OPIS PRZYPADKU

Rhabdomyolysis induced by lipid-lowering therapy in patients with end-stage renal failure maintained on continuous ambulatory peritoneal dialysis – clinical implications

Rabdomioliza indukowana lekami hipolipemizującymi u chorych z terminalną niewydolnością nerek leczonych ciągłą ambulatoryjną dializą otrzewnową – wnioski kliniczne

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ABSTRACT

The cases of rhabdomyolysis induced by lipid-lowering therapy in three patients with end-stage renal failure undergoing continuous ambulatory peritoneal dialysis (CAPD) are presented. In most of the cases, the diagnosis of rhabdomyolysis was not problematic regarding their typical clinical symptoms and laboratory examinations. One patient, presumably due to diabetic neuropathy, did not experience typical muscle pain but only asthenia, abdominal pain and an enhanced serum kinase creatine level. Lipid-lowering drug cessation and intensification of the CAPD scheme were effective in all the cases. In certain cases LDL-apheresis was required. The high frequency of lipid disturbances and an enhanced cardio-vascular risk among CADO patients are reasons for the wide-spread use of lipid-lowering agents in this group of patients. Analysis of potential drug interactions, and diagnostic alertness (with watchful observation of atypical symptoms) are required because of the possibility of rhabdomyolysis occurrence as a side effect of this method. Interruption of lipid-lowering therapy with intensification of the peritoneal dialysis scheme are sufficiently effective treatment of iatrogenic rhabdomyolysis among CAPD patients. Persistent hyperlipidaemia with an individual's predisposition to myolysis after different lipid-lowering agents remain a therapeutic problem.

KEY WORDS
rhabdomyolysis, lipid-lowering therapy, side effects, end-stage renal failure, continuous ambulatory peritoneal dialysis

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STRESZCZENIE

Praca przedstawia przebieg rabdomiolizy wywołanej stosowaniem farmakoterapii hipolipemizującej u trzech chorych ze schyłkową niewydolnością nerek, leczonych nerkozastępczo metodą ciągłej ambulatoryjnej dializy otrzewnowej (CADO). Dwóch chorych prezentowało klasyczne objawy kliniczne rabdomiolizy, co w połączeniu z wynikami badań laboratoryjnych stanowiło oczywistą podstawę rozpoznania. W przypadku trzeciego chorego, prawdopodobnie w efekcie współistniejącej neuropatii cukrzycowej, nie występowały typowe bóle mięśniowe, a jedynie osłabienie mięśni, bóle brzucha i podwyższony poziom kinazy kreatynowej w surowicy. U wszystkich chorych uzyskano poprawę w wyniku odstawienia leku hipolipemizującego i intensyfikacji schematu dializy otrzewnowej. W wybranych przypadkach w dalszej obserwacji konieczne było zastosowanie LDL-aferezy.

Duża częstość występowania zaburzeń lipidowych oraz zwiększone ryzyko schorzeń sercowo-naczyniowych wśród chorych leczonych nerkozastępczo są powodem szerokiego stosowania leków hipolipemizujących w tej grupie osób. Możliwość wystąpienia rabdomiolizy jako powikłania takiego leczenia wymaga od lekarza analizy potencjalnych interakcji lekowych oraz czujności diagnostycznej, w tym bacznej obserwacji atypowej symptomatologii.

Przerwanie leczenia hipolipemizującego oraz intensyfikacja dializy otrzewnowej są wystarczająco efektywnym sposobem leczenia jatrogennej rabdomiolizy u chorych CADO. Problemem terapeutycznym nadal pozostaje utrzymująca się hiperlipidemia, przy równoczesnej osobniczej skłonności do występowania miolizy po różnych preparatach z grupy leków hipolipemizujących.

SŁOWA KLUCZOWE

rabdomioliza, terapia hipolipemizująca, objawy uboczne, terminalna niewydolność nerek, ciągła ambulatoryjna dializa otrzewnowa

INTRODUCTION

Disturbances in lipid metabolism belong to the most common facets of chronic renal disease [1]. Therefore lipid reduction treatment is one of the most essential therapeutic approaches in patients with end-stage renal disease (ESRD) [2,3]. Despite numerous clinical benefits, pharmacological lipid-lowering management is associated with a certain risk of rhabdomyolysis – a life-threatening complication developed mainly after hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors [4]. Remaining on other drugs such as warfarin, cyclosporin, erythromycin, a dihydropyridine derivative or gemfibrozil creates a potential risk of rhabdomyolysis [5,6,7]. In patients with chronic renal failure in whom impaired renal function is accompanied by functional disturbances of other organs, both clinical manifestations, and consequences of rhabdomyolysis may be particularly serious. Although Navaneethans' review from 2009 (Cochran Database) showed the safety of statins in this high-risk population and a similar occurrence of rhabdomyolysis and elevated liver function tests with statins in comparison to a placebo [8], the clinical aspects of rhabdomyolysis in patients treated with continuous ambulatory peritoneal dialysis (CAPD) are largely unknown.

Herein we report 3 cases of rhabdomyolysis after different classes of lipid-lowering drugs in patients with chronic renal failure remaining on continuous ambulatory peritoneal dialysis. See Table I for the patients' data on admission and on discharge.

CASE 1

49-year old male with hypertensive nephropathy, several cardiovascular risk factors including: obesity (BMI – 34 kg/m^2), diabetes as well as a history of myocardial infarction and stroke, treated with CAPD was eligible for lipid-lowering treatment because of significant mixed hyperlipidaemia (total cholesterol serum level – 7.6 mmol/l, tryglicerides serum levels – 11.1 mmol/l) resistant to nonpharma-

cological management. Combined treatment with simvastatin (20 mg daily) and acipimox (500 mg daily) was initiated. Three weeks later, the patient complaining of severe pain in the lower limbs and lumbar regions, nausea, as well as vomiting, was admitted to the local clinic. General tenderness to palpation was the only new symptom revealed by clinical examination. In light of anamnestic and clinical data, iatrogenic rhabdomyolysis was the preliminary diagnosis, which was then confirmed by laboratory investigations (creatine kinase serum level – 12 790 U/l). Stopping the lipid-lowering treatment together with intensification of CAPD (increased to 12.5 liters daily volume of glucose dialysis solution) and small doses of analgesic drugs (selective cyclooxygenase inhibitor – rofecoxibe) resulted in regression of the symptoms and significant clinical improvement. After one week of hospitalisation, the creatine kinase serum concentration decreased to 560 U/l.

Considering the high lipid serum levels after 3 months of regular ambulatory monitoring, a new attempt at lipid-lowering therapy was taken (phenofibrate – 200 mg daily). After 10 days of this treatment the patient was admitted to the clinic with diffuse, general myalgia and severe hypotension (systolic blood pressure – below 100 mmHg). The patient's history, clinical manifestation and laboratory examinations (creatine kinase serum level – 13 570.3 U/l) indicated rhabdomyolysis. The interventions were similar to the management during previous hospitalisation and resulted in clinical improvement. Considering the implications of persistently high lipid levels, lack of effect of nonpharmacological management together with potential hazards of further lipid-lowering agents, LDL-apheresis was launched. There were no adverse effects after 2 sessions of LDL-apheresis. The patient was discharged from the clinic after 11 days of hospitalisation and was monitored in the ambulatory clinic.

CASE 2

46-year old male with hypertension, ischaemic heart disease, 20-year history of type 1 diabetes and end-stage renal failure due to diabetic nephropathy has been treated with continuous ambulatory peritoneal dialysis for 3 years. Despite nonpharmacological lipid-lowering management, his cholesterol serum concentration tended to increase and reached the level at which pharmacological therapy was absolutely required (cholesterol serum level – 7.13 mmol/l). His triglycerides serum level was 0.58 mmol/l. In light of this, treatment with simvastatin (20 mg daily) was started. After 13 days of this management, a high creatine kinase serum level (7 350 U/l) was revealed during a routine ambulatory appointment. Apart from non-specific general weakness, no major symptoms were reported. Clinical evaluation did not contribute to the diagnosis. In light of the anamnestic data and laboratory results, rhabdomyolysis was diagnosed. Cessation of pharmacological treatment with simvastatin and intensification of CAPD (increased number and volume of exchanges) led to significant clinical improvement and a decrease in the creatine kinase serum concentration (238 U/l). The patient was discharged from the clinic after 7 days of hospitalisation. Since then he has been monitored regularly in the outpatient clinic. His cholesterol serum concentration decreased to 6.2 mmol/l on a restricted dietary regime.

CASE 3

55-year old hypertensive, obese, diabetic female with ischaemic heart disease and chronic renal had been successfully treated with CAPD for eleven months. Hypercholesterolemia, apparent prior to the onset of CAPD (cholesterol serum level – 6.19 mmol/l), tended to increase during renal replacement therapy, reaching the level of 8.25 mmol/l. At the same time, the triglycerides serum concentration was 3.84 mmol/l. Pharmacological treatment with fenofibrate (200 mg daily) was initiated. 12 days later the patient was admitted to the local clinic with asthenia and abdominal pain. No significant abnormalities were revealed during clinical evaluation. Routine laboratory analyses indicated a high creatine kinase serum level (11 300 U/l). In the light of these data, after the exclusion of other potential reasons leading to the increase in the creatine kinase serum concentration, rhabdomyolysis was revealed with subsequent fenofibrate cessation and intensification of CAPD (increased frequency and dwell volume). After 10 days of hospitalisation the creatine kinase serum concentration was 215 U/l and clinical improvement was evident. As the cholesterol serum concentration still exceeded the accepted levels (10.75 mmol/l), LDL-apheresis was initiated, and after three sessions no significant adverse symptoms were noticed.

Table I. Clinical and laboratory data on admission (A) and on discharge (D)
Tabela I. Dane kliniczne i laboratoryjne chorych przy przyjęciu na oddział oraz przy wypisie

	Case 1/I		Case 1/II		Case 2		Case 3	
Age (yrs.)	49		49		46		55	
Gender (M/F)	M		M		M		F	
Parameters	A	D	A	D	A	D	A	D
SBP/DBP (mmHg)	140/80	140/90	90/50	110/80	140/90	150/90	160/110	170/105
Serum cholesterol (mmol/l)	6.78	5.89	7.85	6.56	6.23	7.69	6.22	10.75
Serum tryglicerides (mmol/l)	4.06	4.92	7.4	4.91	0.9	1.76	3.84	2.68
Serum creatinine (μmol/l)	1292.4	1240.0	892.6	912.11	565.8	622.0	688.6	826.3
Serum BUN (mmol/l)	22.17	14.69	14.06	15.38	28.17	22.72	19.0	18.82
Serum potassium (mmol/l)	4.6	4.49	5.1	5.11	5.7	4.97	4.8	5.26
Serum natrium (mmol/l)	146.0	134.0	140.0	143.0	137.0	138.0	140.0	149.0
Serum bicarbonates (mmol/l)	19.5	23.0	19.5	23.5	25.3	25.8	22.5	23.1
Serum hemoglobin (mmol/l)	5.83	6.45	6.83	5.15	7.45	7.45	5.65	6.08
Serum creatine kinase (U/L)	12790.0	93.6	13570.3	129.7	7350.0	153.4	11300.0	128.9

Abbreviations:
Case 1/I – first admission; Case 1/II – second admission; M – male; F – female; A – results on admission D – results on discharge; BUN – blood urea nitrogen

DISCUSSION

All three cases presented above reflect a typical clinical profile of uraemic patients developing rhabdomyolysis after lipid-lowering treatment. Insufficient renal function, numerous coexisting diseases, multiple drug regimes seem to create the potential risk of rhabdomyolysis in this group of patients. This complication may occur not only after HMG-CoA reductase inhibitors but also following acipimox as well as fibric acid derivatives [9]. Clinical manifestation is usually apparent within the first few weeks after the onset of lipid-lowering treatment. In most of the cases, the diagnosis was not problematic regarding the typical clinical symptoms associated with a spectrum of skeletal muscle complaints and laboratory examinations. However, it should be noted that some patients (particularly those with advanced diabetic nephropathy) might not experience typical muscle pain [10]. None of the presented cases was fatal, although the risk of death related to rhabdomyolysis is significant [4]. Management including lipid-lowering drug cessation, intensification of CAPD and analgesic drugs seems to be safe and effective. Nevertheless, use of the latter should be extremely careful in light of their ability to induce anuria in patients with chronic renal failure [11]. In the presence of pain, selective inhibitors of cyclooxygenase seem to be a preferable option in patients with chronic renal failure in whom the renal production of prostanoids is *a priori* impaired [11]. The intensification of CAPD may be particularly important in order to control electrolyte disturbances and limit the exposure to myoglobin, which deteriorates the remaining renal function [12]. Although recent hopeful data concerning eicosapentaenoic acid and vitamin D suggest new potential therapeutic ways to prevent iatrogenic rhabdomyolysis, there are no sufficient ways to exclude this potential side-effect among CKD patients [13,14,15].

Considering the risk of rhabdomyolysis after lipid-lowering agents in hypercholesterolemic, uraemic patients in whom it was previously detected, LDL-apheresis is a promising therapeutic option. Significant reduction of atherogenic factors, a decrease in LDL-oxidation, improvement of endothelial function, together with good tolerability have been reported in hypercholesterolaemic patients treated with LDL-apheresis [16,17]. Since data regarding its safety and effectiveness in patients with chronic renal failure are limited, more evidence for its use in this group of patients is required.

Nevertheless, efforts to improve adherence to nonpharmacological lipid-lowering management should be always undertaken in the light of several beneficial effects not only on lipid metabolism.

CONCLUSIONS

1. As the aetiology of a post lipid-lowering agent's myopathy is multifactorial, it is important to evaluate the patient's clinical status with particular emphasis on comorbidities and pharmacological regiment.
2. The diagnostic alertness for iatrogenic rhabdomyolysis particularly among patients administered higher lipid-lowering drug doses or polypharmacy are required.
3. The interruption of lipid-lowering therapy with intensification of the peritoneal dialysis scheme are sufficiently effective treatment of iatrogenic rhabdomyolysis among CAPD patients.
4. Persistent hyperlipidaemia with an individual's predisposition to myolysis after different lipid-lowering agents still remains an unresolved therapeutic problem.

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