TOXIC EFFECT OF ANDROGENIC ANABOLIC STEROIDS: TWO CLINICAL CASES

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Abstract
In this study two cases of methandienone misuse were presented. Six weeks later the patients were admitted to the hospital with jaundice (skin and sclera), dermal itching and acholic feces. In both cases severe hyperbilirubinemia was found which persisted in next 30 days. The treatment of toxic effects after androgenic anabolic steroid misuse includes combination of extracorporeal detoxification of cumulated bilirubin, hyperbaric oxygen therapy and hepatoprotective agents. Both patients were discharged with a fully recovered liver function.

Key words androgenic anabolic steroids, methandienone, hyperbilirubinemia, hyperbaric oxygen therapy

INTRODUCTION
Androgenic-anabolic steroids (AASs) are synthetic analogues of the male sex hormone testosterone – a natural androgenic steroid. AASs display anabolic and androgenic (virilizing) effects. The first AAS was produced in 1953 - 19-nortestosterone, which has three to five times stronger muscle building (anabolic) effect than natural testosterone and up to three times reduced androgenic activity. Now, over 1000 derivatives are synthesized by the pharmaceutical companies which differ in their androgenic and anabolic effects (1).

The effects of AASs are the main reason for their usage in different target groups as culturists, bodybuilders, fitness maniacs, people suffering from muscle dysmorphism, as well as people from the army – rangers and others. In the same groups the AASs misuse is highest (2).

However, an increase number of signals about pro-hormones presences in food additives are observed without listing them in the ingredient list (3,4). The usage of AASs is associated with plenty of side effects and increased health risk.

Most of these side-effects are dose-dependent: elevated blood pressure (5) and alterations in the structure of the heart (6), and sudden cardiac death (7), harmful changes in cholesterol (8), blood sugar levels, increased the risk of cardiovascular disease (9) or coronary artery disease (10,11), acne (12). There are sex-specific side-effects: gynecomastia (13), testicular atrophy (14), enlarged clitoris, reduced sexual function and temporary infertility (15-17). There are described psychiatric effects: mania, hypomania and increased aggressiveness (18), psychosis and suicide, symptoms of dependence and withdrawal (19).

The prevalence of their acute toxic effects is different to be distinguished alone as insufficient literature data and clinical experience (20).

The most frequently mentioned in the literature as AASs’ misuse are compounds: methandienone, nandrolone, oxandrolone, stanozolol, oxymetholone. The acute toxicity of methandienone is associated with ischemic insult (21), cholestatic icterus and acute liver failure (22), acute renal damage with tubular necrosis (23,24), IgA nephropathy (25), acute pancreatitis (23), neurotoxicity with accelerated neurodegenerative diseases (26). The toxic effects of the other AASs also include pulmonary embolism in patients with protein C deficiency (27), myocardial infarction and acute liver failure, especially in combination with other psychoactive compounds as ephedrine, gamma-hydroxybutyrate (28,29), cardiac arrest (30).
CASE REPORTS

Case 1. 28-years-old man was admitted in the clinic after two months usage of AAS (methandienon). He complains from generalized itching, loss of appetite, icterus, acholic feces, and darkness of the urine (within a month). From the medical check: an intensive scleral and dermal icterus. A weak abdominal pain on palpation was noticed. A liver edge was palpable 4 cm below the costal margin. Normal peristaltic was found and succusio renalis - bilaterally negative. The patient was afebrile.

Laboratory data: Urine – positive for bilirubin and urobilinogen. Blood count and hemostasis – no significant abnormalities, in reference range. Increased erythrocyte sedimentation rate – up to 80 mm/h during the hospital stay. Clinical chemistry – the most significant deviations in bilirubin and transaminases are shown in Fig. 1, 2, respectively.

The other tested parameters with deviations during the clinical course are shown in Table 1. C-peptide, creatine-phosphokinase, amylase, creatinine and urea, as well as blood ionogram were in reference range during the stay. Immunology – complement C3 and C4 values were 4.04 g/L and 0.63 g/L, respectively, were indicative for acute phase disturbances at hospitalization; IgG, IgA and IgM – in reference range; ANA /AMA / ASMA tests were negative. Hepatitis antibodies were negative. No data about leptospirosis. Microbiology – hemoculture and uroculture – no bacterial growth. ECG showed regular sinus rhythm without repolarization changes. The X-ray study of lung and heart did not identified any pathological changes. Abdominal sonography revealed an enlarged liver – up to 180 mm (right midclavicular line) and normal echogenicity at arrival and with an increased parenchymal echogenicity when discharged. Spleen 127/40 mm, v. portae 12 mm, gall bladder, pancreas and kidneys were without pathological changes.

Table 1. Laboratory data of Case 1 at arrival (initial), maximum deviation during the hospital stay and final (when discharged).

<table>
<thead>
<tr>
<th>Lab. test</th>
<th>Units</th>
<th>Initial</th>
<th>Maximum (on day)</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>[mmol/L]</td>
<td>5.8</td>
<td>21.1 /10 day/</td>
<td>6.1</td>
</tr>
<tr>
<td>Total Protein</td>
<td>[g/L]</td>
<td>75</td>
<td>51 /30-th day/</td>
<td>79</td>
</tr>
<tr>
<td>Albumin</td>
<td>[g/L]</td>
<td>46</td>
<td>37 /30-th day/</td>
<td>56</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>[mmol/L]</td>
<td>6.4</td>
<td>10.9 /12-th day/</td>
<td>7.0</td>
</tr>
<tr>
<td>HDL</td>
<td>[mmol/L]</td>
<td>No data</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td>[mmol/L]</td>
<td>No data</td>
<td>5.15</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>[mmol/L]</td>
<td>5.7</td>
<td>2.14</td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td>[U/L]</td>
<td>412</td>
<td>No data</td>
<td></td>
</tr>
</tbody>
</table>

Clinical course. The patient was stable during the whole hospital stay. On the 18th day after hospitalization a fever (38 °C) period began. Increased number of white blood cells and accelerated sedimentation rate of the red blood cells were registered. The microbiological tests were negative without any additional complains. After the 40th day of the stay the urine tests were normal. The increased blood glucose level persisted to the 10th day and after that was in reference range. The deviation in the lipid profile was not corrected. The decreased amount of total protein and albumin were compensated on day 45th. The hyperbilirubinemia and the corresponding icterus were persisted up to day 60th. Initially, bilirubin fractions had a parallel time-course kinetic and after the day 20th the direct bilirubin predominated over indirect bilirubin. The maximum deviation for the transaminases was 3-4 over the upper reference value for ASAT and 5 times for ALAT, respectively. The alkaline phosphatase had a maximum two-fold increase over the reference, but the ratio between ALAT and alkaline phosphatase was lower than 2.

Fig. 1. Bilirubin profile of Case 1 during the hospital stay.

Fig. 2. Enzyme activity of ASAT, alkaline phosphatase (AlkPhosph) and γ-glutamyltransferase (GGTP) of Case 1 during the hospital stay.

Therapy. The aim of the therapy was to reduce the toxic effects, to support the liver function and to increase the regeneration process of the damaged liver tissue. The therapeutic protocol includes: extracorporeal detoxification – plasmapheresis (six procedures of plasma exchange and slow continuous ultrafiltration (SCUF), combined with Human Albumin substitution); carbohemoperfusion (three procedures); hyperbaric oxygen therapy (10 procedures; 60 min; 1.8-2.5 ATA); supportive therapy as infusion of electrolytes, carbohydrates (lavelose), Aminosteril N-Hepa 8%; hepatoprotective agents as Essential, Legalon 140, Ursofalk, Transmetil; corticosteroids; gastroprotective therapy; antibiotics (sulperazone; amikacine); Insulin Actrapid HM; vitamins; individual diet plan including probiotics (Biomilk Hepanorm).
The intensive therapy including extracorporeal detoxification and hyperbaric oxygen therapy was applied in the first 20 days of the hospital stay till the total and direct bilirubin were reduced to 300 mmol/L and 150 mmol/L, respectively.

The patient was discharged on 68th day, recovered from the disease.

**Case 2.** 32-years-old man was admitted to the hospital after 45 days misuse of methandienone in elevated dosage in a total amount of 1000 mg. The patient had jaundice and complained from generalized itching, urine darkness, acholic feces. From the medical check an intensive icterus of the sclera and skin was noticed. The patient had normal heart function (72 bpm, 130/80 mm Hg), the abdomen allowed deep palpation with normal peristaltic, liver was not enlarged on palpation, and negative succus renalis on both sides.

**Laboratory data:** Urine – positive for bilirubin and urobilinogen. Blood count displays leukocytosis (17.2 G/L) and increased erythrocyte sedimentation rate (up to 36 mm/h). Blood coagulation was in reference range. Clinical chemistry – the parameters with deviations are shown on Table 2. During the hospital stay there was increase in blood glucose up to 9.4 mmol/L and disturbances in the lipid metabolism. The time-course of bilirubin and transaminases with alkaline phosphatase are shown on Figs. 3,4. The amount of C-reactive protein was in normal range. HIV, HAV, HBV, HCV and Wasserman tests were negative.

**ECG** was normal. The X-ray study of the chest was normal. Abdominal sonography: the liver is moderately enlarged with diffuse increased echogenicity without inflammatory changes. The spleen had a size 130/50 mm; v.portae – 12 mm; gall bladder – a concrement (7 mm) in the lumen is described; kidneys – diffuse increased echogenicity of the parenchyma.

**Table 2.** Laboratory data of Case 2 at arrival (initial), maximum deviation during the hospital stay and final (when discharged).

<table>
<thead>
<tr>
<th>Lab. test</th>
<th>Units</th>
<th>Initial</th>
<th>Maximum (on day)</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>[mmol/L]</td>
<td>/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Protein</td>
<td>[g/L]</td>
<td>70</td>
<td>51 /30-th day</td>
<td>61</td>
</tr>
<tr>
<td>Albumin</td>
<td>[g/L]</td>
<td>40</td>
<td>34 /30-th day</td>
<td>39</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>[mmol/L]</td>
<td>8.05</td>
<td></td>
<td>6.89</td>
</tr>
<tr>
<td>LDL</td>
<td>[mmol/L]</td>
<td>0.78</td>
<td>0.79</td>
<td>0.92</td>
</tr>
<tr>
<td>HDL</td>
<td>[mmol/L]</td>
<td>4.5</td>
<td>5.95</td>
<td>4.03</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>[mmol/L]</td>
<td>6.0</td>
<td>6.24</td>
<td>4.27</td>
</tr>
<tr>
<td>LDH</td>
<td>[U/L]</td>
<td>291</td>
<td>585 /30-th day</td>
<td>492</td>
</tr>
</tbody>
</table>

**Clinical course:** The patient was stable during his hospital stay. The urine analyses became normal on the 25th day. The skin itching was disappeared on 30 - 35th day. On the 30th day acne was found and erosive balanitis, also. The disturbances in the lipid status were not compensated. The amount of total protein and albumin were in the lower range of the reference values during the whole stay. The jaundice was disappeared on 40th day, however, the prevalence of direct bilirubin was notable. The ALAT was higher than ASAT (2-3 fold increase), as two-fold and five-fold increase for ASAT and ALAT was measured, respectively. The alkaline phosphatase was also increased (2-3 times over the reference), but the ALAT/alk. phosphatase ratio was lower than 2.

**Fig. 3.** Bilirubin profile of Case 2 during the hospital stay.

**Fig. 4.** Enzyme activity of ASAT, alkaline phosphatase (AlkPhosph) and γ-glutamyltransferase (GGTP) of Case 2 during the hospital stay.

**Therapy.** The supportive therapy of the liver function was leading here. 13 procedures of extracorporeal detoxification were performed – plasmaferesis (plasma exchange and plasma adsorption of bilirubin using Plasorba BR-350). The plasma substitution was performed using freshly-frozen plasma and Human albumin 4%. Ten procedures of hyperbaric oxygen therapy were applied. The supportive electrolyte and carbohydrate parenteral infusions of monosaccharides, electrolytes, and drugs as Aminosteril N-Hepa 8%, Transmetil, Legalon 140, Essentiale, Ursofalk, ACC 200, folic acid, corticosteroids, antihistamines (Ewofax), vitamins were applied. The patient was on individual diet plan. Plasma-exchange procedures and oxygen therapy were performed till the total bilirubin amount was reduced with 350 mmol/L and direct bilirubin – with 250 mmol/L, respectively.

The patient was discharged with a normal liver function on the 44th day.
DISCUSSION

The study describes two clinical cases of androgenic anabolic steroid – methandienone – misuse. In general, both cases present resistant disturbance of the liver function which is difficult to be compensated.

The leading diagnosis in the introduced cases was toxic hepatitis induced from drug misuse. The initial symptoms started six weeks after the first use of the AAS and the jaundice is the first clinical symptom of liver dysfunction. The extreme hyperbilirubinemia is found in both patients with corresponding signs of bilirubin-excretion disturbances (jaundice, acholic feces). In the first case, diabetes was found and treated as accompanied disease. Concomitant cytolytic and cholestatic effects were observed, without significant influence on the synthetic liver function. A continuing dyslipidemia was found in both patients. The laboratory data presents a bi-phasic profile in ASAT/ALAT values without any clinical symptoms associated in the peak-period.

The complex therapy in both clinical cases had three main targets: i) to support continuously the liver function aiming to compensate the severe hepatobiliary disturbances; ii) to shorten the endotoxic influence of hyperbilirubinemia using powerful extracorporeal detoxification methods; and iii) to control the tissue and cellular hypoxia using hyperbaric oxygen therapy.

Conclusion

Methandienon is an androgenic anabolic steroid, which is one of the most frequent misused anabolic steroids. The toxic effect results in acute and prolonged hepatotoxicity (most probably in dose-dependent manner). The illness is characterized by stable condition of the patient with hepatobiliary disturbances without development of liver insufficiency.

The treatment requires specific and complex therapy based on detoxification of endogenous bilirubin as well as applying of intensive hepatoprotective and supportive protocol.

Acknowledgement

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Sažetak

U ovom radu su prikazana dva slučaja zloupotrebe metandienona. Šest nedelja kasnije bolesnici su primljeni u bolnicu sa žuticom (koža i beonjače), svrabom kože i aholičnim fecesom. O oba slučaja dokazana je ozbiljna hiperbilirubinemia, koja je bila prisutna sledećih 30 dana. Lečenje tok- sičnih efekata nastalih nakon zloupotrebe androgenih anaboličkih steroida podrazumevalo je kombinaciju ekstrakorporalne detoksifikacije kumulo-vanog bilirubina, hiperbaričnu kiseoničnu terapiju i hepatoprotektivne agense. Oba bolesnika su otpuštena sa potpuno oporavljenom funkcijom jetre.
REFERENCES