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Paracetamol Bioavailability Study by Means of Salivary Samples

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Abstract: Bioequivalence of two different marketed paracetamol tablets, Decamol (500 mg, B.N., 4151, Megapharm) and Otamol (500 mg, B.N, 41093, Al-Quds-pharm), were compared to the innovator product, Dexamol (500 mg, B.N.12603, Dexxon). The bioavailability study was carried out in healthy volunteers in a crossover sequence using saliva drug levels as a parameter. *In vitro* studies, it was shown that all three products, Decamol, Otamol and Dexamol, were pharmaceutically equivalent. The bioavailability data obtained could be correlated to the *in vitro* data of the three tablet brands. *In vivo* investigations indicated no statistically significant differences in the bioavailability of Decamol and Otamol from Dexamol tablets. Therefore, all the three products are considered bioequivalent.

Key words: Paracetamol, bioavailability, salivary samples, bioequivalence

INTRODUCTION

Paracetamol is the most common analgesic/antipyretic agent which widely used to treat mild to moderate pain. It is rapidly absorbed and has a half-life of around 2 h (Dougall *et al*., 1983; Nimmo and Prescott, 1978). Serum concentrations between 10 and 20 μg mL^{-1} are generally considered to be therapeutically effective, while>150 μg mL^{-1} may produce hepatic necrosis (Winek, 1976).

Pharmacokinetics of paracetamol in humans was found to be affected by formulation (Steinigen, 1988; Degen and Maier, 1984; Haile *et al*., 1992; El-Sousi *et al*., 2002). The present study examines the relative bioavailability of two generic formulations of paracetamol tablets (Decamol and Otamol) in comparison to the innovator's brand (Dexamol). Assessment of the bioequivalence of two locally manufactured tablet brands was undertaken with reference to an imported tablet brand. Both *in vivo* and *in vitro* data were generated. The *in vivo* data involved saliva concentration data in ten volunteers. The use of saliva concentration data for bioavailability assessment of paracetamol was considered feasible since the ease of collection and analysis of saliva samples beside the good correlation between saliva and plasma concentration of paracetamol (Cardot *et al*., 1985). Free Paracetamol in saliva was assayed in the present study using a simple and sensitive colorimetric method (Price *et al*., 1983).

MATERIALS AND METHODS

Subjects: Ten healthy female volunteer with ages ranging 19-24 years and weighs from 55-80 kg, were selected on the basis of acceptable medical histories and normal physical examination. All subjects gave their informed written consent to participate in the study after detailed explanation of the objective and nature of study. The protocol was approved by the General Director of Pharmacy, Ministry of Health, Palestinian National Authority.

Materials: Brand A was Dexamol, 500 mg, B.N.12603, Dexxon. Brand B was Decamol, 500 mg, B.N.4151, Megapharm and brand C was Otamol 500 mg, B.N.41093, Al-Quds Pharm. All chemicals were of spectro quality or analytical grade.

Methods: *In vitro* studies were carried out at the Middle East Pharmaceutical and Cosmetics Laboratories, Gaza, Palestine. Tests performed were appearance, friability, disintegration time, mean tablet weight, content uniformity and dissolution rate as specified by USP27-NF22 monograph for paracetamol tablets. For assay, ten tablets from each formulation were powdered and the average weight of one tablet was determined by UV spectrophotometer method according to USP27-NF22 monograph.

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Dissolution rate (Apparatus 2: 50 rpm) was determined using a tablet dissolution tester (USP24), Electro lab. TDT, India. The dissolution medium was 900 mL of phosphate buffer (pH 5.8). Dissolution samples were analyzed using UV spectrophotometer at 243 nm.

In vivo study was executed in a three-way randomized crossover design. Each brand was administered orally as a single dose (two tablets, 1 g) in the sequence described in Table 1. All subjects were instructed to abstain from medications for one week prior to and throughout the study. Seven-day wash-out periods separated the study days. Subjects fasted overnight before each drug administration and food was not allowed for 3 h thereafter. Each tablet was administered with approximately 150 mL of water. Saliva samples (3 mL) were collected immediately before and at 0.5, 0.75, 1.0, 1.25, 1.5, 3.0, 6.0 and 8.0 h after drug administration.

To each 1.0 mL standards (5.0, 10.0, 15.0, 20.0 and 25.0 μg mL^{-1} Paracetamol) and to each 1.0 mL saliva samples, 1.0 g of anhydrous sodium sulfate was added and extracted three times with 5.0 mL portion of ether. The ether layer was collected and evaporated. The residue was dissolved in a 1.0 mL 0f (1:1) HCl and heated on a boiling water bath for 30 min the solution is cooled to room temperature and diluted with 2.0 mL water. One milliliter of 1% o-cresol and 2.0 mL of concentrated ammonium hydroxide were added. After 30 min the absorbance of blue color was measured using UV-visible spectrophotometer. Finally the Paracetamol concentration was determined from the linear calibration curve.

The pharmacokinetic parameter, i.e., maximum salivary concentration (C_{max} μg mL^{-1}), mean time to maximum saliva concentration (T_{max}, h) and area under the saliva concentration-time curve (AUC_{0-8} μg mL^{-1} h) were observed. The area under the saliva concentration-time curve was calculated using the trapezoidal rule.

Differences between saliva concentration and other parameters were compared using two-way analysis of variance (ANOVA) and paired t-test. A $p<0.05$ was considered to be the level of significance.

RESULTS AND DISCUSSION

Demographic data and sequence of administration of paracetamol dose to ten healthy female subjects are shown in Table 1. The *in vitro* data for the three paracetamol formulations are shown in Table 2. Each brand met all the specifications as stipulated by USP77-NF22 for paracetamol tablets. A comparison of physical parameters indicated that the *in vitro* availability of paracetamol formulations is in the order:

Decamol > Dexamol > Otamol

In Fig. 1, it was shown the mean saliva concentrations of paracetamol at each sampling time following oral administration of the three brands to ten healthy female volunteers. Paracetamol saliva concentration did not show any significant difference between the three brands at each sampling time except at 0.5, 0.75 and 1.0 h, respectively. At 0.5 h, according to t-test, there was significant difference between Decamol and Dexamol brands and between Decamol and Otamol. However, no significant difference was observed between Dexamol and otamol brands. At 0.75 h, there was significant difference between otamol and Dexamol brands and between Otamol and Decamol brands. However, no significant difference between Dexamol and Decamol brands was observed. At 1.0 h, there was no significant difference among the three brands.

The bioavailability parameters for the three brands i.e., maximum salivary concentration (C_{max} μg mL^{-1}), time to maximum saliva concentration (T_{max}, h) and area under the saliva concentration- time curve (AUC_{0-8} μg mL^{-1} h) are listed in Table 2.

A comparison of the mean % AUC values in Table 2 indicated that the bioavailability of the three brands is in the order: Decamol > Dexamol > Otamol which correlated

Table 1: Demographic data and sequence of administration of dexamol, Decamol and otamol to ten healthy female volunteers

				Period		
Volunteers	Age (Year)	Weight (kg)	Height (cm)	1	2	3
1	20	55	155	A	C	B
2	20	78	170	A	C	B
3	23	60	160	A	C	B
4	22	80	175	A	C	B
5	20	66	165	B	A	C
6	21	71	160	B	A	C
7	19	55	160	B	A	C
8	22	66	165	C	B	A
9	23	70	167	C	B	A
10	24	67	160	C	B	A
mean	21.4	66.8	163.5			

A = Dexamol 1g; B = Decamol 1 g; C = Otamol 1 g

Table 2: Bioavailability and *in vitro* data for paracetamol formulations (1 g) under study

Formulation	C_{max} (μg mL^{-1})	T_{max} (h)	AUC_{0-8} (μg mL^{-1}h)	% AUC	Tablet weight (mg)	Assay UV (%)	Disintegration time (min)	% of dissolution at 30 min
Dexamol	19.50±1.08	0.75	33.88±2.80	100	545	103.3	6.00	95.10
Decamol	20.33±0.93	0.50	35.23±1.73	104	521	101.7	3.00	98.46
Otamol	17.56±0.87	1.00	30.50±1.66	90	616	104.4	20.0	80.00

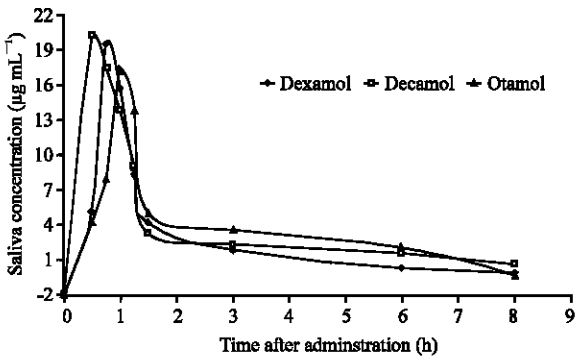

Fig. 1: Mean saliva concentration-time curves after administration (1 mg) of Dexamol, Decamol and Otamol to ten healthy female volunteers

the *in vitro* data. No significant differences were found between the three brands with respect to C_{max} and AUC_{0-8} but T_{max} values showed significant differences based on t-test and ANOVA method.

Based on mean values of AUC_{0-8} oral bioavailability of Decamol and Otamol was 104.0 and 90.0%, respectively, relative to Dexamol (innovator brand). Thus, bioavailability of Decamol and Otamol tablets were not significantly different from Dexamol tablets. Therefore all three products are considered bioequivalent.

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