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Dextromethorphan as a potential neuroprotective agent with unique mechanisms of action.

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Abstract

BACKGROUND: Dextromethorphan (DM) is a widely-used antitussive. DM's complex central nervous system (CNS) pharmacology became of interest when it was discovered to be neuroprotective due to its low-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonism.

REVIEW SUMMARY: Mounting preclinical evidence has proven that DM has important neuroprotective properties in various CNS injury models, including focal and global ischemia, seizure, and traumatic brain injury paradigms. Many of these protective actions seem functionally related to its inhibitory effects on glutamate-induced neurotoxicity via NMDA receptor antagonist, sigma-1 receptor agonist, and voltage-gated calcium channel antagonist actions. DM's protection of dopamine neurons in parkinsonian models may be due to inhibition of neurodegenerative inflammatory responses. Clinical findings are limited, with preliminary evidence indicating that DM protects against neuronal damage. Negative findings seem to relate to attainment of inadequate DM brain concentrations. Small studies have shown some promise for treatment of perioperative brain injury, amyotrophic lateral sclerosis, and symptoms of methotrexate neurotoxicity. DM safety/tolerability trials in stroke, neurosurgery, and amyotrophic lateral sclerosis patients demonstrated a favorable safety profile. DM's limited clinical benefit is proposed to be associated with its rapid metabolism to dextrorphan, which restricts its central bioavailability and therapeutic utility. Systemic concentrations of DM can be increased via coadministration of low-dose quinidine (Q), which reversibly inhibits its first-pass elimination. Potential drug interactions with DM/Q are discussed.

CONCLUSIONS: Given the compelling preclinical evidence for neuroprotective properties of DM, initial clinical neuroprotective findings, and clinical demonstrations that the DM/Q combination is well tolerated, this strategy may hold promise for the treatment of various acute and degenerative neurologic disorders.

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