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Full Length Research Paper

Efficacy and tolerance of combination of Cytidine 5 ' monophosphate (CMP) and Uridine-5 ' Triphosphate Trisodium (UTP) in patients with diabetic neuropathy: results of a study conducted in Dakar-Senegal

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Diabetic neuropathy is the earliest and most common chronic complication of diabetes. There are numerous therapeutic methods, but most of them present a problem of efficacy and tolerance. NUCLEO CMP FORTE ® is a combination of nucleotides (Cytidine 5'- Monophosphate Disodium and Uridine -5' Triphosphate Trisodium). Several preclinical studies have demonstrated the effect the combination of CMP and UTP in the regeneration of the myelin sheath and nerve cells. The aim of this study was to evaluate the efficacy and safety of the combination of CMP and UTP in the treatment of diabetic neuropathy. In a prospective study, we conducted a 3- month clinical trial of the combination of CMP and UTP in 75 patients with diabetic neuropathy. The methods of investigation were clinical (Visual Analogous Scale, Neuropathy Disability Scale and Neuropathy Symptom Scale), electrophysiological (electromyography) and biochemical (liver and kidney function tests). The patients (68) had a mean age of 56 years. They were mostly female (72%), had diabetes 2 (95.6%) and all types of neuropathic pain. The medication had improved the sensory disorders as well as the intensity of pain in diabetic neuropathy patients. There was also a significant increase in sensory conduction velocity in the right median nerve and left sciatic nerves during the electromyographic tests. No clinical or biological side effects have been noted. The combination of CMP and UTP is useful in the treatment of diabetic neuropathy. We recommended its use for diabetic patients with neuropathy.

Key words: Neuropathy, diabetes, CMP, UTP, Senegal.

INTRODUCTION

Diabetic neuropathy is typically the earliest and most common chronic complication of diabetes. According to WHO, 347 million people were expected to have diabetes worldwide in 2008 (Danaie et al., 2011). Diabetic neuropathy is a result of nerve damage caused by diabetes, and affects up to 50 % of diabetics (Muller, 2002). This pathology can occur either in type 1 or 2 diabetes, but also in aged or young patients (Bansal et al., 2014; Jaiswal et al., 2013). Approximately 40–50% of the patients developing DPN further develop painful diabetic neuropathy (Veves et al., 2008). The severity of this complication is mainly linked to the clinical consequences

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thereof (trophic disorders, neuropathic pain, severe dysautonomic illnesses) (Boulton et al., 2005). The essential element of management is the treatment of the chronic neuropathic pain. Many neurogenic pain medications (antidepressants and antipsychotics) aroused but all these medications have notable side effects (Boulton et al., 2005; Hartmann et al., 2012; Javed et al., 2015; Mibielli et al., 2010; Saeed et al., 2014). NUCLEO CMP FORTE® is a combination of nucleotides (disodium cytidine 5'- monophosphate and disodium uridine -5'- triphosphate) recommended in the treatment of neuropathies. Several preclinical studies have demonstrated the effect of the combination of CMP and UTP (Cytidine 5' Monophosphate Disodium and Uridine 5' Triphosphate Trisodium) in the regeneration of nerve cells by stimulating the synthesis of phospholipids and sphingolipids (the major components of neuronal cell membranes and myelin sheath (Durany, 2005; Martianez et al., 2012). Clinical trials on the combination of CMP and UTP have resulted in an efficacy of this treatment on the pain as well as on the sensory conduction velocity in poly-neuropathies (Gallai et al., 1992; Muller, 2002). As a follow up to these studies, we conducted a three-month clinical trial of the combination of CMP and UTP in diabetic neuropathy in collaboration with the FERRER Pharmaceutical Laboratory. The objective was to evaluate the efficacy and safety of treatment with the combination of CMP and UTP in patients with diabetic neuropathy.

PATIENTS AND METHODS

Patients

We conducted a clinical trial to evaluate the efficacy and tolerance of the combination of CMP and UTP. Thus, patients with diabetic neuropathy were followed during 90 days. We included in the study any diabetic patient (type 1 or 2) with a clinically diagnosed diabetic neuropathy and a pathological electromyography (EMG) who agreed through a signed informed consent to participate in the study. Patients were recruited during consultation at the Department of Internal Medicine/Marc Sankale Diabetes Center, Abass Ndao Hospital Center, Dakar-Senegal. This Center is a tertiary and university one dedicated to diabetes specifically with activities related to health care, counsel and secondary prevention on diabetes to patients with either diabetes or glucose intolerance. The exclusion criteria were: patients of less than 18 years old, pregnant or breastfeeding women, patients with neurological or systemic disease or other factor involving changes that may interfere with the neuropathy; patients with an allergy or intolerance to nucleotides; patients on a neuro-protective treatment. Recruitment was carried out at the Department of Neurology, Fann University Hospital and the Marc Sankalé Diabetes Center, Abass Ndao Hospital, Dakar, Senegal. Withdrawal criteria were: the non administration of the drug, voluntary withdrawal, important and serious side effects and diagnosis of severe inter-current affection.

METHODS OF INVESTIGATION

The evaluation of neuropathy was done clinically through neurological examination, the Visual Analogous Scale (VAS) as well as with the following scales: Neuropathy Symptom Score (NSS) and Neuropathy Disability Score (NDS). For the VAS, score was determined and the intensity of the neuropathic pain scaled as followed: score at VAS ≤ 4 (mild pain), score VAS = 5-7 (moderate pain), score VAS > 7 (very severe pain). Each patient was clinically evaluated regularly three times: before treatment, at day 45 of treatment and at the end of treatment (day 90). Blood and urine tests were performed before and at the end of treatment to detect potential biological and biochemical adverse effects including liver, kidney and blood cells. Thus, biological analyses were performed concerning Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Serum creatinin, Glycated hemoglobin (HbA1c), fasting blood glucose and a complete blood count (CBC). The laboratory Standards are as follow: glucose: 0.7 to 1.10 g / l, glucated hemoglobin (HbA1c): 4.2 to 6.2%, creatinin: 6 to 13 mg / l, Aspartate Aminotransferase (AST) < 35 UI / l and Alanine Aminotransferase (ALT) < 40UI / l. Two Electromyography (EMG) tests were performed in each patient (before and at the end of treatment). We carried out the recording of the Sensitive Conduction Velocity (SCV) at the right and left sural nerve, the right and left musculo- cutaneous nerves, the right median nerve and the left ulnar nerve. The recording of the Motor Conduction Velocity (MCV) was performed on the right and left lateral popliteal nerve, the right and left internal popliteal sciatic nerves, the right median nerve and the left ulnar nerve. Muscle detection was made on the left leg muscles and the right medial gastrocnemius muscle. The sympathetic skin reflex allowed us to assess the autonomic efferent.

Medications

Each patient received a daily dose of 15mg (i.e. 3 capsules / day) through oral continuous intake for 90 days. The daily dose was administered three times daily by a nurse: 1 capsule at 8AM, 2 PM and at 8 PM. Whether or not attributed to the medication, any adverse effect was assessed during the follow up of the patient. Whenever present, informations on the type of adverse effect, date of occurrence, severity, and the likelihood of its relation to the medication were recorded.

Statistical Analysis

The entry and processing of the data were performed with

with the SPSS for Windows version 18.0. Univariate analyses were performed to compute frequency, means with standard deviation. With the bivariate analyses, mean scores before and after treatments were compared for any patient included in the study using the T Test and results expressed with a Confidence Interval of 99 %.

RESULTS

We included 75 patients at the beginning of the study but 7 of them were withdrawn from it for reasons non attributable to the drug use. Finally the full follow up rate concerned 68 patients corresponding to a 90.66% follow up rate. The patients had a mean age of 56 years (extremes of 21 and 76 years) and were mostly female (female: 49 or 72%). They had mostly type 2 Diabetes (95.6 %). Neuropathic pain was present in all the patients followed by paresthesias (97.05%), hyperesthesia (44.4%) and allodynia (39.7%) (Table 1). Pain was judged intense (35.3%) and moderate (58.8%) by the patients. The mean NDS score before treatment was 5.82. Biological tests before treatment were documented in all the patients with the following results: mean glycemia: 208 (±0.92) mg/dl, mean HbA1C: 9.06% (±2.88), mean creatinin: 9.6 mg/dl (±3.2), liver function with AST (mean: 26.74 UI/l ± 3.14) and ALT (mean: 24.03UI/l ± 2.86) (Table 4). Improvement was observed with the sensory disorders (Table 2), the intensity and severity of the neuropathic pain (Table 3) and the mean sensory conduction velocity (Table 5). By the way, the mean NDS score varied from 5.82 to 4.52 before and after treatment ($P<0.000$. Frequency of autonomic dysfunction varied from 35.3% to 17.6% before and after treatment ($P<0.01$). No neuropsychiatric, skin, digestive and cardiovascular adverse effects were noted clinically in patients during and after treatment. The medication did not have any side effect in the kidney and liver function when comparing the biological tests before and after treatment (Table 4).

DISCUSSIONS

The population for the study of the clinical trial was set to 75 patients. Seven patients were withdrawn from the study for reasons not attributable to the combination of CMP and UTP. Thus, 68 patients underwent testing to the end, which means a follow-up rate of 90.66 %. The follow-up rate of our sample (90.66 %) is higher than 80% usually acceptable (Bouvenot et al., 2002).The mean age of our patients was 56 years, ranging from 21 to 76 years. This high mean age was found in several studies on diabetic neuropathy (Abougalambou and Abougalambou, 2012; Adonkounou et al., 2008; Hussein, 2013). This can partly be explained by the frequency of neuropathy in type 2 diabetes that occurs in adulthood on the one hand, and also the fact that occurrence of neuropathy is related to duration of diabetes on the other hand (Hartmann et al., 2012). The sex ratio in our study was 2.6 for female. Diabetic neuropathy seems to be more frequent in female as observed in Germany (Muller, 2002). This female predominance is confirmed by other authors (Abougalambou and Abougalambou, 2012). But, diabetes occurs either in male than female groups worldwide. Diabetes type 2 was more prevalent in our study population (95.6 %). This high prevalence of type 2 diabetes has been reported by several authors (Hartmann et al., 2012; Pirart, 1978). Among the sensory disturbances observed (neuropathic pain, hyperesthesia, paresthesia, hypoesthesia surface, proprioceptive allodynia and hypoesthesia), a significant regression was observed for hypersensitivity (from 44.11 % to 14.70%), hypoesthesia surface (from 26.47% to 5.88 %), allodynia (from 39.70 % to 2.94 %) and deep hypoesthesia (from 19.11% to 5.88 %). The combination of CMP and UTP resulted in a statistically significant decrease ($p < 0.01$) in the intensity of the neuropathic pain. The mean intensity score on VAS decreased significantly during treatment. This result is identical to what was observed during a study conducted in Germany among neuropathic pain patients: 6.02 before treatment and 4.04 at the end of treatment (Muller, 2002). Before treatment, the majority of patients (58.8%) had moderate neuropathic pain while 35.3% of patients had a very severe pain. After 45 days of treatment, moderate pain remains predominant (63.2%) but the proportion of very intense pain significantly decreased from 35.3 % to 10.3 %. This decrease in the intensity of pain was confirmed at the end of treatment (90 days) by the predominance of mild pain (64.7 %) and the proportion of very intense pain (1.5 %). The objective assessment of patient symptoms was achieved through the NDS score. We observed a significant decrease in the mean score of the NDS meaning an improvement during treatment. In Germany, the mean score decrease observed before and after treatment was not statistically significant (Muller, 2002). The combination of CMP and UTP was well tolerated by patients. No neuropsychiatric, skin, digestive and cardiovascular adverse effects were observed in our patients. The treatment did not lead to impaired renal function (serum creatinin) or liver dysfunction (ALT and AST). The mean values of creatinin, AST and ALT remained within standards before and after treatment. The EMG exploration showed a statistically significant increase ($P< 0.001$) of sensory conduction velocity in the median and left sciatica nerves. Improvement in the sensory conduction velocity of the left sciatic nerve was similar to what was observed in Germany (Muller, 2002). In our study, sensory conduction velocity of the left sciatic nerve has evolved from 37.39 m / s before treatment to 40.10 m / s at the end of treatment. In Germany, the values have changed from 37.5 m / s to 39.9 m / s^2 (Muller, 2002). The EMG autonomic affection has been

halved after treatment from 35.3 % to 17.6 %. This electromyographic improvement of the autonomic affection confirms the regression of the autonomic disorders (intestinal and tachycardia) observed clinically.

Whatever the results obtained during this study, there are some limits. Due to the subjective nature of the symptoms reported by patients, the scales used for the evaluation of the pain may not produce consistent results and may lack the sensitivity to track any objective changes in neuropathy status. This could also be , partly because these scales assess pain status and are thus subjective, measuring largely positive symptoms [Dyck *et al.* 2007]. The second aspect of the limits is related to the development of diabetic pain neuropathy. Symptoms can be lacking or not so severe to preoccupying diabetic patients. As we used subjective scales, the results obtained could be biased. In the other hand, some patients could have majored their symptoms for more care during the study. This can lead to false score during evaluation. However, neuropathy caused by small-nerve fibers is frequent during diabetes.

CONCLUSION

The combination of CMP and UTP has demonstrated its efficacy on sensory disorders as well as on the intensity of the pain in diabetic neuropathy. It had no significant effect on some autonomic disorders (orthostatic hypotension, erectile dysfunction and incomplete urinary retention). It increased in sensory conduction velocity in the right median and left sciatic nerves. It was well tolerated clinically and biologically. We recommend its use for treating diabetic neuropathy.

Conflict of Interest. None

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ANNEX

Table 1. Characteristics of the patients.

Sensory disorders	Number of cases	Percentage (%)
Mean age: 56 years (±5.4)		
Female	49	72%
Diabetes2	65	95.60
Neuropathic pain	68	100
Hyperesthesia	30	44.11
Paresthesia	66	97.05
Superficial hypoesthesia	18	26.47
Allodynia	27	39/70
Propioceptive hypoesthesia	13	19/11

Table 2. Evolution of sensory disorders with treatment.

Sensory disorders	Before treatment Number of cases (%)	After treatment Number of cases (%)
Neuropathic Pain	68 (100%)	65 (95.58%)
Hyperesthesia	30 (44.11%)	10 (14.70%)
Paresthesia	66 (97.05%)	64 (94.11%)
Superficial hypoesthesia	18 (26.47%)	04 (5.88%)
Allodynia	27 (39.70%)	02 (2.94%)
Propioceptive hypoesthesia	13 (19.11%)	04 (5.88%)

P< 0.000005

Table 3. Comparison of patients according to the intensity and severity of pain before and after treatment.

Neuropathic pain	Before Treatment Number of cases (%)	At Day 45 of treatment Number of cases (%)	At Day 90 of treatment Number of cases (%)	P value
Pain intensity				0.001*
Mild pain	4 (5.9%)	18 (26.5%)	44 (64.7%)	
Moderate pain	40 (58.8%)	43 (63.2%)	23 (33.8%)	
Intense pain	24 (35.3%)	07 (10.3%)	01 (1.5%)	
Pain severity				0.00*
Mean score	6.15	5.03	4.21	

*Difference statistically significant.

Table 4. Values of biological tests before and after treatment.

Biological Test	Before treatment	After treatment	P value
Glucose			
Mean ((±)	2.08 (±0.92)	1.90 (±0.92)	NS
HBA1C			
Mean ((±)	9.06 (±2.88)	8.24 (±2.88)	NS
Creatinin			
Mean ((±)	9.60 (±3.2)	7.89 (±2.49)	NS
AST			
Mean ((±)	26.74 (±3.14)	22.6 (±2.40)	NS
ALT			
Mean ((±)	24.03 (±2.86)	24.33(±2.85)	NS

NS= Difference not statistically significant.

Table 5. Comparison of mean sensory conduction velocities before and after treatment.

VCS according to treatment	Before treatment	After treatment	P value
Right Median	45.04	47.88	0.000*
Left ulnar 50	50.12	50.28	NS
Left musculocutaneous	42.61	42.36	NS
Right musculocutaneous	43.66	44.02	NS
Left Sciatic	37.39	40.10	0.000*
Right Sciatic	39.35	41.30	NS

*Difference statistically significant.
NS: No significant difference.