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PHARMACOKINETICS AND DISPOSITION

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Intraindividual variability of paracetamol absorption kinetics after a semi-solid meal in healthy volunteers

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Abstract *Objective*: The absorption kinetics of paracetamol is dependent on gastric emptying and its measurement was proposed as a non-invasive method to estimate gastric emptying rate. The objective of this study was to evaluate the intraindividual variability of paracetamol absorption kinetics after a semi-solid meal.
Methods: The pharmacokinetics of paracetamol was studied on two occasions in 15 healthy volunteers without *Helicobacter pylori* antibodies. A 1-g dose of paracetamol was given as a solution together with a standardised semi-solid meal and the subjects stayed in the supine position.
Results: For most of the subjects, the time course of paracetamol concentrations was similar on the two occasions. The intraindividual variability was low, with coefficients of variation of 38.3%, 8.0% and 3.8% for time to maximum plasma concentration, maximum concentration and area under the plasma concentration – time curve until 6 h, respectively.
Conclusion: The assessment of paracetamol absorption kinetics is reproducible when the drug is given together with a semi-solid meal in *Helicobacter pylori*-negative healthy subjects.

Key words Paracetamol, Absorption

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Introduction

The absorption kinetics of paracetamol is dependent on gastric emptying [1, 2] and its assessment was, therefore, proposed as a non-invasive method to estimate gastric motility [3-5]. In previous studies of gastric emptying, paracetamol was administered to fasting subjects [1, 5–7] or with a liquid [2, 4, 8, 9], semi-solid [10, 11] or solid [3] meal. The results vary with study design, since gastric emptying is influenced by the type of meal (solid, liquid), its weight and its caloric content [12].

Studies using a solid meal may be difficult to interpret since specific interactions between solid and liquid phases are observed [13, 14]. Semi-solid meals are closer to ''normal'' (everyday life) meals than liquid meals. Therefore, in the case of patients with dyspepsia or upper gastrointestinal symptoms related to meals, a semi-solid meal is more likely to reproduce the phenomenon usually experienced. The aim of our study was to estimate the intraindividual variability of the absorption kinetics of paracetamol when administered with a semi-solid meal.

Methods

Subjects

Since an effect of *Helicobacter pylori* on gastric emptying cannot be excluded [15, 16], subjects infected with this bacteria were not included in the study. Thirty-five healthy subjects were pre-included and tested for the absence of *Helicobacter pylori* antibodies by means of an ELISA (Institut Pasteur, Paris): 15 (14 males and 1 female) had negative serology and therefore participated in the study. They gave written informed consent after the study had been approved by the regional ethics committee (Comité consultatif de protection des personnes dans la recherche biomédicale de Franche-Comté). The mean (range) age was 37 (20–51) years, body weight 77 (60–100) kg and height 177 (168–196) cm. All were found to be healthy by routine clinical examination and laboratory tests, including measurement of blood glucose. They had no medical history, except for an appendectomy in two subjects and the surgical cure of an inguinal hernia in one subject. The ultra-

sound examination of the abdomen was normal in all subjects except for one who had a single kidney. None of the subjects was a smoker and none had taken drugs for at least 1 week before the study.

Protocol

Paracetamol pharmacokinetics was studied on two occasions separated by a 1-week interval (studies were performed on the same day of the week for each volunteer), except for subject 9, for whom the interval was 10 days. After overnight fasting, the subjects were given 1 g paracetamol (Efferalgan, effervescent tablets, UPSA, France) dissolved in 100 ml water at 0800 hours. The drug was taken together with a standardised semi-solid meal, consisting of a mixture of two doses of vanilla flavour Nutricrémal (Sodiétal, Saint-Malo, France), 10 g sunflower oil and 28 g maltose dextrin, corresponding to 18% proteins, 31% lipids and 52% carbohydrates, for a total of 504 kcal and a volume of 280 ml. Another 100-ml glass of water was given just after the meal and also 2 h later; a non-standardised lunch was served in the research unit 4 h after dosing. Since the absorption of paracetamol is altered by posture and activity [7], the subjects stayed in the supine position, on the right side, for the first 2 h and only modest activity was allowed for the next 4 h. Blood samples were collected via an indwelling cannula into heparinised tubes before and 0.5, 1, 1.5, 2, 3, 4 and 6 h after paracetamol intake. After centrifugation, plasma samples were stored at −20 °C until analysis.

Paracetamol assay

Plasma concentrations of paracetamol were measured by means of a high-performance liquid chromatography (HPLC) method, modified from those described by Adriaenssens et al. [17] and Kamali et al. [18]. After centrifugation of blood samples, β-OH-ethyltheophylline was added to the plasma as internal standard and proteins were precipitated by 6% perchloric acid. After centrifugation, the supernatant was directly injected into an ultrasphere ODS-5-μm, 4.6 mm × 15 cm Beckman column and the absorbance was measured at a wavelength of 249 nm. Calibration curves were linear between 0 $\mu g \cdot ml^{-1}$ and 20 $\mu g \cdot ml^{-1}$, with a limit of detection of 0.5 $\mu g \cdot ml^{-1}$ and an interassay coefficient of variation (CV) of 4.0% and 0.7% at 2 $\mu g \cdot ml^{-1}$ and 10 $\mu g \cdot ml^{-1}$, respectively.

Pharmacokinetics and statistical analysis

Peak plasma concentration (C_{max}) and the time to reach peak concentration (t_{max}) of paracetamol were noted. The area under the plasma drug concentration – time curve from 0 h to 6 h (AUC_{6h}) was calculated using the linear trapezoidal method. The terminal elimination rate constant (λ_z) was estimated by linear regression of the log–linear portion of the terminal elimination phase. Both AUC_{6h} and AUC extrapolated to infinity (AUC_∞) were calculated. Intra- and interindividual variation in these parameters was estimated using one-way analysis of variance based on two replicates for each of the 15 subjects. CVs for intraindividual variation (CV_W) and interindividual variation (CV_B) were calculated as:

$$CV_W = \frac{\sqrt{MS_W}}{\bar{x}}$$

$$CV_B = \frac{\sqrt{(MS_B - MS_W)/n_o}}{\bar{x}}$$

where MS_W is the mean sum of squares within subjects, MS_B the mean sum of squares between subjects, $\bar{x}$ the overall mean for all observations and n_o the number of replicates per subject (in our case, two) [19]. Intraindividual differences were analysed using the Wilcoxon signed rank test.

Results

For most of the subjects, the time course of plasma concentrations observed during the two different dosings were similar (Fig. 1). The subjects who had dissimilar plasma concentrations (mainly subjects 2 and 6) were not different from the others and their experiments were uneventful. Double peaks were observed in a number of cases. For subject 3, who had identical paracetamol concentrations 0.5 h and 1 h after the first dosing, t_{max} was arbitrarily chosen to be 0.75 h. The interindividual variability of C_{max} and AUC_{6h} was about 30%, whereas the intraindividual variability of these two parameters was low: 8.0% and 3.8% for C_{max} and AUC_{6h}, respectively (Table 1). Estimation of AUC_∞ was less reliable since mean (SD) extrapolated AUC was 39 (6)% and 38 (10)% of AUC_∞ for first and second dosings, respectively. Inter- and intraindividual variability of t_{max} was high; however, intraindividual differences were not statistically significant.

Discussion

Scintigraphic methods using a radiolabelled meal are, at present, the "gold standard" in the measurement of gastric emptying [20]. These techniques are, however, limited by the necessary equipment and the possibility of artefacts. The use of a drug (i.e. paracetamol) has the theoretical advantage of giving more relevant information on drug fate during the process of drug absorption. Paracetamol is mostly not absorbed in the stomach but rapidly absorbed in the small intestine. Scintigraphic studies have shown that its absorption rate and its bioavailability are dependent on gastric emptying [1, 2]. A correlation was observed between mean gastric-emptying time of a liquid meal, measured by a scintigraphic method, and t_{max}, AUC_{4h} and k_a [2, 4]. This correlation between the gastric-emptying profile determined by gamma-camera imaging and paracetamol absorption kinetics was confirmed in healthy subjects pretreated with levodopa and carbidopa [5].

The t_{max} was previously found to range from 0.25 h to 3 h (fasting state) [1, 6, 7] or 0.25 h to 2 h (liquid meal) [2, 8, 9]. Studies using a semi-solid meal did not measure paracetamol concentrations beyond 1.5 h, a time corresponding to t_{max} in several of the subjects studied [10, 11]. If blood sampling is frequent enough during the first 2 h, double peaks are observed [5]. In the present study, we chose to measure paracetamol concentrations over a period of 6 h and yet have a sampling schedule compatible with future application of the test to patients. As a consequence, very early peaks and rapid fluctuations of paracetamol concentrations may have been overlooked. Nevertheless, t_{max} values (Table 1) were in agreement with the literature and we were able to observe double peaks in a number of patients (Fig. 1).

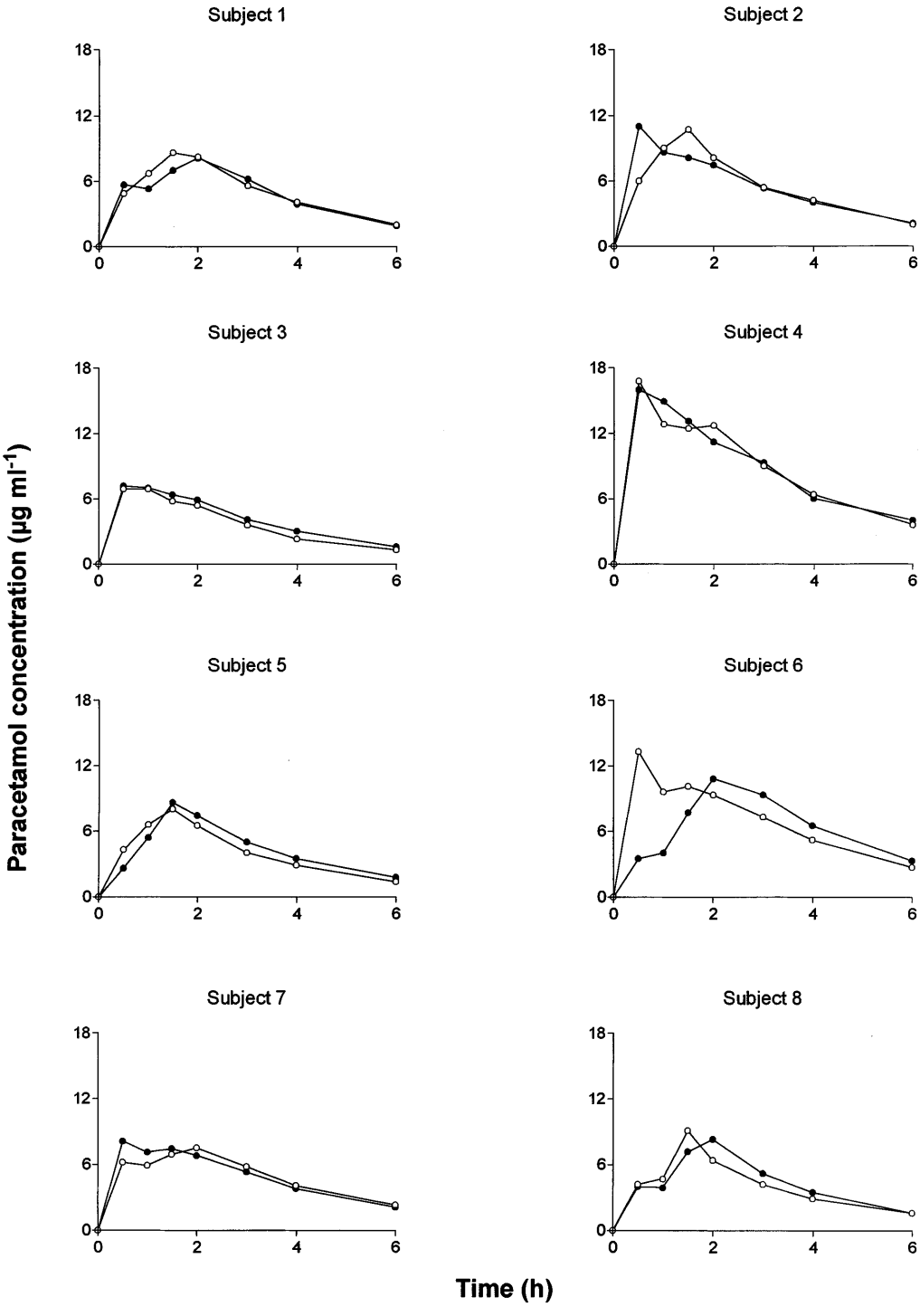

Fig. 1 Plasma concentrations following the administration of 1 g paracetamol for each of 15 healthy subjects on two different occasions. First dosing (○), second dosing (●). Subject 4 was female

Our study shows that the intraindividual variability of C_{max} and AUC_{6h} for paracetamol is less than 10% in healthy volunteers who are *Helicobacter pylori*-negative. Since the variability of $t_{½}$ (assessing metabolism and distribution) was low (Table 1), both C_{max} and AUC_{6h} may be sensitive indicators of alterations in absorption kinetics. Half-lives of paracetamol were shorter than those reported in the literature. This may be explained by our sampling schedule (sampling until 6 h), which also led to large extrapolated AUC. The sensitivity and specificity of paracetamol absorption kinetics have to be confirmed in studies involving patients with impaired gastric motility. Because of its acceptability, this test can be easily performed and repeated.

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Fig. 1 (Contd.)

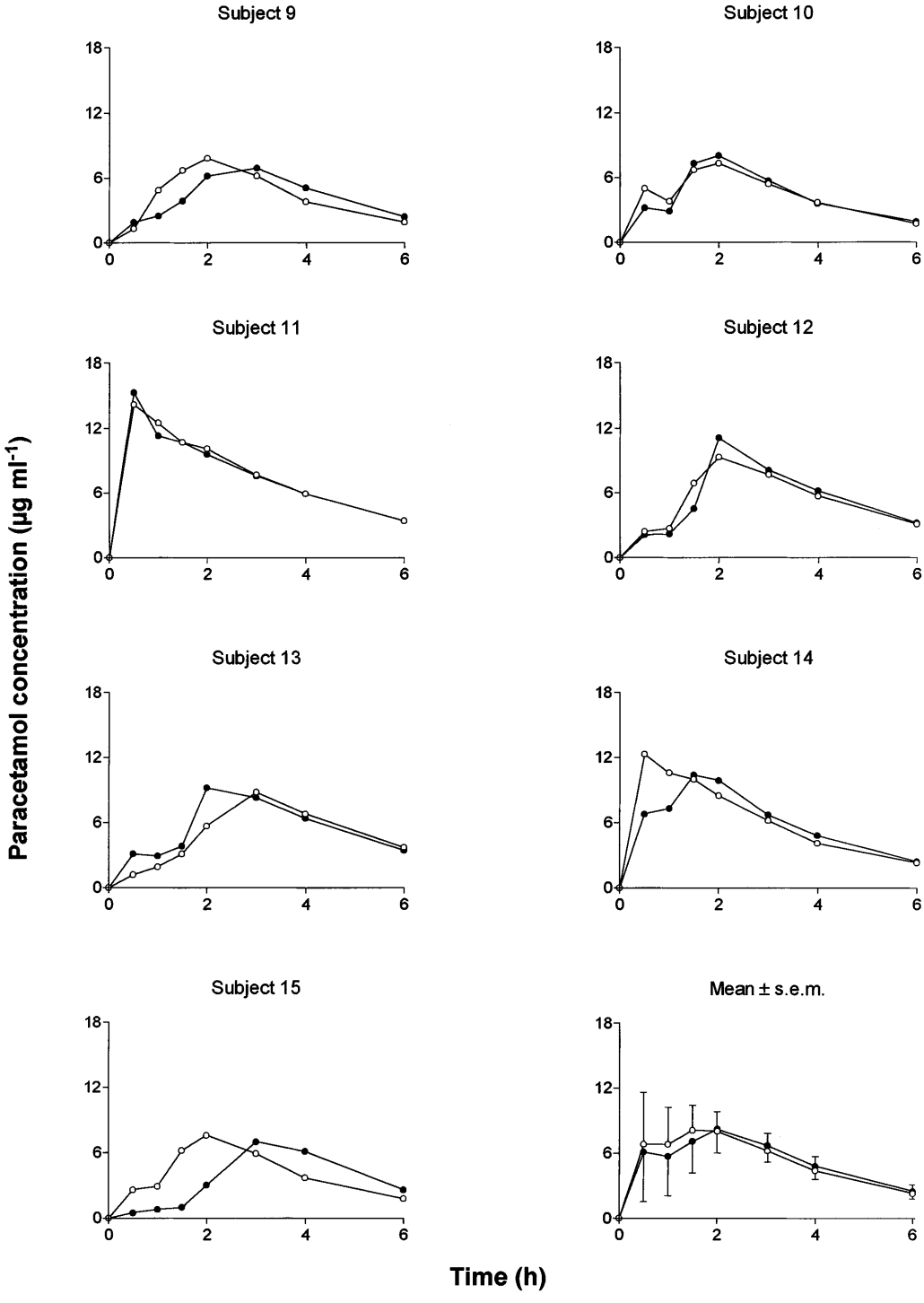

Table 1 Pharmacokinetic parameters of paracetamol, calculated after a duplicate 1-g oral dosing of 15 healthy subjects. *CV* coefficient of variation, t_{max} time to peak plasma concentration, C_{max} peak plasma concentration, *AUC* area under curve, $t_{1/2}$ half-life

	First dosing	Second dosing	CV_W (%)	CV_B (%)
t_{max} (h)	1.5 (0.5–3.0)	2.0 (0.5–3.0)	38.2	38.2
C_{max} ($\mu g \cdot ml^{-1}$)	9.9 (3.0)	9.7 (2.8)	8.0	28.3
AUC_{6h} ($\mu g \cdot h \cdot ml^{-1}$)	32 (9)	32 (8)	3.8	26.8
$t_{1/2}$ (h)	0.91 (0.77–1.11)	0.88 (0.77–1.12)	6.0	9.6
AUC_{∞}($\mu g \cdot h \cdot ml^{-1}$)	53 (16)	53 (17)	5.9	30.7

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