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# COMPARISON OF PARACETAMOL PHARMACOKINETICS IN PANADOL® AND PANADOL EXTRA®

***M.T. Bakare-Odunola and A. Abubakar**
*Department of Pharmaceutical and Medicinal Chemistry,*
*Faculty of Pharmaceutical Sciences,*
*Ahmadu Bello University, Zaria-Nigeria*

**Abstract**
The influence of caffeine (60mg) was studied on the pharmacokinetic characteristics of paracetamol (1000mg single dose) in six healthy male human volunteers. A double beam spectrophotometer was used to analyse salivary paracetamol concentrations. Caffeine caused a significant ($p< 0.05$) decrease in the saliva concentration of paracetamol ($C_{max}$) and area under salivary paracetamol concentration curve (AUC). There was no statistically significant increase in elimination half-life ($t_{1/2el}$) and clearance (Cl) of paracetamol in man. There was statistically significant increase in half life of absorption of paracetamol ($t_{1/2ab}$) from Panadol Extra®. The results indicated impaired absorption of paracetamol from Panadol Extra®. 

**Key words:** *Paracetamol; caffeine; pharmacokinetics; saliva*

## INTRODUCTION

Paracetamol (Acetaminophen) is one of the most commonly used analgesic, antipyretic drugs worldwide, and it is widely available by prescription and over the counter (OTC). Panadol Extra® is paracetamol (500mg) co-formulated with caffeine (30mg). It is widely used by manual workers in Nigeria; for the treatment of mild to moderate pain of various etiologies.

Caffeine has been an additive in analgesic for many years. However, the effects of caffeine on paracetamol have not been seriously investigated since a pooled analysis conducted in 1984 (Zhang, 2001). Because the absorption of paracetamol is so dependent on gastric emptying, other drugs that alter gastric emptying can change its pharmacokinetics (Toes *et al*., 2005).

Administration of 3g of ascorbic acid after an oral dose of 1g of acetaminophen has been shown to prolong the amount of time paracetamol stays in the body (Houston and Levy, 1976). The effect of caffeine (60mg) on the pharmacokinetics of acetaminophen 1000mg was studied (Igbal *et al*., 1995); with the results showing significant increase in serum AUC, $C_{max}$ and a decrease in serum paracetamol clearance (CL). In a toxicological study of paracetamol and caffeine, a decrease in the toxic action of paracetamol with decreased paracetamol levels was observed (Rainska Giezek, 1995). Delayed administration of paracetamol 1h after cimetidine resulted in significant ($P < 0.05$) reduction of the peak salivary concentration ($C_{max}$) and the absorption rate constant ($K_{ab}$) (Garba *et al.*, 1999).

Paracetamol tablets administered with Zobo drink produced increased elimination half-life (Kolawole and Maduenyi, 2004). Co-administration of paracetamol with rifampicin, isoniazid, chloramphenicol, anti-epileptic

* Corresponding author. E-mail:mojitaibat@yahoo.com; Tel: +234-(0)-803-589-6043, +234-(0)-802-663-9300
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drugs and antiviral drugs should be avoided (Crippin, 1993; Toes *et al.,* 2005). Metoclopromide increased the absorption of paracetamol (Nimmo *et al.,* 1973), whereas excretion and plasma concentration may be altered when co-administered with probenecid. Cholestyramine also reduced the absorption of paracetamol (Toes *et al*., 2005).

This study was carried out to compare the pharmacokinetic profile of paracetamol in Panadol® and Panadol Extra®.

## MATERIALS AND METHODS

### Materials

Acetaminophen powder was donated by the Department of Pharmaceutical Chemistry, A.B.U., Zaria. The Panadol® Batch no 013N (acetaminophen) tablets (Smithkline Beecham: Manufacturing date 02/05; Expiring date 02/08); Panadol Extra® tablets Batch no 022N (Smithkline Beecham: Manufacturing date 04/05; Expiring date 04/08) were obtained from a pharmacy retail outlet in Zaria-Nigeria.

A SP8 100 UV Spectrophotometer (Pye-Unicam LTD. York Street, Cambridge, England CB12PX) was used to analyse paracetamol concentrations in saliva. The tablets dissolution apparatus made by Erweka Germany was used to carry out dissolution studies. All chemicals and reagents were of analytical grade and obtained from the Department of Pharmaceutical Chemistry.

### Methods

Quality control assessment of tablets, identification tests, assay for content of active ingredients and dissolution rate test for Panadol® and Panadol Extra® tablets were carried out according to the BP (1993) procedures.

Six healthy human male volunteers ages 29.60 $\pm$ 1.50 (Mean $\pm$ S.E.M) and weighing 65 $\pm$ 2.5kg, height 1.67 $\pm$ 0.15m participated in the study, and their written consents were obtained. They were all students of the Ahmadu Bello University. Volunteers were clinically certified fit for the study and were asked to abstain from taking any drug for at least 2 weeks before the commencement of the study. They were all non-smokers and did not take alcohol. A wash out period of 2 weeks was allowed between the phases of the study.

The first phase of the study involved the ingestion of a 1g dose of paracetamol tablets with 200ml of water after overnight fasting. Food was withheld for the next 3h. Saliva samples (4 ml) were immediately collected prior to the drug ingestion and at times 5, 10, 15, 20, 30, 60, 90, 180 and 240 min. Saliva release was achieved with the aid of chewing semi-solid paraffin. The saliva samples were then stored at -20$^0$C, pending analysis. The second phase involved the ingestion of a 1g dose of Panadol Extra® (paracetamol 1 g with caffeine 60 mg) after overnight fasting. Food was withheld for the next 3 h as before and saliva samples were collected as described above.

### Analysis

Method of (Garba *et al.*, 1999) was adopted for the analysis of paracetamol concentrations in the saliva samples. Saliva samples (2 ml) were placed in a 10 ml centrifuge tube and ethyl acetate (5 ml) was added. The mixture was vortex-mixed for 1 min and centrifuged at 2500 rpm for 5 min. The ethyl acetate layer was removed and its absorbance measured at 262 nm, using 1 cm silica cuvettes with a double beam SP8 -100 UV Spectrophotometer. The calibration curve for standard paracetamol powder in saliva was prepared and the method validated using the same analytical procedure as described above.

### Preparation of calibration curve and validation of method

The calibration curve was constructed by spiking drug free pooled saliva of subjects with standard solution of paracetamol (5 mg/ml) to obtain concentration range of 0 - 50 ìg/ml. Each sample was analysed in duplicate using UV-spectrophotometer, and following the analytical procedure described. The procedure was

repeated five times per each day of analysis. Results are expressed as mean ± S.E.M. They have been analysed for statistical significance by Student's t-test for paired data. A p-value of < 0.05 was considered statistically significant.

**Pharmacokinetic analysis**

The concentrations of paracetamol in saliva sample at the specified time intervals were generated from the calibration curve. The pharmacokinetic parameters were obtained using WINNONLIN Non Compartmental analysis program. Residual method was used to obtain lag time using the saliva-time curves as base data. $K_{ab}$ and $K_{el}$ were calculated from $t_{1/2ab}$ and $t_{1/2el}$ respectively.

## RESULTS AND DISCUSSION

Results of identification tests, assay for content of active ingredients and dissolution rate tests of paracetamol in Panadol® and Panadol Extra® complied with the specification in the B.P 1993 (Table 1). A calibration curve for paracetamol in saliva (10 - 50 ìg/ml) with a good correlation (0.99) was obtained. The day to day coefficient of variation was generally less than 1.05%. Method validation data are shown on Tables 2 and 3. The estimated mean salivary pharmacokinetics of paracetamol in Panadol® and Panadol Extra® are shown on Table 4. The mean saliva-time profiles for paracetamol in the samples are shown in Figure 1.

From the mean salivary pharmacokinetic data, there were significant ($P < 0.05$) reduction by 10.15% and 12.25% in salivary AUC, and $C_{max}$ of paracetamol in Panadol® and Panadol Extra® respectively. The reduction in $K_{el}$ led to increase in $t_{1/2el}$. However, the salivary $t_{1/2ab}$ and Cl for paracetamol in Panadol Extra® were also increased.

The pharmacokinetic results demonstrated an interaction between paracetamol and caffeine which was indicated by decreased saliva paracetamol levels and a smaller area under the curve of changes of paracetamol levels in the group given Panadol Extra®. It also indicated faster elimination of paracetamol. The increased clearance may indicate induction of paracetamol metabolism by caffeine, leading to reduction in salivary paracetamol concentration as observed in the results of this study.

**Table 1:** Results of quality control assessment of tablets

| S/No. | Quality assessment | Panadol® | Panadol Extra® |
|---|---|---|---|
| 1. | Identification test | Positive | Positive |
| 2. | Mean percentage content ± S.E.M | 101.6 ± 0.58 | 100.2 ± 0.25 |
| 3 | Mean percentage release after 45 min ± S.E.M | 87.30 ± 2.95 | 82.37 ± 1.27 |

n = 6

**Table 2:** Extraction Recovery of Paracetamol

| S/No. | Spiked concentration (ìg) | Mean % Recovery ± S.E.M (n = 2) |
|---|---|---|
| 1. | 10 | 95.60 ± 0.05 |
| 2. | 20 | 96.48 ±0.03 |
| 3. | 30 | 97.90 ± 0.10 |
| 4. | 40 | 98.63 ± 0.03 |
| 5. | 50 | 97.45 ± 0.05 |

**Table 3:** Validation of Method

| S/No. | Concentration spiked (ig /ml | Mean Concentration obtained (ig/ml) ± S.E.M (n = 5) |
|---|---|---|
| 1. | 10 | 9.35 ± 0.42 |
| 2. | 20 | 19.53 ± 0.78 |
| 3. | 30 | 28.79 ± 0.89 |
| 4. | 40 | 39.39 ± 0.17 |
| 5. | 50 | 49.56 ± 0.66 |

**Table 4:** Mean Salivary Pharmacokinetic profile of Panadol® (Paracetamol 1 g) and Panadol Extra® (Paracetamol 1g with caffeine 60 mg) in healthy subjects

| Pharmacokinetic Parameters | Panadol® ± S.E.M | Panadol Extra® ± S.E.M | % changes | *P* -value |
|---|---|---|---|---|
| Lag time (h) | 0.26 ± 0.04 | 0.32 ± 0.06 | 23.00 | P > 0.05 |
| $K_{ab}$ ($h^{-1}$) | 2.26 ± 0.48 | 2.82 ± 1.04 | 24.48 | P > 0.05 |
| $t_{1/2ab}$ (h) | 0.35 ± 0.05 | 0.39 ± 0.09 | 11.43 | P < 0.05 |
| $T_{max}$ (h) | 0.27 ± 0.028 | 0.47 ± 0.028 | 74.00 | P > 0.05 |
| $C_{max}$ (i g/ml) | 26.00 ± 2.55 | 23.36 ± 0.86 | 10.15 | P < 0.05 |
| $AUC_{0-4h}$ (i g.h/ml) | 62.45 ± 10.02 | 54.80 ± 11.09 | 12.25 | P < 0.05 |
| $K_{el}$ ($h^{-1}$) | 0.36 ± 0.045 | 0.30 ± 0.11 | 16.67 | P = 0.05 |
| $t_{1/2el}$ (h) | 2.25 ± 0.48 | 3.60 ± 0.99 | 60.00 | P > 0.05 |
| Cl (ml/h) | 16.80 ± 52.30 | 22.68 ± 3.15 | 35.00 | P > 0.05 |

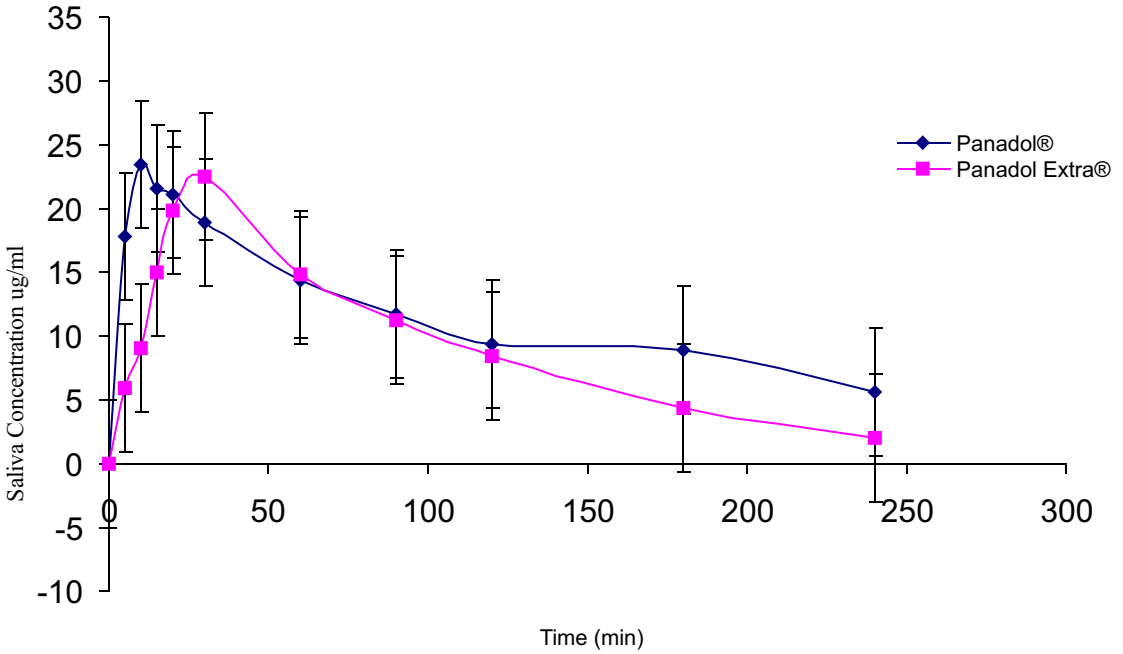


**Fig. 1:** Salivary Concentration-Time Profile ± S.E.M of Panadol®(Paracetamol 1 g) and Panadol Extra® (Paracetamol 1 g with Caffeine 60 mg) in Human Volunteers

## Conclusion

The study has shown that there were significant differences in the $C_{max}$ and AUC of paracetamol in Panadol® compared with that of Panadol Extra®.

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