

Comparable unbound fluconazole levels in plasma, lung and soft tissues of healthy and septic rats

Mauric O, **Kugler SA**, Thallinger C, Joukhadar. SM, Joukhadar C, Traunmüller F. *Comparable unbound fluconazole levels in plasma, lung and soft tissues of healthy and septic rats*. Österreichischer Infektionskongress Saalfelden 2010

Objective

We investigated the pharmacokinetic profile of fluconazole in the interstitium of healthy lung and skeletal muscle after a single intravenous dose of 6mg/kg. The secondary objective was to explore whether severe experimental inflammation exerts significant effects on the time-concentration course of fluconazole.

Methods

A total of 29 rats were included into this descriptive, controlled pharmacokinetic analysis. In 17 anesthetized healthy rats, thoracotomy, microdialysis probe insertion into lung and skeletal muscle tissue and other study related procedures were performed. In a total of 12 rats, Escherichia coli derived lipopolysaccharide (LPS) was injected at an intraperitoneal dose of 250µg and developed clinical symptoms of severe systemic inflammatory response within 4h.

Results

The pharmacokinetic profiles of fluconazole in lung and skeletal muscle tissue were descriptively almost identical to free time-versus-concentration profiles in plasma. No obvious difference in main pharmacokinetic parameters was detected between healthy rats and rats presenting with severe symptoms of systemic inflammatory response. Area under the concentration-vs.-time curve from 0-6h (AUC₀₋₆; mg*min/L) was 35.2 (n=17) for healthy free and infected plasma, 47.4 (n=8) for healthy lung tissue, 39.1 (n=12) for healthy muscle tissue, 52.9 (n=3) for inflamed lung tissue and 41.5 (n=11) for inflamed muscle tissue. Corresponding values for C_{max} (mg/L) were 8.4 for healthy free plasma, 11.0 for healthy lung tissue, 8.8 for healthy muscle tissue, 9.2 for inflamed free plasma, 11.8 for inflamed lung and 9.4 for inflamed muscle tissue. Half-lives ranged between 12.3-22.4h for all compartments tested.

Conclusions

In summary, we demonstrated that free time-vs.-concentration profiles of fluconazole in plasma are almost identical to interstitial time-vs.-concentration profiles of the ventilated lung and skeletal muscle in healthy and inflamed conditions. Therefore the concentration of fluconazole in plasma may serve as an estimate for appraising the fluconazole concentration of the interstitial fluid in lung tissue and skeletal muscle.