Adrogolide HCl (ABT-431; DAS-431), a Prodrug of the Dopamine D1 Receptor Agonist, A-86929: Preclinical Pharmacology and Clinical Data

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ABSTRACT

Adrogolide (ABT-431; DAS-431) is a chemically stable prodrug that is converted rapidly (<1 min) in plasma to A-86929, a full agonist at dopamine D1 receptors. In vitro functional assays, A-86929 is over 400 times more selective for dopamine D1 than D2 receptors. In rats with a unilateral loss of striatal dopamine, A-86929 produces contralateral rotations that are inhibited by dopamine D1 but not by dopamine D2 receptor antagonists. Adrogolide improves behavioral disability and locomotor activity scores in MPTP-lesioned marmosets, a model of Parkinson’s disease (PD), and shows no tolerance upon repeated dosing for 28 days.

In PD patients, intravenous (i.v.) adrogolide has antiparkinson efficacy equivalent to that of L-DOPA with a tendency towards a reduced liability to induce dyskinesia. The adverse events associated with its use were of mild-to-moderate severity and included injection site reaction, asthenia, headache, nausea, vomiting, postural hypotension, vasodilatation, and dizziness.

Adrogolide can also attenuate the ability of cocaine to induce cocaine-seeking behavior and does not itself induce cocaine-seeking behavior in a rodent model of cocaine craving and relapse. In human cocaine abusers, i.v. adrogolide reduces cocaine craving and other cocaine-induced subjective effects. The results of animal abuse liability studies indicate that adrogolide is unlikely to have abuse potential in man. Adrogolide has also been reported to reverse haloperidol-induced cognitive deficits in monkeys, suggesting that it may be an effective treatment for the cognitive dysfunction associated with aging and disease.
Adrogolide undergoes a high hepatic “first-pass” metabolism in man after oral dosing and, as a result, has a low oral bioavailability (≤4%). This limitation may potentially be circumvented by oral inhalation formulations for intrapulmonary delivery that greatly increase the bioavailability of adrogolide. As the first full dopamine D₁ receptor agonist to show efficacy in PD patients and to reduce the craving and subjective effects of cocaine in cocaine abusers, adrogolide represents an important tool in understanding the pharmacotherapeutic potential of dopamine D₁ receptor agonists.