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Editorial

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Amyotrophic Lateral Sclerosis Disease: Analytical Methods of Measurement of Therapeutic Agents against the Disease in Biological Fluids

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Amyotrophic lateral sclerosis (ALS) is an irreversible most common motor neuron disease in which the upper and lower motor neurons in the motor cortex, brain stem and spinal cord degenerate leading to progressive paralysis and death probably arising from respiratory failure [1-3].

The disease is caused by genetic mutations [4,5], oxidative stress [6], inflammation [7], loss of neurotrophic factors [8], glutamate excitotoxicity [9], mitochondrial dysfunction [10].

Alpha-amino-3-hydroxy-5- methyl-4-isoxazole propionic acid (AMPA) receptors mediate glutamate-induced excitotoxicity in neurodegenerative diseases [11].

The clinical symptoms typically manifest as focal weakness in one limb, however other symptoms such as spasm, poor reflexes, frontotemporal lobe dysfunction with cognitive and behavioral abnormalities, bulbar presentation resulting in dysarthria, dysphagia, and respiratory dysfunction can be observed in ALS patients [12].

The molecular mechanisms linked with neurodegeneration in ALS patients may include: astrogliosis, cytoskeleton and axon-transport defects, disturbed RNA metabolism, excitotoxicity, impaired proteostasis, mitochondrial dysfunction and neuroinflammation [5].

The diagnosis of the disease depends mostly on the correct exclusion of other diseases with similar clinic expression through natural history of the patient, clinical examination, electrophysiological studies [13,14]. In addition, the intra and inter variability between ALS patients make create non-availability of specific disease marker [12].

Clinical treatment of amyotrophic lateral sclerosis is mostly done using riluzole. However, other clinical therapeutic agents available are edaravone and nuedextaTM (contains dextromethorphan and quinidine sulfate as active ingredients). Literature has revealed several potential therapeutic agents that are undergoing phase II and III clinical trials and they include withaferin A (inhibitor of nuclear factor-kappa B activity), ibudilast (immunomodulator), mexitil (anti-arrhythmic agent), rasagiline (mitochondrial protectant), retigabine (anticonvulsant agent), tocilizumab (protein biologic), arimoclomol (proteostasis agent), masitinib (immunomodulator), talampanel, (non-competitive antagonist of alpha-amino-3-hydroxy-5- methyl-4-isoxazole propionic acid, AMPA), nurowu (neuro protectant-stem cell therapy), anti-oxidative agents such as resveratrol, bromocriptine, WN1316 (2- [mesityl(methyl)amino] -N- [4-(pyridin-2-yl)-1H-imidazol-2-yl] acetamide trihydrochloride) and anti-inflammatory agents such as N-acetyl-L-tryptophan (inhibitor of cytochrome release and an antagonist of neurokinin 1 receptor).

The objective of the study was to provide information on the analytical methods of determining clinical active agents (riluzole and endaravone) against such disorder in biological fluids. Monitoring of these drug levels in biological fluids is very vital in order to ensure that required therapeutic levels are maintained during treatment. Typical of such biological fluids are whole blood, plasma, serum, saliva, urine, cerebrospinal fluids etc.

Spectroscopic and chromatographic methods are mainly the bioanalytical methods utilized in the determination of riluzole and endaravone in biological fluids. Spectroscopic methods due to insufficient sensitivity and specificity are not often utilized.

Some reported chromatographic techniques using different conditions for sample preparation, analyte extraction, separation and detection to determine these two clinical active agents in biological fluids are presented. Amongst them are high performance liquid chromatographic methods (HPLC) which are either hyphenated or non-hyphenated. Hyphenation is an on-line combination of a separation technique and one or more spectroscopic detection techniques [15]. The determinations include:

Riluzole

(a) human plasma: (i) Hong-Wen *et al.*, [16] and Van Kan *et al.*, [17] by non-hyphenated HPLC methods, (ii) Chandu *et al.*, [18] and Rao *et al.*, [18] by hyphenated HPLC method.

(b) human serum: (i) Van Kan *et al.*, [17] by non-hyphenated HPLC method.

Edaravone

(a) human plasma: (i) Gandhimathi *et al.,* [19] by reverse phase high performance thin layer chromatography (RP-HPTLC)

(b) human serum: (i) Wei and Xiao [20] by non-hyphenated HPLC.

Conclusion

Amyotrophic lateral sclerosis, a rapidly advancing fatal neurodegenerative disease that is progressive, has riluzole and edaravone as current clinical therapeutic agents. Mostly non-hyphenated and hyphenated HPLC analytical techniques are used to determine both therapeutic agents in biological fluids. Hyphenated method happens to be the preferred method probably due to its accuracy, specificity, selectivity, high sensitivity and high sample throughput. Finally, the reported analytical methods to determine riluzole and endaravone respectively in biological fluids may not be exhaustive however it shows that hyphenated HPLC is the analytical method of interest.

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