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Human positron emission tomography studies of brain neurokinin 1 receptor occupancy by aprepitant

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Abstract

Background

Aprepitant is a highly selective substance P (neurokinin 1 [NK_1] receptor) antagonist that significantly improves the pharmacotherapy of acute and delayed highly emetogenic chemotherapy–induced nausea and vomiting, probably through an action in the brain stem region of the central nervous system. Here, we report the use of positron emission tomography imaging with the NK_1 receptor binding–selective tracer [^{18}F]SPA-RQC to determine the levels of central NK_1 receptor occupancy achieved by therapeutically relevant doses of aprepitant in healthy humans.

Methods

mg and placebo (n = 4). In each study, dosing was once daily for 14 consecutive days. Data from both studies were combined for analyses. The ratio of striatal/cerebellar [^{18}F]SPA-RQ (high receptor density region/reference region lacking receptors) was used to calculate trough receptor occupancy 24 hours after the last dose of aprepitant.

Results

Brain NK_1 receptor occupancy increased after oral aprepitant dosing in both a plasma concentration–related (r = .97; 95% confidence interval [CI] = .94–1.00, p < .001) and a dose-related (r = .94; 95% CI = .86–1.00, p < .001) fashion. High (≥90%) receptor occupancy was achieved at doses of 100 mg/day or greater. The plasma concentrations of aprepitant that achieved 50% and 90% occupancy were estimated as approximately 10 ng/mL and approximately 100 ng/mL, respectively.

Conclusions

Positron emission tomography imaging with [^{18}F]SPA-RQ allows brain NK_1 receptor occupancy by aprepitant to be predicted from plasma drug concentrations and can be used to guide dose selection for clinical trials of NK_1 receptor antagonists in central therapeutic indications.

Keywords

Substance P · depression · neurokinin 1 receptor (NK_1), aprepitant

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