Brief Communication

Management of Primary Adrenal Insufficiency: Review of Current Clinical Practice in a Developed and a Developing Country

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Abstract

Treatment of primary adrenal insufficiency (PAI) requires lifelong hormone replacement with glucocorticoids (GCs) and mineralocorticoids. Impaired quality of life and increased standardized mortality ratio in these patients emphasize the importance of tailoring therapy to individual needs. Role of education is paramount in improving patient compliance and in anticipating and preventing adrenal crises. Although discovery of synthetic GCs was a major breakthrough in treatment of patients with this life-threatening condition, management of PAI continues to be challenging. The obstacles for clinicians appear to vary widely across the globe. While optimization and individualization of therapy after diagnosis of PAI remain the main challenges for clinicians in the developed world, doctors in a developing country face problems at almost every stage from the diagnosis to the treatment and follow-up of these patients; cost of therapy, lack of resources, and funding are the main hindrances. Adherence to therapy and patient education are found to be common issues in most parts of the world. This commentary highlights the challenges from both developed and developing country's perspective in treating PAI; it also provides an update on current management scenario and future treatment options.

Keywords: India, management, primary adrenal insufficiency, recent advances, United Kingdom

Introduction

Adrenal insufficiency (AI) is a life-threatening condition. The 2-year mortality in primary AI (PAI) exceeds 80%.[1] Health-related quality of life (QoL) is impaired in these patients, and there is two-fold increase in standardized mortality ratio (SMR) due to cardiovascular and infectious diseases in patients with PAI. As there are no known risk factors for susceptibility to adrenal crisis, patient education remains the main preventive strategy.[2]

In this brief review, the management approach to patients with PAI will be discussed. The focus of this article is to give a glimpse of the challenges of management of AI in a developed country like the UK and a developing country like India. We will also give a peek of recent advances in the management of PAI.

Management of Primary Adrenal Insufficiency

Glucocorticoid (GC) is secreted in a pulsatile (ultradian) and circadian fashion, reaching a peak in the morning and nadir at midnight. The preferred choice of GC replacement is hydrocortisone (HC) or cortisone acetate (CA). Both HC and CA are taken in 2–3 divided doses, with the first dose on waking up in the morning and the last dose 4–6 h before bedtime. Monitoring of GC replacement relies on clinical assessment.[3]

Fludrocortisone is used for mineralocorticoid replacement in PAI as a single morning dose of 0.05–0.20 mg. Blood pressure, electrolytes, and plasma renin activity (PRA) are used to monitor treatment adequacy.[4]

Dehydroepiandrosterone (DHEA) replacement is not advised routinely in patients with AI. However, it could be tried in women with hypopituitarism and concomitant AI who have more severe androgen deficiency and in some patients with

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persistent and severely impaired QoL and reduced libido despite optimized replacement therapy.[5]

All patients and their partners/caregivers should be educated to recognize an imminent adrenal crisis and to adjust the GC doses appropriately including the use of parenteral GC. All patients with AI should receive a "steroid emergency card" which provides information on the treatment.[5]

Management of Primary Adrenal Insufficiency: The UK Perspective

For the treatment of both primary and secondary AI in the UK, HC is prescribed routinely; prednisolone is occasionally used in patients noncompliant to multiple daily dose schedules or those with severe late evening or early morning symptoms not responding to multiple daily doses of HC. In cases of PAI, fludrocortisone is added. DHEA replacement is not undertaken routinely in clinical practice in the UK. Clinical assessment including body weight, postural blood pressure, energy levels, and signs of frank GC excess is used for monitoring GC replacement. Mineralocorticoid replacement is primarily monitored by clinical assessment and blood electrolyte measurements.

Apart from the education provided by the medical staff, support is also available to patients with adrenal failure from the support groups (e.g., Addison's disease self-help group in the UK and Ireland) through their online forum, through local meetings and newsletters.[6]

A recent issue in the management of patients with PAI in the UK has been a substantial hike in the price of immediate release HC by more than 12,000%, and the price of generic 10 mg HC tablets has increased from 70p a pack in April 2008 to £88 per pack by March 2016. Alternate strategies are being looked at and a small subset of clinicians in the UK have started to use prednisolone as the initial GC replacement therapy, cost being one of the reasons among others.[7]

A European open-ended observational study of AI management and outcomes (European Adrenal Insufficiency Registry) is an ongoing registry and should provide further data on the relative benefits of various GC replacement therapies in AI (also includes the novel modified-release preparation of HC).[8] Modified-release HC is considered orphan drug and is currently not recommended for routine prescribing in the UK as there is limited evidence on efficacy and safety.[9] Moreover, the drug has not been found to be cost effective.[10]

Management of Primary Adrenal Insufficiency: The Indian Perspective

The management of PAI is challenging in India with obstacles at every stage right from the diagnosis to the treatment and subsequent follow-up of the patient. The clinical diagnosis of PAI is often missed by general physicians.[11]

Tetracosactide (cosyntropin; synacthen) is not easily available in India for ACTH stimulation test, and we often use intramuscular ACTH stimulation test for diagnosis of AI.[12]

The biggest obstacle for treatment of PAI in India is the limited availability of oral HC tablets. Oral HC is available in urban areas; however, many of our patients come from rural areas, where the availability of this drug is limited. Hence, many physicians prefer using prednisolone for the management of PAI. There is also a substantial difference in cost of these medications. Oral HC in dose of 20 mg/day will cost a patient Rs. 14 per tablet while the equivalent dose of prednisolone of 5 mg will only cost 60 paisa per tablet.

A lot of work needs to be done about patient education and adherence to medications. We have often seen patients skipping medications and landing up in emergency care unit with adrenal crisis. Although we insist on training all our patients for "sick-day rules," the guidance is not always followed by the patient.

Fludrocortisone is commonly prescribed by us in PAI with titration done based on clinical parameters and PRA. The cost and availability of PRA is another obstacle in management. DHEA is not easily available in India, and with limited indications for its use in PAI, the use of DHEA is rarely given a priority in clinical practice.

Recent Advances and Future Directions

The management of PAI has seen some exciting new developments in the recent years. A novel once-daily, dual-release HC (PLENADREN; ViroPharma, Maidenhead, UK) was developed in the recent years to obtain more physiological circadian-based S-cortisol exposure-time profile. The tablet contains an immediate release coating surrounding an extended release core providing high levels of cortisol during the morning, followed by a gradual decrease throughout the day.[1]

Another oral timed-released HC preparation called CHRONOCORT (available from Diurnal Limited, Cardiff, UK) simulates the physiological release of cortisol more closely as it has sustained release and enteric coats which can provide differing release profiles. When given in a twice daily toothbrush regimen (20 mg at 23:00 and 10 mg at 7:00 h), it has shown in *in vivo* and *in vitro* studies to provide a pharmacokinetic profile similar to the normal physiological diurnal rhythm of cortisol.[13]

Conclusion

Synthetic GCs have been a landmark discovery enabling patients with life-threatening PAI to survive; however, the management of PAI continues to be challenging. There is substantial difference in the management of PAI between developed and developing countries; however, patient education and adherence to treatment are a common problem

faced by endocrinologists dealing with these patients in most regions worldwide.

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Conflicts of interest

There are no conflicts of interest.

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