Pharmacokinetics and saliva secretion of paracetamol in healthy male Nigerians

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Summary
A preliminary pharmacokinetic study of paracetamol was carried out in Nigerians for whom it is normal to consume paracetamol or its combination during almost any type of symptoms. After a single oral dose of 1000mg of the drug to eight adult male volunteers, paracetamol was measured in plasma and saliva using high-performance liquid chromatography.

The plasma profile showed a biexponential decline after peak absorption. Some of the pharmacokinetic parameters compared with previous results from Caucasians and Asians although some differences were observed. The absorption of paracetamol was rapid with mean t\textsubscript{max} of 0.875 ± 0.44h (range, 0.5 - 1.5h) and was 20 times faster than elimination rate. The C\textsubscript{max} varied between 11.46 and 26.44 μg/mL\textsuperscript{1} with three of the subjects having C\textsubscript{max} greater than the 20 μg/mL\textsuperscript{1} limit for therapeutic level. The elimination half-life was slightly longer than previous reports, with four subjects having t\textsubscript{1/2} above 3h. The t\textsubscript{1/2} was found to correlate significantly (p <0.01) with the mean residence time (MRT), an indication that MRT can be used where t\textsubscript{1/2} cannot be evaluated. The oral clearance was slightly lower (about 25%) than earlier reports in some Caucasians and Asians.

The absorption parameters from saliva (C\textsubscript{max}, t\textsubscript{max}, AUC and saliva levels) correlated well (r = 0.88 to 0.999) with those from plasma. The plasma levels were higher than saliva in all the subjects studied with variable S/P ratio of 0.64 ± 0.1 in contrast to earlier reports of S/P ratios above unity.

In conclusion, the pharmacokinetics of paracetamol in Nigerians shows possibility of higher plasma levels and slower clearance from the body.

Keywords: Paracetamol, Pharmacokinetics, Saliva

Résumé
Les pharmacokinetiques et la secretion du salive Paracetamol chez les (hommes) nigerians en bonne santé.

Une etude pharmacokinetique préliminaire du paracetamol a été effectuée sur des Nigerians chez qui c'est normal de consommer paracetamol ou sa combination pendant Presque n'importe quel type des symptomes. Après une seule dose par voie orale de 1000 mg d’une drogue pour huit adultes hommes volontaires, paracetamol était mesure en plasma et en salive tout en utilisant liquide chromatographique d’une performance très élevée.

Le profil de la plasma a indiqué une diminution biexponentielle après une forte absorption. Quelques uns des paramètres du pharmacokinetiques ont été comparés avec les résultats précédents des blancs et des indiens quoique quelques differences aient ete remarqués. L’absorption du paracetamol était rapide avec un moyen de max de 0.875 + - 0.44h (de l'ordre, 0,5 - 1,5h) et était vingt fois plus rapide que le taux de l'élimination. Le Cmax varie entre 11,46 et 26,44 μg/mL avec trois des sujets ayant Cmax plus élevé qui le 20 μg/mL limite pour le niveau thérapeutique. L’élimination demi-vie était légèrement plus long plus que des résultats précédents, avec quatre patients ayant t1/2 au dessus de 3hrs. On a remarqué que le t1/2 était en correlation sensiblement (P <0.01) avec le temps moyen de la demeure (MRT) (Mean Residence Time), une indication que le MRT pourrait être utilisé là où le t1/2 ne peut être évalué. La clairance orale était légèrement en baisse (environ 25%) plus que des rapports précédents chez quelques blancs et indiens.

Les paramètres de l’absorption de salive (Cmax, tmax, AUC et les niveau de salive) étaient très bien en correlation avec (r = 0.88 a 0.999) avec ceux du plasma. Les niveaux de plasma étaient plus élevés que le salive chez tous les patients étudiés avec une proportion S/P variable de 0,64 + -0,1 par rapport aux résultats précédents d’une proportions /P au dessus de l’unité.

En conclusion, le pharmacokinetics de paracetamole chez des Nigerians montre la possibilité des niveaux élevés de plasma et une clairance graduelle dans le corps.

Introduction
Paracetamol (N-acetyl p-aminophenol) is the most widely used non-prescription analgesic and antipyretic medication in Nigeria and is also one of the most commonly available pharmaceutical products in the Nigerian drug market.\textsuperscript{1} It is readily available over the counter and is found in the drug market under several brand names and in many proprietary combinations with other drugs. The importance of characterising differences in drug disposition and response among patients of various backgrounds has been highlighted by many authors.\textsuperscript{2, 4} The disposition of paracetamol has for a long time been widely reported among Caucasians and Asians.\textsuperscript{3, 10} In one of the studies, it was found that oral clearance was approximately higher in Caucasians than Asians,\textsuperscript{3} while Yin et al, 2001\textsuperscript{10} observed that oral clearance was 16 - 56% lower in Hong Kong Chinese as compared with Caucasians and Australian Chinese. Despite the popularity of paracetamol in Nigeria and in Africa in general, only little information is available on its full pharmacokinetics in human.

The pharmacokinetics of paracetamol is reported to be dose-dependent with its elimination half-life increasing significantly during overdosage of the drug.\textsuperscript{11} Death due to
paracetamol poisoning and overdose has been widely reported in Britain and USA, but in Africa due to dearth of information, the actual incidence of paracetamol poisoning, its morbidity and mortality are hardly known. Changes in plasma concentrations of paracetamol have been used to indicate possible hepatic necrosis. It is therefore needful to have a baseline data on pharmacokinetics of paracetamol in this African population.

The use of saliva for therapeutic drug monitoring has been receiving increasing attention. As a non-invasive and painless method, saliva sampling is less discomforting and risky than blood sampling. It also does not carry the risk of infection such as HIV/AIDS. The relationship between saliva and plasma or serum levels of paracetamol has been reported. While some of these workers reported significant correlation between some of the parameters from saliva and plasma (or serum) concentration, there was no agreement that saliva could be used for pharmacokinetic studies due to lack of correlation and high variable saliva to plasma (S/P) ratios. While the earlier studies were carried out by non-specific and non-sensitive spectrophotometric assay methods, the later were carried out in haemodialysis patients and in subjects who took overdose.

The main aim of this study was to evaluate the disposition of paracetamol in healthy Nigerians and to carry out a preliminary investigation into the relationship between saliva and plasma - derived pharmacokinetic parameters using a HPLC method.

Materials and methods

The study was undertaken at Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria, and was part of the bioavailability and bioequivalence studies of different brands of paracetamol in healthy volunteers. Ethical permission for the study was given by the Obafemi Awolowo University Teaching Hospital Ile-Ife.

Subjects

Eight healthy adult male volunteers between ages 24 and 34 years (mean, 26.8 ± 3.3 years) and weighing between 65 and 79kg (mean, 68 ± 4.8kg) participated in the study after giving written informed consent. All participants were non-smokers and they abstained from other medications and alcohol prior to and throughout the duration of the study.

Drug administration and sampling

All patients observed an overnight fast and each received 2 x 500mg paracetamol tablets (Pizermol, Pfizer Nig. Plc) with 200mL of water. Food was withheld until 4h post dose. Blood samples were withdrawn from a forearm vein prior to and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24h after drug administration. The blood samples were immediately centrifuged for 10min at 3,000 rev/min to obtain plasma.

In three out of the eight subjects, after a washout of the mouth with water, stimulated saliva (about 5mL) was collected into universal bottles at the same time as venous blood, by sucking a sterilized glass head. The pH of the saliva samples was taken. All plasma and saliva samples were stored at -20°C until analysis.

Analytical method

A modification of the HPLC method described by Amer et al, 1981 was used for the analysis of paracetamol in plasma and saliva. The drug and internal standard, 2-acetamidophenol (2-AAP) were extracted with ethyl acetate. The extract was dried under nitrogen at 50°C and the residue reconstituted in methanol. An aliquot (20μL) was chromatographed on a C18 reversed-phase column (5μm) run with a mobile phase of phosphate buffer - acetonitrile - methanol - perchloric acid (86:8:6:1). The detection was by UV fixed at 254nm. Calibration curves in plasma and saliva were linear (r=0.999) in the range of 0 to 15μg/mL. The limit of detection was 50ng/mL. Interassay coefficients of variations were less than 10% in both plasma and saliva at concentrations 2 and 10μg/mL.

Pharmacokinetic and data analysis

Pharmacokinetic parameters were calculated from plasma and saliva drug concentration - time data (t_max, C_max, AUC, t1/2, Vd, CL, MRT) by non-compartmental methods. The t_max, and C_max were obtained directly from drug concentration profiles as the time required to reach the highest concentration and the highest concentration respectively. The absorption rate constant (ka or α) was calculated by method of residuals, while the elimination rate constant (kel or β) was calculated by least squares method. The absorption and elimination half lives were calculated as In(α) (or 693/α) and In(β) (or 693/β) respectively. The area under the curve (AUC) and the area under the first moment curve (AUMC) were estimated by trapezoidal methods ([C_i + C_{i+1}/2(t_{i+1} - t_i)]). The percentage of AUC extrapolated from 12h to infinity was between 4 and 13% in all subjects. The mean residence time (MRT) was estimated as AUMC/AUC. Oral clearance (CL/F) was calculated as Dose/AUC.

All results were expressed as mean ±SD. The correlation data generated were analysed using linear regression. Values of p <0.05 were considered as significant.

Results

The mean plasma concentration - time profile for paracetamol in the eight volunteers is shown in Figure1. Table 1 shows the subject characteristics and kinetic parameters of paracetamol. There was inter-individual variability in some of the pharmacokinetic data obtained, especially in the maximum plasma concentration (C_max). The C_max varied from 11.46 to 26.44 μg/mL (mean, 17.96 ± 5.98μg/mL).

The mean concentration time profiles in plasma and saliva in three volunteers are shown in Figure 2. The plasma paracetamol levels were higher than the saliva levels and were nearly parallel to each other. Table 2 shows the comparison of some pharmacokinetic parameters derived from both saliva and plasma in three of the subjects. The t_max from both saliva and plasma were nearly indistinguishable, varying between 0.5 and 1.5 in both saliva (mean, 1.00±0.41h) and plasma (mean, 1.17±0.47h). The C_max and AUC values from plasma were consistently higher in the three subjects than saliva with mean C_max S/P ratio of 0.60±0.03μg/mL, mean AUC S/P ratio of 0.70±0.18μg.hmL, and mean S/P ratio of 0.64±0.10.
Table 1 Pharmacokinetic parameters of paracetamol derived from plasma after a single oral administration of 1000 mg to eight volunteers

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>t_{max} (h)</th>
<th>C_{max} (µg/mL)</th>
<th>AUC</th>
<th>t_{1/2α} (h)</th>
<th>t_{1/2β} (h)</th>
<th>MRT (h)</th>
<th>CL/F (mL/min·kg)</th>
<th>Vd (L/kg)</th>
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<tr>
<td>I</td>
<td>27</td>
<td>65</td>
<td>0.5</td>
<td>18.10</td>
<td>51.26</td>
<td>0.13</td>
<td>3.44</td>
<td>5.06</td>
<td>5.00</td>
<td>1.45</td>
</tr>
<tr>
<td>II</td>
<td>34</td>
<td>65</td>
<td>1.5</td>
<td>13.67</td>
<td>55.29</td>
<td>0.12</td>
<td>3.53</td>
<td>4.35</td>
<td>4.63</td>
<td>1.58</td>
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<tr>
<td>III</td>
<td>28</td>
<td>65</td>
<td>0.5</td>
<td>12.46</td>
<td>46.51</td>
<td>0.15</td>
<td>2.52</td>
<td>4.19</td>
<td>5.51</td>
<td>1.20</td>
</tr>
<tr>
<td>IV</td>
<td>24</td>
<td>68</td>
<td>1.0</td>
<td>25.42</td>
<td>57.90</td>
<td>0.19</td>
<td>2.95</td>
<td>4.67</td>
<td>4.23</td>
<td>1.13</td>
</tr>
<tr>
<td>V</td>
<td>24</td>
<td>79</td>
<td>1.5</td>
<td>14.05</td>
<td>58.11</td>
<td>0.17</td>
<td>2.40</td>
<td>4.15</td>
<td>3.63</td>
<td>0.53</td>
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<tr>
<td>VI</td>
<td>27</td>
<td>68</td>
<td>1.0</td>
<td>11.46</td>
<td>45.58</td>
<td>0.16</td>
<td>2.60</td>
<td>4.32</td>
<td>5.38</td>
<td>1.44</td>
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<tr>
<td>VII</td>
<td>26</td>
<td>72</td>
<td>0.5</td>
<td>26.44</td>
<td>84.29</td>
<td>0.13</td>
<td>4.60</td>
<td>5.80</td>
<td>2.75</td>
<td>2.10</td>
</tr>
<tr>
<td>VIII</td>
<td>24</td>
<td>67</td>
<td>0.5</td>
<td>22.06</td>
<td>54.03</td>
<td>0.16</td>
<td>3.87</td>
<td>5.20</td>
<td>4.96</td>
<td>1.24</td>
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<tr>
<td>Mean</td>
<td>26.75</td>
<td>68.63</td>
<td>0.875</td>
<td>17.96</td>
<td>56.62</td>
<td>0.15</td>
<td>3.24</td>
<td>4.72</td>
<td>4.51</td>
<td>1.33</td>
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<tr>
<td>SD</td>
<td>3.33</td>
<td>4.81</td>
<td>0.44</td>
<td>5.98</td>
<td>12.13</td>
<td>0.02</td>
<td>0.76</td>
<td>0.59</td>
<td>0.94</td>
<td>0.45</td>
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</table>

Table 2 Comparison of absorption characteristics of paracetamol derived from plasma and saliva concentrations after single oral dose of 1000 mg of the drug to three volunteers

<table>
<thead>
<tr>
<th>Subject</th>
<th>Plasma C_{max} (µg/mL)</th>
<th>Plasma AUC (µg·h/mL)</th>
<th>Plasma AUC_{1/2} (µg·h/mL)</th>
<th>Saliva C_{max} (µg/mL)</th>
<th>Saliva AUC (µg·h/mL)</th>
<th>Saliva AUC_{1/2} (µg·h/mL)</th>
<th>AUCs/AUCp</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>1.5</td>
<td>13.67</td>
<td>50.76</td>
<td>1.5</td>
<td>14.05</td>
<td>53.69</td>
<td>0.77</td>
</tr>
<tr>
<td>V</td>
<td>1.5</td>
<td>14.05</td>
<td>53.69</td>
<td>0.5</td>
<td>22.06</td>
<td>50.16</td>
<td>0.49</td>
</tr>
<tr>
<td>Mean</td>
<td>1.17</td>
<td>16.59</td>
<td>51.54</td>
<td>1.17</td>
<td>16.59</td>
<td>51.54</td>
<td>0.70</td>
</tr>
<tr>
<td>SD</td>
<td>0.47</td>
<td>4.73</td>
<td>1.89</td>
<td>0.47</td>
<td>4.73</td>
<td>1.89</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Fig. 1 Mean plasma concentration-time curve after a single oral administration of 1000mg paracetamol to eight volunteers

Fig. 2 Plasma and saliva levels of paracetamol after a single oral administration of 1000mg of the drug to volunteers.

Discussion

The profile in Figure 1 shows a biexponential decline after peak absorption and this agrees with the observation of Aneer et al., 1981. 10 Inter-subject variations in paracetamol disposition have been documented. 7, 21 The absorption of paracetamol from the table t was relatively rapid with peak plasma concentrations generally attained within 0.5 to 1.5h in all volunteers (mean of less than 1h). The absorption rate was approximately 20 times faster than the elimination rate as indicated by the average absorption half-life of about 9min (0.15± 0.02h) and elimination half-life of over 3h (3.24± 0.76h) (Table 1).

Fig. 3 A plot of saliva paracetamol concentrations against simultaneous plasma levels monitored after a single oral administration of 1000mg of the drug to volunteers.

Therapeutic levels of paracetamol have been suggested to be between 10 - 20 µg/mL in plasma after taking 1000mg dose. 23 In the present study, three out of the eight subjects (about 38%) had C_{max} values greater than 20µg/mL. The mean resident time (MRT) ranged from 4.19 to 5.20h (mean, 4.72± 0.59 h) and this was found to correlate significantly with the elimination half-life (r = 0.09, p < 0.05). This indicates that in situations where the t_{1/2} cannot be determined for paracetamol, the MRT can be used and vice versa. MRT, which describes the average time for all the drug molecules to sojourn in the body is usually directly proportional to t_{1/2} for drugs that are administered by intravenous route (iv) and which exhibit one compartment model, 21 but oral administration of paracetamol seems to obey this principle from this study.

The pharmacokinetics of paracetamol may not be
significantly different from that in other races such as Caucasians and Asians, however, slight differences were observed in some of the parameters. The $t_{1/2}$ reported in the present study appears to be slightly higher than those from Caucasians and Orientals. After therapeutic doses of paracetamol in adults is usually between 1.5 and 3 h (with mean values of 2 h), but in this case, four out of the eight volunteers (50%) had $t_{1/2}$ above 3 h. High plasma concentrations and long elimination half-life ($t_{1/2} > 4 h$) have been used to indicate possible liver damage. In the present study, the subject (VII) with the highest Cmax of 26.44 μg/mL-1 also had the longest $t_{1/2}$ of 4.6 h (Table 1).

The oral clearance (CL/F) (4.51±0.94 mL/min·Kg-1) was about 25% lower than various reports from Caucasians and Chinese with mean oral clearance above 6 mL/min·Kg-1 in the two races. However, a parallel study with other races is needed to confirm this observation. In another comparison study on disposition of paracetamol among factory workers in London, oral clearance in Caucasians were approximately 25% higher than in Asians. Also significant differences have been observed in the urinary excretion of paracetamol between Spanish, Caucasians and Blacks. Some other evidence suggests that paracetamol pharmacokinetics is minimally affected by race.

There were intra- and inter-individual variations in the saliva to plasma (S/P) ratios but the variations were independent of sampling time over the 0-12 h interval. Statistical comparisons were not performed due to the small sample size (n = 3). The relationship between saliva and simultaneous plasma concentrations of paracetamol was linear with a significant correlation (r) of 0.89 (p < 0.001) as shown in Figure 3. The correlation between saliva and plasma AUC and Cmax were 0.823 and 0.999 respectively.

In the present study, the similarity in $t_{1/2}$ of both saliva and plasma indicates that equilibrium is reached rapidly between them, in line with Posti’s hypothesis that saliva be regarded as an integral part of the central compartment, rather than a ‘deep’ pharmacokinetic compartment.

The consistently higher levels of paracetamol obtained from plasma than in saliva are in contrast to the reports of Lee et al, 1996 and Bruner et al, 1998. These authors observed higher, variable and unpredictable S/P ratios (range, 2.1 to 2.9) and AUC/S/P ratios (range, 1.39 to 2.3) respectively. While Lee et al studied chronic dialysis patients with end stage renal failure, Bruner et al carried out their study in volunteers who took 2 G single dose of paracetamol. There is therefore the possibility of dose-dependent disposition of paracetamol in these two situations as reported by Prescott, 1983, which can possibly lead to active secretion of the drug into saliva.

The significant correlation between saliva and plasma levels (r = 0.89) is also an indication of passive diffusion of the drug from plasma to saliva. However, the considerable intra- and inter-individual variations in S/P ratio may imply that other factors may be at work.

In conclusion, this study has evaluated the pharmacokinetics of paracetamol in Nigerians showing possibility of higher plasma levels and slower clearance.

References


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