THE CLINICAL PHARMACOLOGY OF CHLORAMBUCIL AND PREDNIMUSTINE

In their recent letter concerning the clinical pharmacokinetics of chlorambucil, and its prednisolone ester prednimustine, Plym Forshell and colleagues (1983) raise a number of interesting points.

First, these authors cite the activity of low dose prednimustine (8–32 mg) against chronic lymphocytic leukaemia and non-Hodgkin's lymphoma as evidence of alkylating activity in man. This contention is purely circumstantial and overlooks other possible mechanisms of action, e.g. the release of prednisolone which is known to have activity against these tumours (Sawitsky *et al.*, 1977; Jones *et al.*, 1972). Indeed, the observation that bone marrow toxicity is minimal in patients treated with continuous low dose prednimustine is support for the view that significant levels of alkylating species are *not* achieved.

Second, as was suggested (Newell *et al.*, 1983), and as has subsequently been shown (Ehrsson *et al.*, 1983), at higher doses of prednimustine (100 mg) alkylating species, i.e. chlorambucil, are detectable in patients' plasma. However, the important observation remains that the intact steroidal ester is undetectable (Ehrsson *et al.*, 1983) confirming earlier studies in rodents (Newell *et al.*, 1981). Thus prednimustine is acting as a chlorambucil, and presumably prednisolone, pro-drug. Given (a) the low bioavailability of chlorambucil when administered as prednimustine (ca. 20%, Ehrsson *et al.*, 1983; Newell *et al.*, 1983), and (b) the highly variable and in some patients extensive faecal excretion of unchanged prednimustine (Konyves *et al.*, 1975), it would appear to be a relatively poor pro-drug. These observations lead to the recommendation that for diseases where chlorambucil and prednisolone therapy are indicated the two agents should continue to be given separately (Newell *et al.*, 1983).

Although there is clearly also variability in plasma levels following oral chlorambucil (Ehrsson *et al.*, 1983; Alberts *et al.*, 1979) it is difficult to attribute this to poor absorption from the gastrointestinal tract. In two patients comparison of i.v. and p.o. chlorambucil indicated good bioavailability (> 70%) (Newell *et al.*, 1983) whilst in two of three patients treated i.v. and p.o. with ring [¹⁴C]-chlorambucil urinary excretion of ¹⁴C was greater following oral administration (McLean *et al.*, 1979). Thus variable metabolism is a more probable explanation for the variability in plasma levels following p.o. chlorambucil. This is not necessarily deleterious since the only chlorambucil metabolite identified to date in man, phenyl acetic mustard (Newell *et al.*, 1978; McLean *et al.*, 1979; Alberts *et al.*, 1980), is an active alkylating agent.

Finally, Plym Forshell and colleagues (1983) state that in one study prednimustine was superior to a combination of chlorambucil plus prednisolone, both in terms of greater efficacy and reduced toxicity (Lober *et al.*, 1983). We are unable to comment on this interesting observation as these data have not been published.

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