

Adrenal suppression following herbal remedy for rheumatoid arthritis

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Received: 06-04-2014

Revised: 08-08-2014

Accepted: 31-10-2014

ABSTRACT

A patient suffering from rheumatoid arthritis who had extreme adrenal suppression as a result of chronic use of herbal medicines presented with complications of adrenal suppression such as muscle weakness. He also had psychiatric disturbances such as confusion and suicidal tendency. Steroids in the herbal medication were found and hence there exists a need for investigation into their safety and efficacy.

Key words: Adrenal suppression, complementary alternative medicine, rheumatoid arthritis

INTRODUCTION

Millions of people are opting for herbal medication, and its use is increasing in both western and Asian countries, including India. The population in developing countries relies on herbal medication for their primary healthcare needs. The popularity of these medications is due to the fact that they are considered “natural” and do not involve any risks. The Complementary Alternative Medicines (CAM) for rheumatic diseases includes thermotherapy, acupuncture/acupressure, massage and herbal supplements. Among the rheumatic disorders, rheumatoid arthritis is the most common form of arthritis. The patients on

CAM believe that it is effective, convenient and safe and has fewer side-effects. For the management of chronic pain, most of the arthritis patients prefer CAM. Pain causes considerable distress and functional impairment. In India, herbal remedies are a widely used mode of CAM.^[1] In most of the cases, physicians were not informed about the use of CAM,^[2] and few patients continue the medications for many years and come with further complications. In this regard, this case report describes adrenal suppression due to a herbal medication.

CASE REPORT

Case 1

A 49-year-old male presented with polyarthritis and secondary adrenal suppression. He was symptomatic for the former condition for more than 10 years. His serum cortisol levels were extremely low (serum 0.32 µg/mL, normal levels 6.2–19.4 µg/mL), C-reactive protein levels were serum 0.8 mg/mL (normal levels <0.6 mg/dL) and he had vitamin D deficiency (serum 11.93 ng/mL, deficient <20, insufficient

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.155493

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21–29, normal optimal 30–70, toxic >100 ng/mL), erythrocyte sedimentation levels were 44 mm/h (normal levels 3–10 mm/h), uric acid levels were serum 11.1 mg/dL (normal levels 2–7 mg/dL) and rheumatoid factor was negative (serum 10 IU/mL, normal levels <20 IU/mL). He was on herbal medicine (powder) before presenting to the rheumatology unit, which he was taking for many years. He had symptoms of adrenal suppression, mainly muscle weakness and suicidal tendency, and few other psychiatric disturbances and family history did not present with any of the above symptoms. His concurrent medications included methotrexate 10 mg/week, colchicine 0.5 mg twice daily, febuxostat 40 mg once daily, deflazocort 12 mg twice daily and rabeprazole 20 mg once daily. The patient was on herbal medication for 3 years, and stopped it eventually. Then, he was put on deflazacort for 12 weeks at 12 mg twice daily and now the dose is tapered to 6 mg/day. Deflazacort, an intermediate-acting corticosteroid, has been prescribed to minimize the probable withdrawal symptoms due to the probable presence of dexamethasone or betamethasone (long-acting steroids) presumably in the herbal medication.^[3]

Case 2

A 38-year-old male presented with polyarthritis, was on herbal medication (powder) and was suffering from rheumatoid arthritis since 5 years. Because there was no improvement in his clinical features, he presented to the rheumatologist. He was having early morning stiffness, fatigue, joint swelling and joint deformity. His laboratory investigations revealed a positive increase in rheumatoid factor (46 IU/mL, normal <20 IU/mL). His concurrent medications include methotrexate 10 mg, folic

acid 5 mg once daily, prednisolone 5 mg once daily, famotidine 40 mg once daily and cholecalciferol granules (30,000 IU) twice a week.

The herbal samples of the patients were analyzed by mass spectrometry in the Sophisticated Analytical Instrument Facility, Indian Institute of Technology, Chennai. Our aim was to identify whether the steroid substances were present in the herbal preparation. The herbal sample of both cases was screened for the presence of steroidal compounds such as prednisolone (360.44), deflazocort (441.52), hydrocortisone (362.46), dexamethasone (392.46), betamethasone (392.46) and phytosterols such as β -sitosterol (414.70) and stigmasterol (412.69). In the positive ion mode, the sample of case 1 revealed the presence of steroidal compounds by the mass 393.81, which may be dexamethasone or betamethasone [Figure 1]. The positive ion mode of case 2 does not reveal any steroidal compound [Figure 2]. Both the samples show the presence of other mass interferences that may be either phytoconstituents or impurities.

DISCUSSION

We have described the presence of adrenal suppression following ingestion of a herbal medication. In spite of lack of controlled trials to validate herbal medicine for their efficacy and safety, their use is increasing. Understanding the mechanism of action, standardization, high complexity of ingredients and different formulations poses a great challenge in their quality control. The contributing reasons

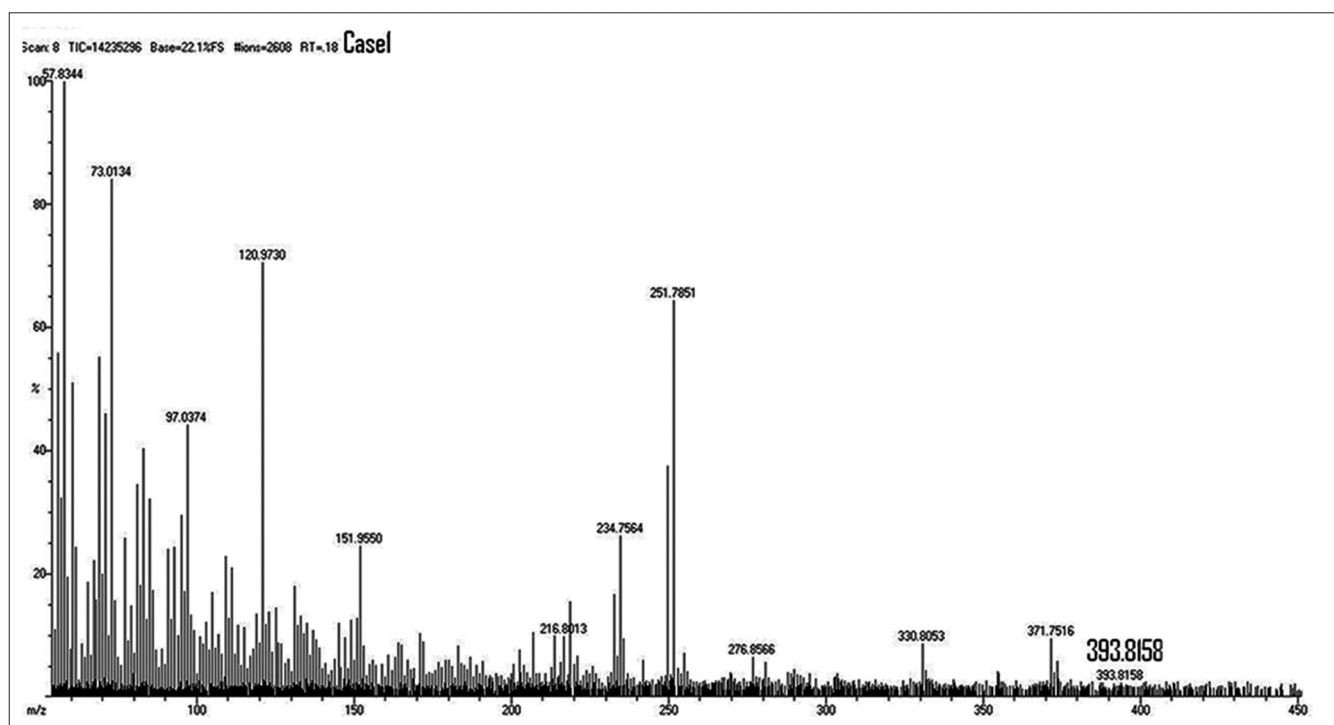


Figure 1: Mass spectrometry of Case 1, who was on herbal medication

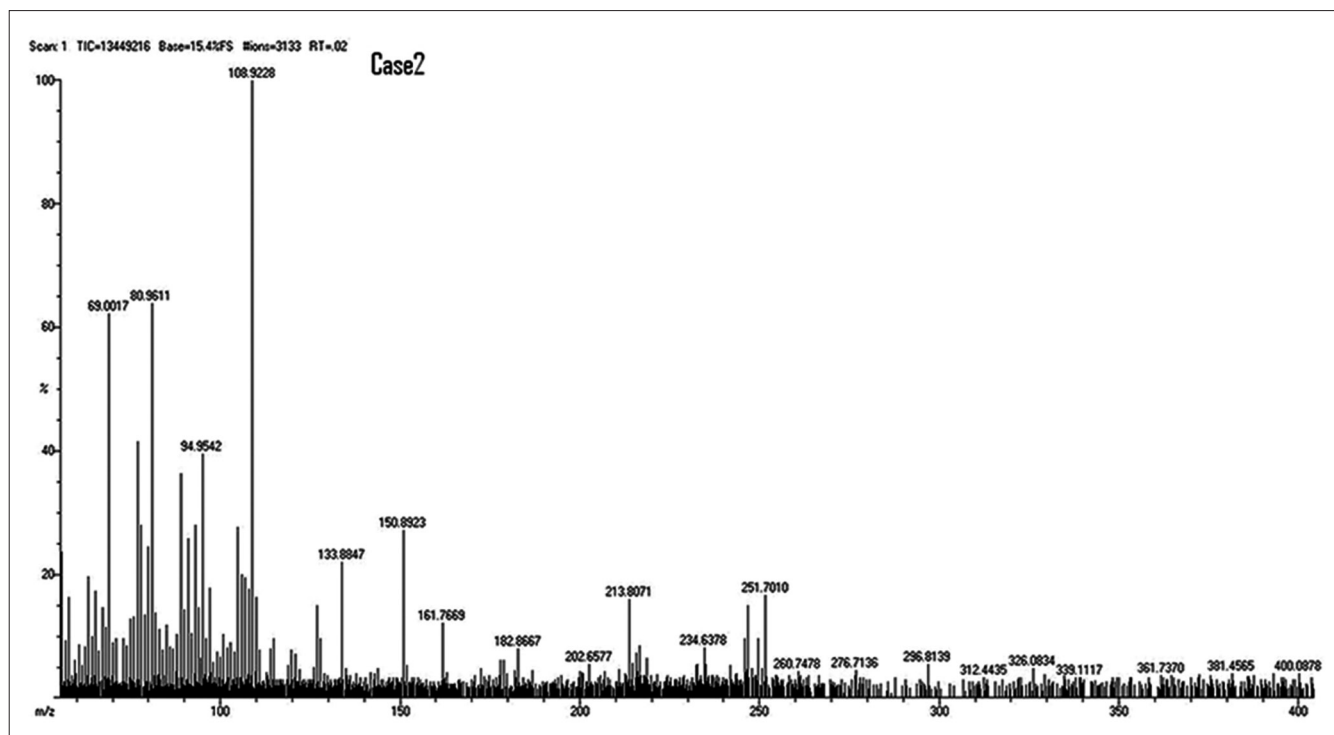


Figure 2: Mass spectrometry of Case 2, who was on herbal medication

are lack of clarity of herbal formulae in the formulation, presence of impurities, higher intake (particularly powders), herb–drug interactions if they take concurrent medications and adulteration.^[4] Previous reports have highlighted that herbal remedies may contain steroids.^[5] Because the therapeutic methods routinely used in the treatment of rheumatoid arthritis have several limitations such as a burdensome and unpleasant therapeutic experience, or may have adverse effects, patients turn to alternative medicine in the hope to find effective treatment and rapid results. The major causes of adulteration of herbal remedies with steroids for potent relief and non-steroidal anti-inflammatory drugs for prompt relief from pain, incorrect dosing and potential hazardous substances such as metals, pathogenic organisms and agrochemical residues could be the reasons for adverse effects.

Corticosteroids are used for a wide variety of inflammatory disorders like rheumatologic, dermatologic, pulmonary, hematologic and gastrointestinal disorders. Long-term use of steroids is associated with adverse effects such as adrenal suppression, hyperglycemia, dyslipidemia, osteoporosis and immunosuppression.^[6] Administration of corticosteroids can also lead to central nervous system side-effects.^[7]

While under therapy, the first patient developed symptoms of adrenal suppression and the second patient had no improvement in therapeutic outcome. The steroidal compound adulterated in the herbal medication may be betamethasone or dexamethasone. Despite this, we are unable to identify any other recognizable steroids.

In the present study, the symptoms of adrenal suppression could have precipitated or exacerbated neuropsychiatric disturbances such as depression and insomnia due to Hypothalamus-Pituitary-Adrenal (HPA) suppression. The depressive symptoms also reflected suicidal tendency and the patient could survive by administration of glucocorticoids throughout his life. Cortisol levels reduce in a patient on steroid therapy with HPA axis suppression. One may not know the dosage equivalent of steroids present in the herbal formulation from the concentration as assessed by mass spectrometry. Neuropsychiatric disturbances like mania and, rarely, depressive illness is not a part of steroid withdrawal symptoms as assessed by the low cortisol levels. Rather, if a patient is under stress and is on long-acting steroid therapy withdrawn abruptly, then the symptoms of acute adrenal insufficiency such as cardiovascular collapse and not neuropsychiatric disturbances will manifest. Even if suppression has occurred, we have tried to minimize this using substitution of long-acting with intermediate acting drugs.^[8]

Adrenal suppression following ingestion of herbal remedies is of major concern, and abrupt withdrawal of such products could precipitate adrenal failure with the potential for fatality. The consulting physicians and pharmacists in drug counseling should be aware of such consequences. While interacting with the patients, the use of alternative medicine should be explored and awareness regarding the proper usage, adverse effects and drug interactions should be explained to them.

In spite of taking herbal medication, the second patient did not have clinical improvement as steroids were not detected in the herbal medications for this patient. This supports the fact that steroids could be one of the active principles in the herbal medication.

Stringent policies for specifying the actual ingredients, methods of maintaining quality, conditions for storage, drug interactions and shelf-life in alternative medications should be defined. Underestimation of herbal safety should be taken care of and proper analysis of adulterations could improve the quality of life of rheumatoid arthritis patients. Patients should be made aware of the potential hazards of alternative medicine and should be encouraged to consult their physicians before their use.

CONCLUSION

Pharmacovigilance of herbal remedies is essential and stringent criteria applicable for western medicine should be applicable to herbal medicine before they can be advocated for rheumatoid arthritis patients.

ACKNOWLEDGMENTS

The authors take this opportunity to express their thanks to Dr. Ramanujam, Dr. B. Balaji, Mr. Sivaselvakumar, Mr. J. Sivaraman,

Mrs. Andhuvan and Dr. V. Sankar for providing guidance and continuous encouragement.

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How to cite this article: Premkumar B, Murthy MS, Rajagopal K, Nagaprabu VN, Ponugupati SM. Adrenal suppression following herbal remedy for rheumatoid arthritis. *J Pharmacol Pharmacother* 2015;6:110-3.

Source of Support: Nil, **Conflict of Interest:** None declared.