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Mini-Review

# Amifampridines (3,4 Diaminopyridine and 3,4 Diaminopyridine Phosphate): Drugs of Choice for Lambert-Eaton Myasthenic Syndrome

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## ABSTRACT

Amifampridines have been known to be effective as symptomatic treatment of Lambert-Eaton myasthenic syndrome since 1983. Food Drug Administration (FDA) approved amifampridines, the most studied safe and effective drugs in the neuromuscular diseases, are available for the general use for symptomatic treatment of LEMS, 60 years after the first description of LEMS and 40 years after the first trial of 3,4-DAP in LEMS.

**Keywords:** Aminopridines; 3,4-Daiaminopyridine (DAP); Dysautonomia; Lambert-Eaton Myasthenic Syndrome (LEMS)

## INTRODUCTION

Amifampridines have been known to be effective as symptomatic treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) since 1983. Because of delay in the randomized, placebo-controlled, trials, Food Drug Administration (FDA) approval has been lacking until 2018. In this review, I will summarize the effectiveness and safety profile of amifampridines for the symptomatic treatment of LEMS.

## LITERATURE REVIEW

Lambert-Eaton Myasthenic Syndrome (LEMS) is a rare presynaptic neuromuscular junctional disorder induced by voltage gated calcium channel antibody. Since the first description of LEMS, the frequent association of Small Cell Lung Cancer (SCLC) has been well known, being observed in 75% of LEMS cases in 1960's and 50% of LEMS cases in the recent days [1,2]. SCLC was detected in 50% of paraneoplastic LEMS cases at the time of diagnosis of LEMS. Almost always SCLC was found within two years of diagnosis of LEMS [3].

By blocking voltage-gated calcium channel, Ca++ uptake in the pre-synapses is decreased, eventually decreasing the release of Acetylcholine (ACh) from the synaptic vesicles and, thus, inducing muscle weakness.

The most common symptoms of LEMS are proximal muscle weakness, especially in the legs, and easy fatigability [4]. In view of easily fatigability and muscle weakness, Myasthenia Gravis (MG) was often considered as the possible diagnosis and, in fact, turned out to be the most common misdiagnosis in patients with LEMS. However, unlike MG, oculo-bulbar symptoms as the initial symptom is rare in LEMS. Tensilon test which is positive in 90%-95% of cases in MG is only positive in 33% of cases in LEMS [5].

Triad of findings in LEMS is proximal muscle weakness, weak or absent reflexes, and dysautonomia [4]. In MG, reflexes are normal. The common dysautonomic symptoms are dryness of mouth, orthostatic hypotension, and erectile dysfunction in LEMS. Thus, it is important to ask a question on dysautonomic symptoms in cases suspected of LEMS. The pathognomonic simple diagnostic test for LEMS is documentation of Post-Exercise Facilitation (PEF) in muscle strength or reflexes [6]. After brief 10 second exercise of muscle, one can document an improvement of muscle strength or reflexes in LEMS. Unfortunately PEF was observed only in 1/3 of LEMS patients [6].

Repetitive Nerve Stimulation (RNS) test is the key diagnostic test in LEMS. Unlike MG, abnormality is found universally in all muscles [4,7]. Thus, the abductor digiti minimi muscle testing is usually enough to make the diagnosis of LEMS. Triad findings in the RNS test are the low CMAP amplitude, decrement at the Low Rate of Stimulation (LRS) and incremental response after brief exercise or at the High Rate of Stimulation (HRS). For the adequate technical test, the brief 10 s exercise and 2.5 m wait

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period between the tests are recommended [8,9]. For the diagnostic marker of LEMS, an incremental response ≥ 100% was used in the past but the recent studies showed that an incremental response ≥ 60% was considered to be sufficient for the diagnosis of LEMS with 96% sensitivity and 98% specificity [4,10].

VGCC antibody test was positive in 90% of LEMS patients [11]. In view of low specificity (3%), one has to be careful in making the diagnosis of LEMS with positive VGCC antibody alone [12]. Detection of SCLC can best be done by the high resolution CT scan of chest and positron emission body scan [3].

Treatment of LEMS consists of symptomatic treatment, immunotherapy, and tumor therapy. Being an immune-mediated disease, immunotherapy is essential. Among the various immunotherapies, IVIG is the only treatment which showed a better outcome in comparison with placebo treatment [13]. Aggressive therapy for cancer is also essential because LEMS symptoms improve and paraneoplastic LEMS patients live longer than SCLC patients alone [14,15].

For symptomatic treatment, the ideal drug is the VGCC agonist [16]. However, such drug is not available as yet. Thus, the VGKC blocking agents have been the next best choice. By blocking voltage dependent K channel and inhibiting reporalization at the nerve ending, they induce the opening of slow VGCCs and increase calcium influx into the nerve terminal, subsequently leading to exocytosis of ACh containing synaptic vesicles and increasing ACh at the synapsis.

Guanidine HCl, one of four VGKC blocking agents, has been approved by the FDA for symptomatic treatment for LEMS prior to 1962 when only safety information was necessary for approval. It was the first drug used for LEMS from the beginning and studied in case series. Guanidine HCl has been used in 47 LEMS patients with clinical improvement in most cases and electrophysiological improvement in two studies [17]. Because of rare bone marrow suppression and renal insufficiency which seem to be dose-related, guanidine HCl was precluded from general use for LEMS from early 1990. However, Oh et al. reported a combination of low dose guanidine (1 gm a day) and liberal dose of pyridostigmine in nine LEMS patients with an improvement in muscle strength and CMAP amplitude without any serious side reaction in nine patients [17].

The second VGKC blocker tried in LEMS was 4-aminopyridine in 1977 [18]. In open trial, 9 patients showed clinical and electrophysiological improvement. However, seizures occurred in two patients due to easy crossing of the blood-brain barrier of 4-aminopyridine. Thus, 4-aminopyridine is discontinued in LEMS.

The third VGKC blockers are aminopyridines: 3,4-Diaminopyridine (DAP) and 3,4-DAP phosphate (3,4-DAPP). 3,4-diaminopyridine (DAP), which is known to be more potent in neuromuscular transmission and less convulsant than 4-aminopyridine, was first tried in 3 LEMS patients in 1983 with clinical and electrophysiological improvement [19]. Since then, 128 patients were treated in open trials with 3,4-DAP with improvement in muscle strength or daily living in 123 (96%) patients [16]. Six randomized, placebo-controlled trials in total 297 patients showed a significant difference in favor of 3,4-DAP over placebo in primary end-points (Quantitative Myasthenia Gravis [QMG] score and CMAP amplitude) [16]. However, seizure occurred in four patients. One patient had brain metastasis. Other three had ≥ 80 mg of 3,4-DAP a day. In one of three patients's toxic level of aminophylline was found. Since then, 80 mg of 3,4-DAP was set as the daily maximum dose.

In 1990, FDA granted an orphan drug designation to 3,4-DAP to Jacobus Pharmaceuticals company (JPC). However JPC never applied the new drug approval until 2018 and instead provided 3,4-DAP free of charge to patients under "Independent New Drug (IND) program for many years. Finally in 2019, FDA approved 3,4-DAP (JPC; Rizurg) for pediatric usage.

3,4-DAP phosphate (3,4-DAPP) is 3,4-DAP with added phosphate. Compared with 3,4-DAP, it is more stable and can be stored at room temperature [16]. 3,4-DAPP was approved by the European Medicine Agency around 2010 under the "exceptional circumstance" for LEMS on the basis of previous trials with 3,4-DAP without any further study [16]. With this approval, the price of 3,4-DAPP was increased dramatically (for example, 50-fold increase in United Kingdom), receiving widespread publicity The second VGKC blocker tried in LEMS was 4-aminopyridine in 1977.

## DISCUSSION

Two recent randomized, placebo-controlled, multicenter trials (n=64) compared 3,4-DAPP with placebo for treating LEMS by using QMG and subjective global score of improvement as the primary end points and clinical global impression of improvement and walking tests (timed 25-foot walk test or 3 times up and go test) as the secondary endpoints [16,20]. All of the primary and secondary endpoints showed statistically significant improvement with 3,4-DAPP over placebo. In 2018, FDA approved 3,4-DAPP (Catalytic Pharmaceutical Co CPC); Firdapse) for LEMS. However, the price of 3,4-DAPP remained "high": $180/10 mg tablet for Firdapse and $ 80/10 mg tablet for Rizurgi. Both manufacturers claim cost assistance to patients with limited resources.

The recommended daily dose of amifampridines (3,4-DAP and 3,4-DAPP) is less than 80 mg a day, divided into 3 or 4 times a day due to the shorter action of the drug [16,20]. Two most common side reactions are tolerable paresthesia around mouth and fingers and gastrointestinal distress. No other major side reaction including a prolongation of Q-T interval in the ECG, a potential side-reaction, has been reported. For long-term administration, amifampridines can be supplemented with a liberal amount of pyridostigmine.

## CONCLUSION

Finally, FDA approved amifampridines, the most studied safe and effective drugs in the neuromuscular diseases, are available for the general use for symptomatic treatment of LEMS, 60 years after the first description of LEMS and 40 years after the first trial of 3,4-DAP in LEMS.

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