ABSTRACT. Objective. To determine whether multiple dosing of acetaminophen would result in drug accumulation in polymedicated elderly patients with rheumatic pain.

Methods. Twelve inpatients (11 women), aged 89 ± 4 years, weight 59 ± 10 kg, receiving 3 to 8 concomitant medications, entered the study. Their creatinine clearance according to the Cockroft-Gault formula was 42 ± 12 ml/min. The pharmacokinetics of 1 g acetaminophen was evaluated after the first dose (D1) and after the last dose (D7) during a 3 times daily regimen of 1 g for 5 consecutive days.

Results. The plasma pharmacokinetic profile of acetaminophen did not change significantly at D7 compared to D1. No significant within-patient differences were observed, especially with respect to plasma elimination half-life (2.74 ± 0.48 and 2.77 ± 0.32 hours, respectively), area under the concentration-time curve (82.5 ± 21.1 and 90.1 ± 15.2 µg•h/ml, respectively), and apparent oral clearance (3.68 ± 0.85 and 3.28 ± 0.52 ml/min/kg, respectively).

Conclusion. No drug accumulation occurred during multiple dosing with acetaminophen in these very old subjects. On the basis of pharmacokinetic data alone, a dose regimen of acetaminophen 1 g tid seems to be appropriate in such patients. (J Rheumatol 2001;28:182–4)

Key Indexing Terms: ACETAMINOPHEN POLYPHARMACY ELDERLY PHARMACOKINETICS OSTEOARTHRITIS

Acetaminophen (paracetamol) proved to be effective in relieving mild to moderate nociceptive pain of various etiologies. In recommended therapeutic dosages (3–4 g daily for adults), it is usually well tolerated and is virtually devoid of clinically relevant drug–drug interactions. Accordingly, acetaminophen is the recommended initial drug of choice for systemic treatment of noninflammatory rheumatic pain, especially in elderly patients.

However, there may be concerns about possible drug accumulation in these patients as a result of the physiological changes that occur with aging, including reduced liver and renal functions. Single dose studies investigated the pharmacokinetics of acetaminophen in the elderly. It is uncertain whether their findings can be extrapolated to the more usual clinical setting of longterm multiple drug administration.

Thus, it has been suggested to carry out studies of single dose versus multiple pharmacokinetics in small groups of elderly patients to explore the validity of such extrapolation. We investigated whether accumulation of acetaminophen occurs in the very elderly undergoing multiple drug treatment and receiving a multiple dose regimen of acetaminophen 1 g tid for rheumatic pain.

MATERIALS AND METHODS

This study was conducted in accordance with the standard code of ethical practices. The protocol was approved by the Regional Ethics Committee of Paris – Hôtel Dieu, France.

Patients. Twelve mobile inpatients (11 women, one man), aged 84 to 95 years (mean ± SD 89 ± 4), weighing 45 to 74 kg (59 ± 10 kg) entered the study after giving informed consent in writing. All were receiving longterm therapy with either 3 (n = 5), 4 (n = 3), or 5 to 8 (n = 4) medications, mainly for cardiovascular disorders (n = 9), mild depression (n = 8), or insomnia (n = 7). Their treatment was unchanged throughout the study. Smokers and patients receiving enzyme-inducing drugs as well as patients with unstable or active diseases were excluded. Standard laboratory tests (blood cell count, aminotransferases, serum albumin, and creatinine) were within the accepted reference range for this age group. The mean calculated creatinine clearance (Cockroft-Gault equation) was 42 ± 12 ml/min (range 29–61 ml/min). All participants complained of mild to moderate pain related to osteoarthritis of the hip and/or knee.

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knee (n = 10) or periarthritis of the shoulder (n = 2). Thus acetaminophen was used as an analgesic.

Protocol. The patients were given acetaminophen 1 g (2 × 500 mg Dafalgan® capsules) with 150 ml tap water in the morning (8:00 AM) and evening (8:00 PM) of Day 1. Then they received 1 g acetaminophen 3 times daily for 5 consecutive days, followed by a single dose of 1 g on the morning of Day 7. Blood samples were collected before morning dosing and at 0.5, 1, 1.5, 2, 4, 6, 8, and 10 h post dose on Days 1 and 7. Samples were centrifuged for 10 min at 3000 rpm, and plasma was removed and stored at −20°C until analysis. For both pharmacokinetic evaluations, patients were required to fast overnight and they remained fasted for 2 h after dosing.

Analytical procedure. Acetaminophen was assayed by high performance liquid chromatography. Briefly, acetaminophen and the internal standard (ß-hydroxy-ethyl-theophylline) were chromatographed on a C18 µBondapak® column (300 × 3.9 mm) with a mixture of acetonitrile and phosphate buffer 0.01 mol/l at pH 4 (910/90, v/v) as the mobile phase (flow rate 1.2 ml/min). The UV detection was at 254 nm following liquid-liquid extraction with diethyl ether. Standard curves done in plasma were linear in the range of 0.5 to 25 µg/ml. The limit of detection of the assay was 0.1 µg/ml. The intra- and inter-day coefficients of variation for acetaminophen 0.75, 4.5, and 15 µg/ml were < 5% in plasma.

Pharmacokinetic and statistical analyses. Pharmacokinetic analysis was carried out with Siphar® software (Simed, Créteil, France) according to a non-compartmental model. The area under the plasma concentrations versus time curve (AUC) was calculated by the trapezoidal rule and extrapolated to infinity. The elimination half-life (t1/2) was estimated by log-linear regression. Apparent oral clearance (Cl/f) was calculated as dose/AUC per body weight. The maximum plasma concentration (CMax) and the corresponding sampling time (TMax) were the observed values. The data were compared using Student’s paired t test, except for TMax (nonparametric Wilcoxon test). The level of significance was taken as p < 0.05.

RESULTS
All subjects complied with the protocol. No drug related adverse event was recorded during the study. The mean plasma concentrations versus time on Day 1 (first dose) and Day 7 (last dose) are depicted in Figure 1. The corresponding pharmacokinetic variables are presented in Table 1. There was no significant difference between the first and the last dose of acetaminophen in any variable (CMax, TMax, t1/2, AUC, Cl/f). The trough levels of acetaminophen averaged 1.3 ± 0.4 µg/ml (range 0.7–1.8 µg/ml) on Day 7, whereas the drug was undetectable in all samples drawn prior to initial dosing on Day 1. Finally, there was no acetaminophen accumulation in any patient.

DISCUSSION
A number of single dose pharmacokinetic studies of acetaminophen in the elderly have been published7-13. They revealed that the rate and extent of drug absorption was not substantially altered by the aging process7,10. Conversely, a more or less marked decline in acetaminophen plasma clearance combined with an increase in its elimination half-life has

![Figure 1. Mean plasma concentrations of acetaminophen, 1 g tid, after the first dose (D1) and repeated administration (D7).](image-url)

<table>
<thead>
<tr>
<th>Variable</th>
<th>D1</th>
<th>D7</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMax, µg/ml</td>
<td>23.1 ± 5.1 (13.6–31.0)</td>
<td>23.9 ± 5.4 (16.5 ± 35.0)</td>
<td>0.57</td>
</tr>
<tr>
<td>Tmax, h</td>
<td>1.0 ± 1.0 (0.5–4.0)</td>
<td>0.9 ± 0.5 (0.5–2.0)</td>
<td>0.75</td>
</tr>
<tr>
<td>t1/2, h</td>
<td>2.77 ± 0.32 (2.33–3.46)</td>
<td>2.74 ± 0.48 (2.00–3.54)</td>
<td>0.81</td>
</tr>
<tr>
<td>AUC, µg·h/ml</td>
<td>90.10 ± 15.16 (60.89–109.39)</td>
<td>82.54 ± 21.09 (57.67–134.65)</td>
<td>0.28</td>
</tr>
<tr>
<td>Cl/f, ml/min/kg</td>
<td>3.28 ± 0.52 (2.66–4.13)</td>
<td>3.68 ± 0.85 (2.10–5.42)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
usually been observed in this population, compared to young adults\textsuperscript{9,13}. In this respect, the mean apparent plasma clearance found in our patients was about half to two-thirds of that currently reported in healthy young adults (5–6 ml/min/kg) who were given 1 g acetaminophen orally\textsuperscript{7,11}. Similarly, the mean elimination half-life we observed (2.7 h) appeared to be prolonged, compared to the usual values of about 2 h in young subjects\textsuperscript{11,15}.

The decline in acetaminophen clearance in the elderly is probably multifactorial. Since this compound is extensively metabolized, primarily to the glucuronide and sulfate conjugates, prior to excretion in the urine, it can be hypothesized that age-associated changes in acetaminophen clearance might result from impaired hepatic conjugation. Interestingly, it has been shown that conjugation by glucuronidation is impaired in the elderly as a result of the decline in liver volume with age\textsuperscript{13}. This feature is the major contributor to the decline in the clearance of acetaminophen in healthy elderly subjects\textsuperscript{13}. Additional factors, including associated diseases, concomitant medications, and general physical status, may influence drug disposition\textsuperscript{6}. This is supported by studies showing that the decrease in acetaminophen plasma clearance and increase in its plasma half-life are less pronounced in fit, active elderly subjects than in their frail, immobile counterparts\textsuperscript{12,13}. The fall of acetaminophen clearance in the latter appears to result from both the decline in liver size and reduced activities of conjugating enzymes compared to young people\textsuperscript{13}.

However, these single-dose pharmacokinetic studies did not settle the question of whether adjustment of acetaminophen dosage is necessary in elderly patients receiving chronic therapy\textsuperscript{9,11,12}. The patients we studied are representative of a growing segment of the elderly population insofar as all were at least 84 years of age, received multiple drug therapy for various medical conditions, and experienced noninflammatory rheumatic pain\textsuperscript{6,16}. As expected, they presented with mild to moderate renal insufficiency according to the equation of Cockcroft and Gault\textsuperscript{14}. We found comparable pharmacokinetic profiles after the first dose (D1) and the last dose (D7) in these patients, who were given 1 g acetaminophen 3 times a day for 5 consecutive days. Furthermore, the trough levels on Day 7 (1.3 ± 0.4 µg/ml) were close to the daily pretreatment plasma concentrations (1.1 ± 0.3 µg/ml) observed in young healthy volunteers treated with a similar dose regimen for 10 days\textsuperscript{17}. In summary, despite decreased acetaminophen plasma clearance compared to young healthy adults, no drug accumulation appeared to occur in any of our patients over the study period. However, possible accumulation of the polar glucuronide and sulfate conjugates of acetaminophen cannot be excluded, inasmuch as such accumulation has been observed in patients with moderate to severe chronic renal failure\textsuperscript{17}.

Based on trough levels and comparing single dose and multiple-dose pharmacokinetic variables, no accumulation of acetaminophen was noted over the study period of treatment, suggesting that a dose regimen of acetaminophen 1 g tid would be appropriate in very old patients with pain related to degenerative arthritis. Further, this dose regimen appears to be virtually devoid of significant hepatotoxicity\textsuperscript{18,19}. Whether this is also true at maximum dosage (4 g daily) cannot be determined based on this study.

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