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Paracetamol bioavailability from an elixir, a suspension and a new alcohol-free liquid dosage form in humans

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Summary

Paracetamol (acetaminophen) bioavailability and pharmacokinetics were examined following oral administration of 1.44 g single doses of paracetamol alcohol-free solution A, suspension B and an elixir C to 8 healthy male volunteers. The drug plasma concentrations were measured using an HPLC method. The mean *AUC* (μg/h/ml), peak plasma concentration (*PPC*; μg/ml) values (X $\pm$ S.E.) obtained following dosing with A (78.11 $\pm$ 5.88 μg/h/ml^{-1} and 23.36 $\pm$ 1.71 μg/ml) were significantly higher than those for B (65.12 $\pm$ 4.55 μg/h/ml and 17.67 $\pm$ 1.97 μg/ml). The (*PPC*) was reached in a shorter time after dosing with A (52.50 $\pm$ 9.4 min) compared to B (86.25 $\pm$ 15.5 min) and C (67.5 $\pm$ 13.6 min). The rate of paracetamol absorption, K_a (h^{-1}) was highest after dosing with A (3.58 $\pm$ 0.52 h^{-1}) followed by C (3.09 $\pm$ 0.48 h^{-1}) and then B (2.81 $\pm$ 0.56 h^{-1}).

Introduction

Paracetamol (acetaminophen) is one of the most popular over-the-counter analgesic and antipyretic drugs. Currently paracetamol is available in different dosage forms, tablets, capsules, drops, elixirs, suspensions and suppositories. Paracetamol elixir and drops usually contain ethanol among other ingredients to solubilize the water-insoluble drug. The British Pharmacopoeia (1980) adopted a formula for paediatric elixir containing 10% v/v of ethanol.

The disposition, metabolism, pharmacokinetics and bioavailability of paracetamol have been the subject of a number of studies (Endi et al., 1984; Jackson et al., 1984; Wojcicki and Gawronska-Szklarz, 1984). These indicate that following oral administration paracetamol is rapidly and almost completely absorbed from the gastrointestinal tract. Gastric emptying is reported to influence paracetamol absorption in humans and that drugs which increase gastric emptying such as metoclopramide increase the rate of paracetamol absorption (Nimmo et al., 1973). Drugs which decrease gastric emptying such as ethanol delay the drug absorption (Nimmo, 1975). In addition, Goldfinger et al. reported that patients taking

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paracetamol in combination with drugs known to induce hepatic microsomal enzymes, e.g. ethanol, have reduced margins of safety for paracetamol-induced hepatotoxicity, associated with increased metabolism of the drug by hepatic microsomes (Goldfinger et al., 1978; Kromhout, 1979; Light 1980; McClain, 1980).

A paracetamol alcohol-free liquid dosage form has recently been introduced in Jordan; the exclusion of alcohol, provided that it does not affect the drug and/or the formulation stability is expected to have substantial advantages.

(i) Reduced hepatotoxicity; liver microsomal enzymes are no longer induced and hence lesser amounts of the toxic metabolite are produced.
(ii) More complete absorption of certain drugs, e.g. paracetamol which would not be affected by alcohol-induced delayed gastric emptying.
(iii) No risk for alcohol-sensitive patients, e.g. epileptics.
(iv) Enhanced acceptability of drugs by certain societies where for religious and social reasons alcohol intake is prohibited. The issue of availing alcohol-free medications has been raised by a number of societies (Karrar, 1983).

The present study reports the bioavailability of paracetamol from three liquid/semi-liquid dosage forms, an elixir, a suspension and a newly introduced alcohol-free syrup in healthy adult male volunteers.

Materials and Methods

Materials

Paracetamol alcohol-free syrup (A, Batch No. 29/1/84) was kindly supplied by the Jordanian Pharmaceutical Manufacturing Co. (JPM, Amman, Jordan). Paracetamol suspension (Brand Calpol B; batch no. A0536, Wellcome Laboratories, U.K.) and elixir (Brand Panadol C; batch no. 316/518, Sterling Winthrop, U.S.A.), were purchased from commercial sources. Paracetamol, acetanilide, methanol, ethyl acetate (HPLC grade), and/or ether and Analar Acetic acid were all obtained from BDH Chemicals, Poole, U.K.

Volunteers

Eight healthy and informed male volunteers participated in the trials. Their ages and body weights ranged between 20 and 46 years, and 60 and 80 kg, respectively. The study was carried out under medical supervision and health was confirmed by urine and stool examination, haematological testing, liver and kidney function tests. The volunteers were given numbers from 1 to 8.

Trial conditions

The three products, A, B and C were administered orally in single doses of 60.0 ml each (equivalent to 1.44 g, from a 120 mg/5 ml elixir or suspension) to fasting subjects. No food and/or fluids, except drinking water was taken 2.0 h post-dosing. The volunteers were instructed not to take any medication a week before and during the trials. The trials were conducted using a cross-over design with a wash-out period of 7 days.

Blood collection

Blood samples (10 ml each) were collected using an indwelling catheter from an arm vein at the following times: 0.5, 1.0, 1.5, 2.0, 2.5, 5.0, 7.0, 9.0 and 12.0 h post-dosing. A blank control blood sample (20 ml) was collected just before drug administration. The samples were collected in heparinized tubes and the plasma was separated immediately by centrifugation and stored at $-70\,^{\circ}C$ awaiting analysis.

Assay

(a) Apparatus

The HPLC method consisted of the following apparatuses: Pye Unicom PU 4010 pump, LC-UV variable wavelength detector operated at 250 nm and a CDPA computing integrator, a Rheodyne 7125 injection valve fitted with a 20 μl loop and a 150×5 mm (i.a.). Hypersil ODS 5 μl (Shandon) column. The mobile phase consisted of 25% methanol and 0.1% ethyl acetate in 1% acetic acid. The flow rate was 1.5 ml/min.

(b) Method

A modified method similar to those reported previously was used (Hong et al., 1976; Howie et

al., 1977); to 1.0 ml of plasma obtained from subjects receiving the drug and/or 1.0 ml of spiked blank plasma was added acetanilide (100 μl, 100 μg/ml in distilled water) and thoroughly mixed. The mixture was extracted with Analar ether (5.0 ml × 2) via whirlmixing (1.0 min) and centrifugation (5.0 min, 2500 rpm) each time. The combined ether extracts were evaporated to dryness in a waterbath (30 °C) using a gentle stream of nitrogen, resolubilized in 1.0 ml of the mobile phase and injected onto the HPLC column.

All-glass distilled water was used throughout the analysis. All glassware used was acid washed (50% Hd). The mobile phase was filtered through a millipore filter (cat. no. HVLP 04700) and constantly degassed with helium during the HPLC run.

Determination of pharmacokinetics and bioavailability

The pharmacokinetic parameters determined include: the area under the plasma concentration vs time curve (*AUC*; μg/h/ml), peak plasma concentration (*PPC*; μg/ml), peak plasma concentration time (*PPCT*; min), absorption rate constant (K_a; h^{-1}), elimination rate constant (K_e; h^{-1}), and plasma half-life ($t_{1/2}$; h). The *AUC* was measured by the trapezoidal method. The pharmacokinetics analysis was performed using the ESTRIP computer program (Brown and Manno, 1978). This program computes lag time to onset of absorption, and fits a polyexponential equation to the data. From this the rate constants of absorption and elimination could be obtained.

The bioavailability of paracetamol from each of the three products A, B and C was assessed using the plasma levels. The extent and rate of bioavailability were described by the *AUC* (μg/h/ml) and the *PPC* (μg/ml) together with the *PPCT* (min) and K_a, respectively (Ritchell, 1976).

Statistical analysis

The calibration curves were subjected to linear regression analysis. Paracetamol plasma concentrations and pharmacokinetic parameters were analysed using the Student's paired *t*-test.

Results and Discussion

A reliable HPLC method was devised which was capable of measuring small changes in plasma drug administration. The method involved some modifications of the existing techniques (Hong et al., 1976; Howie et al., 1977), namely the use of a reverse-phase technique using acetanilide as the internal standard. With this system it was possible to measure concentrations as low 100 ng/ml. Between-assay coefficient of variation and intra-assay variation were 6% and 2%, respectively. Acetanilide was chosen as internal standard because it was chemically close in structure to paracetamol and stable on storage. The response was linear over a range of 'spiked' paracetamol stan-

TABLE 1

Paracetamol mean values (± S.E.) of the area under the plasma concentration–time curve (AUC), peak plasma concentration (PPC), peak plasma concentration time (PPCT min), absorption rate constant (K_a), elimination rate constant (K_e) and plasma half-life ($t_{1/2}$), obtained after oral administration of 1.44 g single doses of paracetamol alcohol-free elixir A, conventional suspension B and elixir C to 8 healthy adult male volunteers

Parameter	Product A	Product B	Product C
AUC (μg/h/ml)	78.11 ±5.88 *	65.12 ± 4.55 *	72.27 ± 5.02
PC (μg/ml)	23.36 ±1.71 *	17.67 ± 1.97 *	21.69 ± 1.56
PPCT (min)	52.50 ±9.40	86.25 ±15.46	67.50 ±13.60
K_a (h^{-1})	3.58 ±0.52	2.81 ± 0.56	3.09 ± 0.48
K_e (h^{-1})	0.217 ± 0.016	0.282 ± 0.037	0.232 ± 0.012
$t_{1/2}$ (h)	3.30 ±0.21	2.81 ± 0.46	3.04 ± 0.16

* The mean *AUC* and *PPC* (±S.E.) obtained after the administration of product A were significantly higher than those obtained after B ($P = 0.05$, d.f. = 7).

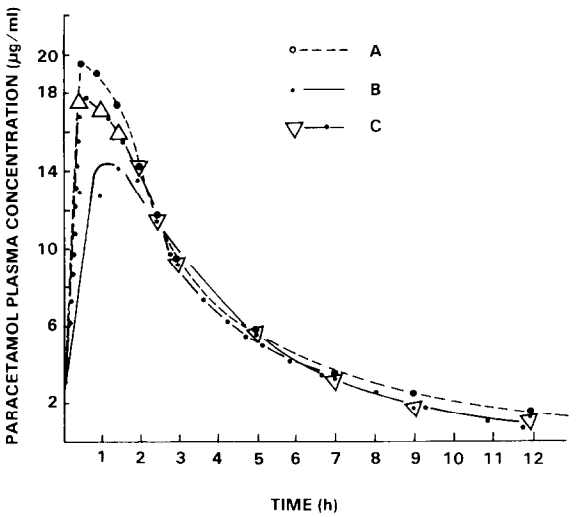

Fig. 1. Paracetamol plasma concentration (µg/ml)–time (h) curves obtained after oral administration of 1.44 g single doses of paracetamol alcohol-free elixir. A (○------○) conventional; suspension B (*———*) and elixir C (▽———▽) to 8 healthy adult male volunteers. (Each curve represents the mean of 8 runs.)

dards in a plasma using a range from 0.0 to 20.0 µg/ml. This range of standards was used to calibrate the CDP4 computing integrator, thus calculating the results of unknown plasma paracetamol concentrations as µg/ml.

The pharmacokinetics of paracetamol obtained following oral administration of the suspension B and the elixir C to healthy adult male volunteers (Table 1) were in good agreement with previously reported data (Endi et al., 1984). The three products A, B and C produced plasma concentration vs time curves of similar shapes in particular after the PPCs were reached, in the distribution and elimination phases (Fig. 1). Starting from about 2.0 h post-dosing, the products A, B and C produced almost equal mean paracetamol plasma concentrations at 2.5, 3.0, 5.0, 7.0, 9.0 and 12.0 h (Fig. 1). These results indicate that the three products were bioequivalent with regard to the profiles of paracetamol distribution and elimination. This finding was also indicated by the pharmacokinetics of distribution and elimination obtained (Table 1) where the 3 products have produced comparable paracetamol mean K_e and $t_{1/2}$ values.

The mean *AUC* and *PPC* values obtained following the administration of product A: 78.11 $\pm$ 5.88 µg/h/ml and 23.38 $\pm$ 1.71 µg/ml were significantly higher than those obtained after product B: 65.12 $\pm$ 4.55 µg/h/ml and 17.67 $\pm$ 1.97 µm/ml (Table 1). Product C was neither significantly different from A nor B with regard to the *AUC* and *PPC*. The three products A, B and C gave comparable values for the *PPCT* and K_a: 52.50 $\pm$ 9.40 min and 3.58 $\pm$ 0.52 h^{-1}; 86.25 $\pm$ 15.46 h^{-1} and 2.81 $\pm$ 0.56 h^{-1}; 67.50 $\pm$ 13.60 min and 3.09 $\pm$ 0.48 h^{-1}, respectively (Table 1). Similar findings were obtained for three products regarding the K_e and $t_{1/2}$ (Table 1). The results obtained indicate:

(i) paracetamol was bioavailable to a greater extent and at a higher rate from product A, the alcohol-free elixir, compared to the suspension B;

(ii) the conventional elixir C might reasonably be considered bioequivalent to the alcohol-free elixir A and the suspension B; the extent and rate of paracetamol bioavailability from the product C were slightly less than those from A and slightly higher than those from B (Table 1);

(iii) paracetamol had the highest rate of absorption from the alcohol-free elixir A ($K_a = 3.58 \pm 0.52$ h^{-1}), followed by the conventional elixir C, then last came the suspension B; and

(iv) paracetamol was cleared from plasma at comparable rates of elimination (K_e and $t_{1/2}$) for the three products.

With regard to paracetamol bioavailability the alcohol-free product A, the suspension B and the conventional elixir C could be ranked in the order, A > C > B. These results demonstrated that the exclusion of alcohol from the paracetamol elixir did not interfere with the drug absorption from the gastrointestinal tract into the systemic circulation but on the contrary the alcohol-free formulation A has had enhanced bioavailability.

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