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Impact of experimental variables on the protein binding of tigecycline in human plasma as determined by ultrafiltration

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Abstract

Tigecycline, a tetracycline derivative, shows atypical plasma-protein-binding behavior. The unbound fraction decreases with increasing concentration at therapeutic concentrations. Moreover, uncertainty exists about the magnitude of tigecyline's protein binding in man. Unbound fractions between 2.5 and 35% have been reported in plasma from healthy volunteers, and between 25 and 100 % in patients, respectively. In the present study, the protein binding of tigecycline has been investigated by ultrafiltration using different experimental conditions. Whereas temperature had only a marginal influence, the unbound fraction at 0.3/3.0 mg/L was low at pH 8.2 (9.4/1.9%) or in unbuffered pooled plasma (6.3/1.2%), compared with plasma buffered with HEPES to pH 7.4 (65.9/39.7%). In experiments with phosphate buffer and/or EDTA, the concentration dependency was markedly attenuated or abolished, which is compatible with a cooperative binding mechanism involving divalent cations such as calcium. The unbound fraction in clinical plasma samples from