Effect of Ibuprofen on Protein Binding of Warfarin in Human Serum

Keyphrases □ Ibuprofen—effect on protein binding of warfarin, human serum □ Binding—warfarin to serum protein, effect of ibuprofen, humans □ Warfarin—serum protein binding, effect of ibuprofen, humans □ Anti-inflammatory agents—ibuprofen, effect on protein binding of warfarin, human serum □ Anticoagulants—warfarin, serum protein binding, effect of ibuprofen, humans

To the Editor:

Ibuprofen is a widely used anti-inflammatory, which is extensively bound to plasma proteins (1). Studies in rats showed that ibuprofen can displace warfarin from serum protein binding sites and that this displacement causes an increase in the total body clearance of warfarin and in the anticoagulant effect produced by a given concentration of total (free and protein-bound) drug (2).

Theoretical considerations indicate that the displacement of a drug from protein binding sites should be associated with a transient and intermittent increase in the pharmacological effect (3, 4). However, no such potentiation was observed in humans with respect to the anticoagulant effect of warfarin when ibuprofen was administered in doses of up to 2.4 g/day (5). In view of the recent tendency to use even larger doses of ibuprofen for the treatment of inflammatory disease, it was considered advisable to determine the relationship between ibuprofen concentration and protein binding of warfarin in human serum.

Blood was obtained from five healthy adult females who were taking no drugs other than oral contraceptives. Serum was separated and pooled. Racemic ^{14}C-warfarin (1.34 μg/ml) and ibuprofen (0–200 μg/ml) were added, and the free fraction of warfarin was determined in duplicate by equilibrium dialysis (6).

The pooled serum contained 4.18% albumin and 8.46% total protein. The free fraction of warfarin in the absence of ibuprofen was 0.00978, equivalent to 99.022% protein binding. The free fraction increased continuously with the increasing ibuprofen concentration (Fig. 1). At the highest concentration of ibuprofen (about 200 μg/ml), the warfarin free fraction was 0.0198, *i.e.*, twice as large as in the absence of ibuprofen.

It is estimated that the steady-state serum concentration of ibuprofen produced by administration of 600 mg every 6 hr to adult patients is about 30–40 μg/ml (2). At this concentration, ibuprofen increases the warfarin free fraction in human serum by only about 10% so that no significant potentiation of anticoagulant effect should be apparent. However, a doubling of the dose will cause an appreciable displacement of warfarin and may be expected to produce a measurable potentiation of anticoagulant effect.

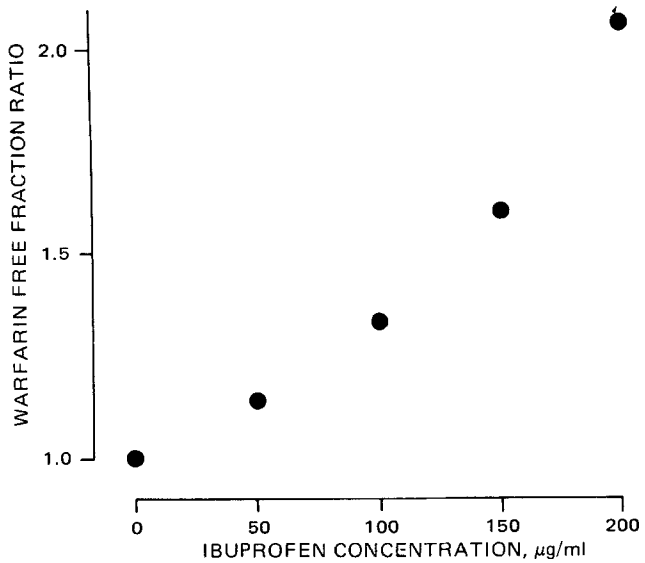

Figure 1—*Effect of ibuprofen on protein binding of warfarin in pooled human serum. Shown is the relationship between the warfarin free fraction ratio (with ibuprofen/control) and the ibuprofen concentration.*

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