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# Pharmacokinetics of acetaminophen in Hong Kong Chinese subjects

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**Abstract**

The pharmacokinetics of acetaminophen have been well studied in different populations, especially in Caucasians. However, limited studies on acetaminophen pharmacokinetics have been conducted in the native Chinese and few such data have been reported in the English language literature. Previous published studies suggested that environmental and genetic factors may cause inter-individual difference in acetaminophen disposition, thus we investigated the pharmacokinetics of acetaminophen in Hong Kong Chinese subjects. A single 500 mg oral dose of acetaminophen was administered to 12 healthy male Chinese subjects under fasting conditions. Multiple blood samples were obtained after drug administration. Plasma acetaminophen concentrations were determined using HPLC, and its main pharmacokinetic parameters were generated. In comparison to other published data, acetaminophen half-life was considerably longer (15–62%), and oral clearance was lower (16–56%) in Hong Kong Chinese as compared to Australian Chinese, Caucasians (USA, UK, Australia), and subjects from Pakistan, Denmark, Spain and South Africa. Similarities however were found in the pharmacokinetic parameters between Hong Kong Chinese and Mainland Chinese subjects. The observed pharmacokinetic parameters of acetaminophen in Hong Kong Chinese subjects may be different from other ethnic populations. Further studies are needed to verify this hypothesis. 

*Keywords:* Acetaminophen; Pharmacokinetics; Ethnic difference

Acetaminophen (paracetamol, *N*-acetyl-*p*-aminophenol) is an analgesic and antipyretic agent used widely in both Asian and Western countries. Although the pharmacokinetics of acetaminophen have been well studied in various populations, especially in Caucasians, very limited data from the native Chinese population have been reported in the English Language literature.

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In view of the possible differences of drug disposition among different ethnic populations, the present study was to investigate the pharmacokinetics of acetaminophen in Hong Kong Chinese subjects.

This clinical study protocol was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. Written informed consent was obtained from each subject prior to enrollment in the study.

A total of 12 healthy male volunteers with a mean age of $24.1 \pm 7.1$ years, weight of $62.7 \pm 5.6$ kg and height of $170.6 \pm 4.4$ cm participated in the study. All subjects underwent a physical examination, ECG evaluation, haematological and blood chemistry test, and a thorough medical history to determine all inclusion criteria were met. All subjects were non-smokers and free from any prescription and non-prescription medications two weeks before the study.

A single 500 mg oral dose of acetaminophen (500-mg Panadol® tablet, Smithkline Beecham Int.) with 240ml water was administered after an overnight fast of 10 h. Blood samples were collected pre-dose and at 0.25, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10 h after dosing. The plasma was separated immediately and stored at $-30$°C until analyzed.

Acetaminophen concentrations in plasma were determined by a reversed-phase HPLC method. The limit of detection was 0.02 μg/ml, and the limit of quantification was 0.2 μg/ml for acetaminophen. The assay method provided an average recovery of 106.17, 101.05 and 102.46%, within-run variation of 3.97, 1.95 and 3.29%, and between-run variation of 2.59, 2.75 and 4.14%, respectively, for plasma samples of acetaminophen at concentration of 0.2, 2 and 20 μg/ml.

Pharmacokinetic parameters such as peak plasma concentration ($C_{max}$), the time to reach peak plasma concentration ($T_{max}$), terminal elimination rate constant ($K_{el}$), area under the plasma concentration–time curve ($AUC_{0-t}$, $AUC_{0-\infty}$), apparent total clearance ($CL/F$), and apparent volume of distribution ($V_d/F$) were generated using the standard non-compartmental analysis.

All subjects compiled with the protocol and completed the study. Fig. 1 shows the mean plasma concentration–time profile of acetaminophen in 12 subjects. The estimates of acetaminophen pharmacokinetic parameters are: $C_{max}$, $7.56 \pm 2.18$ μg/ml; $T_{max}$, $0.77 \pm 0.45$ h; $AUC_{0-t}$, $27.61 \pm 4.76$ μg h/ml; $AUC_{0-\infty}$, $30.84 \pm 5.73$ μg h/ml; $T_{1/2}$, $2.91 \pm 0.45$ h; $CL/F$, $0.27 \pm 0.04$ l/h/kg; $V_d/F$, $1.10 \pm 0.12$ l/kg. Relatively large inter-subject variability in acetaminophen absorption was observed. Double-peaks in the concentration-time profiles occurred in three out of 12 subjects, which may be a result of the delayed gastric emptying (Clements et al., 1978).

Main pharmacokinetic parameters of acetaminophen reported in various studies were compared and summarized in Table 1. The mean half-life of acetaminophen was 32, 27–62, 54, 21, 15–21 and 21% longer in Hong Kong Chinese than that in Australian Chinese, Caucasians (USA, UK, Australia), and subjects from Pakistan, Denmark, Spain and South Africa, respectively. The mean value of $CL/F$ was 27, 25–27, 56 and 16% lower

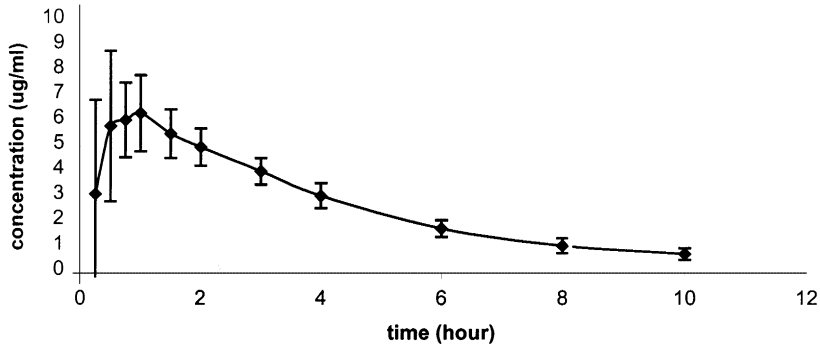


Fig. 1. Mean plasma concentration–time profiles of acetaminophen in 12 study subjects.

Table 1
Comparison of acetaminophen pharmacokinetic data from similar studies in different ethnic populations

| Subject source | Subject | Dose (mg) | $K_{eL}$ (1/h) | $T_{1/2}$ (h) | CL/F (l/h/kg) | $V_d$/F (l/kg) |
|---|---|---|---|---|---|---|
| HK Chinese | 12 (M), 24.1 ± 7.1 years | 500 | 0.24 ± 0.04 | 2.91 ± 0.45 | 0.27 ± 0.04 | 1.10 ± 0.12 |
| Mainland Chinese-1 (Zhao et al., 1995) | 8 (M), 27.2 ± 6.6 years | 500 | 0.24 ± 0.06 | 3.17 ± 1.13 | 0.32 ± 0.06 | 0.84 ± 0.27 |
| Mainland Chinese-2 (Tan and Chan, 1995) | 10 (M) | 500 | 0.24 ± 0.04 | 3.00 ± 0.60 | 0.28 ± 0.09 | 0.93 ± 0.30 |
| Australian Chinese (Osborne et al., 1991) | 12 (M), 18–31 years | 2 × 500 | | 2.2 ± 0.4 | 0.37 ± 0.10 | |
| USA Caucasians (Borin and Ayres, 1989) | 15 (9 M, 6 F), 30.3 ± 6.6 years | 500 | 0.40 ± 0.26 | 1.80 | | |
| USA Caucasians (Sahajwalla and Ayres, 1991) | 8, 22–29 years | 2 × 325; 2 × 500 | 0.38 ± 0.08; 0.32 ± 0.04 | 1.85; 2.20 | | |
| UK Caucasians (Kamali, 1993) | 10 (5 M, 5 F), 20–29 years | 3 × 500 | 0.32 ± 0.02 | 2.12 ± 0.15 | 0.37 ± 0.03 | 1.0 ± 0.05 |
| Australian Caucasians (Osborne et al., 1991) | 12 (M), 20–32 years | 2 × 500 | | 2.3 ± 0.4 | 0.36 ± 0.09 | |
| Parkistan (Iqbal et al., 1995) | 10 (M), 22–32 years | 500 | 0.42 ± 0.05 | 1.89 ± 0.27 | 0.62 ± 0.05 | 1.25 ± 0.25 |
| Denmark (Haderslev et al., 1998) | 10 (4 M, 6 F), 30–38 years | 2 × 500 | 0.29 (0.27–0.36) | 2.4 (1.9–2.5) | 0.32 (0.28–0.35) | 1.11 (0.73–1.26) |
| Spain (Pedraz et al., 1988) | 6 (4 M, 2 F), 24.5 ± 2.9 years | 500 | | 2.53 ± 0.28 vs. 2.40 ± 0.26[a] | | |
| South Africa (Malan et al., 1985) | 6 (M) | 2 × 500 | | 2.4 ± 0.4 | | |

$K_{eL}$, terminal elimination rate constant; $T_{1/2}$, terminal elimination half-life; CL/F, apparent total clearance; $V_d$/F, apparent volume of distribution.
[a] Data from two commercial tablets.

in Hong Kong Chinese than that in Australian Chinese, Caucasians (UK, Australia), and subjects from Pakistan and Denmark, respectively (Malan et al., 1985; Pedraz et al., 1988; Borin and Ayres, 1989; Osborne et al., 1991; Sahajwalla and Ayres, 1991; Kamali, 1993; Iqbal et al., 1995; Haderslev et al., 1998). The mean value of $V_d/F$ was similar among these populations. However, when compared to the pharmacokinetic data reported in the Chinese language studies, similarities in acetaminophen pharmacokinetics were found between Mainland Chinese and our study subjects (Zhao et al., 1995; Tan and Chan, 1995).

Previous study has demonstrated that acetaminophen is eliminated mainly by metabolism, which involves minor microsomal oxidation and primary glucuronidation (55%) and sulphation (33%) (Cummings et al., 1967). It is unclear if there are differences in the oxidative and/or conjugative metabolism which are related to our observed difference in acetaminophen disposition. It is also unknown if other genetic and/or environmental factors that may affect the metabolism of acetaminophen. Nevertheless, our results in the present study appear to support the previous observations that acetaminophen clearance was slower in Asians than in Whites and that the half-life was longer. Environmental factors, including contrasting use of social drugs like ethanol, hormonal contraceptives and the presence or absence of meat in the diet have been suggested to contribute to these differences (Mucklow et al., 1980).

The difference in the bioavailability ($F$) of acetaminophen might also contribute to the observed difference in the value of $CL/F$, as in the present study clearance (CL) was not determined separately from $F$. Racial difference in acetaminophen absorption is not expected since its absorption is a passive process. However, acetaminophen undergoes significant hepatic first-pass metabolism (Chiou, 1973), and this process may contribute to a difference in the bioavailability between different populations. Further studies, however, are needed to investigate such difference.

In conclusion, the pharmacokinetic parameters of acetaminophen in Hong Kong Chinese subjects may be different from other populations. Further direct comparative studies are needed to verify this point.

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