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Adrogolide HCl (ABT-431; DAS-431), a Prodrug of the Dopamine D_1 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 D_1 receptors. In *in vitro* functional assays, A-86929 is over 400 times more selective for dopamine D_1 than D_2 receptors. In rats with a unilateral loss of striatal dopamine, A-86929 produces contralateral rotations that are inhibited by dopamine D_1 but not by dopamine D_2 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, vasodilitation, 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 re-

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ported 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 D_1 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 D_1 receptor agonists.

INTRODUCTION

Dopamine exerts its effects in the central nervous system (CNS) through two distinct receptor families, the dopamine D_1-like and the dopamine D_2-like receptor families. The former includes the D_1 and D_5 receptor subtypes and the latter includes the D_2, D_3, and D_4 receptor subtypes (12,10). D_1 and D_2 receptors predominate in the striatum, nucleus accumbens, and olfactory tubercle; the D_1 receptor is also abundantly expressed in the amygdala. This distribution of dopamine D_1 and D_2 receptors and previous animal studies with partial D_1 agonists like SKF-38393 suggest that a full D_1 agonist like A-86929 may have potential utility in the treatment of Parkinson's disease (PD), drug addiction, certain types of cognition dysfunction and attention deficit hyperactivity disorder (ADHD).

At present, the gold standard for the treatment of PD is levodopa (L-DOPA) (20,6,33). While this dopamine precursor is efficacious in the treatment of PD, its long-term use is complicated by the early development of side effects that include dyskinesia, hallucinations, and "on-off" motor phenomena that become progressively more prominent with duration of use and the need to increase dosing as tolerance occurs. It has also been suggested that L-DOPA may promote disease progression by facilitating free radical production that can accelerate the neurodegenerative process.

The most commonly used alternative or adjunctive therapies for PD are directly acting dopamine D_2 receptor selective agonists (33). These include pergolide, ropinerole, bromocriptine, and lisuride. In general, dopamine D_2 agonists lack the efficacy of L-DOPA, and based on available human data, they appear unlikely to replace it as the preferred therapy. They are generally used in early stages of the disease to delay the need for L-DOPA or as an adjunct to L-DOPA with the aim of reducing the need for high doses of L-DOPA.

The first test of the potential role of a dopamine D_1 receptor agonist in PD was made with SKF-38393, a partial dopamine D_1 agonist that has proven to be inactive in nonhuman primate models of Parkinson's disease (4). The dopamine D_1 ergot-based partial agonist CY 208–243 was effective in nonhuman primate models and although it had minimal efficacy in PD patients due to pharmacokinetic issues (34), it demonstrated the underlying potential of a full dopamine D_1-like agonist. Because adrogolide was very effective in nonhuman primate animal models of PD, the efficacy, safety, and pharmacokinetics of adrogolide were studied in PD patients.

In addition, since cocaine is a potent inhibitor of dopamine reuptake in the brain and the reinforcing effects of cocaine are thought to be mediated through activation of dopamine receptors, dopamine receptor agonists have been the focus of potential pharmacotherapies for cocaine addiction. Both dopamine D_1 and D_2 receptor agonists are self-administered by animals, suggesting that both receptor subtypes mediate the reinforcing effects of cocaine and that both classes of compounds would be reinforcing in humans (28,36). However, studies using a reinstatement model of cocaine-induced craving in rats demonstrate an important functional difference between the two types of dopamine agonist. The dopamine D_2 receptor agonists 7-OH-DPAT and quinpirole *enhance* cocaine self-administration and mimic the actions of cocaine, while dopamine D_1 agonists (e.g., SKF-82958 and SKF-81297) do not mimic cocaine and actually *suppress* cocaine-induced cocaine seeking behavior (29). Similarly, in clinical studies, dopamine D_2 agonists like pergolide and bromocriptine were found to be ineffective in curbing cocaine craving in cocaine users (13,17–19,24). Adrogolide, a more efficacious dopamine D_1 receptor agonist than either of the SKF-compounds, was studied in the rat reinstatement model and in human cocaine abusers to determine its potential to suppress cocaine craving.

Adrogolide, a chemically stable prodrug of the substituted quinoline, A-86929, is converted rapidly in plasma to A-86929, its active entity. This review will describe the results of non-clinical pharmacology studies of adrogolide and of A-86929 and the results of clinical studies of adrogolide in PD patients and cocaine abusers.

Chemistry

A-86929 and adrogolide HCl (ABT-431), a diacetyloxy prodrug of A-86929, were synthesized at Abbott Laboratories (22). Adrogolide is composed primarily of A-93431.1 (>98%) and minor amounts (% each) of A-86929.1 and the two monoesters of A-86929.1 (Fig. 1; the ".1" suffix indicates HCl salt). Adrogolide provides greater long-term solid state chemical stability than the parent catechol and is converted rapidly in plasma by the action of nonspecific esterases to A-86929, the pharmacologically active entity. Adrogolide is synthesized as a single enantiomer (*R* isomer) with enantiomeric purity of greater than 99%.

IN VITRO AND *IN VIVO* ANIMAL PHARMACOLOGY

Receptor Binding Profile

The affinities of A-86929 for the various dopamine receptor subtypes were measured in rat striatal and cloned human receptor membranes using standard radioligand binding techniques (Table 1) (32). A-86929 is best described as a dopamine D_1/D_5 receptor ligand. It has high affinity for dopamine D_1 receptors in the rat striatum, cloned human dopamine D_1 receptors expressed in HEK cells, and cloned human dopamine D_5 receptors expressed in CHO cells. In rat striatal tissue, the affinity of A-86929 for dopamine D_1 receptors is 20-fold greater than its affinity for dopamine D_2 receptors. In cloned human dopamine receptors, the affinity of A-86929 for dopamine D_1 receptors is 15-fold, 20-fold, and 7-fold greater than its affinity for D_2, D_3, and $D_{4.2}$ receptors, respectively. A-86860, the (+)enantiomer of A-86929, has significantly less affinity than A-86929 for all the re-

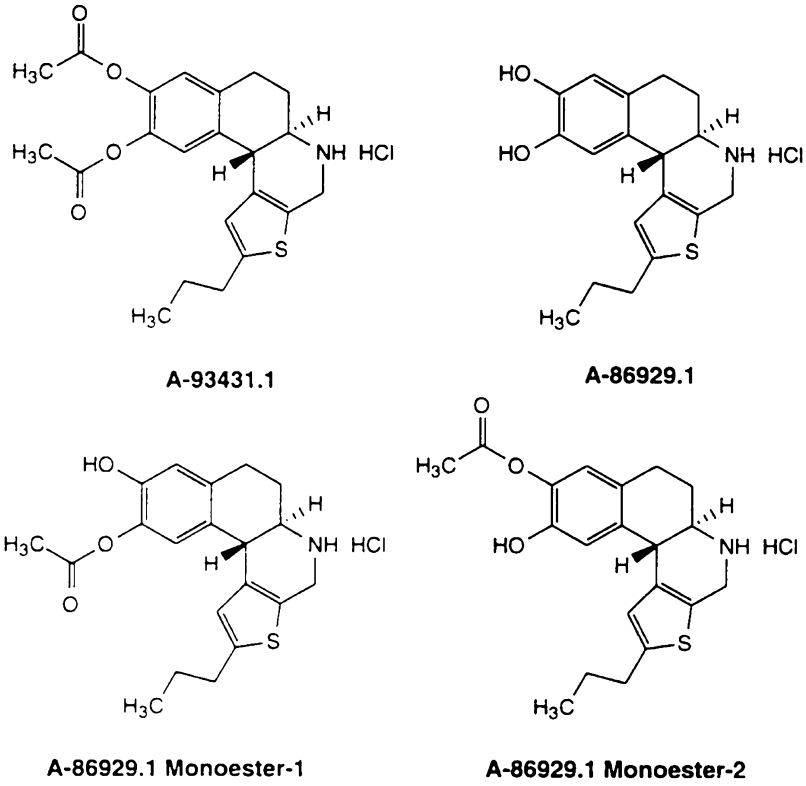

Fig. 1. Adrogolide (ABT-431): A-93431.1 and A-86929.1. **A-93431.1:** (–)-trans 9,10-diacetyloxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride; **A-86929.1:** (–)-trans 9,10-dihydroxy-2-propyl-4,5,5a,6,11b-hexahydro-3-thia-5- azacyclopent-1-ena[c]phenanthrene hydrochloride; **Two monoesters of A-86929.1:** 1) (–)-trans 9-acetyloxy-10-hydroxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride, 2) (–)-trans 9-hydroxy-10-acetyloxy-2-propyl-4,5,5a,6,7,11b-hexahydro-3-thia-5-azacyclopent-1-ena[c]phenanthrene hydrochloride.

ceptors listed in Table 1 with the exception of the $D_{4.2}$ receptor for which A-86929 (K_i = 350) and A-86860 (K_i = 380) have similar affinities, indicating stereoselectivity in the receptor interaction.

TABLE 1. Dopamine receptor binding profile of A-86929

Dopamine receptors	Binding affinity (K_i, nM)[a]
D_1 (rat striatum)	18 ± 1.8 (33)
D_1 (human clone)	51 ± 4.2 (15)
D_5 (human clone)	15 ± 5.2 (7)
D_2 (rat striatum)	360 ± 22 (44)
D_2 (human clone)	750 ± 110 (33)
D_3 (human clone)	1000 ± 100 (5)
$D_{4.2}$ (human clone)	350 ± 12 (4)

[a] Values represent mean ± S.E.M. with numbers of experiments in parentheses.

In Vitro Functional Activity

A-86929 is a full agonist at the dopamine D_1 receptor as assessed by adenylate cyclase assays using goldfish retina, rat striatal tissue, and cloned human D_1 receptors (Table 2) (32). A-86929 showed high potency and full intrinsic activity relative to dopamine in these assays. The EC_{50} value of A-86929 at cloned human dopamine D_1 receptors was more than 400 times greater than that observed at the cloned human dopamine D_2 receptor, and the potency of A-86929 was nearly 10-fold greater at the human dopamine D_5 than at the dopamine D_1 receptor.

Effects in 6-OHDA-Lesioned Rats

Rats with unilateral 6-hydroxydopamine (6-OHDA) lesions were used to evaluate the *in vivo* dopaminergic effects of adrogolide and A-86929 (32). Parenteral administration of direct and indirect acting dopamine receptor agonists produces contralateral rotations in 6-OHDA-lesioned rats (15). Adrogolide and A-86929 produced a robust contralateral rotation with ED_{50} values of 0.54 and 0.24 μmol/kg, subcutaneously (s.c.), respectively; these values were not significantly different from one another. A dose of 1 μmol/kg, s.c., of either compound produced approximately 5–6 h of rotation. The dopamine D_1 selective antagonist *R* (+)SCH 23390 blocked the rotation produced by A-86929, while the dopamine D_2 selective antagonist, haloperidol, was without effect, indicating that the rotation is mediated through stimulation of D_1 receptors. The number of rotations did not decline following each of three daily injections (9:00, 12:00, and 15:00 h) of A-86929 at 0.11 and 0.22 μmol/kg, s.c., for 10 days. On the tenth treatment day, the total number of rotations after each of the three daily injections of 0.22 μmol/kg, s.c., was greater than that after each injection on day 1, suggesting the development of response sensitization (2).

Effects on Cognition

Co-administration of intramuscular (i.m.) adrogolide (0.00001–0.0001 mg/kg) and haloperidol (0.07–0.20 mg/kg, i.m.) for 3–7 months prevented haloperidol-induced deficits in the spatial working memory and object working memory of monkeys (7), an effect that has been attributed to a downregulation of dopamine D_1 receptors that develops fol-

TABLE 2. Functional activity of A-86929 in dopamine receptor-regulated cAMP production

Receptor	EC_{50} (nM)[a]	IA (%)[b]
Goldfish D_1	39 ± 5.1 (17)	92 ± 3.9 (17)[b]
Rat striatum D_1	40 ± 14 (5)	120 ± 8.5 (5)[b]
Human D_1-HEK	9.0 ± 1.4 (41)	120 ± 3.5 (41)[b]
Human D_5-CHO	1.1 ± 0.21 (6)	110 ± 8.0 (6)[b]
Human D_2 short LTK	3900 ± 740 (24)	81 ± 5.2 (24)[c]

[a] Values represent mean ± S.E.M. with numbers of experiments in parentheses conducted in triplicate.
[b] Intrinsic activity expressed in percentage relative to 10 μM dopamine.
[c] Intrinsic activity expressed in percentage relative to 1 μM quinpirole.

lowing the long-term blockade of dopamine D_2 receptors. Adrogolide may be an effective treatment for age- and disease-related cognitive deficits.

Seizures and Hyperactivity in Rodents

A-86929 and adrogolide produced seizure-like activity in mice with ED_{50} values of 7.1 and 2.7 μmol/kg, respectively, beginning 30 to 40 min after dosing; these ED_{50} values were not significantly different (31). Pretreating the mice with a subthreshold dose of A-86929 (1.0 μmol/kg, s.c.) for 4 days did not affect seizure threshold when the animals were subsequently challenged with higher doses of the compound. The seizure-like activity elicited by A-86929 (20 μmol/kg) was completely blocked by the D_1 selective antagonist, SCH 23390 (0.3 μmol/kg, s.c.), indicating that the seizures in mice were associated with activation of the D_1 receptor. A-86929 and adrogolide produced seizures in young rats with ED_{50} value of 34.2 and 35.6 μmol/kg, s.c., respectively, and A-86929 produced seizures in adult rats with an ED_{50} value of 345 μmol/kg, s.c. SCH-23390 (0.03–0.3 μmol/kg, s.c.) and haloperidol (2.8 μmol/kg, s.c.) reduced the seizure activity produced by A-86929 (100 μmol/kg, s.c.) in rats. A-86929 significantly increased the locomotor activity of rats after acute administration at doses of 2, 4, and 8 μmol/kg, s.c., and daily during repeated dosing for 6 days at 3 and 6 μmol/kg, s.c. (31). As with seizures, SCH 23390 (0.01–0.10 μmol/kg, s.c.) and haloperidol (0.1 and 1 μmol/kg, s.c.) blocked the effects of A-86929.1 (1.0 μmol/kg, s.c.) on locomotor activity.

Adrogolide and A-86929 have proconvulsant activity and are behavioral stimulants like other dopamine D_1 receptor agonists (1,5,21). Although the CNS stimulant effects of adrogolide and A-86929 are due to dopamine D_1 receptor stimulation, the observation that both the dopamine D_1 and D_2 antagonists block seizures and hyperactivity suggests a dynamic interaction between the receptor subtypes. The large difference between the ED_{50} values for the proconvulsant effects (ED_{50} values of 34.2 μmol/kg, s.c., in young rats and 345 μmol/kg, s.c., in adult rats) and behavioral stimulant effects (2, 4 and 8 μmol/kg, s.c.) of A-86929 and the ED_{50} value of A-86929 for producing contralateral rotation in 6-OHDA lesioned rats (0.24 μmol/kg, s.c.) suggests a sufficiently high therapeutic ratio for clinical safety.

EFFICACY IN AN ANIMAL MODEL OF PARKINSON'S DISEASE AND IN PARKINSON'S DISEASE PATIENTS

Efficacy in MPTP Lesioned Monkeys

MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is toxic to dopamine-secreting nigrostriatal neurons. It produces behavioral deficits in man and nonhuman primates that closely resemble those seen in PD and are blocked by dopaminergic agents, such as L-DOPA (35). Doses of 0.3 and 1 μmol/kg, s.c., of adrogolide and 0.1, 0.3, 1, and 3 μmol/kg, s.c., of A-86929 significantly decreased behavioral disability scores and in-

creased locomotor activity in a dose-dependent manner after acute administration to the MPTP-lesioned common marmosets (32). The minimally effective doses for adrogolide and A-86929 were 0.30 μmol/kg, s.c., and 0.10 μmol/kg, s.c., respectively, with a duration of action of 3 to 5 h. There was no evidence of tolerance developing to A-86929 (1 μmol/kg, s.c.) in the marmosets following administration three times daily at 4-h intervals for 30 consecutive days. Similar results were obtained in MPTP-lesioned pig tailed macaques and cynomolgus monkeys (2,11).

Forebrain dopamine levels were reduced on one side of the brain in macaque monkeys by unilateral intracarotid infusions of MPTP causing these animals to rotate away from the lesioned side when challenged with a direct-acting dopamine agonist. In these animals, A-86929, administered at doses of 0.03, 0.10, and 0.30 μmol/kg, i.m., produced significant, dose-dependent increases in contralateral rotations; the duration of action was also dose-dependent (2). When a dose of 0.30 μmol/kg of A-86929.4 was administered three times daily at 3-hour intervals for 10 days, the first daily injection tended to elicit greater contralateral rotation compared with the second and third daily injections. These results indicate the ability of A-86929 to maintain behavioral efficacy during subchronic administration.

After weekly s.c. injections of MPTP, cynomolgus monkeys exhibited stable parkinsonism-like behavioral disabilities. The repeated administration of L-DOPA to these monkeys induced abnormal involuntary movements that closely resembled the dyskinesias observed in L-DOPA-treated PD patients. L-DOPA-primed monkeys are also highly sensitive to the induction of dyskinesias when challenged with dopamine agonists (11). Doses of 0.1, 0.3, 1.0, and 3.0 μmol/kg, s.c., of A-86929 administered to L-DOPA-primed, MPTP-lesioned cynomolgus monkeys improved parkinsonian features and significantly lowered disability scores. Disability scores after doses of 0.3, 1.0, and 3.0 μmol/kg, s.c., were not significantly different from those obtained following a standard beneficial dose of L-DOPA + benserazide (100/25 mg/subject, p.o.). Doses of 1.0 and 3.0 μmol/kg, s.c., also significantly increased locomotor activity. The increase in locomotor activity at the dose of 3.0 μmol/kg, s.c., was equal to that achieved following administration of L-DOPA/benserazide (100/25 mg). The duration of action of the higher doses of A-86929 was approximately 4 h. At doses of 0.1, 0.3, 1.0, and 3.0 μmol/kg, the dyskinesias elicited by A-86929 were significantly less pronounced than those observed with the standard beneficial dose of L-DOPA/benserazide. Increasing the dose of A-86929 tended to increase the dyskinesia score, although the dyskinesia at the highest dose (3.0 μmol/kg, s.c.) was still less severe than that observed with L-DOPA/benserazide.

Taken together, the results of studies in nonhuman primate models of Parkinson's disease indicate that A-86929 produces a dose-related antiparkinsonian effect equal in quality to that of L-DOPA, but with less dyskinesia. The repeat dosing studies indicate that the risk of developing tolerance to A-86929 is low. Another full dopamine D_1 agonist, A-77636, was also efficacious in the nonhuman primate model of Parkinson's disease (16). In contrast to the 4-h duration of action of A-86929, A-77636 had a duration of action greater than 20 h and showed tolerance with repeated administration. Thus, A-86929 is a suitable clinical candidate to test the hypothesis that a full dopamine D_1 agonist has efficacy with less dyskinesia than L-DOPA in the treatment of PD.

Parkinson's Disease Patients

In a phase I study, the safety and pharmacokinetics of an i.v. formulation of adrogolide were investigated in a randomized, double-blind, placebo-controlled, parallel-group, dose titration study in 13 L-DOPA–treated PD patients conducted at a single center (3). Doses of adrogolide, infused over a 1-h period were increased daily for at least 6 days to 7.5 mg in group 1 and 20 mg in group 2. Blood samples were obtained prior to, during, and after infusion of adrogolide for determination of A-86929 plasma concentrations. Thirteen patients received adrogolide and one received placebo. The adverse events reported by 4 or more of the 13 patients were: injection site reaction (11/13; 85%), asthenia (8/13; 62%), headache (8/13; 62%), nausea (5/13; 38%), vomiting (4/13; 31%), postural hypotension (4/13; 31%), vasodilatation (4/13; 31%), and dizziness (4/13; 31%). The majority of adverse events were mild to moderate in severity, and one patient withdrew due to severe nausea and vomiting. No clinically meaningful changes in vital signs, electrocardiogram or laboratory tests were noted. In general, adrogolide was well tolerated in this study when administered daily in single 60-min i.v. infusions in doses up to 20 mg. After i.v. infusion of single rising doses of adrogolide from 2.0 to 20.0 mg, dose-normalized area under the curve of A-86929 increases a little less than proportionally with increasing dose. The 13% and 7% increases in mean plasma clearance after dose increases from 2.0 to 7.5 mg and 10.0 to 20.0 mg, respectively, were not deemed to be clinically significant. The apparent terminal phase half-life was approximately 3–4 h at doses of 10.0–20.0 mg. Mean total plasma clearance was high, exceeding hepatic blood flow and ranging from a mean of 142–182 L/h/70 kg.

In a phase IIA study, the safety, tolerability, pharmacokinetics, and efficacy of an i.v. formulation of adrogolide were studied in a multicenter, double-blind, placebo-controlled, dose-ranging study in 14 L-DOPA–responsive PD patients (25). For 6 days, each patient received a single 60-min i.v. infusion daily of increasing doses of adrogolide (5, 10, 20, 30, and 40 mg) randomly interspersed with placebo after a 12-h L-DOPA holiday. The results from both the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS) and tapping section of the Rating for Parkinsonism and Dyskinesia (RPD) indicated that adrogolide improved PD symptoms in a dose-dependent manner when administered as an i.v. formulation. There was a significant difference between the response to placebo and adrogolide (10 to 40 mg) on the UPDRS percent medium improvement score. The maximum improvement occurred at 30 mg of adrogolide with no further improvement at 40 mg and was similar in magnitude to that obtained with L-DOPA (median dose of 300 mg). Additionally, adrogolide produced less dyskinesia than L-DOPA, as assessed by RPD-Dyskinesia scores. Dyskinesia was more commonly observed at the higher doses of adrogolide and was more likely to be dystonic than choreic in type. Mean dose-normalized C_{max} was generally linear as the dose of adrogolide increased from 10 to 40 mg. C_{max} averaged 2.5 to 3.1 ng/mL/mg, with a T_{max} at 50 min after the start of infusion. Terminal phase half-life was approximately 3 to 4 h.

Adrogolide was generally well-tolerated by the patients in this study. All treatment-emergent adverse events were assessed to be mild or moderate in severity. There were no reports of severe, serious, or unexpected adverse events related to adrogolide administration. No patients withdrew from the study due to adverse events or for other reasons. The most common adverse events were injection site reactions (11 patients; 92%) and headaches and nausea (9 patients each; 75%). Hypotension and vomiting were reported by

six patients each (50%). The physical examination, neurological examination, ECG, and EEG results were unremarkable and there were no clinically significant findings in relation to hematology, urinalysis, and biochemistry results.

In another clinical study that was specifically designed to compare the effects of acute challenges with L-DOPA and adrogolide in dyskinetic Parkinson patients, adrogolide was again as effective as L-DOPA in alleviating parkinsonism but, in contrast to the first study, it was observed to cause an equal amount of dyskinesia at antiparkinson doses (26). In this study, patients were administered a single, rising, i.v. dose of adrogolide (5, 10, 20, and 40 mg) on 4 of 5 treatment days and oral L-DOPA on any one of the 5 days, and dyskinesias were assessed before and for 3 h after dosing. The severity of dyskinesias in patients who responded with a full antiparkinson effect at any one of the doses of adrogolide was comparable with the dyskinesia caused by an effective dose of L-DOPA.

EFFICACY IN AN ANIMAL MODEL OF COCAINE CRAVING AND IN HUMAN COCAINE ABUSERS

Effects in an Animal Model of Cocaine Craving

Self et al. (30) evaluated the effects of adrogolide on cocaine craving and relapse using the reinstatement paradigm in rats. The reinstatement paradigm is considered a valid model of drug craving and relapse in humans (27). In this model, in which rats are trained to self-administer cocaine, doses of 0.7, 2.3, and 7 μmol/kg, s.c., of adrogolide did not induce cocaine-seeking behavior when cocaine was unavailable for self-administration. Doses of 0.2, 0.7, 2.3, and 7 μmol/kg, s.c., attenuated the ability of cocaine itself to induce cocaine seeking behavior during abstinence (30). The effects of adrogolide on cocaine-seeking behavior were specific to cocaine reinforcement as the rats reduced their operant behavior maintained by food reinforcement after the administration of adrogolide. Pretreatment with adrogolide (7 μmol/kg, s.c.) also delayed the start and disrupted the regularity of cocaine self-administration. There was no evidence of tolerance to this effect of adrogolide over 4 days of testing. Taken together, the results of the reinstatement studies indicate that adrogolide has therapeutic potential in treating cocaine addiction.

Effects in Cocaine Abusers

Following the positive outcome in the rodent model of cocaine craving and relapse, the effects of adrogolide on cocaine-induced craving and high were evaluated in human cocaine abusers. The effects of adrogolide on the reinforcing, cardiovascular, and subjective effects of cocaine were investigated in nine experienced cocaine smokers in a randomized, blinded study that also used a serial visual analog scale to measure cocaine-induced subjective effects (14). I.v. doses of 2 and 4 mg/100 mL of adrogolide were administered over a 1-h period immediately before smoked cocaine (12 and 50 mg). Although adrogolide did not decrease smoked cocaine self-administration, both doses of adrogolide significantly decreased the subjective ratings of high, stimulated, liking, quality, and potency of the 12-mg smoked cocaine dose. The 4-mg dose of adrogolide also decreased the subjective effects of liking following the 50-mg smoked cocaine dose. The most frequently re-

ported side effects after the 4-mg dose of adrogolide were headache and nausea. These doses of adrogolide tended to increase heart rate and decrease systolic and diastolic pressures after smoked cocaine had increased both parameters. Taken together, the results of these clinical studies indicate that adrogolide attenuates the subjective effects of cocaine and, thus, has potential use as pharmacotherapy in cocaine abusers.

EFFECTS IN STUDIES OF ABUSE LIABILITY

Because there is evidence that dopamine D_1 receptor agonists are self-administered by rats (28), the potential abuse liability of adrogolide was assessed in tests of nonprecipitated withdrawal, conditioned place preference, and self-administration (9). No clear signs of substance withdrawal, as measured by decreases in food consumption, body weight, or rectal temperature, occurred in rats during an 8-day withdrawal observation period following twice daily dosing for 10 days with adrogolide at two doses, 0.3 or 3 mg/kg, i.p. The twice-daily dosing of adrogolide for 4 days at the same doses did not produce a conditioned place preference in rats. Conditioned place preference was tested in a two compartment apparatus. Rats did not spend more time in the compartment clearly associated with adrogolide injections when given a choice between that compartment and the adjoining neutral compartment. Self-administration studies were performed in rats and monkeys. At doses of 0.01, 0.03, and 0.1 mg/kg/infusion, rats did not initiate the self-administration of adrogolide or substitute the self-administration of adrogolide for cocaine (0.25 mg/kg/infusion). Intravenous doses of 0.05, 0.1, and 0.2 mg/kg/infusion of adrogolide were not self-administered by rhesus monkeys that had been trained previously to self-administer cocaine (0.03 mg/kg/infusion) intravenously under a fixed-ratio 30 schedule. The results of these studies and those of the reinstatement studies indicate that adrogolide is not likely to have abuse potential in man. In this regard, adrogolide differs from SKF-77434 and SKF-82958, dopamine D_1 agonists that are self-administered by rats (28). The reinforcing effects of these agonists may be related more to their D_2 than D_1 receptor activity, as neither SKF-77434 nor SKF-82958 are as selective for the dopamine D_1 receptor as adrogolide (1,28). The lack of abuse potential is an important characteristic of adrogolide, indicating that it would not itself induce a cocaine-like subjective effect and, thus, become a substitute for cocaine.

FORMULATION STUDIES

Adrogolide was administered by i.v. injection in the proof of principle clinical studies because it undergoes extensive first-pass metabolism after oral dosing. The oral bioavailability in man is less than 3.5% when dosed as a solution. Chen et al. (8) have reported that a gingival adhesive tablet designed to give a sustained sublingual release of adrogolide resulted in an improved bioavailability of 10% to 13% of a 5 mg i.v. reference dose. The intrapulmonary route of administration in which an alcoholic solution (60% EtOH) of adrogolide was delivered as bolus inhalations of 1, 2, 4, and 8 mg produced a mean absolute pulmonary bioavailability of 82–107% of a 5 mg i.v. dose (23). An aerosol suspension formulation in which adrogolide was dispersed in tetrafluoroethane, HFC-134a,

with poloxamer 124 and vitamin E had a lung bioavailability of 34% of a 0.5 mg A-86929 equivalent per kg, i.v. dose in dogs and up to 25% of a 5 mg A-86929 equivalent i.v. dose of A-86929 in man (37). These studies indicate that the pulmonary delivery systems may be a suitable alternative to oral delivery of adrogolide.

SUMMARY

Adrogolide, a prodrug, is rapidly converted in plasma to A-86929. A-86929 has high affinity and functional selectivity for the dopamine D_1 receptor. The clinical studies of adrogolide were the first controlled studies to demonstrate the potential efficacy of a selective dopamine D_1 receptor full agonist in Parkinson's disease patients and cocaine abusers. The i.v. administration of adrogolide produced an antiparkinsonian effect in patients in a safe and well-tolerated manner with a tendency toward less dyskinesia compared with L-DOPA and decreased the subjective effects of i.v. and smoked cocaine in experienced cocaine abusers. Although there were a relatively large number of adverse events reported in these clinical studies, the events were mild to moderate in severity. The most common adverse events were injection site reactions and headaches and nausea. The clinical studies were performed using i.v. dosing of adrogolide because of its poor oral bioavailability. Oral inhalation formulations of adrogolide for the intrapulmonary delivery greatly increase the bioavailability of adrogolide and may be suitable alternatives to oral dosing. As the first potent and full dopamine receptor agonist to be extensively characterized in both non-clinical and clinical studies, adrogolide has provided a greater appreciation of the pharmacological potential of dopamine D_1 receptors compounds in the treatment of CNS disorders.

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