RARE SIDE-EFFECTS OF FENOFIBRATE

R. RABASA-LHORET, M. RASAMISOA, A. AVIGNON, L. MONNIER

SUMMARY - Fibrates are widely prescribed as hypolipidemic drugs and are considered as safe. We report the case of a 69 year-old woman who probably developed a major allergic reaction following a Fenofibrate prescription (generic form) of 300 mg per day. Clinical features included asthenia, hyperthermia (40.5°C) and slight muscular pain. Biological abnormalities were mildly elevated muscular enzymes and pancytopenia rapidly developed. All bacteriologic, virologic, immune and radiologic investigations were normal. Evolution was spontaneously favorable with Fenofibrate withdrawal. This is the first reported case of major fever and pancytopenia following a Fenofibrate prescription. Adverse effects of Fenofibrate are briefly reviewed and their usual favorable outcomes following drug removal are outlined.

Key-words: fenofibrate, adverse effects, pancytopenia, fever.

RE´ SUME´ - Effets secondaires rares avec le Fénofibrate. Parmi les traitements hypolipidémiants les fibrates sont largement prescrits et considérés comme sûrs. Nous rapportons l’observation d’une femme de 69 ans qui dans les suites de la prescription de 300 mg/j d’une forme générique du Fénofibrate a probablement développé une réaction allergique majeure. Le tableau clinique associe une altération de l’état général, une hyperthermie (40,5 °C) et des myalgies. Biologiquement on retrouve une myolyse modérée et rapidement la patiente développe une pancytopenie. L’ensemble des investigations bactériologiques, virologiques, immunologiques et radiologiques est resté négatif. L’évolution a été spontanément favorable à l’arrêt du traitement. Il s’agit du premier cas d’hyperthermie majeure avec pancytopenie rapporté lors de l’utilisation du Fénofibrate. Les effets secondaires des fibrates sont présentés de même que leur évolution le plus souvent favorable à l’arrêt du traitement.

Mots-clés : fénofibrate, effets secondaires, pancytopenie, fièvre.

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Dietary failure to normalize dyslipidemia usually results in pharmacological interventions. The choice of medication should be based on efficacy, safety (adverse effects and drug interactions) and absence of contraindications. Two classes of lipid-lowering drugs are widely used: HMG-CoA reductase inhibitors and fibrates. HMG-CoA reductase inhibitors are potent hypocholesterolemic drugs. However fibrates are recommended in patients exhibiting high triglycerides levels and/or low HDL cholesterol [1-3]. Although fibrates are considered as safe, we report one case with major side-effects that could be related to Fenofibrate treatment [4].

A sedentary 69 year-old woman with familial history of premature cardiovascular disease underwent a cholecystectomy ten years ago. At the same time a dyslipidemia was diagnosed and smoking intoxication was stopped. In March 2000 a Fenofibrate treatment (300 mg/d, generic form) was initiated because of a persisting type IV hyperlipidemia despite well-conducted dietary measures (Total-Cholesterol: 2.26 g/l; Triglycerides: 3.56 g/l; HDL-cholesterol: 0.30 g/l). Treatment was started while patient was taking no other medication. No travel abroad was reported since years. Pre-treatment laboratory values included routine haematology, inflammatory and hepatic investigations that all were normal. Ten days after treatment onset, dizziness, asthenia and hyperthermia appeared and the patient was referred to emergency ward. Major hyperthermia (40.5°C), tachycardia (120/min) and slight muscular pain were noted. Biochemistry showed a moderate transaminase increase at two-fold upper limit of normal (ULN), moderately elevated creatine phosphokinase (CPK) (1.5 ULN) and lactico dehydrogenase (3 ULN) (Table I). Haematology revealed moderate thrombocytopenia (121.000/mm³; N > 150.000), normal fibrinogen and elevated C-reactive protein (CRP: 38 mg/l; N < 5). Evolution showed persistent hyperthermia for 5 days, majoration of myolysis with increase of CPK up to 8-fold ULN, majoration of transaminases up to 5-fold ULN and CRP (maximum: 102 mg/l) abnormalities. Pancytopenia rapidly appeared with anaemia (haemoglobin 10.4 g/dl; N > 12), leucopenia (1400/mm³ with 71% neutrophiles) and thrombocytopenia (72.000/mm³) (Table I). Large bacteriologic, virologic and immune investigations were all normal. Abdomino-renal echography and electromyography revealed no abnormalities. Therapeutic attitude consisted in removal of Fenofibrate and symptomatic treatment (hydration). Evolution was spontaneously favorable with normalization of all clinical and biological abnormalities within 15 days.

When hypercholesterolemia is not the major lipid abnormality, fibrates are widely prescribed [1, 2, 4, 5]. Tolerance is usually good, with most side-effects being transient or reversible [4, 6-8]. The most common side-effects are gastrointestinal problems (abdominal discomfort, diarrhea and constipation) and occur in approximately 5% of patients. Reports including asthenia, headache, loss of libido, impotence, dizziness and insomnia are observed in 3 to 4% of treated-patients. In approximately 1% of patients, muscle tenderness developed and was often accompanied by elevated CPK. Myolysis cases have been reported during fibrate treatment and could be more frequent during fibrate-HMG-CoA reductase association [1]. In approximately 2% of patients, a skin rash can appear. Liver changes include increase in incidence of elevated transaminases usually transient with isolated cases of hepatitis [4, 8]. There have been two reports

<table>
<thead>
<tr>
<th>Dates</th>
<th>D-10</th>
<th>D 0</th>
<th>D 1</th>
<th>D 2</th>
<th>D 3</th>
<th>D 5</th>
<th>D 7</th>
<th>D 10</th>
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<tr>
<td>T° (°C)</td>
<td>40.5</td>
<td>38.9</td>
<td>39.3</td>
<td>37.8</td>
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<td>37.2</td>
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<td>Hb(g/100ml)</td>
<td>14.0</td>
<td>12.7</td>
<td>12.5</td>
<td>12.0</td>
<td>11.1</td>
<td>10.4</td>
<td>12.1</td>
<td>12.3</td>
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<tr>
<td>White cells (/mm³)</td>
<td>8100</td>
<td>4400</td>
<td>4000</td>
<td>1600</td>
<td>1400</td>
<td>2900</td>
<td>5800</td>
<td>6800</td>
<td>7800</td>
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<tr>
<td>Neutrophiles (/mm³)</td>
<td>6300</td>
<td>3460</td>
<td>1280</td>
<td>994</td>
<td>1635</td>
<td>2800</td>
<td>1381</td>
<td>774</td>
<td>5000</td>
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<td>Platelets (x1000/mm³)</td>
<td>271</td>
<td>121</td>
<td>94</td>
<td>72</td>
<td>73</td>
<td>131</td>
<td>318</td>
<td>439</td>
<td>380</td>
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<tr>
<td>CPK (40-290 UI/l)</td>
<td>400</td>
<td>3130</td>
<td>2410</td>
<td>1433</td>
<td>745</td>
<td>144</td>
<td>79</td>
<td>42</td>
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<td>1798</td>
<td>2685</td>
<td>3025</td>
<td>2500</td>
<td>2064</td>
<td>1381</td>
<td>774</td>
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<td>ALAT (5-40 U/l)</td>
<td>18</td>
<td>99</td>
<td>126</td>
<td>111</td>
<td>103</td>
<td>206</td>
<td>178</td>
<td>124</td>
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<tr>
<td>ASAT (7-56 U/l)</td>
<td>12</td>
<td>62</td>
<td>59</td>
<td>61</td>
<td>60</td>
<td>120</td>
<td>143</td>
<td>79</td>
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<tr>
<td>CRP (0-5 mg/l)</td>
<td>38</td>
<td>102</td>
<td>77</td>
<td>56</td>
<td>33</td>
<td>19</td>
<td>13</td>
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</table>

When hypercholesterolemia is not the major lipid abnormality, fibrates are widely prescribed [1, 2, 4, 5]. Tolerance is usually good, with most side-effects being transient or reversible [4, 6-8]. The most common side-effects are gastrointestinal problems (abdominal discomfort, diarrhea and constipation) and occur in approximately 5% of patients. Reports including asthenia, headache, loss of libido, impotence, dizziness and insomnia are observed in 3 to 4% of treated-patients. In approximately 1% of patients, muscle tenderness developed and was often accompanied by elevated CPK. Myolysis cases have been reported during fibrate treatment and could be more frequent during fibrate-HMG-CoA reductase association [1]. In approximately 2% of patients, a skin rash can appear. Liver changes include increase in incidence of elevated transaminases usually transient with isolated cases of hepatitis [4, 8]. There have been two reports...
of possible haematologic abnormalities including anaemia and leucopenia [6, 7]. To our knowledge major fever and pancytopenia were never observed previously. All fibrates are involved in these reactions, the most frequently involved being the most widely prescribed (i.e., Fenofibrate) [9]. Other lipid-lowering agents like statins are usually well tolerated and have an excellent safety record [10].

Effects of fibrates are mediated, at least in part, through alteration in transcription of genes encoding for proteins that control lipoprotein metabolism [2]. Fibrates activate specific transcription factors belonging to the nuclear hormone receptor superfamily, named as peroxisome proliferator-activated receptors (PPARs) [1, 2]. The PPAR-α form mediates fibrate action on HDL-cholesterol levels via transcriptional induction of synthesis of the major HDL apolipoproteins, apo-AI and apo-AII [1, 2, 5]. Fibrates lower hepatic apoC-III production and increase lipoprotein lipase mediated lipolysis via PPAR [1, 2]. Finally fibrates interfere with fatty acid metabolism resulting in a decrease in VLDL production [1, 2].

PPAR-α is expressed by various tissues including skeletal muscle, liver, kidney, central nervous system and vascular endothelial cells [11-13]. In hematologic system PPAR-γ are expressed in spleen, bone marrow, monocytes and macrophages [14, 15]. Both PPAR-α and PPAR-γ are involved in mediating inflammatory processes [16-18] and cellular apoptosis [15, 16]. Thus in this case Fenofibrate through PPARs could potentially interfere at various levels with blood cell production and/or destruction. Hyperthermic reaction could be a non specific reaction to this major allergic reaction but could also have been triggered by the PPARs role in inflammatory process and/or central thermic regulation.

Although causal relationship cannot be ascertained, the medical presentation of this patient is compatible with a major allergy to Fenofibrate. This case illustrates the fact that adverse events secondary to treatments with fibrates have usually a good reversibility when the medication is stopped [7].

REFERENCES


5 Rader DJ, Haffner SM. Role of fibrates in the management of hypertriglyceridemia. Am J Cardiol, 1999, 83, 30F-35F.


