Multiple Sclerosis and Related Disorders 21 (2018) 42–45

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Case report

Dimethyl fumarate in a patient with multiple sclerosis and type 1 diabetes mellitus: The importance of ketonuria

Ewa Krzystanek[a,*], Przemyslawa Jarosz-Chobot[b]

[a] Department of Neurology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland
[b] Department of Children's Diabetology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Poland

ARTICLE INFO

Keywords:
Dimethyl fumarate
Diabetes mellitus
Multiple sclerosis
Ketonuria
Adverse reaction

ABSTRACT

Background: Dimethyl fumarate (DMF) is approved for use in patients with relapsing-remitting multiple sclerosis (MS). Its mechanism of action is still not well understood, but besides the immunological pathways in MS, it may also affect the metabolism of normally functioning internal organs, tissues and cells.

Case presentation: We report on the case of 29-year-old woman with satisfactorily-controlled type 1 diabetes (T1D), who was diagnosed as having MS. After administration of DMF she experienced intense, adverse gastro-intestinal reactions together with ketonuria up to 160 mg/dL. The highest ketone concentrations in the urine were observed approximately 2 h after each DMF dose and always with co-existing adverse reactions. Dose reduction did not improve symptoms and treatment had to be stopped. Twelve hours after the last dose of DMF all laboratory results returned to normal ranges and all gastro-intestinal adverse reactions were resolved within the following 24 h.

Conclusion: This is a first report of ketonuria in a MS-patient with T1D treated with DMF. Patients with MS and co-existing metabolic diseases, which are not contraindicated for DMF treatment, represent a unique opportunity to address questions regarding the possible mechanisms of action of DMF on the cellular metabolism. The use of DMF in patients with metabolic diseases needs closer attention.

1. Background

Dimethyl fumarate is approved in the United States and in Europe for use in patients with relapsing-remitting multiple sclerosis (MS). It acts via the activation of the nuclear factor (erythroid-derived 2), related factor 2 (Nrf2) response pathway, the primary cellular defense against the cytotoxic effects of oxidative stress (Linker et al., 2011). Such a model of action, however unique among other drugs for MS, is unspecific for MS pathology, because it affects not only cells related to immunological processes in MS, but also numerous normally functioning body cells and tissues. One of the affected physiological pathways may be the oxidation of fatty acids, mainly carried out in the mitochondria of hepatocytes, which leads to production of so-called ketone bodies (e.g. hydroxybutyrate, acetoacetate and acetone).

Although different adverse reactions (AR) had been reported after administration of DMF, such as flushing, gastrointestinal (GI) complications, pruritis, rash or erythema, the reason of their occurrence is still not clearly determined. After several cases of liver injury in patients treated with the DMF that were reported in the postmarketing setting, the prescribing information for the DMF has been updated recently to include a warning of potential liver injury. One of the initial symptoms of severe metabolic imbalance in patients taking DMF may be the presence of ketone bodies in the blood or in the urine. According to European labelling, ketonuria may be detected in up to 45% of patients taking DMF (EMEA, 2017; FDA, 2013), however, the data from the clinical trials are not conclusive in the matter of the clinical importance of such findings (Fox et al., 2012; Gold et al., 2012), and there is still lack of any postmarketing, real-world observations.

Routine laboratory testing during DMF treatment is usually carried out on a monthly-basis, rather than daily or hourly. Therefore, important metabolic fluctuations after each DMF dose may be overlooked in routine clinical practice. Patients with other co-existing metabolic diseases, which are not contraindicated for DMF treatment, represent a unique opportunity to address questions regarding possible mechanisms of action of DMF on the cellular metabolism. About 0.85% of MS patients suffer from type 1 diabetes mellitus (T1D) (Langer-Gould et al., 2010). Both of these diseases belong to the autoimmunological spectrum and share several similarities in immunological and epidemiological features (Tettey et al., 2015). At present, there is no clear recommendation on how to treat a patient with MS and T1D (Comi et al.,

* Corresponding author.
E-mail address: ewa26@mp.pl (E. Krzystanek).

https://doi.org/10.1016/j.msard.2018.02.007
Received 22 August 2017; Received in revised form 20 January 2018; Accepted 5 February 2018

2017). Considering ketoacidosis as a possible life-threatening condition in patients with T1D, administration of DMF for the treatment of MS in such a specific population of patients requires closer attention regarding clinical relevance of post-DMF ketonuria.

2. Case presentation

A 29-year-old female patient, who has suffered from T1D for 20 years, was diagnosed with MS according to McDonald's 2010 criteria (1 relapse, many T2-hyperintense and T1-gadolinium enhancing lesions in the first brain MRI, EDSS 3.5). The patient was treated with multiple insulin doses (MDI) injected subcutaneously: Apidra SoloStar (Sanofi-Aventis, Germany) 8U three times a day as meal boluses and Lantus SoloStar (Sanofi-Aventis, Germany) 18U once daily in the evening (basal insulin). The dosing of insulin was additionally adjusted ad hoc according to the actual level of capillary blood glucose, determined on each measurement with electronic personal glucose meter performed directly before each meal (GlucoSense Pro, Genexo, Poland) and only when the level was over 200 mg/dL. Her glycated hemoglobin HbA1c was 8.3%. The patient regularly monitored the level of glucose and ketone bodies in her urine with a semi-quantitative visual strip test (Keto-Diastix, Bayer Diagnostics, Ireland), usually 4–6 times a day, and registered them in the self-control diary, along with the levels of glycaemia. The levels of glycaemia, glycosuria and ketonuria and major ARs registered on the selected days during treatment with DMF are presented in the Table 1

She started DMF with a titration dose (120 mg BID) within the first week, followed by a dose of 240 mg BID. She took the drug always with meals – breakfast and dinner, as indicated in the patient's information leaflet. She ate meals regularly: breakfast at 9:00 a.m., lunch between 2:00–4:00 p.m., dinner about 7:30 p.m., and administered insulin precisely right before each meal. At the beginning of the first week she experienced nausea, vomiting, abdominal pain and diarrhea (12 stools per day), which decreased within a few days. After dose escalation, the symptoms intensified again, especially in the second and third week, with nausea, malaise, permanent generalized weakness, loss of appetite, vomiting and abdominal pain. After 35 days the dose was decreased to 240 mg once daily in the evening, to minimize ARs appearing during the day. During DMF treatment, the level of urine ketones ranged from 5 mg/dL to 160 mg/dL, mostly without glycosuria, with the highest ketone concentrations around 2 h after each DMF dose and always with co-existing GI ARs. She drank approximately 2.5 L of water daily and her body weight was stable. Her insulin requirements remained stable at a level of 0.7 U/kg of body weight, just as they were before initiating DMF therapy.

Because of persisting ARs and ketonuria, DMF was discontinued 41 days after the first dose administration. Twelve hours after the last dose of DMF all laboratory results returned to normal ranges and all GI adverse symptoms were resolved within the following 24 h. After 10 days of observation, interferon beta-1a intramusculary was started without any AR. During the following 8 months of observation there was no ketonuria detected at any day.

As GI disorders are quite frequent upon DMF initiation and in most cases gradually resolve within time, no specific evaluation of the ARs was performed. Our patient was not febrile at any time and did not travel during the period of treatment with DMF. Arterial blood gasometry or stool studies were not performed and a full chemistry panel, along with complete blood count and urinalysis was performed just before the reduction of DMF dose to 120 mg once daily. All results of this test were within normal limits.

3. Discussion

The oral drug seemed to be the best option for our MS patient with T1D, because she had to administer numerous insulin injections each day. Moreover, diabetes mellitus is not contraindicated for DMF treatment. The explanation of ARs and ketonuria in relation to abnormal glucose metabolism in our patient was difficult, because there was no pattern or consistency between the observed parameters, where ketonuria was present for many hours each day, but only a few times with coexisting hyperglycemia and very rarely with glycosuria during 43 days of therapy. Since ketone bodies are often detected during prolonged fasting, alcohol abuse, hypoglycemia and hyperglycemia (> 300 mg/dL), we initially suspected fasting caused by nausea and abdominal pain. However, our patient was very cooperative and, despite ARs, ate, drank approximately 2.5 L of water per day and administered insulin regularly, thus we assumed this reason to be less likely. In the setting of vomiting, the patient may have still had inadequate carbohydrate intake despite regular food intake, leading to ketonuria, but vomiting was very sporadic, with nausea and abdominal pain as main ARs. The only significant association observed was coincidence between ketonuria and DMF administration, therefore in our opinion, the main reason for ketonuria was DMF intake.

Orally administered DMF undergoes rapid presystemic hydrolysis by esterases and is converted into its primary metabolite, monomethyl fumarate (MMF), which is also active. Dimethyl fumarate is not quantifiable in plasma, thus all pharmacokinetic analyses related to DMF were performed with plasma MMF concentrations. The T_{max} of MMF is 2–2.5 h. In our patient, the highest level of urine ketones was observed up to 2 h post DMF intake. Moreover, the patient complained the most of nausea, malaise and abdominal pain about 1.5–3 h after DMT intake, therefore, we hypothesize that GI symptoms could be related to high level of ketones.

Clinical symptoms of elevated level of ketones in the blood may be a specific smell of urine, nausea, vomiting, diarrhea, abdominal pain, polyuria or thirst and dry mouth. It should be especially alarming for a clinician in the case of a diabetic patient, because of possible life-threatening condition known as diabetic ketoacidosis (Grabacka et al., 2016). In our patient external insulin was fully available and regularly used in MDI model, with individual doses adjusted according to every measurement of glycaemia, therefore ketoacidosis was much less likely. Additionally, no other clinical or laboratory symptoms of ketoacidosis were observed.

The mechanism of ketonuria in patients with MS taking DMF is not clear and clinical data regarding its use in patients with diabetes mellitus is lacking. Results of experimental studies suggest, that Nrf2-pathway modulation may also interfere with diabetes mellitus. It has vasodilatory properties (Lu et al., 2017) and may limit diabetes-associated vascular injury (Sharma et al., 2017). It may also prevent mitochondrial damage to inhibit the development or progression of diabetic retinopathy (Kowluru and Mishra, 2017) and may protect against acute oxidative stress-induced pancreatic ß-cell damage (Fu et al., 2015). On the other hand, in the developing tubular cells it may induce nephrogenic diabetes insipidus (Suzuki et al., 2017) and interfere with the inhibition of renal Nrf2 (in rat renal proximal tubular cells) and angiotensinogen gene expression regulated by insulin (Ghosh et al., 2017). As we did not observe any additional serious accompanying disorders or deviations from the normal state, and after discontinuation of DMF ketonuria was not observed, we suspect that Nrf2-pathway modulation could be the reason of ketonuria in our patient with MS and T1D.

4. Conclusions

The oral drug seemed to be the best option for our MS patient with T1D, because of necessity of numerous insulin injections. Unfortunately, the drug's not well understood mechanism of action resulted in metabolic dysregulation in this well-controlled diabetic patient. In our opinion, DMF should not be recommended in patients with MS and T1D until the effects of the drug on metabolic pathways is better understood. Further investigations are necessary regarding the causes of ketonuria in patients with MS treated with DMF. The question

Table 1
The levels of glucose in the blood, ketone bodies and glucose in the urine and major adverse reactions registered on the selected days during DMF treatment in the self-control diary of a 29-years-old female patient with MS and type 1 diabetes mellitus.

DMF dose	Day of treatment	Time of a day	Breakfast	+2 hours	Lunch	+2 hours	Dinner	
		Parameter	9:00 a.m.	11:00 a.m.	2:00–4:00 p.m.	4:00–6:00 p.m.	7:30 p.m.	10:00 p.m.
120 mg BID (breakfast, dinner)	**3**	**Glycaemia**	182	178	111		136	151
		Ketonuria		80		5		
		Glycosuria		0		0		
		ARs				Flushing		
	5	**Glycaemia**	234	254	256		180	60
		Ketonuria		80		80		
		Glycosuria		0		0		
		ARs		bloating				
	7	**Glycaemia**	397	319	161		69	157
		Ketonuria	160					
		Glycosuria	1000					
		ARs	vomiting					
240 mg BID (breakfast, dinner)	**10**	**Glycaemia**	150	110	123		161	128
		Ketonuria		160		80	5	
		Glycosuria		0		0	0	
		ARs	Nausea when fasting, abdominal pain till evening					
	11	**Glycaemia**	295	119	126		134	183
		Ketonuria		40		5		
		Glycosuria		0		0		
		ARs	Bloating, belching					
	12	**Glycaemia**	274	151	142		136	155
		Ketonuria		40				
		Glycosuria		0				
		ARs	Bloating, belching					
	13	**Glycaemia**	198	116	136		98	73
		Ketonuria	160			5		
		Glycosuria	0			0		
		ARs	Bloating, belching					
	16	**Glycaemia**	209	136	141		139	164
		Ketonuria		80		80		
		Glycosuria		0		0		
		ARs		Severe abdominal pain, nausea, vomiting				
	21	**Glycaemia**	107	158	173	57	148	
		Ketonuria	160			15		
		Glycosuria	0			0		
		ARs	Abdominal pain, nausea					
	26	**Glycaemia**	119	83	302	132	56	164
		Ketonuria	160	80	160			80
		Glycosuria	0	0	0			0
		ARs	Severe nausea		vomiting			
	27	**Glycaemia**	174	335	124	52	149	156
		Ketonuria	80	160	80	5	15	
		Glycosuria	0	0	0	0	0	
		ARs	Nausea, abdominal pain all day					
	28	**Glycaemia**	231	170	107	59	110	162
		Ketonuria	160	160	5	5		
		Glycosuria	100	100	0	0		
		ARs	Nausea, loss of appetite		malaise			
	29	**Glycaemia**	271	103	105	180	163	
		Ketonuria	80	160	15	5		
		Glycosuria	0	0	0	0		
		ARs	loss of appetite, nausea, sleepiness all day					
	30	**Glycaemia**	159	213	114	84	148	152
		Ketonuria	80	160	40	5		
		Glycosuria	0	0	0	0		
		ARs	Nausea, heartburn most of the day					
	33	**Glycaemia**	118	108	137	149	303	
		Ketonuria	80	15	5	160	160	
		Glycosuria	0	0	0	0	0	
		ARs				Nausea and vomiting		
	34	**Glycaemia**	201	172	170	104	133	86
		Ketonuria	160	160	80	15	80	15
		Glycosuria	0	0	0	0	0	0
		ARs	Nausea, abdominal pain					
	35	**Glycaemia**	164	157	175	87	147	166
		Ketonuria	80	80	80	40	40	40
		Glycosuria	0	0	0	0	0	0
		ARs	Nausea all day, fatigue					

(*continued on next page*)

Table 1 (*continued*)

DMF dose	Day of treatment	Time of a day Parameter	Breakfast 9:00 a.m.	+2 hours 11:00 a.m.	Lunch 2:00–4:00 p.m.	+2 hours 4:00–6:00 p.m.	Dinner 7:30 p.m.	10:00 p.m.
240 mg OD (dinner)	**36**	**Glycaemia**	177		168	123	128	171
		Ketonuria	15		5	0	5	5
		Glycosuria	0		0	0	0	0
		ARs						
	39	**Glycaemia**	231	187	176		142	163
		Ketonuria	80	80	80		80	40
		Glycosuria	0	0	0		0	0
		ARs	Nausea					
	42	**Glycaemia**	184	148	185	68	166	185
		Ketonuria	80	5	0	5	5	0
		Glycosuria	0	0	0	0	0	0
		ARs	Nausea, abdominal pain					
	43	**Glycaemia**	210	196	156		148	159
		Ketonuria	40	80	0	15	5	0
		Glycosuria	0	0	0	0	0	0
		ARs	Headaches					
No drug	**44**	**Glycaemia**	99	179	164		111	110
		Ketonuria	5		40		0	5
		Glycosuria	0		0		0	0
		ARs						

Note: All values are given in mg/dL. Glycaemia was assessed in the capillary blood with electronic personal glucose meter, ketone bodies and glucose levels in the urine were assessed with semi-quantitative visual strip test. DMF tablets were taken always with meals – breakfast and dinner, when twice daily (BID) and with dinner, when once daily (OD). ARs – adverse reactions, DMF – dimethyl fumarate.

of how does DMF stimulate the ketogenesis is still open.

Acknowledgements

We would like to thank our patient, whose co-operation and meticulousness allowed us to draw attention to such an important problem.

Consent

Written informed consent was obtained from the patient for the publication of this case report.

Conflicts of interest

E Krzystanek received travel support and/or compensation for lectures and/or participation in advisory boards from Biogen, Genzyme, Merck Serono, Novartis, Roche, and Teva, which have been exclusively used for the support of research activities.

P Jarosz-Chobot does not report any conflicts of interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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