed consent form, and recruiting materials were approved by the Ethics Committee of Sokoto State Ministry of Health Nigeria.

Blood sampling

The volunteers were fasted 11-h preceding acetaminophen administration to 3 h after administration. A cannula was inserted into a forearm vein to facilitate the sampling of venous blood. A single dose of acetaminophen, 1 g orally with 300 ml of distilled water by 8 A. M administered. Four participants per day were studied. Blood was obtained before acetaminophen administration and 15, 30, and 45 min, and 1, 2, 3, 4, 5, and 6 h after the administration. At each time point, 5 mL of the whole blood from each participant were collected.[17] After centrifugation (3000 rpm, 10 min), plasma samples were harvested and stored in a freezer at − 4 before analysis.

Acetaminophen plasma concentrations were determined by validated reverse-phase high-performance liquid chromatography (HPLC) Food and Drug Administration (FDA) guidelines.[18] This method was developed by Pharmaceutical Product Development (Middleton, WI, USA) and validated over a calibration range of 100–50,000 ng/mL for acetaminophen using 0.100 mL of plasma containing K_2EDTA. The method was validated for linearity, precision, accuracy, ruggedness, recovery, and specificity.

Chromatographic conditions

The acetaminophen separation and quantification were done with HPLC. It consisted of a Degasser Shimadzu DGU-20A (Shimadzu Corporation, Japan), Shimadzu LC 10 AI solvent delivery system equipped with ultraviolet–visible variable wavelength detector Shimadzu FCV 10 AL VP (Shimadzu Corporation, Japan), Sample Cooler, and Auto Sampler SK-10AR. It was fitted with column C18 (4.0 mm × 150 mm × 5.0 µm). The mobile phase was prepared by mixing acetonitrile and water 50:50 (v/v). Acetaminophen and acetofenitidin internal standard were detected at 270-nm wavelength. The flow rate was 0.3 ml/min.

Stock and standard solution preparation

It was prepared with 100 mg of acetaminophen accurately measured using validated weighing balance, into a volumetric flask containing 100 mL of acetonitrile to give 1 mg/ml. From this stock, 1 mg was added to 10 ml of acetonitrile to obtain 100 µg/mL, to obtain 50 µg/mL, 2.0 ml of water was added to 2.0 ml of the 100 µg/mL. To obtain 25 µg/mL, 2.0 ml of water was added to 2.0 ml of the 50 µg/mL.

Quality control preparation

These preparations were gotten by spiking 100 µg of standard solution into 1.9 ml of plasma (matrix) that was harvested from donors' blood after vortex and centrifuged at 8000 g. This was to obtain concentrations range of 12.5 mg/L, 25 mg/L, and 50 mg/L and were stored at −20°C.

Data analyses and statistics

During data cleaning, one participant's data were found as an outlier and were not included in the analysis. The remaining 19 participants' data generated from chromatograms were analyzed using noncompartmental analysis with a linear trapezoidal method with PKSolver version 2.0 Software which was validated for C_{max}, T_{max}, $t_{1/2}$, area under the curve (AUC) $_{0-6,}$ MRT, Vz/F, and CL/F. Mean, standard deviations, and coefficient of variations were calculated for the participants.

Table 1: Demographic characteristics of participants (*n*=19)

Variable	Range	Mean±SD
Age (years)	19-46	26.5±8.4
Weight (kg)	35-13	66.3±23.3
Height (m)	1.5-1.8	1.7±0.9
BMI (kg/m^2)	13.7-37.2	22.4±6.3

The mean body mass index of the participants is within the nonobese range. BMI: Body mass index; SD: Standard deviation

Results

Results are displayed in Tables 1-3.

Discussion

The linear trapezoidal rule, a noncompartmental analysis method employed in this study for the determination of secondary parameters, revealed the proportion of study participants with C_{max} was greater than the upper limit of the therapeutic range [Table 2] and was close to 36% reported previously in the Nigerian Yoruba ethnic group.[12] Other pharmacokinetic parameters such as T_{max} and C_{max} were also similar. However, another similar study in Jos, Nigeria, revealed higher mean C_{max}, T_{max}, and Cl/F parameters than the findings in the index study.[19] This further demonstrated variability in the metabolism of acetaminophen among ethnic groups within the same country. Conversely, a comparable study in Mozambique reported a contrasting result in which none of the participants was found to have plasma levels beyond the therapeutic range (mean C_{max} = 12.4 mg/L).[20]

The mean peak plasma values (17.5 µg/mL) observed in this study were lower than 23.8 µg/mL among the Chinese population earlier documented. However, the time to attain a peak of 0.84) was close to 0.66 h reported.[21] Time to attend peak plasma concentration reflects absorption rate and together with elimination rate considerably varies

Table 2: Pharmacokinetic parameters of individuals by two-stage approach

ID	Age (years)	BMI (kg/m^2)	Gender	T_{max} (H)	C_{max} (µg/ml)	AUC_{0-6} (µg/ml*h)	$T_{1/2}$ (H)	MRT (H)	C1/F (µg/µg/ml*h)	V_z/F (µg/ml/h)
1	38	21.8	Female	0.75	19.29	53.33	2.9	4.5	13.8	57.3
2	40	37.2	Female	0.25	9.67	31.88	6.3	9.7	13.9	125.4
3	20	24.2	Male	0.5	10.41	34.2	2.9	4.4	21.9	94.6
4	21	20.4	Male	0.5	15.48	47.59	4.3	6.5	12.3	76.4
5	42	33.3	Female	0.5	12.81	31.4	2.7	4.6	22.6	87.9
6	22	23.0	Female	0.25	17.49	31.40	12.86	18.9	8.3	154.4
7	34	24.2	Female	0.25	15.12	47.77	3.8	5.6	13.7	74.5
8	24	20.7	Female	1	27.18	85.64	1.0	2.76	10.9	16.4
9	19	13.7	Female	0.5	24.6	71.12	2.7	4.3	10.5	41.5
10	22	21.0	Female	1	21.24	58.45	1.9	3.2	15.2	40.8
11	24	27.3	Female	2	20.82	75.25	1.4	3.4	12.1	23.6
12	25	17.7	Male	0.75	14.55	63.48	3.5	5.8	10.1	50.8
13	20	17.9	Male	0.75	24.63	80.34	3.4	6.1	8.6	42.4
14	22	15.0	Male	2	13.46	57.5	4.6	7.4	9.7	64.8
15	20	23.2	Male	1	14.5	53.6	4.4	6.7	10.9	68.9
16	23	17.5	Male	0.25	21.65	73.68	5.4	7.8	7.4	58.2
17	23	18.2	Male	2	13.51	60.64	3.2	5.1	11.8	54.1
18	21	18.8	Male	1	12.22	53.10	6.4	9.8	8.3	76.9
19	23	18.9	Male	0.75	16.99	65.34	5.4	7.9	8.1	63.7
Mean±SD	25.4±8.42	21.8±6.3		0.84±1.09	17.3±27.03	56.6±151.2	4.2±4.2	6.5±3.6	12.1±4.2	66.9±32.9
CV (%)		28.1		103.8	117	167.6	61.9	55.4	34.7	49.2

Six out of 19 participants have higher than maximum therapeutic plasma concentration (>20 µg/ml). ID: Identity; T_{max}: Time taken to attain maximum plasma concentration; C_{max}: Maximum concentration attained in plasma concentration–time curve; AUC: Area covered by plasma concentration–time curve following drug administration; $t_{1/2}$: Half-life; MRT: Mean resistance time; Cl/F: Drug clearance; V_z/F: Apparent volume of distribution; SD: Standard deviation; CV: Coefficient of variation

Table 3: Gender comparison of pharmacokinetics parameters by two-stage approach

Gender	Tmax (h)	Cmax (µg/mL)	$AUC_{0\text{-}6\ (\mu g/mL*h)}$	$T_{1/2\ (h)}$	MRT (h)	Cl/F (µg/µg/mL*h)	V_2/F (µg/mL/h)
Male	1	22.6	121.5	6.7	10.1	34.9	3.6
Female	0.5	12.7	54.0	2.5	4.2	52.2	14.4

There is obvious gender variation in the primary pharmacokinetic parameters as displayed above. Except for clearance and volume of distribution, estimates for the pharmacokinetic parameters are higher in males than females. T_{max}: Time taken to attain maximum plasma concentration; C_{max}: Maximum concentration attained in plasma concentration–time curve; AUC: Area covered by plasma concentration–time curve following drug administration; $t_{1/2}$: Half-life; MRT: Mean resistance time; Cl/F: Drug clearance; V_z/F: Apparent volume of distribution

among populations. The mean time to attain maximum plasma concentration found in our study participants was quite lower than 1.48 ± 0.61 reported by Raffa *et al*. and higher than 0.25 ± 0.02 documented by FDA.[22]

The mean half-life of acetaminophen following oral administration of therapeutic dose was reported as 2 h in the range of 1.5–3 h in a study done previously.[23] Tobacco smoking, alcohol, and oral contraceptives have all been shown to prolong the half-life of acetaminophen.[24] Our findings in this study revealed that more than half of the respondents have acetaminophen half-lives greater than 3 h. However, the shorter half-life observed in females compared to their male counterparts was quite in agreement with what was reported in African-Americans.[25] However, this value was quite higher than 2.0 ± 0.4 and 2.9 ± 0.9 reported in preceding studies.[17,26]

This is worrisome as higher plasma concentration coupled with prolonging half-life (>4 h) are strong predisposing determinants for possible liver damage.[27] The greater majority of the population freely consumes acetaminophen as an OTC drug as a single drug or in combination. This necessitates the dire need to focus attention on the dosage regimen for acetaminophen in this part of the world. The mean area under concentration–curve time (90.2 µg/mL*h) observed in this study was similar to the one reported in a preliminary study earlier reported.[12] This may not be surprising because the study participants were within the same country, and absorption and elimination which are key determinants of AUC did not remarkably differ. However, the finding was close to 57.6 ± 10.4 µg/mL*h but sharply disagrees with 38.8 ± 4.3 documented in previous studies, respectively.[15,26]

Our findings on clearance and apparent volume of distribution were quite lower when compared to the values documented by other workers.[28] Despite variation in the study participants and geography, our findings were close to the ones reported in previous studies.[29,30] This observation has reechoed the variability in the pharmacokinetics of acetaminophen within and between populations.

Conclusion

Clearance from the plasma tends to be more for females than their male counterparts. A good proportion of Hausa/Fulani is susceptible to acetaminophen toxicity at a therapeutic dose.

Ethical clearance

The ethical clearance was granted by Sokoto state Ministry of Health, Nigeria.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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