

3,4-diaminopyridine Phosphate in the Treatment of Lambert–Eaton Myasthenic Syndrome

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Abstract

3,4-diaminopyridine (3,4-DAP, amifampridine) is the leading treatment for Lambert–Eaton myasthenic syndrome (LEMS), an autoimmune disorder with impaired neuromuscular transmission, for which few effective medications are currently available. 3,4-DAP has been available as a therapy for LEMS in special treatment programmes for approximately 25 years. As an unlicensed drug, doses for oral administration are required to be compounded by local, hospital or other compounding pharmacies from the base chemical. Administering the correct dose of 3,4-DAP is critical; overdosing can increase the risk of seizures and other adverse events, while underdosing can result in a substantial loss of efficacy or even treatment failure. Two recent studies, have shown a wide variation in the 3,4-DAP content of compounded preparations (22.2–125.2 %, n=9) and (53.5–128.5 %, n=21), thereby reflecting the possibility of patients receiving dosages that might be above safety limits or even markedly below efficacy limits. This inconsistency results from the variable quality and instability of the base chemical and compounding errors. A formulation of 3,4-DAP phosphate salt has now been licensed in Europe and the US with orphan medicinal product status and appears to be as efficacious as the base in relieving the symptoms of LEMS.

Keywords

Amifampridine, compounded drugs, Lambert–Eaton myasthenic syndrome, potassium ion channel blockers, neuromuscular transmission, myasthenia gravis

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Lambert–Eaton myasthenic syndrome (LEMS) is a rare neuromuscular disorder affecting around 1/100,000 people in Europe, although because it may go undiagnosed in many patients, its true prevalence may be considerably higher.¹ LEMS results from insufficient synaptic release of acetylcholine, which disrupts peripheral cholinergic neurotransmission. This is caused by autoimmune antibodies directed against the P/Q-type voltage-gated calcium channels (VGCCs). The loss of functional VGCCs reduces the calcium-dependent quantal release of the neurotransmitter acetylcholine. This lowers the safety margin for synaptic transmission at both the neuromuscular junction and certain autonomic nerve terminals leading to muscular weakness and symptoms of autonomic dysfunction.^{2–5}

Over half the patients with LEMS, particularly male smokers aged over 50 years, present with an underlying malignancy, usually small cell lung cancer (SCLC).^{6,7} However, there are also case reports on a wide variety of lung and non-lung malignancies observed in LEMS patients such as breast cancer⁸ and neuroblastoma.⁹ The peak age of onset of non-tumour LEMS is 35 years with a second peak at 60 years, whereas paraneoplastic LEMS occurs primarily in middle-aged and older adults, with a median age of onset of 58 years.¹⁰ Non-paraneoplastic LEMS can be associated with other organic-specific autoimmune

disorders.¹¹ Paraneoplastic cerebellar degeneration can also occur in cancer-associated LEMS cases.¹²

The diagnosis of LEMS can be challenging, since the clinical presentation of sub-acute progressive fatigue and weakness is unspecific. As a result, diagnosis is often delayed from many months up to even decades.¹¹ The symptoms of LEMS are frequently mistaken for those of myasthenia gravis or depression. In a recent study, initial misdiagnosis occurred in 58 % of British and Dutch cases.¹³ The most common clinical presentation of LEMS is proximal muscle weakness (more pronounced in the hip girdle than in the shoulder girdle). Tendon reflexes are reduced or absent, but it is important to note that they may be preserved early in the course of the illness. Cranial muscles may also be involved with symptoms such as ptosis, facial weakness, dysphagia, dysarthria and difficulty chewing. Cranial muscle weakness is usually milder than in myasthenia gravis and it occurs after the onset of limb-girdle weakness. Additional symptoms of autonomic dysfunction include reduced salivation, erectile dysfunction, dryness of the eyes and reduced sweating.¹⁴ The presence of an annoying dry mouth in patients with unexplained muscular fatigability is a diagnostic 'red flag' for LEMS. Diagnosis of LEMS is based upon assessment of clinical symptoms in conjunction

Table 1: Summary of Randomised, Placebo-controlled or Active Controlled Trials with Compounded 3,4-diaminopyridine in the Treatment of Lambert–Eaton Myasthenic Syndrome

| Study and Reference | Design | Treatments and Numbers of Patients | Endpoints | Results |
|------------------------------------|---|---|---|--|
| Oh et al., 2009 ⁴⁹ | Randomised, double-blind, cross-over drug trial (randomised phase: 308 days, follow-up 3–4 months) | 3,4-DAP (30 mg titrated to max 80 mg/day, oral) (n=7) or placebo (n=7) | SS Score, LEMS Classification, Muscle Strength Score, QMG Score, RNS test and SFEMG (to determine CMAP) | Significant improvements with 3,4-DAP for SS Score, LEMS Classification, Muscle Strength Score, QMG Score and CMAP (p=0.0112, -0.0246). Not all patients preferred 3,4-DAP. AEs: paraesthesia, difficulty sleeping and high blood pressure. 50 % sustained improvement during follow-up |
| Wirtz et al., 2009 ³⁰ | Randomised, double-blind, double dummy, cross-over (open-label in follow-up) single dose only | 4 treatment groups (n=9): 3,4-DAP, 3,4-DAP 10 mg, pyridostigmine 2 x 1 mg, 3,4-DAP + pyridostigmine, placebo | Isometric muscle strength, CMAP amplitude | Differences from placebo seen with 3,4-DAP and combination but not with pyridostigmine. Combination therapy did not have supra-additive effect. AEs: peri-oral and lingual paraesthesias; upper arm pain (study drug injection site) |
| McEvoy et al., 1989 ⁴⁸ | Open-label phase to determine 3,4-DAP dose (8 days) for randomised, double-blind cross-over phase (3 days) (open label in follow-up, ≥3 months) | 3,4-DAP titrated to 100 mg/day or as tolerated or placebo (and 3,4-DAP ± pyridostigmine oral in follow-up) (n=12) | NDS, isometric muscle strength, CMAP amplitude, autonomic function | Significant improvements with 3,4-DAP compared with baseline and placebo in NDS, isometric muscle strength and CMAP amplitude (p<0.001–<0.05) in cross-over phase. In open-label phase, NDS decreased with increasing 3,4-DAP doses. AEs: paraesthesia, epigastric distress, sleeping problems and rhinorrhoea. One seizure during follow-up |
| Sanders et al., 1993 ³⁰ | Randomised, double-blind cross-over (1 week) with follow-up (4–45 months) | 3,4-DAP max 100 mg/d (oral) or placebo; 3,4-DAP 15–50 mg/d (oral) + pyridostigmine in follow-up (n=10) | QMG Score | Significant improvement in QMG Score (p=0.01). Symptomatic improvement in 96 % of patients. AEs: transient peri-oral paraesthesias and seizures in 2 patients |
| Sanders et al., 2000 ³¹ | Randomised, parallel group study (6 days) with open label follow-up | 3,4-DAP 20 mg three times daily (n=12) or placebo (n=14) (n=25 in follow-up) | QMG Score, CMAP amplitude | Symptomatic improvement in QMG Score and CMAP (p=0.01 and p<0.001, respectively) in 96 % of patients. ≥2-point increase in QMG Score – usually in combination with pyridostigmine. AEs: peri-oral and digital paraesthesias |
| Murray et al., 1984 ⁵² | Randomised, double-blind (single dose) with follow-up (9 months) | 3,4-DAP (20 mg oral) or pyridostigmine (120 mg oral) (n=6) and 3,4-DAP (30–90 mg/d oral in follow-up) (n=9) | Clinical and non-specified electrophysiological measures | Marked clinical and electrophysiological improvement with 3,4-DAP in double-blind phase. Clear improvement in 50 % of patients in follow-up. AEs during follow-up: circum-oral and peripheral paraesthesias |

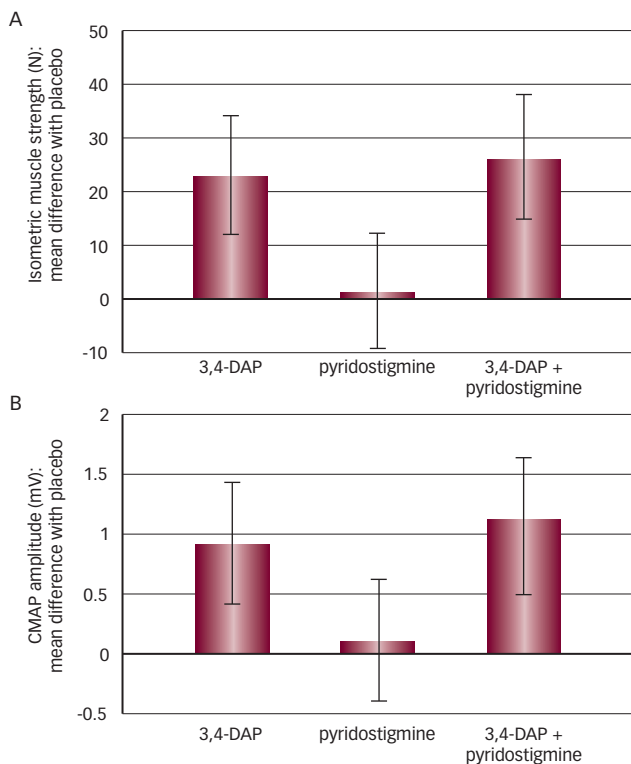
AEs = adverse events (associated with 3,4-DAP treatment); CMAP = compound muscle action potential; 3,4-DAP = 3,4-diaminopyridine; LEMS = Lambert–Eaton myasthenic syndrome; NDS = neurologic disability score; QMG score = quantitative myasthenia gravis score; RNS = repetitive nerve stimulation; SFEMG = single-fibre electromyography; SS Score = subjective symptom score.

with electrophysiological parameters and antibody testing. Electrophysiology testing demonstrates the characteristic so-called Lambert triad, including:

- reduced amplitudes of the compound muscles action potential (CMAP) in the motor conduction velocity studies;
- decremental responses of the CMAP amplitudes to low-frequency (2–3 Hz) repetitive nerve stimulation; and
- marked incremental responses of the CMAP amplitudes to high-frequency repetitive nerve stimulation or voluntary muscle contraction over a brief period of time.¹⁵

If the facilitation is greater than 100 % in most muscles tested or is greater than 400 % in any muscle, the patient almost certainly has LEMS. If facilitation is less than 50 % in all muscles tested, the patient still may have LEMS, especially if symptoms have been present for only a short time.⁴ The diagnosis of LEMS may be confirmed by radioimmunoassay of VGCC antibodies which are believed to be the main pathogenic factors in LEMS,¹⁶ and these are detected in 85 % of patients with clinically and electrophysiologically defined LEMS.^{17,18} In seronegative LEMS patients without detectable VGCC antibodies, the electrophysiological findings are less pronounced.¹⁹ Because of the high prevalence of SCLC in LEMS, it is mandatory to perform a careful tumour screening, especially in

Figure 1: Comparison of Isometric Muscle Strength and Resting Compound Muscle Action Potential Amplitude After Intravenous Administration of Single Doses of 3,4-diaminopyridine, Pyridostigmine or the Combination of Both Drugs in Nine Patients with Lambert–Eaton Myasthenic Syndrome



A: isometric muscle strength; B: resting CMAP amplitudes. The mean difference with placebo is depicted. Error bars represent 95 % confidence intervals. Results were obtained from a double-dummy, double-blind, randomised, placebo controlled, cross-over study. 3,4-DAP = 3,4-diaminopyridine; CMAP = compound muscle action potential. Source: Wirtz et al., 2009.³⁰

patients with a history of smoking. In almost all patients of a recently published Dutch cohort, SCLC was found within one year of diagnosis of the LEMS.²⁰ Computed tomography (CT)-thorax scans detected most of the tumours found and was far more sensitive than chest X-rays.²⁰ [(18)F]fluorodeoxyglucose positron emission tomography (FDG-PET) may have an additive value in tumour screening in selected cases.

Following diagnosis of LEMS, various test instruments can be employed to measure clinical improvement, such as the Subjective Symptoms Score, LEMS Classification, Muscle Strength Score²¹ and Quantitative Myasthenia Gravis (QMG) Score.^{22,23} However, scores developed to evaluate myasthenia gravis patients are only of questionable value to document the impairment in LEMS patients especially due to autonomic dysfunction and lower limb weakness.

Current Treatments for Lambert–Eaton Myasthenic Syndrome

The most widely used treatment for symptom relief of LEMS is 3,4-diaminopyridine (3,4-DAP, amifampridine), which was first suggested to improve muscle strength and autonomic function in a small case series of LEMS patients more than 25 years ago.²⁴

3,4-DAP blocks potassium ion channels in membranes and facilitates synaptic transmission.²⁵ The blocking of potassium ion channels prolongs the depolarisation during nerve action potentials, thereby increasing the

open-time of voltage-gated calcium channels and consequently the influx of calcium ions into the nerve terminal. This increased calcium influx enhances the quantal neurotransmitter release which is calcium dependant. Both 4-aminopyridine and 3,4-DAP have been used to treat LEMS, but 4-aminopyridine is thought to be less effective and has a narrow toxic to therapeutic margin,²⁶ with many neurological side effects reported.²⁷ Due to the rarity of the condition, few randomised controlled trials (RCTs) involving LEMS therapies have been conducted. The potassium channel blocker guanidine hydrochloride has shown limited efficacy in some small studies but it is associated with gastrointestinal, renal and haematological adverse events.^{27,28} Cholinesterase inhibitors such as pyridostigmine bromide have been employed in the treatment of myasthenia gravis for more than 50 years but have only been used in limited numbers of LEMS patients and produce only minimal to moderate responses when used as monotherapy, although they may improve dry mouth.^{4,27,29} A study comparing 3,4-DAP with pyridostigmine in the treatment of LEMS showed that muscle strength and CMAP were significantly improved with 3,4-DAP but not with pyridostigmine and combined treatment with both produced no advantage over 3,4-DAP alone.³⁰ Gastrointestinal cramps and diarrhoea may occur when 3,4-DAP is taken with pyridostigmine and can be minimised by reducing the dose of pyridostigmine.⁴

If 3,4-DAP fails to satisfactorily control the symptoms of LEMS, immunomodulatory therapies may be considered, however, some neurologists also use immune modulation therapy prior to beginning 3,4-DAP treatment. High-dose intravenous immunoglobulin (IVIg) treatment, plasma exchange and immunoabsorption therapy have been evaluated in small trials but require much larger studies to confirm results and support their wider use.^{31–33} Only one RCT involving these therapies has been carried out. It compared IVIg with placebo in LEMS patients and found significant but short-term improvement of limb, respiratory and bulbar muscle strength.³³ Immunosuppressive therapies such as prednisolone or azathioprine have shown efficacy in LEMS but the proportions of patients showing improvements were limited and the effects were short-lived.^{34–37} In LEMS patients corticosteroids can be used when required for the disease treatment; however, immunosuppressants should be avoided before the presence of a tumour is ruled out.³⁸

As in other autoimmune disorders, the anti-CD 20 antibody rituximab is a promising agent also for LEMS. However, there are still only scattered reports on the use of rituximab in LEMS patients.^{35,39} A recently published retrospective data survey including ten patients with myasthenia gravis and two patients with LEMS, found that rituximab treatment resulted in a significant clinical improvement in two-thirds of cases.³⁹ The data from this survey showed that both LEMS patients improved clinically, however, they did not achieve remission.

Anti-tumour treatments are essential for all patients with the paraneoplastic form of LEMS to treat underlying malignancies.⁴⁰ Interestingly, data supports a role for the LEMS-related immune response in suppressing tumour activity which can prolong the survival time of LEMS patients with cancer.^{41,42} Chemotherapeutic agents, such as vincristine, doxorubicin, adriamycin and cyclophosphamide, have shown efficacy against SCLC-associated LEMS but the proportions of patients benefiting were small.^{34,37} Chalk et al.³⁷ evaluated the outcome of 16 patients with LEMS associated with small-cell carcinoma. Thirteen patients received specific tumour therapy and most also received pharmacological and immunological treatment for LEMS. Seven of 11 patients surviving for more than two months after tumour

therapy showed substantial neurological improvement but only one patient was in complete remission seven years after the cancer therapy. In three of these 11 patients, improvement was only transient.

Clinical Evidence Supporting the use of 3,4-diaminopyridine in Lambert–Eaton Myasthenic Syndrome

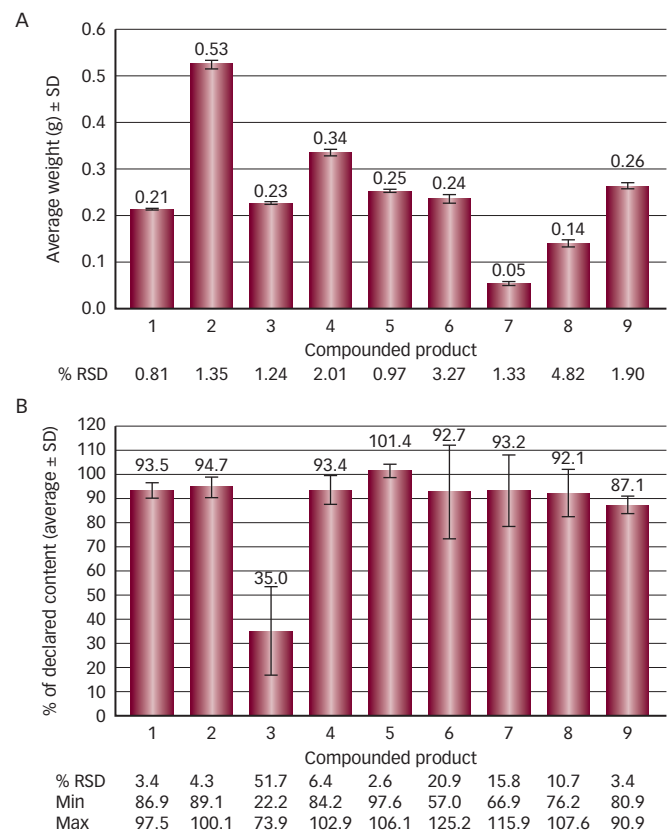
The efficacy and safety of 3,4-DAP in LEMS treatment have been investigated in several small clinical trials. Moderate to marked functional improvement was seen in patients receiving 3,4-DAP at doses of 24–80 mg/day iv or up to 102 mg/day oral in non-randomised trials (n=1–53).^{24,34,43–47} Six RCTs (n=7–26) compared DAP with placebo for treating LEMS over periods up to eight weeks; these are summarised in Table 1.^{30,48–52} 3,4-DAP produced significant improvements compared with placebo in a number of criteria including the Subjective Symptoms Score, LEMS Classification, Muscle Strength Score, QMG Score and amplitudes of the CMAPs (see Figure 1).

All the studies showed that 3,4-DAP was generally well tolerated with a favourable risk:benefit ratio. Few adverse effects were reported, and these were mild, transient and dose-related, and included paraesthesia, heat sensation, difficulty sleeping, light-headedness and fatigue.⁵³ 3,4-DAP can however, increase the risk of seizure especially in patients on high daily doses (80 mg or more) and with brain metastases. Among 669 patients from a French multiple sclerosis clinic treated with 3,4-DAP, less than 20 % of patients presented with adverse drug reactions (ADRs) while using moderate doses of 3,4-DAP (either 20–30 mg daily for multiple sclerosis fatigue, or up to 80 mg daily for patients with LEMS) for periods of up to 51 months.⁵⁴ In this observational, retrospective cohort study, the majority of ADRs were mild to moderate and transient or reversible at the end of treatment or after dose adjustment. Most did not require discontinuation. The most commonly observed ADRs were paraesthesias. In this study there was one case of epileptic seizure, one of hepatotoxicity and one of heart palpitations thought ‘possibly’ to be linked to 3,4-DAP. Overall, the incidence of certain side effects of 3,4-DAP is unknown due to limited clinical experiences. Because of this, treated patients must be monitored regularly including laboratory testing and an electrocardiogram (ECG) is mandatory if there is evidence of cardiac arrhythmias prior to the initiation of treatment. A recent Cochrane review⁵⁵ analysed the results of four of these RCTs in a total of 54 patients with LEMS and concluded that there is limited to moderate high-quality evidence showing that 3,4-DAP for up to eight weeks or IVIG improved muscle strength scores and CMAP in LEMS.

The Problem of Compounding 3,4-diaminopyridine

The use of compounded drug products, produced by the ad hoc mixing of drugs tailored to the specialised medical need of the patient, are still widespread in independent community pharmacies.⁵⁶ The practice is controversial because, by definition, it involves producing a drug for which safety and efficacy have not been demonstrated. Compounding requires high staff competency to assure the quality of the compounded medication. However, compounding pharmacies are not usually equipped to comply with Good Manufacturing Practice (GMP) standards, which require drug products to have an active ingredient range limit of 95–105 % of the declared label content.⁵⁷ Compounded medications may vary significantly in dosage and absorption characteristics, with no independent check of quality or variation. This results in uncertainty in dosing and raises concerns for patient therapy.⁵⁸ There are numerous published cases of problems associated with compounded drugs. The

Figure 2: Analysis of Nine Compounded Products Containing 3,4-diaminopyridine

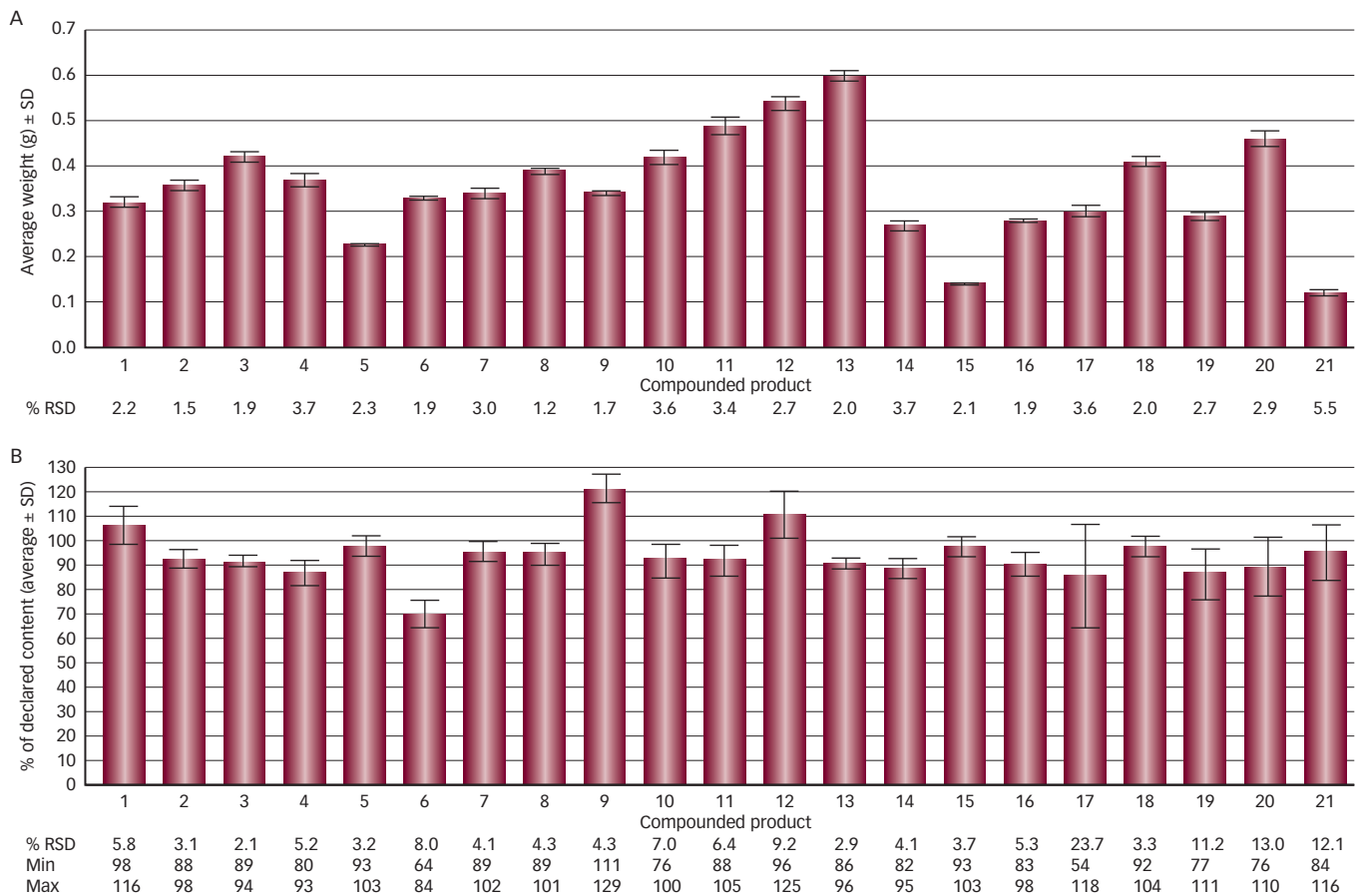


RSD = relative standard deviation; SD = standard deviation. A: weight distribution (average ± SD, n=10) and RSDs; B: percentage of declared 3,4-DAP content (average ± SD, n=10), RSDs and minimum and maximum measured values. Source: Green et al., 2012.⁶⁵

analysis of prescriptions for 0.3 % nitroglycerin ointment found that 29 % of the 24 samples were subpotent and one sample was superpotent.⁵⁹ This product was widely used, with 84,000 prescriptions for this ointment written in 2004 alone. Accidental overdoses of 4-aminopyridine due to pharmacy errors have resulted in life-threatening seizures in MS patients.^{60,61} A survey of compounded drug products including female hormones, local anaesthetics and inhalation drugs, by the US Food and Drug Administration (FDA), found 33 % of products failed testing criteria, either due to sub- or super-potency or lack of uniformity of individual dosage units. Potency ranged from 67.5 to 268.4 % of the amount of drug declared on the product labelling.^{56,62,63}

The quality of compounded drugs creates an important public health concern and is of particular relevance for 3,4-DAP because until recently it has only been available as a compounded product. Its use requires local, hospital or other pharmacies to prepare tablets or capsules from the base compound.⁶⁴ These are used either orally or in the preparation of solutions for intravenous administration. Raust et al. demonstrated that the base form of 3,4-DAP is much less stable under stress conditions than the salt formulation of 3,4-DAP, with 27 % of the base form degraded compared with only 0.1 % of the salted form.⁶⁴ As there exists potential instability of the base compound (which is only stable for up to 12 months) and potential compounding errors in manufacture, these issues have implications for the efficacy and safety of the product. Furthermore, compounded forms of 3,4-DAP do not have appropriate safety monitoring and pharmacovigilance systems in place to capture, analyse and report efficacy and safety data.

Figure 3: Analysis of Twenty-one Compounded Products Containing 3,4-diaminopyridine



RSD = relative standard deviation; SD = standard deviation. A: weight distribution (average ± SD, n=21) and RSDs; B: percentage of declared 3,4-DAP content (average ± SD, n=21), RSDs and minimum and maximum measured values. Source: Green et al., 2011.⁶⁵

A recent study assessed the 3,4-DAP content of tablet or capsule samples prepared in nine different pharmacies in Germany (two), Italy (one), The Netherlands (one), US (four) and UK (one) that claimed to contain 5, 10, 20 or 50 mg of active drug.⁶⁵ Ten samples of each preparation were analysed. The variability in dosage form weight ranged from 0.81 % relative standard deviation (RSD) to 4.82 % RSD. Among the 90 samples tested, the 3,4-DAP content varied from 22.2 to 125.2 % of the declared label content (see Figure 2) and none complied with the GMP standard range of 95–105 % of declared content. There was considerable variation of 3,4-DAP within the content of samples from the same pharmacies. All 10 of the samples from one pharmacy had active drug content well below the stated label content (35.0–57.1 %). There was no evidence of significant levels of degradation products in any of the samples. The variability in compounded 3,4-DAP samples appeared to be mostly the result of heterogeneity of the formulated material.

Similar findings were observed in another recent study of the active content variability of compounded 3,4-DAP in solid oral dosage forms, which evaluated 10 units each of 21 samples obtained from Germany (17), Belgium (two), Italy (one) and Spain (one), within the stated shelf life⁶⁶ (see Figure 3). The variability in dosage form weight ranged from 1.16 % RSD to 5.48 % RSD. Among the 210 units tested, 3,4-DAP content ranged from 53.5 to 128.5 %. No dosage form achieved the GMP standard range of declared content for all ten units tested. All samples of one dosage form contained at least 10 % below the declared content (mean ± standard deviation [SD], 69.8 % ± 5.6 %), and all samples of

another dosage form contained at least 10 % above the declared content (121.8 % ± 5.3 %). The most variable dosage form averaged 85.9 % of declared content but ranged from 53.5 to 118.1 %. There was no evidence of a significant presence of degradation products or related substances in 15 dosage forms. Four dosage forms contained total impurities/degradation peaks that amounted to ≤0.20 % 3,4-DAP equivalent. Two dosage forms contained higher levels of potential impurities/degradation peaks (0.43 % and 1.14 % 3,4-DAP equivalent).⁶⁶

It is evident from these data that compounded formulations of 3,4-DAP can vary widely and that patients may be exposed to unnecessary risks. There is a need for pharmaceutical grade oral dosage forms of 3,4-DAP to ensure efficacy and patient safety (see Figure 3). As a result of a recent review of available efficacy and safety data, 3,4-DAP has been recommended as a first-line treatment of symptomatic LEMS by the European Federation of Neurological Societies.⁵³ The salt species of 3,4-DAP has been shown to have superior stability compared to the base,⁶⁴ and an oral formulation containing 3,4-DAP phosphate salt, equivalent to 10 mg base, is now available. This formulation has obtained the orphan medicinal product status both in the European Union and in the US, and has received marketing authorisation in Europe as Firdapse®. Although the safety and efficacy of 3,4-DAP phosphate has not been directly compared with 3,4-DAP base in a RCT, it has been shown to be essentially bioequivalent with the base preparation,⁶⁷ and has been produced with vigorous quality control and pharmacovigilance standards as required by regulators.

Conclusions and Future Developments

3,4-DAP has proven to be an effective treatment of LEMS in a series of randomised studies. The tolerability has been found to be acceptable and the risk:benefit ratio was favourable. However, the variability of 3,4-DAP found in compounded preparations from different pharmacies and the associated safety risks suggest that compounding can be problematic and that approved products available as accurately measured doses may be a more effective, safe and reliable alternative. The recently licensed 3,4-DAP phosphate salt appears to be as efficacious as the base in relieving the symptoms of LEMS and has an acceptable tolerability profile. Using manufactured doses of 3,4-DAP phosphate salt avoids the problems associated with compounding at local pharmacies and increases efficacy and safety by supplying reliable and consistent doses that are within strict guidelines.

Most adverse effects associated with 3,4-DAP are dose-dependent, and the drug has a narrow therapeutic window. Possible improvement in terms of side effects and LEMS symptoms might be obtained by slow-release tablets, or a combination of 3,4-DAP with other agents. All studies on 3,4-DAP in LEMS conducted to date have included limited patient populations. More clinical trials involving larger numbers of patients are needed to support the general use of 3,4-DAP in LEMS and compare it with other treatments such as the cholinesterase inhibitors, cancer chemotherapeutic agents, immunomodulation and immunosuppression. Recently, a registry for LEMS patients was inaugurated combining patient data from several European countries. This European effort will aid in determining the frequency of adverse effects of 3,4-DAP and will hopefully lead to the improvement of therapy for LEMS patients. ■

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