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Ganaxolone: A New Anti-Epileptic Drug

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ABSTRACT

Abbreviations: AEDs: Anti-Epileptic Medications; PTZ: Pentylenetetrazole; TBPS: t-butylbicyclophosphorothionate; MES: Maximum Electroshock; CNS: Central Nervous System

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Ganaxolone belongs to the epalon family of neuroactive steroids, which allosterically modify the GRC through a specific recognition site. Many Anti-Epileptic Medications (AEDs) target the GABAA system, including benzodiazepines, barbiturates, tiagabine, and vigabatrin [1]. The discovery that naturally occurring epalons, such as 3-hydroxy-5-pregnan-20-one (3,5-P) and 3-hydroxy-5-pregnan-20-one (3,5-P), were active in a variety of animal seizure models, and that this activity was mediated through a novel recognition site on the GRC distinct from the benzodiazepine and barbiturate sites, led to the development of ganaxolone [2]. Synthetic analogues of these naturally occurring epalons have been proposed to provide many of the pharmacological benefits of benzodiazepines and barbiturates without the drawbacks. The 3β-methylated synthetic equivalent of 3α,5α-P(allopregnanolone), a progesterone metabolite, is ganaxolone (3α-hydroxy-3β-methyl-5-pregnan-20-one) [3]. Ganaxolone, like endogenous epalons, is hormone-free and exhibits strong neuroactivity; however, unlike endogenous epalons, ganaxolone is orally accessible. Ganaxolone is now being tested in Phase II trials for the treatment of infantile spasms and complex partial seizures [4]. Ganaxolone is a white, crystalline, nonhygroscopic powder with a molecular weight of 332.54 and a melting point of 190–198°C. Because GNX is insoluble in water, the majority of nonclinical and clinical testing has been done with suspensions or tablets [5]. Marinus Pharmaceuticals is working on new liquid and solid formulations to boost bioavailability and lessen the pharmacokinetic fed/fasted effect [6] (Figure 1).

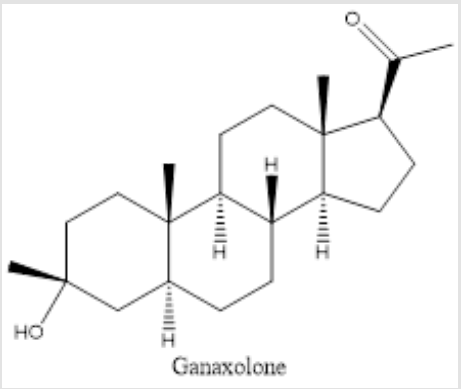

Figure 1.

Pharmacology and Toxicology

In a variety of animal seizure models, ganaxolone has exhibited a broad spectrum of anticonvulsant action. It prevents clonic seizures in mice and rats caused by sc. pentylenetetrazole (PTZ) injection, sc. bicucilline, ip. t-butylbicyclophosphorothionate (TBPS), ip. aminophylline, ip. cocaine, and Maximum Electroshock (MES). Ganaxolone significantly inhibits fully kindled Stage-5 seizures in the rat caused by corneal kindling and clonic convulsions in fully kindled mice caused by PTZ injection [7]. Ganaxolone significantly increased the seizure threshold, as measured by a rise in the amount of intravenously injected PTZ necessary to cause clonus in mice. These findings indicate that ganaxolone inhibits seizure propagation while also raising seizure threshold [8]. Except in the maximal electroshock paradigm, the dosages of ganaxolone that prevented seizures were many times lower than those that caused ataxia in mice and rats on the rotarod. In animal seizure models, ganaxolone's protective index is equivalent to, if not superior to, that of existing AEDs. These findings from a variety of animal seizure models show that ganaxolone has a broad-spectrum anticonvulsant profile that could be useful in treating both generalised and partial seizures, as well as cocaine-induced seizures [9]. Ganaxolone provided protection against behavioural abnormalities caused by PTZ injections in addition to its anticonvulsant benefits. PTZ injections cause stereotypic behavioural symptoms, such as motionlessness, twitches, and tail and hindlimb postural abnormalities, in addition to convulsions. Unlike other AEDs studied, ganaxolone normalised these behavioural effects at the same dose level that was required to prevent seizures. Only phenobarbital (at doses 4-8 times that of an anticonvulsant) prevented a comparable proportion of PTZ-induced behaviours [10].

The most common side effect after therapy in all preclinical investigations was dose-related drowsiness, which was expected given the compound's GABAergic effects. There was no evidence of organ or systemic toxicity related with ganaxolone treatment, whether single-dose or multiple-dose. No haematology or serum chemistry parameters were changed in any of the trials to show functional or anatomical alterations within haematopoietic tissue or any particular organ. In the 6-month investigation, the only organ alterations detected were increased liver and kidney weights and inconclusive changes in renal histology in high-dose (40 mg/kg/day) female rats. There were no functional or serum chemistry changes during this time. After taking oral ganaxolone (10 mg/kg), no alterations in cardiovascular haemodynamics were found in dogs. Unlike other AEDs, ganaxolone's reproductive toxicology investigations in rats and mice revealed no evidence of developmental consequences. Ganaxolone is unlikely to be mutagenic, according to toxicity testing [11].

Clinical Studies

Pharmacokinetics and Safety

Ganaxolone is available in two forms: an oral solution and a tablet. Both formulations have been used in single dosage pharmacokinetic investigations, however multiple dose evaluations have only used the suspension thus far. In Phase I trials, 210 healthy individuals (129 men and 81 women) between the ages of 18 and 59 were given ganaxolone [12]. Plasma concentrations of ganaxolone suspension increased rapidly after a single oral dose, reaching peak levels in 1 to 3 hours. Drug concentrations dropped biexponentially, with an apparent distribution phase lasting 2-9 hours and a long-term elimination phase lasting 16-43 hours. At dosages of 50-600 mg, AUC and Cmax increased linearly and dose proportionally, although plasma levels were lower than predicted at higher doses (900- 1500 mg) [13]. The pharmacokinetic profile of ganaxolone tablets was comparable, with peak plasma concentrations delayed by about 30 minutes. Dosing was done o.d. (50, 200, 500 mg), b.i.d. (300 mg), and t.i.d. (250, 500, 750 mg) in multiple dose trials. There were no unexpected drug accumulations, and steady-state plasma concentrations were attained in 5 days. There was no gender difference in the pharmacokinetic profile of ganaxolone in studies with both male and female volunteers [14]. Plasma concentrations of ganaxolone were approximately five times higher after a meal than when it was given fasting. Healthy individuals were given ganaxolone dosages ranging from 50 to 1600 mg.

The effects of ganaxolone on vital signs, electrocardiograms, physical and neurological tests, serum chemistry, and haematological evaluations were unremarkable across Phase I investigations. Treatment-related adverse events in Phase I clinical investigations were mostly extensions of ganaxolone's GABAergic effects. Somnolence, asthenia, dizziness, headache, stupor (drunkenness), abnormal thinking, and abnormal walking were the most common side effects, which occurred in some patients at higher dose levels [15]. Furthermore, while there was no apparent linear association between plasma concentrations and adverse events, volunteers with the highest plasma levels were more likely to report Central Nervous System side effects (CNS). The majority of the 23 healthy volunteers who had plasma ganaxolone concentrations exceeding 300 ng/ml (301 - 784 ng/ml) after a single dose showed CNS depression adverse effects, including six complaints of severe somnolence. Four of the 23 healthy volunteers with high plasma ganaxolone concentrations, including one with a Cmax of 612 ng/ml, the second highest level seen, reported no treatment-related side effects [16].

Future Directions

With the increase in new AEDs since 1993, a new AED must either demonstrate far greater safety and performance, or fill a need in the market. Claiming a far higher safety profile is a dangerous undertaking, as safety risks are typically not discovered until the drug has been administered to tens of thousands of patients. In terms of efficacy, certain new treatments are clearly more effective in some patients than others, but overall, the efficacy profiles of most new drugs appear to be comparable. The ganaxolone development programme targeted unmet requirements for these reasons. The early focus on infantile spasms is a clear example of an unmet need, as there is currently no FDA-approved treatment for this condition. Although men and women are equally affected by epilepsy, it is estimated that over one million American women of reproductive age suffer from it. Epilepsy affects many women's health difficulties, especially those of reproductive age. Hormones can influence seizure activity significantly. Before or during menstruation, some epileptic women have more frequent or severe seizures. Seizures influenced by the menstrual cycle are known as 'catamenial epilepsy.' Although it is commonly recognised that women's seizures are worse during menses, there is currently no viable treatment for these people [17].

A catamenial seizure pattern affects about one-third of women with intractable epilepsy, with perimenstrual increases being the most prevalent. Seizure exacerbations are linked to a drop in endogenous progesterone levels during the perimenstrual period, and data suggests that exogenous progesterone medication can reduce seizure frequency. Because ganaxolone is a neuroactive synthetic counterpart of allopregnanolone, a naturally occurring progesterone metabolite, it may be especially useful against catamenial seizures. Furthermore, ganaxolone's low teratogenicity makes it a good therapy option for women who are planning to have children. The safety, tolerability, pharmacokinetics, and anticonvulsant effectiveness of ganaxolone as an add-on therapy in women with catamenial epilepsy who are uncontrolled on their current AED regimen are currently being evaluated.

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