

## THE EFFECT OF AZAPROPAZONE ON THE BINDING OF WARFARIN TO HUMAN SERUM PROTEINS

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Azapropazone, a non-steroidal anti-inflammatory agent has been shown clinically to potentiate the action of warfarin (Powell-Jackson, 1977; Green *et al* 1977). One possible mechanism of this drug interaction is a displacement of warfarin from its albumin binding sites by azapropazone giving rise to increased levels of free (non-protein bound), pharmacologically active warfarin in the plasma. Another mechanism may be induced changes in warfarin isomer metabolism by azapropazone. Preliminary investigations (McElnay and D'Arcy, 1977) using pure albumin showed that azapropazone decreased warfarin binding. It was therefore of importance to determine to what extent this displacement occurred in human serum over a range of azapropazone concentrations.

The technique used in the present study was equilibrium dialysis (Harron *et al*, 1978). Blood was obtained from four healthy male volunteers who were not receiving drug therapy. The separated serum was pooled, assayed for protein content and 1 ml samples were then dialysed (30 hours, 37°C) against 1 ml volumes of isotonic phosphate buffer (pH 7.4). The buffer contained racemic  $^{14}\text{C}$ -warfarin ( $1.34 \mu\text{g ml}^{-1}$ ) and azapropazone (0-200  $\mu\text{g ml}^{-1}$ ); these concentrations were used in a previous warfarin/ibuprofen study (Slattery and Levy, 1977). Serum and buffer samples were then assayed using liquid scintillation counting. These assay results allowed the percentage of bound (99.219%) and free (0.781%) form warfarin to be determined. Free fraction ratio values (Slattery and Levy, 1977) for warfarin in combination with azapropazone were then calculated by expressing the increases in free form warfarin, due to azapropazone displacement, as a ratio of the free form warfarin alone. These values (fig.1) increased with increasing azapropazone concentration, giving a doubled value at 200  $\mu\text{g ml}^{-1}$ .

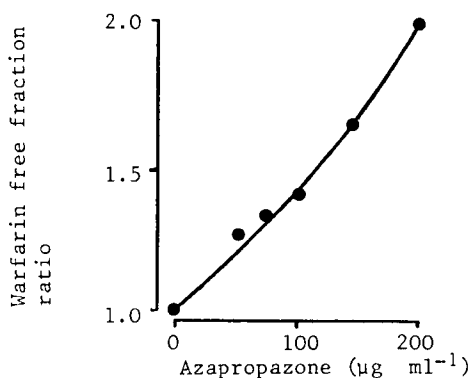


Fig.1. Changes in warfarin free fraction ratios over a range of serum azapropazone concentrations. Serum contained - (1) Albumin  $47 \text{ g L}^{-1}$  (2) Globulins  $24 \text{ g L}^{-1}$ . Each point is the average of 4 individual determinations.

Blood levels of azapropazone on a dosage regimen of 3 x 300 mg daily may reach  $96.5 \mu\text{g ml}^{-1}$  (Leach, 1976); at this concentration the free fraction of warfarin would increase by about 40% and this would be expected to give increased anticoagulation.

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