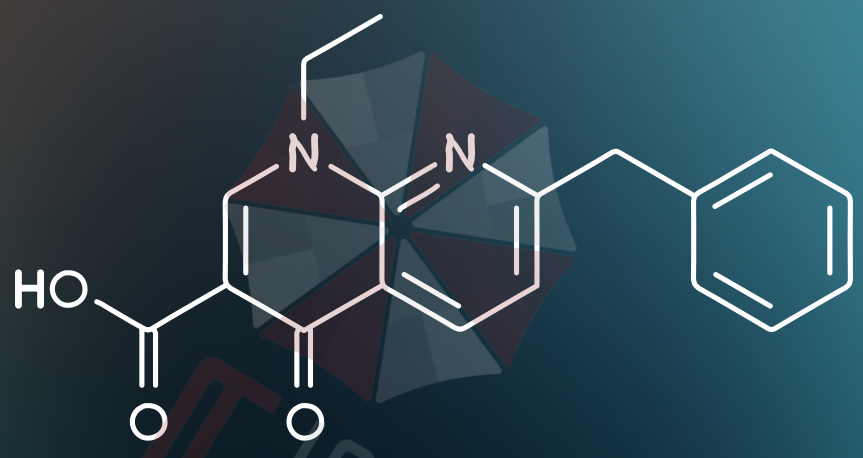

Amfonelic Acid: Preclinical Promise, Clinical Limits

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History

Amfonelic acid (also known as AFA or WIN 25,978) is a compound with stimulating properties. Originally, it was developed in order to generate a new generation of antibiotics, which eventually led to the class of quinolone antibiotics. Many of the quinolone antibiotics were found to have stimulating or repressing effects on the brain besides their antimicrobial properties. Amfonelic acid was discovered in the labs of Sterling-Winthrop in the late 1960`s. It was found to be a potential candidate in the development of stimulating agents as it exhibited greater potency and a more favorable therapeutic index compared to cocaine or amphetamine. Although a few clinical studies were conducted in the 1970s, the chemical's clinical development was halted after it was observed that AFA worsened psychotic symptoms in patients with schizophrenia and caused unwanted stimulant effects in elderly individuals with depression. It was hence deemed unsafe for use in the general population. In the last 25 years, very few new articles investigating the effects of amfonelic acid have been published, showing that clinical interest has shifted towards different classes of stimulants.

Recently, a paper detailed a novel synthesis route for amfonelic acid and close structural analogs.[1]

Pharmacology of Amfonelic Acid

Amfonelic acid acts as a dopamine reuptake inhibitor (DRI). The half-life was reported to be 12 hours in rats. There seems to be only a small amount of interactions with other systems, as there is no interaction with the noradrenaline systems and minimal changes in the metabolism of serotonin. The antimicrobial properties of amfonelic acid seem to be relatively weak with a potency 30-times lower compared to the similar compound nalidixic acid.[2]

Preclinical Trials

In rats, amfonelic acid displays a 50% greater stimulatory potency compared to amphetamine. Otherwise, the behavioral effects of amfonelic acid in rats are comparable to those produced by amphetamine.[3] It was also shown that amfonelic acid has a different mechanism of action, which is less damaging to neurons compared to the classical amphetamines, like methylamphetamine.[4] However, amfonelic acid has a lower toxicity compared to amphetamine, at least in mice. Amphetamine-treated mice showed a death rate of 94% at a dose of 256 mg/kg, while no

deaths were observed when amfonelic acid was administered at a dose of 1024 mg/kg. At 2048 mg/kg amfonelic acid, 6% of mice died after 6 hours. Since amphetamine and amfonelic acid are given at similar doses, amfonelic acid can be inferred to have a more favorable safety profile.[5] Additional studies established the fact that amfonelic acid also caused intense stimulation in a wide variety of animals such as gerbils, dogs and monkeys.[6]

Many anti-psychotic chemical such as haloperidol act as antagonists in the dopamine system. If such chemical are co-administered with the DRI amfonelic acid, their potency increases.[7] In fact, many studies that focus on amfonelic acid in animals have investigates its interaction with other psychopharmacological chemical like resperine.

Administration of methamphetamine (MA) induces damage to dopaminergic neurons. In one experiment with adult rats were treated with MA (10 mg/kg, i.p.) Amfonelic acid (AFA) was administered (20 mg/kg, i.p.) at the same time. The results showed that MA induced the typical damage to dopaminergic neurons. AFA treatment completely prevented the effects of MA on the dopaminergic system, both morphologically and biochemically.[4] The interaction of amfonelic acid with several anti-psychotic chemicals which influence the dopamine brain metabolism has been the subject of several animals studies.[8–11]

Since dopamine is a key contributor to the control over the pituitary gland, it was investigated whether amfonelic acid had a measurable effect on the resale of hormones produced by the pituitary in rats. Intravenous injection of 0.2 mg/kg of AFA had no influence on plasma luteinizing hormone concentration until 60 min after injection when it was significantly elevated. Increasing the dose to 1 mg/kg reduced luteinizing hormone titers at 15 and 30 mins with a return to pre-injection levels by 60 min. AFA also produced a dose-dependent decrease in plasma prolactin levels; the decrease occurred as early as 5 mins after injection. AFA, both at 0.2 and 1 mg/kg doses, was effective in producing a sharp, dose-related rise in plasma growth hormone levels. By contrast, TSH levels were significantly suppressed by both doses of AFA. Hence, it may be possible to induce a release in growth hormone with AFA in humans, but other hormonal systems would also be affected.[11]

Serotonin Metabolism

During the first studies with AFA in animals, it was found that their brain contained an increased amount of metabolites of serotonin. One study concluded that this is likely due to the fact that AFA is responsible for an increase serotonin synthesis, not in delayed breakdown.[12] However, only little data is available on the effects of AFA on the serotonergic system since the focus of research was almost entirely placed on the dopaminergic system.

Interaction With Alcohol

Amfonelic acid (AFA) reduced the hypnotic effect of ethanol in mice. It did not enhance the elimination of ethanol. The stimulation of locomotor activity by amfonelic acid in mice was more sensitive to the blocking effect of ethanol than stimulation induced by amphetamine. It appears that dopamine released by amfonelic acid is responsible for its antagonism of ethanol.[13]

Abusive Potential

Rats could also be trained to self-administer amfonelic acid on a daily basis. These data indicate that amfonelic acid can act as a reinforcer in rats, and further suggest that amfonelic acid may have abuse potential in humans.[14,15] Another study in rats which involved other stimulants besides AFA supported this hypothesis.[16] However, a further study provided evidence that amfonelic acid, as well as other non-amphetamine stimulants, acts by a different mechanism of action than amphetamine does.[17]

Clinical Trials

Only little data is available on human clinical trials with AFA. Most reports data back to the late 1960`s. The only study still available today found little effect of AFA on human depression.[18]

Conclusion

Amfonelic acid is a central nervous system stimulant with direct effects on the dopamine system. It increases the amount of available dopamine in the sympathic cleft and hence leads to a higher amount of dopaminergic signaling in the brain. The compound has comparable

effects to other stimulants like amphetamine (“Speed”), to which it is often compared in many animals studies. Compared to amphetamines, it is slightly more potent but has a much lower toxicity in mice. This seems to be connected to the fact the amfonelic acid has a different mechanism of action compared to amphetamines. Experiments also suggest that the lower toxicity of amfonelic acid is connected to the fact that it does not have the same propensity to kill neurons as ampethamine.

A small amount animal data shows that amfonelic acid interferes with the important hormones produced in the pituitary gland like growth hormone. However, it is not clear if this is transferable to humans or if it produces a noticeable effect. In addition, the shown depression of TSH could lead to problems with the thyroid gland if amfonelic acid was ingested over a longer period of time.

Animal data suggests that amfonelic creates a rewarding effect when injected, meaning that it creates a psychological dependence in mice. Therefore, it is likely that this compound has abusive potential in humans as well.

There is no available data from humans, the little data that is available suggest that amlofenic acid does also produce a stimulating effect in humans, but has little clinical usefulness, at least in treating depressive disorders.

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