Gerontokinetics—a reply

The reappraisal of elderly pharmacokinetics reported by Thompson & Tucker (1992) questioned whether it is ethical to include elderly fit volunteers in new drug development studies when there is little likelihood of obtaining data different from the predictions available from younger subjects. Naturally, I endorse their comments and the reasons for asking the question but I believe that it poses another which seems to deserve discussion in your pages.

It is that if there is no peculiar risk to the fit elderly as they describe them, it appears more logical to recruit them to the exploratory studies on new compounds than the more conventional, younger age group represented by students. The logic extends beyond the simplistic idea that it is more justifiable to expose those who have already had an average life span to unnecessary risk, no matter how small, than the young. The retired elderly may have less acute needs of money so they are under less coercion by the honoraria which are now commonplace. They may have more mature judgement and, specifically, they may be seen to be less inclined to take risks of any kind.

In a practical sense, I find that elderly volunteers are less likely to default on conditions of studies. They appear less likely to consume excessive amounts of alcohol or tobacco. Their retired status makes them available for the repeat dose pharmacokinetic studies which require their residence under constant supervision in the trial premises. They consistently report that they value the camaraderie of trials, which provides them with a positive social benefit from participating.

I would endorse Thompson and Tucker's comment that trials in this group should be included in the development programme of new drugs destined mainly for use in the elderly. Indeed, to protect the young I feel obliged to consider whether such a programme for such a drug should include a majority of volunteers who are fit and between the ages of 60 and 75 years.

Accordingly, I would welcome any clarification of the relative risks to these two age groups which your pages might provide. I believe it would focus upon the differences, if any, in response to drugs of vital organs in the two age groups; particularly myocardial function and circulatory responses to pharmacologically induced changes such as hypotension.

J. A. SUTTON
Interphase UK Ltd,
1 London Road, Hindhead, Surrey GU26 6AB

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Caution in the use of a 100 mg dose of racemic mephenytoin for phenotyping Southeastern Oriental subjects

An oral dose of 100 mg of racemic mephenytoin has been used for phenotyping extensive (EMs) and poor metabolisers (PMs) (Küpfer & Preisig, 1984; Wilkinson *et al.*, 1989). The frequency of poor mephenytoin hydroxylators is much lower in Caucasian (about 3 to 6%) than in Oriental populations (23% for Japanese and 17% for mainland Chinese) (Horai *et al.*, 1989), and the occurrence of sedation or sleepiness is three times higher in PMs than in EMs (Wilkinson *et al.*, 1989). No study on the oxidation polymorphism of mephenytoin has been conducted in Southeastern Oriental subjects. Therefore, we have investigated this polymorphism in Indonesian subjects and assessed possible side-effect(s) of the drug. The protocol was approved by the local ethics committee. Before conducting a more detailed investigation, 10 healthy Indonesians (aged 18 to 50 years and weighing 38 to 60 kg) were invited to participate in a study involving separate phenotyping tests with dapsone (100 mg), metoprolol (100 mg as the tartrate) and mephenytoin (100 mg as the racemate). All drugs were administered orally in the morning and at least 1 week separated the different tests. None of the subjects developed any untoward effects when they received dapsone or metoprolol. However, two of the 10 volunteers developed undesirable effects following the oral 100 mg dose of racemic mephenytoin.

Correspondence: Dr Takashi Ishizaki, Chairman, Clinical Research Institute, National Medical Center, Toyama 1-21-2, Shinjuku-ku, Tokyo 162, Japan

Case 1 was a 28-year-old male laboratory worker weighing 45 kg. He took the drug in the morning after an overnight fast. One hour later he complained of dizziness and then developed drowsiness and intellectual impairment, which were intensified subsequently such

that he could no longer stand up. His blood pressure and heart rate were normal. Seven hours later he could sit up and all of the symptoms had disappeared by the night (approximately 12 h after dosing).

Case 2 was a 31-year-old nonpregnant female laboratory worker weighing 38 kg. One hour after taking the drug in the morning she collapsed on the way to work. She was carried by her husband to the laboratory. On arrival, she looked pale and weak and was sweating profusely. She had to lie on a bed for the rest of the day. The next morning she still complained of lightheadedness, but was able to work.

These individuals comprised two of the three PMs of mephenytoin in the 10 volunteers: 0.27% and 0.45% of the dose were excreted as 4-hydroxymephenytoin and the hydroxylation indices (HI) were 188 ($\log_{10}$ HI = 2.28) and 111 ($\log_{10}$ HI = 2.05) in Case 1 and Case 2, respectively. They are PMs according to either of the criteria normally used (Horai *et al.*, 1989; Jurima *et al.*, 1985; Küpfer & Preisig, 1984). The remaining eight subjects (seven were EMs and one was a PM had only minor complaints (e.g., dizziness) after the mephenytoin dose. The body weight of the third PM subject was 60 kg and he excreted 0.71% of the dose as 4-hydroxymephenytoin and his HI was 70 (log HI = 1.85).

Since a reduction in dose of mephenytoin appears to be appropriate for Indonesian subjects as suggested by the above cases, we studied the use of 50 mg dose for phenotyping. Twenty-three Indonesians, including eight subjects who had previously been phenotyped with a 100 mg dose, participated in the study. The protocol was approved by the same local ethics committee and informed consent was obtained from all subjects prior to the study. The two PMs (Case 1 and Case 2) declined to participate in the reduced-dose study. The eight subjects received 50 mg racemic mephenytoin at least 4 weeks after the previous dose. Another 15 subjects were phenotyped first with 50 mg and then with a 100 mg dose at an interval of at least 4 weeks. All subjects were instructed to take mephenytoin before sleeping (around 22.00 h). Two of the 15 new subjects who took both doses were identified as PMs. None of the 23 subjects developed any untoward or undesirable effects with either 50 or 100 mg racemic mephenytoin when the drug was ingested before sleeping. There was a high correlation (r_s = 0.887, $P < 0.01$) between the log % urinary excretion of 4-hydroxymephenytoin after the two doses. Furthermore, the 50 mg dose did not cause any misclassification of the phenotype.

There are three likely reasons why the two subjects developed side-effects as described in the case reports. Firstly, they were PMs of mephenytoin. It is not surprising that the marked interphenotypic differences in disposition of S-mephenytoin (Wedlund *et al.*, 1985) result in different clinical consequences. In fact, the genetic defect in 4′-hydroxylation was first identified in an index male subject on the basis of his unusual clinical sensitivity to a low dose of mephenytoin (Küpfer *et al.*, 1984). Secondly, because all of the first group of 10 subjects took the drug during the daytime, drug-induced sedative effects would have been apparent, particularly in the two PMs. None of the subjects who took the drug immediately before sleeping developed any undesirable effects. Thirdly, the body weights of the two PMs (45 and 38 kg) were much lower than those of Caucasian subjects previously phenotyped with the standard oral dose of 100 mg racemic mephenytoin (Küpfer & Preisig, 1984; Wilkinson *et al.*, 1989). In fact, the third male PM subject with the heaviest body weight (60 kg) among the first group of 10 subjects complained of only minor side-effects when he received the 100 mg dose of racemic mephenytoin in the morning. This is in accordance with a report by Jurima *et al.* (1985) who pointed out that they had to use 50 mg instead of 100 mg for some volunteers since a few subjects with lower body weight experienced mild sedation after taking a 100 mg racemic mephenytoin. Thus, we feel that 100 mg mephenytoin is excessive in subjects with low body weights, particularly when the drug is ingested during the daytime. We recommend that the mephenytoin dose used for phenotyping in Far Eastern Oriental regions be reduced to half and that it should preferably be administered before sleeping. Designation of the phenotyope is not altered by this procedure.

RIANTO SETIABUDY[1], KAN CHIBA[2], MEIZOH KUSAKA[2] & TAKASHI ISHIZAKI[2]

[1] *Department of Pharmacology, School of Medicine, University of Indonesia, Jakarta, Indonesia and*

[2] *Division of Clinical Pharmacology, Clinical Research Institute, National Medical Center, Tokyo 162, Japan*

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