Letters to the Editors

The influence of body weight on the pharmacokinetics of mefloquine

Antimalarial drugs are usually given on a mg kg^{-1} basis. We have reported previously the population pharmacokinetics of mefloquine derived from data of patients treated for uncomplicated *Plasmodium falciparum* malaria as part of trials conducted between 1990 and 1995 [1]. The patients were from the Karen ethnic minority who lived in camps for displaced persons situated along the western border of Thailand. For the studies conducted after 1994 the number of precise mefloquine tablets given was recorded. The patients received one of two mefloquine (Lariam, 250 mg base tablets, Roche Pharmaceuticals) dosing regimens in combination with artesunate (12 mg kg^{-1} over 3 days): 25 mg kg^{-1} (single dose) or 25 mg kg^{-1} (split dose: 15 mg kg^{-1} on day 0 followed by 10 mg kg^{-1} 24 h later). Using the actual dose (mg) in the population pharmacokinetic model as opposed to the weight adjusted dose (mg kg^{-1}), the relationship between the derived pharmacokinetic parameters and body weight was investigated.

A one-compartment model with first-order absorption and first-order elimination was found to describe the data adequately [1]. As very few mefloquine concentrations were recorded during the absorption phase, the absorption rate constant was set to a constant value of 7.0/day derived from a pharmacokinetic study [2] of patients with malaria from the same population. The fundamental pharmacokinetic parameters used to characterize the one-compartment model were apparent clearance (CL/F) and apparent volume of distribution (V/F). The nonlinear mixed effects modelling procedure [3] of the S-PLUS data programme (S-PLUS 4.5 for Windows, Mathsoft, Inc., Cambridge, Massachusetts) was used to calculate estimates of the population pharmacokinetic parameters (CL/F and V/F) and their respective interpatient variances. Individual pharmacokinetic parameters were obtained as posterior estimates from the nonlinear mixed effects modelling procedure. The model building process and the procedures for accepting and rejecting models were identical to those published previously [1]. Measurements of whole blood mefloquine concentration were performed by h.p.l.c. as described previously [4]. The interassay coefficients of variation were 8.3% and 5.7% at 100 and 1000 ng ml^{-1}, respectively.

For those patients given a single dose of mefloquine as part of combination therapy ($n=74$) the posterior patient specific estimates for CL/F and V/F were significantly positively correlated with body weight. Incorporating body weight as a covariate for both CL/F and V/F in the model reduced the interpatient variability from 66 to 49% for CL/F and from 50 to 34% for V/F. At the minimum (13 kg), mean (25.6 kg) and maximum (43 kg) body weights the respective population estimates of CL/F would be 13.34, 33.0 and 60.14 l day^{-1}, and for V/F would be 192.3, 383.9 and 648.3 l, indicating a linear relationship with body weight. Similar results were obtained for patients receiving a split dose of mefloquine as part of combination therapy ($n=31$) (Table 1).

The original decision to adjust the dose of mefloquine according to body weight was an empirical decision that had not been tested formally. There is no evidence that the clearance of mefloquine is dose-dependent [5]. These

Table 1 Mefloquine population pharmacokinetic parameters for the final models where adjusting for body weight gave improved fits.

	Combined therapy and single dosing (74 patients) Estimate (s.e.)	*90% prediction intervals*	*Combined therapy and split dosing (31 patients)* Estimate (s.e.)	*90% prediction intervals*
CL/F (l day^{-1})*	33.0 (2.4)	14.9, 73.3	23.8 (2.2)	12.9, 43.9
Change in CL/F (l day^{-1}) for an increase of 1 kg in body weight	1.6 (0.3)		0.9 (0.3)	
V/F (l)*	383.9 (18.3)	220.50, 668.24	330.6 (19.2)	217.4, 502.9
Change in V/F (l) for an increase of 1 kg in body weight	15.2 (2.1)		11.9 (2.7)	
k_e (elimination rate)*	0.09/day		0.07/day	
$t_{1/2}$ (elimination half life)*	8.1 days		9.6 days	
σ_ε (ng ml^{-1})	295.6		259.2	

*For a person having a mean body weight; s.e., standard error.

data suggest a linear relationship between clearance, and volume of distribution, and body weight over the range between 13 and 43 kg.

Previous population pharmacokinetic modelling [1], where we used the weight adjusted dose (mg kg^{-1}), found no correlation between body weight and the posterior patient specific estimates for both CL/F and V/F. Thus our present and previous findings confirm that the current recommendations for mefloquine administration, both for nonobese adults and children, that the dose of mefloquine should be adjusted for body weight, are correct. Further studies on heavier adults are needed to determine if this linear adjustment is still appropriate for overweight individuals.

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Paracetamol can exacerbate irradiation-induced DNA damage

Paracetamol is one of the most commonly used drugs for short-term pain relief. If taken in excess, the toxic metabolite (N-acetyl-*p*-benzoquinone imine) is formed. This can be inactivated through conjugation with the antioxidant glutathione but results in glutathione depletion and subsequent oxidative damage to hepatocytes [1]. Although the main route of paracetamol bioactivation is via the P450 cytochrome system in the liver, these enzymes are also present in most other tissues of the body. In tissues where this activity is low (such as the skin and lung), prostaglandin synthetase can catalyse the production of the toxic metabolite [2]. Recent work *in vitro* has shown that glutathione depletion is possible in lung cells incubated with therapeutic concentrations of paracetamol [3]. As glutathione plays an important role in the antioxidant defence of the skin to UVA irradiation [4], anything that depletes cellular glutathione levels could potentially exacerbate the cellular damage caused by such an insult and consequently have detrimental health effects.

Initially, the effect of therapeutic concentrations of paracetamol on irradiation-induced DNA damage was investigated *in vitro* (MRC5 human lung fibroblasts, passage number 22–27, ECACC, UK) in a single experiment repeated on 4 separate days. A preliminary study of the same effect in peripheral white blood cells taken from four human volunteers was also conducted to confirm these findings. In both cases, alkaline single cell gel electrophoresis was employed to detect DNA damage in the form of single strand breaks following an irradiation insult from an unfiltered xenon arc lamp (delivering UVB, UVA and visible light (280–750 nm)) using an irradiance of 4.17 mW cm^{-2}. This method, which was developed from that of Singh *et al.* [5], is both sensitive and well suited for the detection of UVA-induced DNA damage. The DNA damage was quantified using a visual analogue scoring system (based on that of Collins *et al.* [6]) to analyse 60 comets in each sample.

Figure 1 illustrates that cultured human fibroblasts experienced significantly more DNA single strand breaks, following a xenon arc lamp dose of 750 or 1000 mJ cm^{-2}, when the cells had been previously incubated with a concentration of paracetamol similar to that obtained during therapeutic use (20 mg l^{-1} for 1 h) [7]. These findings were confirmed using the same procedure to investigate the effect of the same insult on the peripheral white blood cells of the human volunteers taken both before and after they had received the maximal therapeutic dose of paracetamol for 1 day (1 g once every 6 h for 24 h). The same trend was observed in all of the four subjects studied and was the same as that obtained *in vitro*.

The findings of this study, although only preliminary at this stage, could have implications for the risk of developing skin cancer, particularly in individuals who regularly use paracetamol for pain relief and are subject to excessive solar irradiation exposure. The exacerbation of irradiation-induced DNA damage by paracetamol, as demonstrated

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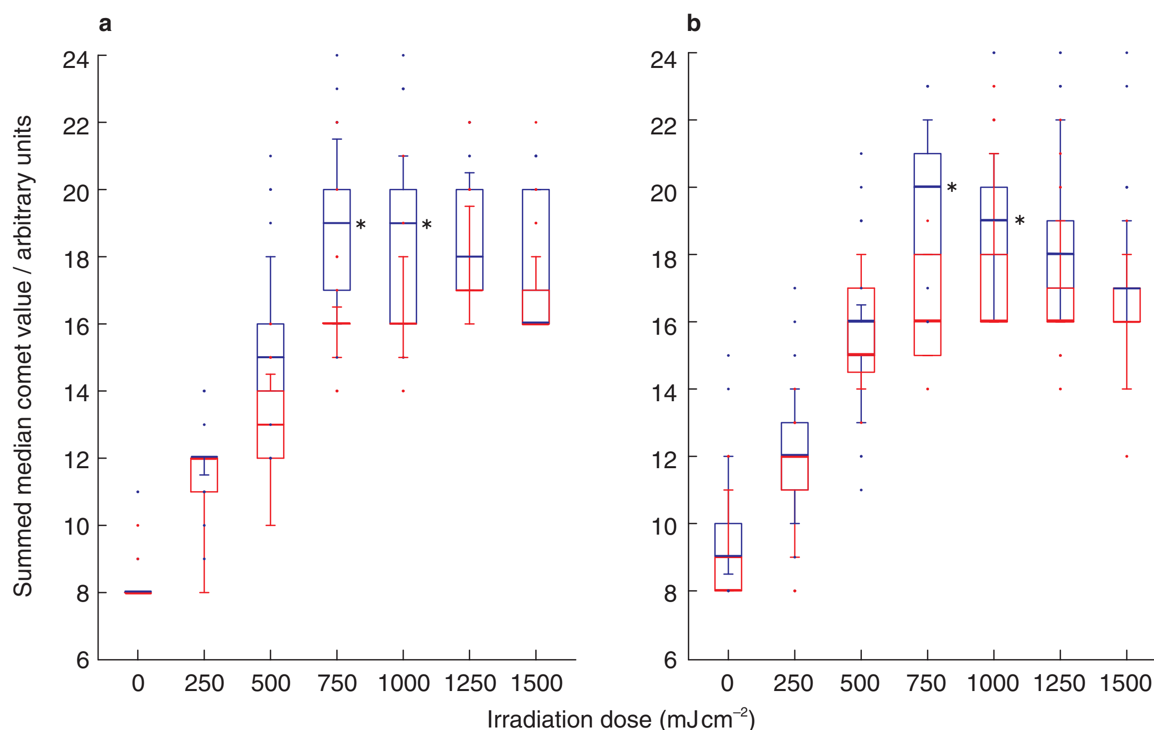

Figure 1 A box-whisker plot of the summed median comet values (indicating the level of DNA single strand breaks) observed by single cell gel electrophoresis of cultured human lung fibroblasts (MRC5) (a) and human peripheral white blood cells (b), following increasing doses of xenon arc lamp irradiation (mJ cm^{-2}). Control cells of both types (red) are compared with cells exposed to therapeutic concentrations of paracetamol (blue). The summed median value of 60 observations in each of four cultures or volunteers is presented as a heavy line. Variance around the median is indicated by a box corresponding to the central 50% of the observations with 10th and 90th percentile whisker caps. Outliers are presented as dots. * indicates statistical significance ($P < 0.05$) between the paracetamol exposed group and its appropriate control, using a Mann–Whitney *U*-test.

here, presents an additional workload for DNA repair mechanisms, but this has yet to be demonstrated in skin cells. Although, glutathione concentrations were not measured in this investigation, it can be postulated that even if a cell is even partially depleted of its protective glutathione by paracetamol prior to an irradiation insult, its DNA would be inherently more susceptible to oxidative damage (known to be caused by UVA light) than those cells not compromised in this manner. Therefore, the combination of both of these effects would result in an increased number of DNA single strand breaks as described. This increase is reversed with continued irradiation and, therefore, it appears that the cell is capable of reacting to the increased clastogenic load in a relatively short space of time.

These findings warrant much further detailed study. Experiments should involve the measurement of glutathione concentrations and include skin cells such as keratinocytes. Studies of this effect in people receiving chronic paracetamol supplementation on a long-term basis would also be informative.

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