BAYESIAN DERIVED PHARMACOKINETIC/PHARMACODYNAMIC VARIABLES FROM WARFARIN THERAPY

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Inter-patient variability of warfarin pharmacokinetic and pharmacodynamic properties precludes a universal response to a fixed dose regimen. The long elimination half-lives of warfarin and the clotting factors combine such that it is many days before a steady-state is attained. Current clinical practice is to estimate the dosage required from the latest clotting time response, represented as the International Normalised Ratio (INR). A model incorporating the pharmacodynamic parameters of warfarin has been proposed to predict clotting time response of warfarin dosing regimens (Theofanous and Barile, 1973). The parameters identified are the degradation rate constant (Kd) of the prothrombin complex activity, the serum warfarin concentration at which the prothrombin complex synthesis rate is zero (Cmax) and a constant, relating to the slope of the log dose-response curve (m). In addition, the pharmacokinetic parameters of warfarin are used to predict the serum warfarin concentration during each dosage interval. During normal clinical practice, the estimation of these parameters is difficult, not practicable and unethical. Computerised methods of parameter estimation, using available patient data, have been used. Bayesian analysis is such a technique, which refines the initial parameter estimates of an individual, derived from population data, into ones of a more individualistic nature (revised estimates). This method (Chrystyn et al, 1988) has been adapted to include the model of Theofanus and Barile with modifications such that only the pharmacodynamic parameters are refined.
Anticoagulant data from 10 patients (3 females), whose mean (sd) age was 63.3 (7.32) years and weight 81.2 (19.89)Kg, have been retrospectively analysed. Initial estimates (IE) of warfarin pharmacodynamic and pharmacokinetic parameters were calculated for each patient, from previously published population data (Svec et al, 1985, Murray et al, 1987). These were refined into revised estimates (RE1), by Bayesian analysis, in the light of each patient's dosing history and an INR value between day 4 and 6 of therapy. Using a measured serum warfarin concentration, revised estimates of warfarin pharmacokinetic parameters were derived for each patient. These values were then used, together with the initial estimates of the pharmacodynamic parameters, to refine the latter into revised estimates (RE2) by Bayesian analysis.
Each set of patient parameters (IE, RE1 and RE2) was used, together with each patients dosage histories, to predict the INR measured between days 11 and 14 of therapy. The mean (sd) value of the INR was 2.88 (0.97). Table 1 details the absolute performance (Sheiner and Beal, 1981) in terms of mean (me) and root mean squared (rmse) prediction errors. This shows that RE2 produced the least biased and most precise predictions.

Table 1: Absolute Performance

	Bias me (sd)	Precision rmse (sd)
IE	-1.38 (0.82)	1.58 (1.76)
RE1	0.33 (1.06)	1.06 (1.36)
RE2	-0.2 (0.56)	0.56 (0.67)

Relative performance reveals that both RE1 and RE2 were significantly ($p < 0.05$) less biased than IE. All other differences were not significant. The RE2 mean (sd) value for Kd was 1.055 (0.061)/day, for Cmax was 2.90 (0.88)mg/L and for m was 38.38 (1.78)%/day.

The large error of the initial estimates reveals that these American derived population values do not apply to the British patient.

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