AN IMPROVED METHOD FOR THE ANALYSIS OF FLURAZEPAM AND ITS MAIN METABOLITE IN HUMAN PLASMA

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Flurazepam has been implicated in dialysis encephalopathy, which occurs in certain patients with advanced renal failure (Taclob & Needle 1976). Hence it is proposed to study the disposition of the drug in such patients.

However, in our hands published methods for the analysis of flurazepam and its N-desalkyl metabolite in human plasma using GLC with electron-capture detection (e.g. De Silva et al 1974) failed to detect these compounds below a concentration of about 10 $\mu g\ ml^{-1}$. Greatly improved sensitivity, adequate for the measurement of therapeutic levels of flurazepam was achieved by rigorous column conditioning: daily silylation with 4 x 5 µl of HMDS followed by overloading the column with the sample compounds (2 x 1 µg). A back extraction method (De Silva et al 1974) was employed for plasma samples. Cross-contamination of samples during the extraction and chromatographic procedures was prevented by exhaustive cleaning and silylation of all glassware including the Hamilton syringe.

Calibration curves were obtained from 'spiked' blood samples for flurazepam and its N-desalkyl metabolite in the concentration range 1-30 $ng\ ml^{-1}$ ($ng\ ml^{-3}$) (flurazepam : $r > 0.99$, $SE < 3.5 \times 10^{-3}$; metabolite : $r > 0.986$, $SE < 4.0 \times 10^{-3}$). The initial lack of sensitivity, similar to that reported for nitrazepam and clonazepam (Kangas 1977), was attributed to considerable adsorption of flurazepam and its metabolites on to the glass GC column, the stationary phase support material and the glassware generally.

The disposition of flurazepam and its N-desalkyl metabolite following a single oral dose (30 mg Dalmane) was followed in three healthy male volunteers (aged 23-34). Peak levels of flurazepam (> 20 $ng\ ml^{-1}$) were found in the plasma of the healthy volunteers 1 - 2 hours following administration using the present column conditioning method. Other reported studies using the basic method have shown only minimal levels (< 3.0 $ng\ ml^{-1}$) for up to 2 hours after administration. In our study some unchanged drug could still be found 12 hours after administration. Disposition of the metabolite in the normal subjects agreed well with those studies previously published ($t_{\frac{1}{2}}$: 64 - 120 hrs).

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