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Editorial

Myasthenia Gravis: Analytical Methods for the Determination in Biological Fluids of First-Line Therapeutic Agents Used in the Management of the Disease

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Editorial

Myasthenia Gravis (MG) an autoimmune disease is the prototype of neuromuscular junction disease caused by auto antibodies against the nicotinic Acetylcholine Receptor (AChR) located in the postsynaptic muscle endplate membrane [1,2]. The autoimmune disorder is characterized by weakness and fatigability of the voluntary muscle arising from the distortion and simplification of the postynaptic muscle membrane and consequent attachment of antibodies and complement to the membrane.

A large number of drugs has been reported to have the potential of inducing myasthenia gravis and they include D-penicillamine, aminoglycoside, fluoroquinolones, tetracyclines, timolol, betaxolol, general anesthetics, chloroquine, sulfonamides, quinidine, barbiturates, gabapentin, phenytoin and calcium channel blockers [3,4].

Myasthenia gravis has been classified on the basis of severity of the diseases into five grades [5]. Such classes include: Grade 0 (asymptomatic), Grade 1 (ocular signs and symptoms); Grade 2 (mild generalized weakness); Grade 3 (moderate generalized weakness, bulbar dysfunction, or both) and Grade 4 (severe generalized weakness, respiratory dysfunction, or both).

The symptoms of myasthenia gravis are specific muscular weakness and fatigability. Ocular symptoms such as ptosis, diplopia, or blurred vision seem to be first manifestation of the disease. Ptosis (weakness of levator palpabrae) which may be unilateral, is a common presenting feature. The diagnosis of myasthenia gravis deals with clinical demonstration of fatigability, while the electro diagnostic, pharmacological and serological tests are adjunct to the diagnosis [6]. Infections, initial high dose steroid therapy, or an inadequate treatment can cause myathenic crisis (exacerbation of myasthenia), a condition that leads to paralysis of respiratory muscles.

Treatment of myasthenia gravis involves use of therapeutic agents (drugs) such as acetylcholinesterase inhibitors, corticosteroids, immunosuppressants, immunomodulating agents and procedures such as plasmapheresis and thymectomy [7]. Initial treatment with drugs usually starts with use of the acetylcholinesterase inhibitor or in combination with corticosteroid. Short-term treatment using immunomodulating agents may be effective in the early stages of treatment or later during an exacerbation. However, for long-term treatment steroid and immunosuppressants are included in the dosage regimen. These first-line drugs namely pyridostigmine bromide (acetylcholinesterase inhibitor), prednisone (corticosteroid), azathioprine (immunosuppressant) are occasionally given in combination with second/or third- line drugs.

In the present paper, analytical methods of choice in the quantification of first- line drugs used to treat myasthenia gravis in biological fluids are considered. Monitoring these drug levels in biological fluids is important to assure appropriate levels are maintained during therapy or treatment.

The bioanalytical methods that have been reported include (i) immunoassay techniques [8,9], electrochemical [10], spectroscopy [11], capillary electrophoresis [12,13] and chromatographic methods.

Despite the availability of a number of analytical methods to determine these first-line drugs in biological fluids, immunoassay methods are rarely used for the analysis due to lack of availability of specific antibodies. Spectroscopic (UV/Vis) methods due to insufficient sensitivity and specificity are not often employed. Capillary electrophoresis (CE) is an attractive alternative to conventional separation techniques such as LC and GC however, its drawbacks in terms of injection modes (hydrodynamic injection or electrokinetic injection), make LC or GC the preferred method of analysis. The advantages of hyphenation of chromatographic methods allow the techniques to enjoy preference amongst analysts. Some reported chromatographic techniques (non-hyphenated or hyphenated) using different conditions for sample preparation, analyte extraction, separation and detection to determine these first-line drugs in biological fluids are presented:

1. Pyridostigmine bromide:

(a) Human Plasma:
(i) non-hyphenated HPLC with UV detector [14-18].
(ii) non-hyphenated GC with nitrogen and phosphorus detector [19]
(iii) hyphenated chromatographic system GC/MS [20,21]
(b) Human Serum:
(i) non-hyphenated HPLC with UV detector [22]

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(ii) non-hyphenated GC with electrochemical detector [23]

2. Prednisone:
(a) Human Plasma:
(i) non-hyphenated HPLC with UV detector [24]
(ii) hyphenated chromatographic system LC-MS/MS [25,26].
(b) Whole blood and urine:
(i) non-hyphenated HPLC with UV detector [24]

3. Azathioprine:
(a) Human Plasma:
(i) non-hyphenated HPLC with UV detector [27,28]
(b) Human Serum:
(i) non-hyphenated HPLC with electrochemical detector [10].
(ii) non-hyphenated HPLC with UV detector [29].

These chromatographic methods are not exhaustive however those presented provide evidence that first-line drugs used to treat myasthenia gravis can accurately and precisely be determined in biological fluids.

Conclusion

Numerous chromatographic methods have been developed to determine in biological samples drugs employed in the treatment of myasthenia gravis. Tandem mass spectrometry (MS/MS) and other hyphenated methods with higher sensitivities are they preferred analytical methods of interest. However, because facilities are not available in clinical or hospital laboratories for these very expensive hyphenated methods, therefore sensitive, rapid, accurate, precise and less expensive chromatographic methods (HPLC, GC, CE) are routinely used in clinical settings for monitoring of these drugs in biological fluids.

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