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Cohort Study

Diabetes Neuropathic Pain: Therapeutic Agents for the Ailment and Analytical Methods for the Measurement of Their Biological Fluids Concentrations

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Abstract

Diabetic neuropathy consists mainly of two types namely, sensorimotor and autonomic neuropathy respectvely. Pain, paraesthesia and sensory loss are common features of sensorimotor neuropathy while malignant arrhythmia, myocardial infarction and sudden death are associated with autonomic neuropathy. The aim of the study was to provide analytical methods employed to measure therapeutic agents utilized in the treatment of diabetes neuropathic pain in biological fluids. The methodology involved obtaining relevant information from scientific journals, reference books in libraries and internet websites. The results indicate that treatment of the ailment mostly involve the use of antiepileptic agents, antidepressants, antihypertensive agents, opioid analgesic agents. Gas or liquid chromatographic methods (hyphenated and non-hyphenated) electrochemical, electrophoresis and spectroscopic methods were found to be the analytical methods used to measure therapeutic agents for diabetes neuropathic pain in biological fluids. Of all these analytical methods, high performance liquid chromatography (liquid chromatographic method) seems to be the analytical method of interest.

Introduction

Diabetes mellitus a clinical syndrome characterized by an increase in plasma blood glucose.

Diabetes neuropathy is a peripheral nerve dysfunction or damage associated diabetes mellitus. Neuropathic pain is a complex phenomenon that is characterized by burning pain as well as allodynia and hyperalgesia involving both the peripheral and central nervous systems.

Diabetes neuropathy is generally classified into:

1. Diffuse neuropathy: consists of (a) distal symmetric polyneuropathy (DSPN), typical example is mixed small and large-fiber neuropathy; (b) autonomic, typical example is cardiovascular autonomic neuropathy (CAN); (c) gastrointestinal, typical example is gastropathy (diabetic gastroparesis); (d) urogenital, typical example is neurogenic bladder (diabetic cystopathy); (e) distal hypohydrosis/anhidrosis, typical example is gustatory sweating.

2. Mononeuropathy (mononeuritis multiplex)-consists of focal neuropathy, typical examples are cranial neuropathies and focal limb neuropathies.

3. Polyradiculopathy or radiculopathy- consists of multifocal neuropathy, typical examples are thoracolumbar radiculoneuropathy and lumbosacral radiculoplexus neuropathy (Bruns-Garland syndrome) [1,2].

The causes of the diabetes neuropathy include hyperglycaemia (resulting in over-activity of polyol pathway through aldose reductase); increase in oxidative stress (leading to increased lipid peroxidation); alteration of fatty acid metabolism (resulting in depletion of γ linolenic acid and PGE1- prostaglandin precursors); decrease in nerve growth factors concentration (namely glial derived neurotrophic factor, ciliary neurotrophic factor, insulin-like growth factors) and inflammatory change in the nerve [3,4].

Diabetes neuropathy is associated with symptoms such as rapid progression of limb weakness, absent ankle reflexes, retinopathy, foot deformity or ulcer, callus, severe and deep aching pain (abnormal discharges from diseased somatosensory neurons are considered to be responsible); weakness (follows the pain that afflicts proximal, but occasional for distal muscles); weight loss etc. [5,6]. These symptoms are generally worse at night leading to sleep disturbance and with painful symptoms during the day, the patient ability to carry out daily activities is diminished [7,8].

The diagnosis of the disease involves assessment of muscle power, pinprick sensation test (small-fiber function), vibration sensation test (large-fiber function), temperature perception test (using object of 10 to 40°C), and joint position test. Other tests may involve skin biopsy for assessing neuropathies with distal loss of unmyelinated nerve fibers, cardiovascular autonomic reflex tests for heart rate responses to deep breathing and standing, blood pressure response to standing, objective gastric emptying test and complete urodynamic test [9,10,11].

The management of diabetic neuropathy will involve:

(i) Prevention:

Screening for symptoms and signs of diabetic neuropathy is very vital, because it assists clinicians to detect the earliest stages of neuropathy. The practice will bring about early intervention by optimizing glucose control and other risk factors, that might contribute to the disease state [12,13].

(ii) Treatment with therapeutic agents:

Pain control is the mainstay of treatment of the disease. However, physiotherapy can offer assistance in more severe cases. Therapeutic agents that have shown efficacy in the treatment of pain associated with the disease are:

1. Amitriptyline: derivative of tricyclic tertiary amine. Chemically defined as 5-(3-dimethylaminopropyliden)-10,11-dihydrodibenzcyclo-heptene. It acts by inhibiting 5-hydroxytryptamine (5-HT) and norepinephrine reuptakes; enhances norepinephrine and 5-HT neurotransmission; promotes low clearance of norepinephrine and 5-HT from the synapse [14,15]. Recommended dose is 150-300mg daily

2. Carbamazepine: derivative of iminostilbene. Chemically defined as benzo[b][1]benzazepine-11-carboxamide. It acts by binding to voltage-dependent sodium channels hence inhibiting spontaneous activity in regenerating small-calibre primary afferent nerve fibers [16,17] Recommended dose is 100-800mg daily.

3. Desipramine: derivative of tricyclic secondary amine. Chemically defined as 3-(10,11-dihydro-5H-dibenzo[b,f]azepin-5-yl)-N-methylpropan-1-amine..Its mechanism of action is similar to amitriptyline [18,19]. Recommended dose is 150-300mg daily.

4. Duloxetine: is a derivative of thiophenepropylamine. Chemically defined as (+) - (S) - N-methyl - γ-(1- naphthyloxy) -2-thiophenepropylamine. It acts as a selective norepinephrine and serotonin reuptake inhibitor [20,21]. The recommended dose is 60-120 mg daily.

5. Gabapentin: derivative of a γ-aminobutyric acid. It is chemically defined as 1-(aminomethyl) cyclohexaneacetic acid. Its mechanism of action is similar to pregabalin [22,23]. Recommended dose is 600–3600mg daily.

6. Irbesartan: derivative of biphenyl tetrazole. Chemically defined as as 2-n-Butyl-4-spirocyclopentane-1-[(2'-tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one. A potent long- acting AII receptor antagonist with high specificity for the AT1 subtype and acts by inhibiting angiotensin II binding to the AT I receptor [24,25]. Recommended dose is150-300mg daily

7. Nortriptyline: derivative of tricyclic secondary amine. Chemically defined as 5-(3-methylaminopropyliden)-10,11-dihydrodibenzcyclo-heptene Its mechanism of action is similar to amitriptyline [26,27]. Recommended dose is 50-150mg daily

8. Pregabalin: is a derivative of gamma-amino butyric acid. It is chemically defined as (3S)-3-(aminomethyl)-5-methylhexanoic acid. It acts by binding with high affinity to the alpha-2-delta protein subunit of voltage-gated calcium channel thereby reducing the release of neurotransmitters, including the excitatory

neurotransmitter l-glutamate [28,29]. The inhibition of glutamatergic transmission is elicited in the spinal cord by direct activation of protein kinase C or nociceptive stimulation. Recommended dose is 150-300mg daily

9. Tapentadol: derivative of phenol propylamine. Chemically, is defined as 3-[(1R, 2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl] phenol. It acts through m-opioid receptor agonism and noradrenaline reuptake inhibition. It is a centrally acting opioid analgesic [30,31]. Recommended dose is 50-100mg daily

10. Tramadol: derivative of phenylcyclohexanol. Chemically is (IRS,2RS)-2-[(Dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol. It acts as a weak m-opioid receptor agonist, norepinerphrine and serotonin reuptake antagonist [32,33]. Recommended dose is 50-100mg daily

11. Venlafaxine: derivative of bicyclic phenethylamine. Chemically it is defined as1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol. It acts a selective norepinephrine and serotonin reuptake inhibitor, however, to a lesser extent, dopamine reuptake in the central nervous system [34,35]. Recommended dose is150-225mg daily

Other drugs of interest for patients whose pain is resistant to the above drugs are mexiletene, citalopram, paroxetine, lamotrigine, topiramate, pethidine, morphine.

To avoid adverse or side effects associated with therapeutic agents as well as inability to produce the required therapeutic responses, monitoring of their plasma concentration levels becomes very important. To achieve the monitoring and determination of plasma drug concentrations analytical methods that are accurate, precise, sensitive, selective and specific are necessary. Such analytical methods may include chromatographic, electrochemical and spectroscopic methods. However, chromatographic methods very often are the analytical methods of interest due their sensitivity and specificity. Chromatographic methods, namely high (or ultra) performance liquid chromatography and gas chromatography are mostly utilized either as hyphenated or non-hyphenated system. Hyphenation is an on-line combination of a chromatographic technique and one or more spectroscopic detection techniques.

Biological fluids are very important to life because they assist in the maintenance of body homeostasis. The fluids mostly analyzed are whole blood, serum or plasma, urine, saliva and cerebrospinal fluid. The present study provides various analytical methods that have been used to measure therapeutic agents for diabetic neuropathic pain in human biological fluids.

Biological fluids and analytical methods reported for the following therapeutic agents include:

1. Amitriptyline: determined in: (a) plasma [36-39] by non-hyphenated system, [40] by hyphenated system, [41] by thin-layer chromatographic system (b) serum [42-44] by non-hyphenated system and [45] by radioimmunoassay system (c) urine [45-47] by radioimmunoassay system and non-hyphenated system, (d) saliva [45] by radioimmunoassay system, (e) human vitreous humor [48] by non-hyphenated system.

2. Carbamazepine: determined in: (a) plasma [49-52] by non-hyphenated system, (b) serum [53-56] by non-hyphenated system, [57,58] by hyphenated system and [59] by spectroscopic system (c) urine [60]

by non-hyphenated system, (d) saliva [53] by non-hyphenated system and (e) breast milk [61] by non-hyphenated system,

3. Duloxetine: determined in: (a) plasma [62,63] by non-hyphenated system, [64-66] by hyphenated system, (b) serum [67-69] by non-hyphenated system.

4. Desipramine: determined in: (a) plasma [70-73] by non-hyphenated system, [74] by hyphenated system, [75] by thin-layer chromatography (b) serum [43] by non-hyphenated system, [76] by hyphenated system (c) urine [46] by hyphenated system.

5. Gabapentine: determined in: (a) plasma [77-80] by non-hyphenated system and [81-83] by hyphenated system, [84] by capillary electrophoresis (b) serum [85-89] by non-hyphenated system and [90-92] by hyphenated system (c) urine [93-95] by non-hyphenated system.

6. Irbesartan: determined in (a) plasma [96-98] by non-hyphenated system [99-102] by hyphenated system (b) serum [103] by non-hyphenated system, (c) urine [104] by non-hyphenated system.

7. Nortriptyline: determined in: (a) plasma [36,37,38,105,106] by non-hyphenated system and [46] by hyphenated system [44] by thin-layer chromatography, (b) serum [38,42,44] by non-hyphenated system and [76] by hyphenated system, [45] by radioimmunoassay system (c) urine [47] by non-hyphenated system, [46] by hyphenated system.

8. Pregabalin: determined in: (a) whole blood [107] by hyphenated system (b) plasma [108,109] by non-hyphenated system, [110-113] by hyphenated system (c) serum [86,114] by non-hyphenated system (d) urine [115] by non-hyphenated system, and [109] by hyphenated system.

9. Tapentadol: determined in: (a) serum [116] by non-hyphenated system, [117] by hyphenated system, (b) urine [118,119] by hyphenated system, (c) saliva [118] by hyphenated system.

10. Tramadol: determined in: (a) whole blood [120] by hyphenated system (b) plasma [121-125] by non-hyphenated system, [126,127] by hyphenated system, (b) urine [123] by non-hyphenated system,

11. Venlaflaxine: determined in: (a) whole blood [128] by hyphenated system (b) plasma [129-131] by non-hyphenated system and [132-136] by hyphenated system, [137] by capillary electrophoresis (b) serum [138] by non-hyphenated system.

The study has shown that therapeutic monitoring of these therapeutic agents will not be a problem since several analytical methods exist for their measurement in biological fluids.

Gas and liquid chromatographic (hyphenated or non-hyphenated) methods including capillary electrophoresis were mostly utilized methods in the analyses of these diabetes neuropathic pain agents. The chromatographic analytical methods have advantages over electrochemical or spectroscopic methods in terms selectivity and sensitivity. However, as the chromatographic methods involve use of expensive and sophisticated equipment analysts in developing and underdeveloped nations, continue to employ spectroscopic methods as the technique of interest due to their cost effectiveness, simplicity, accuracy and precision.

Conclusion

In order to avoid poor quality of life associated with diabetes neuropathic pain, diagnosis and symptomatic treatment are very important. Strict glycaemic control is very vital in the prevention of diabetes neuropathy. The treatment of severe pain associated with the disease involves the use of antidepressants, anticonvulsants, anti-hypertensive agents, opioid analgesic agents. Finally, although chromatographic methods are the best and most important methods of choice, electrochemical and spectroscopic methods still find significant place in the measurement of diabetes neuropathic pain therapeutic agents in biological fluids.

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