

Adrenal crisis following COVID-19 vaccination in steroid dependant patients assessed in the Emergency Department

M. McDermott¹, K. Dalton², J. Legge³.

1. Medicine Department, St. Vincent's University Hospital, Elm Park, Dublin 4, Co. Dublin, Ireland.
2. Medicine Department, Midland Regional Hospital Mullingar, Longford Road, Mullingar, Co. Westmeath, Ireland.
3. Emergency Medicine Department, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland.

Abstract

Introduction

Two patients with adrenal insufficiency presented to the Emergency Department (ED) following vaccination against COVID-19.

Cases

Case 1, presented with dizziness, lethargy, confusion and feeling generally unwell. Case 2, presented with fever, vomiting, dizziness, malaise and feeling generally unwell. Both patients reported feeling well in the days prior to vaccination.

Outcome

No infection was found and both patients were treated as an adrenal crisis and managed with intravenous steroids and fluids. Both patients were referred to the medical team for admission. Case 1 was discharged 1 day later. Case 2 was discharged 2 days later.

Discussion

Vaccination is recommended for high-risk patients, including patients with adrenal insufficiency to prevent severe illness. There are currently no guidelines advising routine stress dosing of steroids around vaccination for these high-risk patients. This may be beneficial for these patients when weighing the risks and benefits in conjunction with the patient's history and with advice from their Endocrinologist.

Introduction

Vaccination is recommended for patients with adrenal insufficiency in order to prevent severe illness during acute infection^{1,2}. There are some documented cases of COVID-19

vaccination precipitating adrenal crisis in steroid dependant patients who have been on steroid replacement therapy for a long period of time^{3,4,5}. In the previous reports the patients improved following treatment for adrenal crisis with intravenous steroids.

As COVID-19 persists in the community and in hospitals, vaccination in order to prevent severe acute illness will likely continue to be a necessary intervention.

Below we present 2 cases of patients with adrenal insufficiency who presented in adrenal crisis following COVID-19 vaccination.

Case One

A female patient in her 80's with a background history of Addison's disease presented the day after COVID-19 vaccination to the ED in a tertiary level hospital. She was known to be steroid dependant. Prior to vaccination the patient was well. Approximately 12 hours after vaccination the patient began to feel unwell. She described feeling generally unwell, dizzy, lethargic, and her family had noted some confusion. They denied any infective symptoms.

The patient had a past medical history of Addison's disease, osteoarthritis and dementia. At baseline this lady was fully orientated. Notably the patient had a previous admission 3 years prior for hypotension following vaccination for which they were admitted for 3 days and treated with intravenous steroids for an adrenal crisis. No infection could be found at that time either.

Her regular medications included hydrocortisone, fludrocortisone, esomeprazole, mirabegron, and bisoprolol. She had no known drug allergies.

On examination the patient was hypotensive and had an altered mental status. The patient exhibited signs of a delirium and this was confirmed in obtaining a collateral history from the next of kin. The examination was otherwise normal.

Case Two

A male patient in his 70's with a background of adrenal insufficiency presented the day after COVID-19 vaccination to the same ED as patient 1. He was known to be steroid dependant. He presented with the complaint of feeling lightheaded and dizzy, vomiting, lethargy, headaches and feeling generally unwell.

He had a past medical history of leukaemia, myocarditis, malignancy of the bladder with ongoing immunotherapy and malignancy of the prostate treated with a prostatectomy. Notably this presentation was this gentleman's third episode of feeling unwell following COVID-19 vaccination with each presentation requiring intravenous steroids.

Regular medications included hydrocortisone, diamicon, esomeprazole, metformin and avelumab.

On examination he was hypotensive and febrile. There were crepitations at the base of the left lung. Otherwise, examination was normal.

Results

Investigation results for case 1 were as follows:

White Cell Count $5.6 \times 10^9/L$.

Haemoglobin 13.3 g/dL.

Platelets $309 \times 10^9/L$.

Sodium 138 mEq/L.

Potassium 3.0 mEq/L.

Creatinine 112 $\mu\text{mol/L}$.

eGFR 39.

C reactive protein 48.7 mg/L.

Urinalysis – mixed growth suggesting contamination.

Chest x-ray – no acute findings.

Case 1 was managed with intravenous fluid resuscitation and intravenous hydrocortisone.

Investigation results for case 2 were as follows:

White Cell Count $51.6 \times 10^9/L$ (previously over 50 due to known leukaemia).

Lymphocytes $47.5 \times 10^9/L$.

Haemoglobin 14 g/dL.

Platelets $208 \times 10^9/L$.

Sodium 149 mEq/L.

Potassium 4.2 mEq/L.

Creatinine 90 $\mu\text{mol/L}$.

eGFR >90.

C-reactive protein 7 ng/L.

Urinalysis – normal.

Chest x-ray – no acute findings.

Case 2 was managed with intravenous fluid resuscitation, intravenous hydrocortisone and an intravenous empirical broad spectrum antimicrobial.

The differential diagnosis in both cases included adrenal crisis and sepsis of unknown source. There have been previously documented cases of adrenal crisis following COVID-19 vaccination in steroid dependant patients^{3,4,5}. However, given the history and exam in both cases, sepsis was an important differential diagnosis to consider.

Given the negative test results above the final diagnosis made in the Emergency Department was post vaccination adrenal crisis for case 1 and case 2. The patients were referred to the medical team on call who admitted the patients and continued their treatment.

Case 1 was admitted under the Endocrinology team who confirmed the diagnosis of post vaccination adrenal crisis that was made in the Emergency Department. She was discharged 1 day later and was feeling well. She was given advice around future vaccinations to stress dosing of her steroids by the Endocrinology team. She had an uncomplicated admission course.

Case 2 was admitted under a general medical team and they continued his treatment for the diagnosis of post vaccination adrenal crisis that was made in the Emergency Department. He was discharged 2 days later following further treatment with intravenous steroids and negative tests for sepsis. He was feeling well. He also had an uncomplicated admission course.

Discussion

At present, guidelines recommend that steroid dependant patients should receive vaccination against COVID-19^{1,2}. Previous case reports^{3,4,5} and the above 2 cases demonstrate the risk of adrenal crisis following vaccination against COVID-19. At present there is no recommendation for routine stress dosing of steroids around vaccination in

order to prevent adrenal crisis, but guidelines do suggest to increase steroid dosing if a steroid dependent patient begins to feel unwell following vaccination¹.

Major *et al* describe 5 cases of adrenal crisis following the first dose of COVID-19 vaccination. The 5 cases present in a similar fashion to the 2 described cases above with fever, lethargy, vomiting and confusion resulting in hospital presentation. The patients were all vaccinated within 24 hours of the onset of symptoms⁶. While Major *et al* describe adrenal crisis in these patients following the first dose of COVID-19 vaccination⁶, the 2 cases described above have a history of similar presentations with previous vaccinations. Patient 1 had a previous admission to the same hospital three years prior requiring intravenous hydrocortisone for post vaccination adrenal crisis. Patient 2 had 3 previous episodes of feeling unwell following vaccination, and described needing intravenous hydrocortisone for each of these events. Ogundipe *et al* describe a case of 2 episodes of presumed adrenal crisis following vaccination in a single patient who received 2 vaccinations against COVID-19 33 days apart. After each vaccination the patient was treated with intravenous hydrocortisone and empiric antibiotics⁷. It appears that there may be a risk of adrenal crisis in steroid dependant patients with each vaccination that they receive.

Markovic *et al* describe a case of adrenal crisis in a patient with hypopituitarism. The presenting complaints in this case are similar to those described above with confusion, lethargy and fever prompting hospital presentation⁴. Patient 2 who is described above informed the ED staff that his steroid dependency was a result of monoclonal antibody treatment which was thought by his managing specialists to have affected his pituitary. Therefore, this was presumed in the ED to be a secondary adrenal insufficiency. Cases of adrenal crisis in primary adrenal insufficiency^{5, 7} and secondary adrenal insufficiency^{3, 4, 5} have been described. It appears that adrenal crisis following vaccination against COVID-19 may affect patients with either primary or secondary adrenal insufficiency.

Kurematsu *et al* describe 3 cases of adrenal crisis following vaccination against COVID-19, and furthermore they explain that adrenal crisis following conventional vaccinations is rare by citing Major and Chako^{3, 6}. The cases reported were similar in fashion to those described above with fever, fatigue, vomiting and delirium prompting a hospital presentation for the cases described. Major and Chako⁶ also state that it is important to counsel steroid dependant patients on how to manage steroids following vaccination.

At present, there are no guidelines suggesting routine increasing of steroid dosing for steroid dependant patients with hypoadrenalism. However, there is advice to increase steroid dosing in this population if they begin to feel unwell following vaccination. Patients who have been previously treated for post vaccination adrenal crisis may be at risk of adrenal crisis with future vaccinations and adrenal crisis may affect those with either primary or secondary adrenal insufficiency. Routine increases in steroid doses following

vaccination may be appropriate for specific patients taking into account their history and experiences with previous vaccinations in conjunction with specialist advice from their Endocrinologist. Increased awareness of post vaccination adrenal crisis may prevent hospital admission in these patients and may also prevent the unnecessary prescribing of antibiotics. Additionally, it may also help to maintain confidence in vaccination programmes amongst this vulnerable group of patients. For other steroid dependant patients, it may be beneficial to alert them to the possibility that they may become unwell following vaccination, educate them on sick day rules, and to make them aware of when to seek medical attention.

Declarations of Conflicts of Interest:

None declared.

Corresponding author:

John Legge,
Emergency Medicine Department,
St. Vincent's University Hospital,
Elm Park,
Dublin 4,
Ireland.

E-Mail: johnleggy@gmail.com

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