JOURNAL OF CRITICAL REVIEWS

ISSN- 2394-5125 VOL 8, ISSUE 02, 2021

Metformin-induced Severe Enteropathy: A Case report

[1]Dr. Mohd Shahril Iman, [2]Dr. Mohammad Che Man, [3]Dr. Nurul Hassanah Muslim, [4]Dr. Shahidah Che Alhadi [5]Dr. Salman Amiruddin.

[1]Klinik Kesihatan Merchang, 21610, Marang, Terengganu. Ministry of Health, Malaysia

[2]Department of Family Medicine, Kulliyyah of Medicine, International Islamic University Malaysia, Indera Mahkota Campus, Pahang, Malaysia.

[3]Klinik Kesihatan UTC Pudu, Wilayah Persekutuan Kuala Lumpur, Malaysia, Ministry of Health. Malaysia.

[4]Department of Surgery, Kulliyyah of Medicine, International Islamic University Malaysia, Indera Mahkota Campus, Pahang, Malaysia.

[5]Fakulti Perubatan Universiti Sultan Zainal Abidin (UniSZA), Jalan Sultan Mahmud, Kuala Terengganu, Terengganu, Malaysia.

imanlurvislam@gmail.com, mohdcheman@iium.edu.my, nurulhassanah901016@gmail.com,shahidahhadi@iium.edu.my ,drsalmanamir82@gmail.com

ABSTRACT

We highlighted a case of an elderly man with uncontrolled diabetes experienced unbearable chronic diarrhoea for 18 months with the extent of wearing diapers daily. He was having numerous investigation to exclude causes such as malignancy and other red flags chronic diarrhoea causes. His abdominal x-ray portrays extensive abnormal gas pattern at small and large bowel but no dilatation yet other examination tests were inconclusive. His symptoms gradually resolved and achieve full recovery after discontinued Metformin. Even though, metformin was widely use, the most common cause of chronic diarrhoea among diabetic patient is still metformin until proven otherwise. Hence, the necessary precaution should be practice as extent of reaction of metformin adverse drug reaction (ADR) to gastrointestinal tract vary commonly mild to moderate and rarely severe reaction. The delay of suspicion of metformin-induced enteropathy was significantly impaired his social life, burden with unnecessary invasive investigation and hinder the management of diabetes to achieve good glycaemic control. This case emphasizes on the crucial aspect of assessing drug history and attempt drug free-interval if suspicion of adverse drug reaction.

Keywords: chronic diarrhoea, Metformin adverse drug reaction, Metformin-induced enteropathy

INTRODUCTION

Metformin is a biguanide class of drugs which becomes favourable choice of drug today due to high safety profile, comparatively cost-effective, weight neutrality, good efficacy as well as potential cardiovascular benefits [1, 8, 9]. Metformin helps in reducing fasting plasma glucose concentrations by 25-30% via hepatic glucose production by altering the mitochondrial functions and activity of AMP Activated Protein Kinase (AMPK) [2, 9]. It also helps in augmented utilization of glucose due to activation of AMPK in skeletal muscles. Metformin helps further more in increasing sensitivity towards insulin [2].

Despite being a widely used as first–line treatment drug in type 2 diabetes with desirable characteristics, nevertheless metformin intolerance associated with gastrointestinal side effects are still poorly understood. Up to 75% of people with diabetes may experience the unwanted side effects, including diarrhoea, nausea, heartburn, abdominal pain, retching and bloating sensation[3]. These could resulted in challenges to treat diabetes itself. The unwanted side effects are distressing that it caused significant decrement in patient's quality of life. Ultimately leading to sub-optimal treatment and poor adherence manifested by ones persistently poor glycaemic control and possibility of increased risk of microvascular complications of diabetes with even higher health care treatment costs due to unnecessary interventions[4]. Approximately, about 40% decrease in adherence therapy has been shown in newly diagnosed patients with type 2 diabetes whom developed GI complications[5].

Diabetic enteropathy is a diabetes complication, classically manifested by diarrhoea, constipation or faecal incontinence. It has multi factorial aetiology, in which disturbance of enteric autonomic system activity that regulates the intestinal motor activity and function may play a role[6]. Diabetic enteropathy becomes a diagnosis of exclusion after other causes have been ruled out such as hypo or hyperthyroidism, inflammatory bowel disease, coeliac disease, exocrine pancreatic insufficiency and adverse drug reaction[7]. Adverse drug reaction such as metformin represent an essential yet easily unrecognised cause of GI complications in diabetic patients.

CASE PRESENTATION

A 59-year-old man with underlying Type 2 Diabetes Mellitus for 20 years and currently on regular basal bolus insulin without oral hypoglycaemic agent. Previously, he is on basal bolus regime and his self-monitoring pre-meal blood glucose was ranged around 9.4 – 29.9 mmol/L and his HbA1c was ranging 9.5% and 17.7% biannually. Treatment approach was changed to combination therapy pre-mixed insulin with metformin because he was less compliance to four times a day insulin injection even though his insulin injection technique was correct.

Since on combination therapy, he experienced gastrointestinal disturbance but not seeking immediate medical attention. He perceived the symptoms result from usage of pre-mixed insulin hence not compliance to insulin therapy.

ISSN- 2394-5125 VOL 8, ISSUE 02, 2021

He had generalized abdominal discomfort, chronic diarrhoea and fecal incontinence. He had passing of loose and watery stool more than 8-12 times/day, no changed in stool colour, no mucus, not passing out worms or per rectal bleeding. The extent of reaction require him to wear diapers every day. He became lethargic, poor appetite and losing weight about 6 kilogram in the past 3 months. There was no alternate constipation, tenesmus, abdominal pain or distension. The examination showed he was lethargic, pink and no signs of chronic liver disease. The abdomen was soft, not tender and no abdominal mass. Per rectal examination, showed good anal tone and no anal mass. The haemoglobin was 14.5g/dL and stool for occult blood was negative. The stool samples for ova and cyst and acid fast bacilli were also negative.

To make matter worse, he refused insulin therapy despite being explained his symptoms were not related with insulin therapy and symptoms persist despite not using insulin. His serial HbA1c biannually were 15.5% and 16.6%. There was postulation of Diabetic Enteropathy causing the gastrointestinal disturbance because of his poor glycaemic control. Hence, the combination therapy was continued in attempt to resolve his symptoms by optimise glycaemic control.

After 7 months on combination therapy and chronic diarrhea still persisted, he was referred to Surgical Clinic (SOPD) general hospital to exclude Colon Cancer because in the presence of gastrointestinal symptoms and the abdominal x-ray portrays extensive abnormal gas pattern at small and large bowel but no dilatation (Figure 1). The colonoscopy revealed normal colon and Contrast Enhanced Computed Tomography (CECT) Abdomen and Pelvis reported no gross evidence of bowel-related mass. Subsequently, the patient was default follow-up for appointment of esophagogastroduodenoscopy (OGDS).

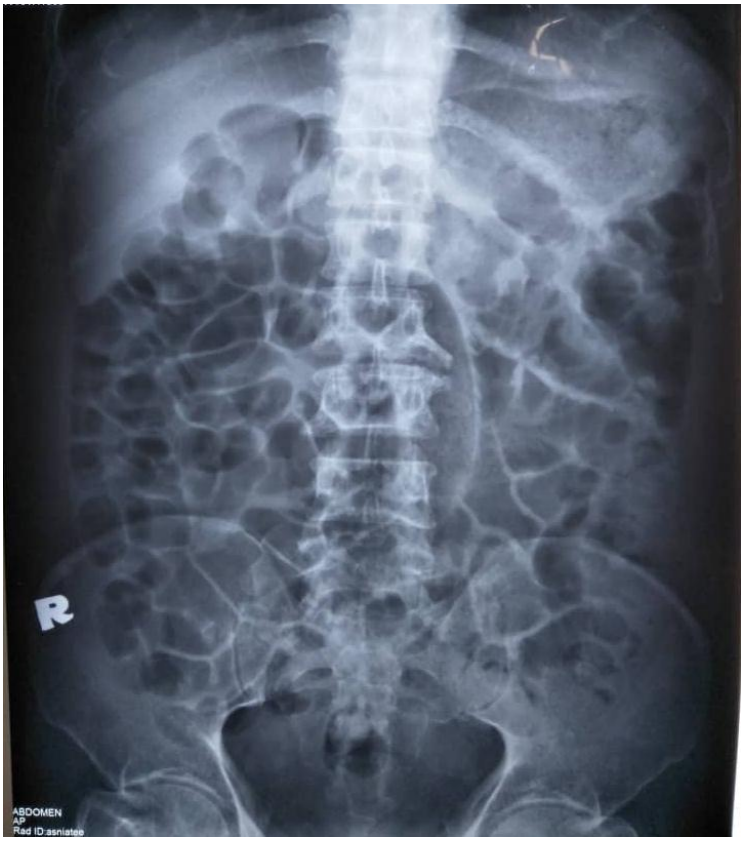

Figure 1: Extensive bowel gas pattern of small and large bowel.

3 months later after defaulted, he was referred to Gastroenterology Clinic to exclude Irritable Bowel Syndrome (IBS) as chronic diarrhoea work-up was inconclusive. T. Mebeverine 135mg TDS were given for 2 weeks showed no response but surprisingly after stopping Metformin, he eventually diapers-free. He had suffered the gastrointestinal symptoms about 18 months before the suspicion of Metformin adverse effect. The symptoms subsided within 2-3 days without further treatment and subsequently achieved full recovery. The report on Metformin adverse drug reaction was submitted to National Centre for Adverse Drug Reactions Monitoring. His latest HbA1c was 9.0% after compliance to premixed insulin and T. Saxagliptin 5mg OD without presence of Metformin.

DISCUSSIONS

Metformin is a first line drug therapy for diabetes mellitus in Malaysian clinical practice [7-9]. Gastrointestinal disturbance is the common and major side effect of metformin [1-10]. The understanding of pharmacological action of metformin is important to correlate with gastrointestinal side effect of Metformin intolerance [8-10]. Metformin key site of action was in the gastrointestinal tract mainly at small intestine [8-10]. It increases glucose uptake in the intestine and subsequently

increases lactate concentration within the enterocyte. Metformin also increases bile acid pool within the intestine, which may affect stool consistency, stimulation of the incretin hormone glucagon-like-peptide-1 (GLP-1) secretion, cholesterol level and alters the microbiome [7-9].

For some patient, Metformin may not only exert glucose-lowering effect by its pharmacodynamics effect but may cause adverse effect to small intestine with varying degree of severity [4]. The mild to moderate symptoms of gastrointestinal disturbance may be neglect by some patient or recognized by patient itself or physician. About 5% of individual cannot tolerate metformin, even at low doses [9]. These adverse effects may relate to drug accumulation in the enterocytes of the small intestine [9]. But the severe adverse reaction may be missed if we only focus on indication of treatment meanwhile not consider possible unwanted effect from medication itself. The challenge in this case was to distinguish the differential diagnosis based on the patient profile and condition. The differential list could be Diabetic Enteropathy, Colorectal Cancer or rarely Inflammatory Bowel Syndrome (IBS).

Furthermore, the abnormal finding on abdominal X-ray was misleading to think of pathological disease rather than suspicion of the metformin adverse effect. As far as concern, the radiological finding on x-ray for metformin-induced enteropathy was not yet published in any literature review. In our case, the patient had extensive bowel gas pattern of small and large bowel with no bowel dilatation. The excess bowel gas may correlate with the disruption in the bacteria normally found in the colon. An alteration in the microbiome by metformin is potential cause of gastrointestinal intolerance [8]. There is radiological finding on PET scan among patient taking metformin having diffusely increased F-FDG (non-metabolised glucose analogue) uptake in the colon and small intestine [8]. It suggest the glucose uptake and utilisation which measure the metabolic activity of the tissue. This confirms that metformin causes increased glucose uptake in the gut [8].

CONCLUSIONS

This case to provide awareness to healthcare provider the importance of adequate knowledge of medication safety profile and proper history taking to identify adverse drug reaction (ADR). The metformin-induced enteropathy is reversible condition. The drug-free interval would help exclude the differential diagnosis if reaction subsided. The ability to determine the adverse drug reaction will avoid harm to the patient.

REFERENCE

1. Madiha Fatima, Saleha Sadeeqa, Saeed Ur Rashid Nazir. Metformin and its gastrointestinal problems: A review, Biomedical Research (2018) Volume 29, Issue 11, April 17, 2018. 10.4066/biomedicalresearch.40-18-526

2. Rena G, Pearson ER, Sakamoto K. Molecular mechanism of action of metformin: old or new insights? Diabetologia 2013; 56: 1898-1906.

3. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15000 adults. Arch Intern Med. 2001;161:1989–1996. doi: 10.1001/archinte.161.16.1989.

4. McCreight LJ, Stage TB, Connelly P, Lonergan M, Nielsen F, Prehn C, Adamski J, Brøsen K, Pearson ER. Pharmacokinetics of metformin in patients with gastrointestinal intolerance. Diabetes, Obesity and Metabolism. 2018 Jul;20(7):1593-601.

5. Florez H, Luo J, Castillo-Florez S, et al. Impact of metformin-induced gastrointestinal symptoms on quality of life and adherence in patients with type 2 diabetes. Postgrad Med 2010;122:112–120pmid:20203462.

6. Chandrasekharan B, Anitha M, Blatt R, et al. Colonic motor dysfunction in human diabetes is associated with enteric neuronal loss and increased oxidative stress. Neurogastroenterol Motil. 2011; 23(2): 131–138, doi: 10.1111/j.1365-2982.2010.01611.x, indexed in Pubmed: 20939847.

7. Tomaszewska A, Mrozikiewicz-Rakowska B, Czupryniak L. Diabetic enteropathy – still undefeated?. Clinical Diabetology. 2017;6(3):105-10.

8. McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. Diabetologia. 2016 Mar 1;59(3):426-35.

9. Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. Diabetologia. 2017 Sep 1;60(9):1586-93.

10. Borg MJ, Bound M, Grivell J, Sun Z, Jones KL, Horowitz M, Rayner CK, Wu T. Comparative effects of proximal and distal small intestinal administration of metformin on plasma glucose and glucagon-like peptide-1, and gastric emptying after oral glucose, in type 2 diabetes. Diabetes, Obesity and Metabolism. 2019 Mar;21(3):640-7.