

Linagliptan-associated delirium in an older patient

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Abstract

Presentation

A 77-year-old man with type 2 diabetes, presented to the Emergency Department with an acute onset of confusion for 24 hours. He was on Metformin but due to nausea, this was switched to Linagliptan two days prior to his presentation. All vital signs were stable including blood sugar. Clinical examination was normal.

Diagnosis

Full blood count, renal, liver and C-reactive protein were all normal. CT brain revealed age-related involutinal changes, while Chest X-ray and MRI brain was normal. His 4AT score was ten and together with his acute change from baseline, a diagnosis of delirium was made.

Treatment

Linagliptan was discontinued and Empagliflozin was commenced with full recovery of the delirium gradually.

Discussion

Linagliptan and delirium may be due to changes to the gut microbiome, disturbing the gut-brain axis increasing inflammation¹. Linagliptan associated delirium has not been previously reported, although with effects of delayed gastric emptying and reduced gut motility, more studies are needed.

Introduction

An older gentleman developed delirium two days after commencing Linagliptan, a dipeptidyl peptidase Inhibitor. This was switched to Empagliflozin, a sodium-glucose co-transporter inhibitor and his delirium slowly resolved. The link between Linagliptan and delirium may be associated with changes to the gut microbiome, whereby the normal gut-brain axis is disturbed causing increased inflammation¹. Additionally, this is the mechanism proposed with several neurological disorders and postoperative delirium²⁻⁵. The gut microbiome is a complex network of bacteria inhabiting the entire gut mucosal surface, important in immune system

development, but subject to variations with advancing age^{6,7}. Linagliptan causing an acute delirium has not been previously reported. With its known effects on gut function via delayed gastric emptying and reduced gut motility, it highlights the need for more gut microbiotic studies to further elucidate less well-known effects.

Case Report

An elderly gentleman with type 2 diabetes, presented to the Emergency Department with an acute onset of confusion for 24 hours. He had been taking Metformin for the previous few weeks, but due to ongoing nausea, this was switched to Linagliptan two days prior to his presentation. He was not taking any other medications. He was independent and driving prior to this. Initial exam showed: Blood Pressure 154/106mmHg, pulse 103/min, respiratory rate 20 breaths/min, temperature 36.3°C, SpO₂ 98% on room air and blood sugar 7.8mmol/L. He was adequately hydrated, with a normal chest examination and 4-AT score of ten. Haemoglobin, white cell count, renal, liver and C-reactive protein were all normal. CT brain revealed age-related involutional changes, while Chest X-ray and MRI brain was normal. Linagliptan was discontinued and Empagliflozin (a sodium/glucose co-transporter inhibitor) was commenced. He was managed with Quetiapine for a short period, however when Parkinsons features were observed (tremor, mild rigidity and gait disturbance), this was stopped. L-dopa was commenced, with full recovery of the delirium over six weeks.

Discussion

There has been increasing interest in the role of gut microbiota dysbiosis in the pathophysiology of delirium^{1,2}. Changes in the gut microbiome have already been proposed in several neurological disorders including Parkinson's and Alzheimer's dementia³. Additionally, studies have shown that patients who developed postoperative delirium had changes in the microbiota⁴. Some studies have explored causative relationships between gut microbiota and geriatric syndromes, although specific links remain elusive requiring further evaluation^{5,6}. Dipeptidyl peptidase-4 (DPP-4) inhibitors work by prolonging the life of incretin hormones such as glucagon-like peptide-1, enhancing secretion of insulin from the pancreas^{7,8}. Additional mechanisms of action include reduced gastric emptying and reduced intestinal motility, with subsequent effects on the microbiome⁸.

We propose that Linagliptin disrupted the microbiome resulting in alterations to the gut brain axis, possibly mediated by GLP-1 or some other process. Such disruptions allow for an overgrowth of a particular group of bacteria within the microbiome adversely influencing the metabolism of butyrate, a short chain fatty acid, allowing the lipopolysaccharide produced to increase intestinal permeability^{7,8}. Inflammatory factors are then permitted to penetrate the

intestinal mucosa and trigger inflammatory signalling, which increases the permeability of the blood brain barrier and initiates neuro-inflammation and nerve damage^{6,7}. The gut microbiome is an intricate network of gut bacteria, important in the development of the body's immune system, yet vulnerable to biodiversity alterations with advancing age^{6,7}. The gut microbiota has been strongly associated with the development of neurological and psychiatric disorders, including Alzheimer's disease, schizophrenia, autism and mood disorders^{7,8}. The fact that our patient was on Metformin may also have significance, as it is thought to influence the gut microbiota composition through direct effects on bacterial growth, and induce changes in the intestinal environment contributing to gastrointestinal adverse effects and patient intolerance of the drug^{9,10}.

In an effort to establish causality, we applied the Naranjo Adverse Drug Reaction algorithm¹¹. This standardized and widely accepted tool is used to determine the likelihood of an adverse drug reaction being drug-induced, and the resulting score of 5 makes this probable. Furthermore, other plausible causes for delirium were ruled out through history, physical examination and investigations, including infection, dehydration, electrolyte disturbances, constipation, glucose abnormalities, hypoxia and urinary retention.

The multiple insinuated mechanisms for delirium are complex and no unifying hypotheses exists, thus conferring a degree of uncertainty in ascribing a single mechanism in any case of delirium. Proposed theories are not mutually exclusive, and delirium may result from the interplay of multiple factors, including predisposing vulnerabilities, acute triggers, and neurobiological mechanisms. DPP4 is expressed in many tissues, including the brain and inhibiting it may alter cytokine signalling and immune regulation in the central nervous system¹⁰, with a potential to disrupt normal functioning, providing a possible alternative mechanism to explain the onset of delirium in this case.

Linagliptan causing an acute delirium has not been reported previously. With its known effects on gut function, it highlights the need for more gut microbiotic studies on this elusive syndrome.

Declarations of Conflicts of Interest:

None declared.

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