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THEOPHYLLINE CONCENTRATION IN SALIVA AS A GUIDE FOR INDIVIDUALIZATION OF ITS THERAPEUTIC USE

Marked interindividual differences have been found in theophylline metabolism in man (Mitenko & Ogilvie, 1973; Piafsky, Sitar, Rangno & Ogilvie, 1977; Plavsic, Bakran & Vrhovac, 1978). It is necessary to individualize treatment with drugs which demonstrate great interindividual variations in pharmacokinetic parameters (Bonora, Ottoboni, Guaglio, Terzoni & Rondanelli, 1980; Chiou, Huang & Huang, 1980; Walther, Meyer, Quedrow, Lenscher, Kohler & Herenburg, 1978). The possibility of using saliva samples for monitoring theophylline treatment has been studied in recent years (Breimer & Danhof, 1980; Horning, Brown, Nowlin, Lartratanangkoon, Kellaway & Zion, 1977). Some authors have found a good correlation between

saliva and serum concentrations of theophylline (Breimer & Danhof, 1980; Horning *et al.*, 1977), but others disagree (Boobis, Trembath, Chambers, Edmunds & Carswell, 1979). It has been shown that concentrations in saliva for weak acidic and basic drugs are equivalent to their free fraction in the serum (Mucklow, Bending, Kahn & Dollery, 1978). Although small interindividual variations in the volume of distribution exist, differences in biological half-lives of theophylline are more important from a clinical point of view (Mitenko & Ogilvie, 1973; Piafsky *et al.*, 1977). The accuracy of the calculation of the biological half-life is dependent upon the number of samples used. In the β -phase of elimination at least three determinations are desirable, but it has been shown that determination of two well-chosen samples may be sufficient (Bonora *et al.*, 1980; Chiou *et al.*, 1980). We have evaluated this for theophylline.

Ten healthy volunteers were fasted overnight and abstained from smoking and caffeine containing drinks during the study. Intravenous aminophylline in a dose of 6 mg/kg was administered over a period of 15 min. Blood (2 ml) and saliva (1 ml) samples were obtained 3 and 6 h after starting the infusion. Each subject's mouth was rinsed and then each chewed parafilm for 5 min before taking saliva. Serum and salivary theophylline concentrations were determined by the RIA method (GammaDab ^{125}I theophylline radioimmunoassay kit, Clinical Assay). Biological half-lives were calculated from the relation $C_2 = C_1 e^{-K_e(t_2-t_1)}$, where C_1 and C_2 are theophylline concentrations in the time t_1 and t_2 after the dose

Figure 1 Correlation between theophylline concentrations in simultaneous serum and saliva samples. $C_{\text{saliva}} = 0.8 + 0.38 C_{\text{serum}}$, $r = 0.93$.

Figure 2 Correlation between theophylline biological half-lives calculated from concentration measurements in serum and saliva. $T_{1/2} \text{ saliva} = 0.6 + 0.88 T_{1/2} \text{ serum}$, $r = 0.95$.

administration and K_e is the constant of its elimination rate (Bonora *et al.*, 1980).

The correlation between theophylline concentrations in the simultaneous serum and saliva samples is

represented in Figure 1. Serum theophylline concentrations were on average 1.95 times higher than the theophylline concentrations in saliva ($r = 0.93$). Figure 2 shows the correlation between the theophylline biological half-lives calculated from concentration measurements in saliva and serum ($r = 0.95$).

Our results accord with other data in the literature (Breimer & Danhof, 1980; Horning *et al.*, 1977). Biological half-lives calculated from measurements of concentrations in serum and saliva have demonstrated good correlation. We suggest that for calculation of intravenous dose, only two theophylline determinations in saliva in the β -phase of the concentration curve need be used. We need to confirm this after oral administration. This method is both cheaper and more comfortable for the patients.

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