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Original Article

# A relative bioavailability study of 500 mg calcium *p*-aminosalicylate film coating tablet in healthy individuals

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ABSTRACT

The purpose of this study is to evaluate the only available calcium *p*-aminosalicylate (Ca PAS) commercial product, which is one of the most commonly prescribed non-surveillance products from the Bureau of National Health Insurance (BNHI) database in Taiwan. An open-randomized, balanced, two-way crossover study was designed to evaluate the relative bioavailability (F) of a 500 mg Ca PAS F.C. tablet with a 500 mg Ca PAS suspension in 13 healthy individuals. Blood samples were collected according to a planned time schedule. The plasma concentrations of PAS were measured by a validated liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS) method. Pharmacokinetic parameters of area under the plasma concentration-time curve from the time zero to the time of last quantifiable concentration ($AUC_{0-t}$), area under the plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration ($C_{max}$), time to reach measured maximum plasma concentration ($T_{max}$), elimination half-life ($T_{1/2}$), and mean residence time (MRT) were determined by non-compartment methods. F was calculated by [$AUC_{0-\infty}$] of the test drug divided by [$AUC_{0-\infty}$] of the reference drug. The mean geometric ratios of pharmacokinetic parameters, including $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ obtained were 0.873, 0.874, and 0.569, respectively. The 90% confidence intervals of ln ($AUC_{0-t}$), ln ($AUC_{0-\infty}$), and ln ($C_{max}$) after being back natural log-transformed were (74.0–103.0%), (74.1–103.0%), and (38.4–84.3%), respectively. The relative bioavailability of the Ca PAS tablet was 87.4%.



## 1. Introduction

The Department of Health in Taiwan initiated the Guidance for Bioavailability (BA)/Bioequivalence (BE) Studies in 1987, to ensure the safety and efficacy of medicines. The BE study is mandated for non-parenteral drugs with systemic effects and proper distinction; these products are called surveillance drugs [1–3]. BA/BE studies are not mandatory in Taiwan for

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products which were licensed before 1987; these medicinal products are named as non-surveillance drugs. With the quality generic concept, evaluation of the BA/BE of commercially available non-surveillance products is also encouraged.

Calcium *p*-aminosalicylate (Ca PAS) is an antimycobacterial agent, which is bacteriostatic against *Mycobacterium tuberculosis*, by preventing the multiplication of bacteria, and is used with other antituberculosis drugs (most often isoniazid) for the treatment of all forms of active tuberculosis (TB), due to susceptible strains of tubercle bacilli. The two major considerations in the clinical pharmacology of Ca PAS are the prompt production of a toxic inactive metabolite under acid conditions and the short serum half-life within 1 hour for the free drug. It is used as a second-line antimycobacterial agent and generally reserved for patients with multidrug-resistant TB (MDR-TB) or patients intolerant to first-line drugs, including isoniazid, rifampin, pyrazinamide, and ethambutol. It also inhibits the onset of bacterial resistance to streptomycin and isoniazid [4–7].

PAS is readily absorbed from the gastrointestinal tract, but may cause irritation of the gastrointestinal mucosa, which leads to increased peristalsis, and thus decreased absorption. Because of this, the drug is best administered with food or an antacid, such as aluminum hydroxide, which decreases irritation but apparently has little effect on maximum plasma concentration ($C_{max}$). Patients with gastric resection were found to have higher serum concentrations of PAS than normal individuals [4]. PAS diffuses widely through body tissues and fluids, although diffusion into the cerebrospinal fluid (CSF) occurs only if the meninges are inflamed. In tissues, high concentrations of PAS are achieved in lungs, kidneys, and the liver. About 15% of the sodium salt and 50–70% of the free acid is bound to plasma proteins. The volume of distribution was 1.43 (L/kg) in 12 healthy volunteers under fasting conditions, after receiving 6 g PAS [8,9].

PAS is considered as an orphan drug, so relevant research reports are few. It is one of the most prescribed non-surveillance drugs from the Bureau of National Health Insurance (BNHI) database and there is only one commercial product available in Taiwan. Additionally, the original product is no longer in the Taiwan market and no BA/BE study has ever been done for this product. Therefore, it was chosen as the candidate in this study to evaluate the relative bioavailability of a 500 mg calcium p-aminosalicylate film coating tablet.

## 2. Materials and methods

### 2.1. Chemicals

The test product, a 500 mg F.C. Ca PAS tablet, and the raw material for preparing the reference product, a Ca PAS suspension, were obtained from PeiLi Pharm. Co, Taichung, Taiwan. The average particle size of the active pharmaceutical ingredient (API) of Ca PAS was around 23.2 μm, measured by using a Coulter counter model: LS-230 (Beckman Coulter Inc., Fullerton, CA, USA). All other chemicals used were commercially available and of analytical grade.

### 2.2. Participants

Eligible participants were screened based on the inclusion and exclusion criteria. They were required to refrain from any prescription drug or herbal products within 14 days prior to dosing. The study protocol was preapproved by the Institutional Review Board (IRB) at the Ching Mai Hospital (Taipei, Taiwan), and all participants gave written informed consent.

### 2.3. BA study

An open-label, randomized, balanced, two-sequence, two-period, crossover design, with at least a 2-day washout period, was carried out at clinical unit. During each treatment period, participants would fast for at least 10 hours before investigational products were administered. They received 500 mg of Ca PAS as one F.C. tablet or suspension with 240 mL water. Participants continued to fast for 4 hours after dosing; drinking water was not allowed during 1 hour before and 2 hours after dosing.

For each treatment period, blood samples were collected for pre-dose (0 hour) in the morning, and 0.167, 0.333, 0.667, 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours after dosing using a heparinized syringe. Each collected blood sample was centrifuged, and the supernatant plasma was placed in an appropriately labeled tube, to be frozen at −20°C until analysis.

### 2.4. Sample preparation and analysis

Each plasma sample (0.2 mL) was extracted with 0.5 mL acetonitrile, followed by centrifugation at 3000 rpm for 10 minutes. Supernatant (100 μL) was then diluted with 500 μL acetonitrile-acetic acid-water (15/0.1/85). Finally, an aliquot (10 μL) was injected onto liquid chromatography coupled with tandem mass spectrometry (LC/MS/MS).

The plasma concentrations of PAS were measured by a validated liquid chromatography coupled with LC/MS/MS method. The concentration of the standard curve ranged from 2 ng/mL to 500 ng/mL. For the plasma sample concentration exceeding the standard curve concentration range, it would be diluted and analyzed to fit the range. MS/MS analysis was performed on an API 4000 triple quadrupole mass spectrometer, which was operated in a turbo ion spray mode with positive ion detection (PE Sciex, Concord, ON, Canada). The samples were delivered into the Electron Spray Ion source using the LC system ($LC\text{-}10AD_{vp}$ pump and $SIL\text{-}HT_A/HT_C$ autosampler, Shimadzu Corporation, Kyoto, Japan). Separation was achieved on a Biosil ODS column (4.6 mm × 150 mm, 5 μm, Biotic Chemical Co., Ltd, Taipei, Taiwan). A data processor was used with Analyst version 1.4 (PE Sciex).

### 2.5. Data treatment

Pharmacokinetic parameters including plasma elimination rate constant ($K_{el}$), time to reach measured maximum plasma concentration ($T_{max}$), measured maximum plasma concentration ($C_{max}$), area under the plasma concentration-time curve from the time zero to the time of last quantifiable concentration ($AUC_{0-t}$), area under the plasma concentration-

**Table 1 – Precision and accuracy of QC samples.**

| | Precision and accuracy of detecting PAS in human plasma | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Within-run ($n = 6$) | | | | Between-run ($n = 30$) | | | |
| PAS (ng/mL) | 2 | 6 | 60 | 400 | 2 | 6 | 60 | 400 |
| Mean | 1.87 | 5.81 | 60.48 | 402.90 | 1.99 | 5.94 | 60.76 | 402.91 |
| CV (%) | 5.7 | 8.3 | 6.2 | 6.6 | 8.7 | 6.6 | 4.4 | 4.3 |
| RE (%) | −6.8 | −3.2 | 0.8 | 0.7 | −0.4 | −1.1 | 1.3 | 0.7 |

CV = coefficient of variation; PAS = *p*-aminosalicylate; RE = relative error.

time curve from time zero to infinity ($AUC_{0-\infty}$), area under the plasma (first) moment concentration-time curve from time zero to infinity ($AUMC_{0-\infty}$), elimination half-life ($T_{1/2}$), mean residence time (*MRT*), and relative bioavailability (*F*) were determined by non-compartmental methods. Pharmacokinetic parameters were described by means ± SD. ANOVA was performed to evaluate the impacts of sequence, subject (within sequence), period and treatment effects on the raw or log-transformed parameters of $AUC_{0-t}$, $AUC_{0-\infty}$, $C_{max}$, *MRT*, and $T_{1/2}$. $T_{max}$ comparisons were made by using the Wilcoxon signed ranks test. Estimates of extent and rate of absorption comparison in terms of $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{max}$ between the test and reference drugs were calculated together with 90% confidence intervals (CI), and tested for significance ($p < 0.05$). In addition, *F* was calculated together also with 90% CI.

## 3. Results

The validation of the standard curve covered a concentration range from 2 ng/mL to 500 ng/mL. Human plasma was spiked with quality control samples, for within-run and between-run validation, at four concentrations, i.e., 2, 6, 60, and 400 ng/mL, as shown in Table 1. The coefficient of variation and relative error values are 4.3–8.7% and −1.1–1.3%, respectively, for between-run validation, and 6.2–8.3% and −6.8–0.8%, respectively, for within-run validations. These results demonstrated that this analytical method can be used for the BA study of PAS.

### 3.1. *Pharmacokinetic data*

Thirteen healthy Taiwanese male volunteers enrolled in the study. The demographics of individuals who completed the crossover study are listed in Table 2. Mean PAS plasma concentration-time data of each sampling time obtained after participants received the reference drug and test drug are listed in Table 3. The plasma concentrations after 6 hours are all below the lower limit of quantitation. Therefore, in Fig. 1, the mean PAS plasma concentration-time profiles presented, only covered up to 6 hours profile. Since the half-life of PAS in this study is below 1 hour, sampling times of 6 hours were enough to describe the pharmacokinetics of PAS in humans.

The mean plasma concentration-time profiles of PAS after the participants received the reference and test drugs are shown in Fig. 1. Pharmacokinetic parameters of PAS are summarized in Table 4. The mean ratio and mean geometric ratio of the reference drug and test drug of $AUC_{0-t}$ are 0.894 and 0.873, respectively, those of $AUC_{0-\infty}$ are 0.894 and 0.874, respectively, and those of $C_{max}$ are 0.615 and 0.569, respectively. The relative bioavailability value of Ca PAS is 87.4 (%).

The results of ANOVA and 90% CI are listed in Table 5. As shown in Table 5, the 90% CI of ln ($AUC_{0-t}$), ln ($AUC_{0-\infty}$),

**Table 2 – Participant's demographic data.**

| Participant no. | Gender | Age (y) | Height (cm) | Weight (Kg) | Period I | Period II |
|---|---|---|---|---|---|---|
| 101 | M | 22 | 168.0 | 52.0 | R | T |
| 102 | M | 27 | 176.0 | 70.0 | T | R |
| 103 | M | 38 | 163.0 | 57.0 | T | R |
| 104 | M | 23 | 173.0 | 68.0 | R | T |
| 105 | M | 25 | 183.0 | 79.0 | R | T |
| 106 | M | 22 | 172.0 | 70.0 | T | R |
| 107 | M | 28 | 168.0 | 64.5 | T | R |
| 108 | M | 25 | 177.0 | 65.0 | R | T |
| 110 | M | 21 | 168.0 | 56.0 | T | R |
| 111 | M | 27 | 168.0 | 67.0 | R | T |
| 112 | M | 30 | 172.0 | 74.0 | R | T |
| 113 | M | 24 | 170.0 | 56.0 | R | T |
| Mean | | 26.0 | 171.5 | 64.9 | | |
| SD | | 4.7 | 5.3 | 8.2 | | |

R = reference; T = test; SD = standard deviation.

**Table 3 – Mean plasma concentration-time data.**

| Time (h) | Reference drug | | | Test drug | | |
|---|---|---|---|---|---|---|
| | Mean | SD | CV (%) | Mean | SD | CV (%) |
| 0 | n. d. | n. d. | n. d. | n. d. | n. d. | n. d. |
| 0.167 | 4299.692 | 1727.986 | 40.2 | 474.634 | 1104.804 | 232.8 |
| 0.333 | 9251.769 | 4028.520 | 43.5 | 2609.908 | 3729.974 | 142.9 |
| 0.667 | 4895.846 | 1148.160 | 23.5 | 4329.154 | 3203.502 | 74.0 |
| 1 | 2700.385 | 671.505 | 24.9 | 3876.846 | 1980.192 | 51.1 |
| 1.5 | 990.615 | 382.051 | 38.6 | 2148.538 | 952.461 | 44.3 |
| 2 | 377.919 | 229.982 | 60.9 | 1149.692 | 786.696 | 68.4 |
| 3 | 53.398 | 49.899 | 93.4 | 150.781 | 126.196 | 83.7 |
| 4 | 9.712 | 9.477 | 97.6 | 19.299 | 13.991 | 72.5 |
| 6 | 0.627 | 1.209 | 192.8 | 1.308 | 1.573 | 120.3 |
| 9 | n. d. | n. d. | n. d. | n. d. | n. d. | n. d. |
| 12 | n. d. | n. d. | n. d. | n. d. | n. d. | n. d. |
| 24 | n. d. | n. d. | n. d. | n. d. | n. d. | n. d. |

CV = coefficient of variation; n.d. = below quantitative limit; SD = standard deviation.

and ln ($C_{max}$) after being natural log-transformed are (74.0–103.0%), (74.1–103.0%) and (38.4–84.3%), respectively. The 90% CI of F of the Ca PAS tablet are (74.6–102.3%) and the mean is 87.4 %.

There were no adverse events during the study, and no indications of clinical problems, such as blood pressure, heart rate, or abnormal body temperature, which caused the withdrawal of the participants. Therefore, we could infer that the doses were tolerable and the trial was safe.

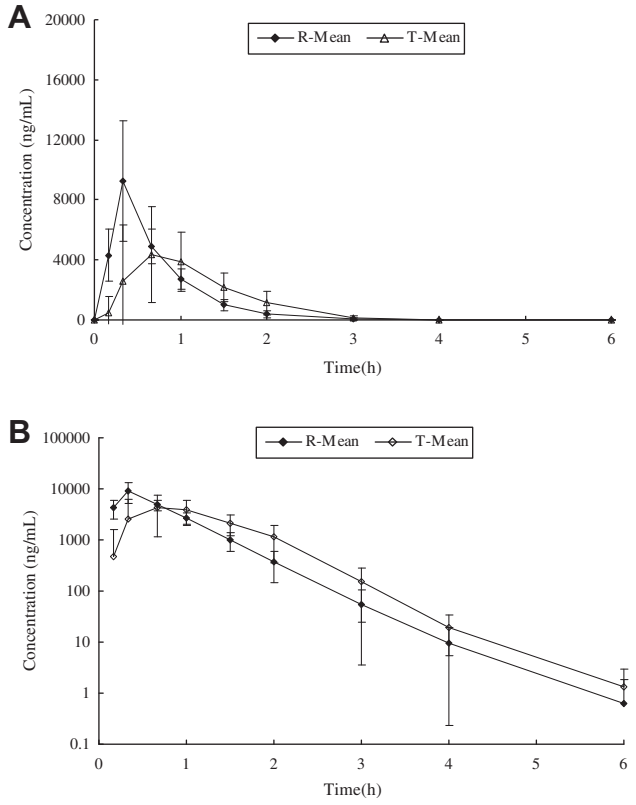


**Fig. 1 – Mean plasma concentration-time profiles after the participants have received the reference and the test drugs.**

## 4. Discussion

PAS inhibits the onset of bacterial resistance to streptomycin and isoniazid. The mechanism of action was postulated to be inhibition of folic acid synthesis (but without potentiation with antifolic compounds) and/or inhibition of synthesis of the cell wall component, mycobactin, thus reducing iron uptake by *Mycobacterium tuberculosis* [4]. Since it has been provided for the patients in Taiwan, it is meaningful to evaluate its BA.

From literature information [7], $T_{max}$ ranged from 2.09 hours to 6.64 hours and $T_{1/2}$ of PAS ranged from 1.21 hours to 3.91 hours. In consideration of the last sampling time, the schedule needed to be long enough to cover > three $T_{1/2}$ after reaching $C_{max}$, and the blood sampling time up to 24 hours should be sufficient for this requirement.

Based on the information from Martindale: The Complete Drug Reference [4], after taking by mouth, PAS and its salts are readily absorbed, and $C_{max}$ occurs after about 1 to 4 hours. Both PAS and its sodium salt are readily absorbed from the gastrointestinal tract, but absorption of the sodium salt is faster and more complete than that of free acid. In addition, it was demonstrated that the *AUC* was similar to all the salt forms (Na, Ca, and K salts) but was greatly different for the free acid, for which it was postulated that dissolution of the relatively insoluble acid was the rate-limiting factor [5]. However, the report by Wan et al [10], in which the bioavailability of PAS and the Na, K, and Ca salts of PAS has been studied, indicated that the absorption of PAS and its salts was essentially complete and dissolution of PAS appears to be a rate-limiting factor in its absorption. The type of administered salt affected the rate of absorption. Although absorption of all four compounds was complete, the areas under the plasma concentration-time curve or the bioavailable drug were dependent on the rate of absorption. The absorption of Na PAS was faster than that for the other two salts.

Granule formulation has been developed and aerosol formulation is developing [11,12] with an expectation of being more effective to use. For lung delivery research [9], PAS was formulated into large porous particles for direct delivery into

**Table 4 – Pharmacokinetic parameters of orally administered 500 mg calcium *p*-aminosalicylate (Ca PAS) [*n* = 13].**

| Parameters | Reference drug | | | Test drug | | | Ratio (T/R) |
|---|---|---|---|---|---|---|---|
| | Mean | SD | CV (%) | Mean | SD | CV (%) | |
| $AUC_{0-t}$ (h*ng/mL) | 6597.1 | 1660.2 | 25.2 | 5897.8 | 2087.3 | 35.3 | 0.916 |
| $AUC_{0-\infty}$ (h × ng/mL) | 6600.9 | 1661.8 | 25.2 | 5901.4 | 2086.6 | 35.4 | 0.916 |
| $C_{max}$ (ng/mL) | 9384.000 | 3815.436 | 40.7 | 5771.615 | 3435.791 | 59.5 | 0.731 |
| $T_{max}$ (h) | 0.392 | 0.124 | 31.7 | 0.962 | 0.420 | 43.7 | |
| MRT (h) | 0.71 | 0.12 | 16.7 | 1.19 | 0.34 | 28.3 | |
| $T_{1/2}$ (h) | 0.38 | 0.08 | 20.2 | 0.40 | 0.09 | 23.6 | |
| $AUC_{0-t}$ /$AUC_{0-\infty}$ | 99.9 | 0.1 | 0.1 | 99.9 | 0.1 | 0.1 | |

$AUC_{0-t}$ = area under the plasma concentration-time curve from the time zero to the time of last quantifiable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; $C_{max}$ = maximum plasma concentration; CV = coefficient of variation; MRT = mean residence time; SD = standard deviation; $T_{max}$ = time to reach measured maximum plasma concentration; $T_{1/2}$ = elimination half-life.

the lungs via inhalation. These particles possess optimized physical properties for deposition throughout the respiratory tract. Systemic drug concentrations peaked at 15 minutes, with a $C_{max}$ of 1171 mg/mL. The results suggest that inhalation delivery of PAS can potentially allow for a reduction in total dose delivered, while providing higher local and similar peak systemic drug concentrations as compared to those obtained upon oral dosing.

From a study be Peloquin et al [9], $T_{max}$ was 4.43 hours (ranging from 2.09 hours to 6.64 hours) in 12 healthy volunteers under fasting conditions, after receiving 6 g PAS granules. $C_{max}$ and $AUC_{0-\infty}$ were 21.4 μg/mL (ranging from 11.4 μg/mL to 79.3 μg/mL) and 140 μg × hour/mL (ranging from 20.8 μg × hour/mL to 255 μg × hour/mL), respectively. In comparison with the reported data [7], the values of $C_{max}$ and $AUC_{0-\infty}$ obtained for both the reference and the test drugs in this study, after the dose was normalized to 500 mg, are slightly smaller. The values of $T_{max}$ and $T_{1/2}$ obtained for both the reference and test drugs in this study are slightly faster than the reported ones, but are consistent with the study of PAS by Wan et al [10]. Based on the study, the type of administered salt affects the rate of absorption. $AUC_{0-\infty}$ or bioavailable drug, are dependent on the rate of absorption [10]. The sodium salt, which could be easily dissolved to affect the rate of absorption of PAS, was used [8]. Ca PAS is known to be less toxic when compared to Na PAS. Because the Ca salt of PAS dissolves more slowly, the rate of absorption is thus slower. Since $AUC_{0-\infty}$ depends on the rate of absorption, $T_{max}$ will be longer; the smaller $T_{max}$ is, the smaller is AUC.

Therefore, different doses, formulations, and salt forms might affect pharmacokinetic profiles, causing the difference in pharmacokinetic parameters obtained in this study (500 mg Ca PAS suspension and tablet) from those reported in the literature (6 g PAS granules).

**Table 5 – Statistical analysis of calcium *p*-aminosalicylate (Ca PAS).**

| Parameter | Mean geometric ratio | 90% CI | | *p* |
|---|---|---|---|---|
| | | Lower bound | Upper bound | |
| Ln ($AUC_{0-t}$) (h*ng/ml) | 0.873 | 74.0 | 103.0 | 0.158 |
| Ln ($AUC_{0-\mu}$) (h*ng/ml) | 0.874 | 74.1 | 103.0 | 0.158 |
| Ln ($C_{max}$) (ng/ml) | 0.569 | 38.4 | 84.3 | 0.026 |
| $T_{max}$ (h) | 1.689 | 143.2 | 194.5 | 0.001 |
| MRT (h) | 1.056 | 93.0 | 118.1 | 0.542 |
| $T_{1/2}$ (h) | 2.453 | – | – | 0.004 |
| $AUC_{0-t}$ /$AUC_{0-\mu}$ | 87.4 | 74.6 | 102.3 | 0.153 |

$AUC_{0-t}$ = area under the plasma concentration-time curve from the time zero to the time of last quantifiable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero to infinity; $C_{max}$ = maximum plasma concentration; F = relative bioavailability; MRT = mean residence time; $T_{max}$ = time to reach measured maximum plasma concentration; $T_{1/2}$ = elimination half-life.

## 5. Conclusion

From this study, the relative bioavailability of Ca PAS tablet compared with suspension is 87.4%.

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