Improved tolerability of ritonavir derived from pharmacokinetic principles

Ritonavir, an inhibitor of the HIV protease enzyme, is one of the most potent drugs available for the treatment of patients with HIV infection [1]. Preliminary data suggest the administration of ritonavir to patients with advanced disease may result in a significant reduction in mortality [2]. The current recommended dose, 600 mg twice daily, has been demonstrated to produce a viral load reduction of $-2.0\log_{10}$ (by RNA PCR) which was sustained at $-0.81\log_{10}$ by 32 weeks [3]. This was associated with an increase in the CD4 count of 230 cells/mm$^3$ above pretreatment levels. We report our experience with this new anti-HIV agent and propose a change in the dosing regimen which could enhance tolerability and yet maintain anti-viral efficacy.

Seventeen patients have been treated with ritonavir 600 mg twice daily over the past 12 weeks. There were 48 adverse events reported by 12 of the patients (70%). In five patients these adverse effects were so severe as to result in the discontinuation of ritonavir therapy (29%). The most frequent adverse effects included nausea (severe, grade 3 in six patients), vomiting (moderate, grade 2 in three patients), perioral and peripheral paraesthesiae (moderate, grade 2 in two patients) and malaise (moderate, grade 2 in four patients). Other adverse effects reported included throat irritation, myositis, pyrexia, stomatitis and insomnia. Two patients lost 3 kg in weight during ritonavir therapy and recovered this on cessation. Of those patients reporting adverse effects, over 70% indicated the onset of symptoms 2 h after each dose and lasting for approximately 4 h. In two patients who wished to discontinue ritonavir treatment we altered the dose regimen to 300 mg every 6 h in view of the apparent relationship between dosing and adverse effects and a knowledge of the pharmacokinetics of ritonavir which has a very short elimination half-life of 3 h. This alteration was associated with a resolution in symptoms enabling these two patients to continue taking ritonavir.

Mindful of the fact that the 90% effective plasma ritonavir concentration has been reported as greater than 2.1 $\mu$g/ml$^1$ after adjusting for binding to plasma proteins, we were concerned that the change in dose schedule would provide satisfactory plasma levels [3]. Using pharmacokinetic data derived from published literature [1, 3, 4] we constructed plasma ritonavir concentration-time profiles that may be expected following the administration of ritonavir 300 mg 6 hourly and 600 mg 12 hourly (Figure 1). The reduced peak plasma concentration following 6 hourly dosing may explain the improved tolerance of ritonavir in our two patients despite taking the same total daily dose of 1200 mg. In addition, the trough levels expected with ritonavir 300 mg 6 hourly do not fall below the 2.1 $\mu$g/ml$^1$ concentration thereby maintaining anti-viral efficacy. In our clinical experience the main problems associated with ritonavir use are patient tolerability and drug interactions resulting from the potent enzyme inhibiting properties of the drug. A change in dose schedule to 300 mg 6 hourly may not influence potential drug interactions but should improve the tolerability of ritonavir enabling patients to benefit from one of the most potent anti-HIV drugs available.

C. MERRY1, 2, M. BARRY1, S. GIBBONS1, F. MULCAHY2 & D. BACK1
1Department of Pharmacology and Therapeutics, University of Liverpool, PO Box 147, Liverpool, L69 3BX and 2Department of Genitourinary Medicine, St James’s Hospital, Dublin, Ireland

(Received 4 July 1996, accepted 29 July 1996)

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Correspondence: Dr M. Barry, Department of Pharmacology and Therapeutics, University of Liverpool, PO Box 147, Liverpool L69 3BX.