

CLINICAL PRESENTATION OF THE ABUSE OF INSULIN: HYPOGLYCAEMIC COMA AND ASPIRATION PNEUMONIA IN NON-PROFESSIONAL BODYBUILDERS

Ivica Petrović¹, Sara Petrović¹, Katarina Vujanac², Marina Petrović², Zorica Lazić²

¹Faculty of Medical Sciences, University of Kragujevac, Kragujevac, Serbia

²Clinical Centre Kragujevac, Clinic for Pulmonology, Kragujevac, Serbia

KLINIČKA PREZENTACIJA ZLOUPOTREBE INSULINA: HIPOGLIKEMIJSKA KOMA I ASPIRACIONA PNEUMONIJA KOD NEPROFESIONALNOG BODIBILDERA

Ivica Petrović¹, Sara Petrović¹, Katarina Vujanac², Marina Petrović², Zorica Lazić²

¹Fakultet Medicinskih Nauka, Univerzitet u Kragujevcu, Kragujevac, Srbija

²Klinički Centar Kragujevac, Klinika za Pulmologiju, Kragujevac, Srbija

Received / Primljen: 28.09.2015.

Accepted / Prihvaćen: 17.10.2015.

ABSTRACT

The use of medications that improve the physical performance of an individual represents a very serious worldwide health problem. The abuse of these medications is increasing. Herein, we describe a patient, at the age of 20, who was hospitalized due to loss of consciousness and difficulty breathing. At admission, the patient was unconsciousness, tahi-dyspnoic, and had a pale complexion and an athletic build. In gas analyses, extremely low saturation was observed, followed by acidosis, heavy hypoxia with normocapnia, higher lactates, hypocalcaemia and severe hypoglycaemia. The patient was treated with a hypertonic solution of glucose and intubated, with the aspiration of sanious content from the respiratory tract. After treatment, the patient woke from coma but was very confused. In the first 6 hours of hospitalization, severe hypoglycaemia occurred several times, despite the continuous administration of glucose. Due to the growth of inflammatory syndrome since the first day of hospitalization, the patient was kept in the hospital for treatment along with the administration of antibiotic treatment. On the fourth day of hospitalization, the patient stated that for the last year, he had been taking testosterone at a dose of 1 g a week, as well as tamoxifen pills and 15 i.j. of fast-acting human insulin (Actrapid[®]) daily for their combined anabolic effect. Hypoglycaemic coma, caused by the abuse of insulin, represents a severe complication in patients, which can be followed by confusion, a slowed thinking process, the weakening of cognitive functions and even death. It is necessary to invest great efforts into the prevention of the purchase of these medications via the Internet or on the black market for purposes of abuse in order to prevent such serious and life-threatening complications.

Key words: bodybuilding, testosterone abuse, insulin abuse, hypoglycaemic coma

SAŽETAK

Upotreba lekova koji poboljšavaju fizičke performanse pojedince predstavlja jako veliki zdravstveni problem u svetu. Zloupotreba ovih lekova je u velikom porastu. Prikazali smo pacijenta, starosti 20 godina, hospitalizovanog zbog gubitka svesti i otežanog disanja. Na prijemu pacijent je bio bez svesti, tahi-dispnoican, blede kože, atletske konstitucije. U gasnim analizama viđena je jako niska saturacija praćena acidozom, teška hipoksija sa normokapnijom, povišeni laktati, hipokalcaemiju i teška hipoglikemija. Pacijent tetiran hipertoničnom rastvorom glukoze, intubiran, sa aspiracijom sukrvičavog sadržaja iz disajnih puteva. Nakon tretmana pacijent se budi iz kome, postaje budan ali jako konfuzan. U prvih 6h hospitalizacije više puta dolazi do pojave teške hipoglikemije i pored kontinuirane administracije glukoze. Zbog rasta zapaljenskog sindroma, od prvog dana hospitalizacije, pacijent je zadržan na bolničkom lečenju uz ordiniranje antibiotske terapije. Četvrtog dana hospitalizacije pacijent navodi da poslednjih godinu dana koristi testosteron u dozi od 1g nedeljno, tablete tamoksifena kao i 15 i.j. brzodelujućeg kristalnog humanog insulina dnevno (Actrapid[®]), radi zajedničkog anaboličkog efekta. Neželjeni efekti preparata koji imaju anabolički efekat mogu biti jako opasni. Hipoglikemijska koma, izazvana zloupotrebom insulina, predstavlja tešku komplikaciju po pacijenta, koja može biti praćena, konfuzijom, usporenošću misaonog toka, slabljenjem kognitivnih funkcija ali i smrtnim ishodom. U budućnosti je potrebno uložiti jako velike napore u cilju onemogućavanja nabavke lekova sa ciljem zloupotrebe, preko interneta, na crnoj berzi, sa ciljem sprečavanja ovako teških, po život opasnih komplikacija.

Ključne reči: bodybuilding, zloupotreba testosterona, zloupotreba insulina, hipoglikemijska koma.

ABBREVIATIONS

AAS - anabolic androgen steroids
GnRH - gonadotropin-releasing hormone
LH - luteinizing hormone

FSH - follicle-stimulating hormone
GH - growth hormone
MV - mechanical ventilation



INTRODUCTION

The use of medications that improve the physical performance of individuals represents a very serious worldwide health problem. The number of sportsmen in semi-professional as well as in popular sports self-administering ergogenic pharmacological agents continues to be an issue. Many athletes use anabolic-androgenic steroids (AAS) to obtain a well-trained, athletic, and healthy-looking body (1). The abuse of these medications is rapidly increasing. The greatest abuse of these medications is in non-professional athletes, especially bodybuilders. The most frequent age that these medications are abused is between 15 and 35 years (2). Professional athletes have a clearly defined plan and program to achieve their goals. In contrast, young people who are involved in sports or just starting to exercise abuse performance-enhancing drugs as a shortcut to their goal. The abuse of these substances is more common in men (3). The most significant factors that influence the decision to abuse ASS are the following: personality, potential side effects, benefit, social influence, and morality. (4, 5) These drugs are purchased via the Internet or on the black market (6, 7).

CASE REPORT

A patient, aged 20, was hospitalized due to the loss of consciousness and difficulty breathing. The data were heteroanamnestically obtained from the father. The loss of consciousness occurred on the day of admission, 5 hours before hospitalization, when the patient complained about hunger, after which he lost consciousness and started breathing heavily. The patient recently used an insulin preparation on his own initiative, for the purpose of gaining muscle mass. At admission, the patient was unconsciousness, tachypneic, dyspneic, had a pale complexion and an athletic build, with body height=185 cm, body weight=104 kg, and BMI=30.72 kg/m². The head and neck were of

usual configuration and shape; the patient displayed dilated pupils, medially located bulbi, no neck rigidity, and stretch marks in the shoulder area. In the lungs there was intensified respiratory murmur, with the presence of a low-toned whistle; heart activity was rhythmic, with clear tones; TA=105/55 mmHg. At the level of the thorax, the abdomen did not displays a peritoneal reaction. An electrocardiogram indicated 112 beats/min, without pathologic changes. Gas analyses (arterial blood) showed very low saturation of 67%, acidosis at pH 7.33, severe hypoxia with normocapnia at pO₂ 4.9, pCO₂ 4.7, bicarbonates at the lower limit of 18.6, hypocalcaemia with ionized Ca 0.99, a limited value of potassium at 3.6, lactates of 8.6, an Hct of 56% and severe hypoglycaemia at 1.6 mmol/L.

Upon admission, the patient was treated with 100 ml of 50% glucose and intubated, with the aspiration of sanious content from the respiratory tract. Due to respiratory insufficiency and coma, the patient was sedated, intubated and put on mechanical ventilation. An urgent endocranial CT was performed to exclude neurologic diseases and was found to be normal. After treatment with a hypertonic solution of glucose, the patient woke from coma but was confused. In the first 6 hours of hospitalization, severe hypoglycaemia occurred several times (two times, 2.0 mmol/l), despite the continuous administration of glucose solution. An RTG of the lungs showed the presence of a blotchy confluent shadow on the right side in the upper and middle lung areas. As the increase in inflammatory syndrome markers from the first day of hospitalization (**Table 1**), given the context of the RTG findings in the lungs, could be explained by the occurrence of aspiration pneumonia, the patient was medically treated via the administration of antibiotic therapy. On the fifth day of hospitalization, the patient was extubated and taken off the mechanical breathing apparatus (**Table 2**). The confusion and bradypsychia of the patient remained until the fourth day of hospitalization, after which the patient reconstructed the events before the loss of consciousness. He stated that for the last year, during training cycles, he had been taking testosterone at a

Table 1. The first laboratory analysis

Analyses	Value	Reference value	Analyses	Value	Reference value
Le	19.4	3.0-10.0x10 ⁹ /L	Amylase S	178	28-104U/L
Er	5.11	4.35-5.72x10 ¹² /L	CK	915	0-170U/L
Hgb	147	138-175 g/L	CK MB	59.2	0-25U/L
Hct	0.426	0.415-0.530	Troponin I	0.127	0-0.04 µg/L
Tr	383	135-450x10 ⁹ /L	proBNP	21	0-125pg/ml
APTT	20.8	25-35s	Ca	1,96	2.0-2.65 mmol/L
INR	1.336	0.9-1.1	K	4.2	3.5-5.3 mmol/L
D Dimer	7206.64	0-500 ng/ml	Na	138	137-147 mmol/L
Urea	2.5	3.0-8.0 mmol/L	CRP	80	0-5.0 mg/L
Creatinine	102	49-106 µmol/L	Pct	0.049	0-0.5 ng/ml
AST	38	0-40IU/L	Albumin	30	35-52 g/L
ALT	35	0-40IU/L	HbA1c	5.1%	4.0-7.0%



Table 2. Gas analyses during hospitalization

Gas analyses	Day I	Day II	Day III	Day IV	Day V	Reference value
pH	7.33	7.46	7.45	7.42	7.47	7.35-7.45
pCO ₂	4.70	4.9	5.9	5.9	5.3	<6.0
pO ₂	4.9	13.7	16.7	13.6	9.9	>10.7
lactates	8.6	1.4	1.4	3.6	1.0	<2.2
HCO ₃	18.6	27.1	29.7	27.5	28.8	18.0-23
Saturation O ₂	67%	98%	99%	98%	96%	>95%
% O ₂ in air	21%	MV - 50%	MV – 50%	MV – 35%	21%	

dose of 1 g a week, as well as 20 mg tamoxifen pills and 15 i.j. of fast-acting regular human insulin (Actrapid®) daily for their combined anabolic effect. The information about this effect of the medications was found on the Internet.

DISCUSSION

Doping in sport has a very long history. Every year, the Medical Committee of the International Olympic Committee issues a publication related to prohibited substances in sport. A large number of people use medications for the purpose of increased combined effects. In addition to the most frequently used anabolic androgen steroids (AAS), other preparations of growth hormone (GH), insulin, 5- α -reductase blockers and luteinizing hormone (LH) are also used. These hormones act synergistically and have an anabolic effect. Anabolism is defined as the state in which there is a positive balance of nitrogenous substances in the organism, and whether there is a stimulation of the protein synthesis in the organism or a decrease in the degradation of already-existing proteins in the organism.

Anabolic androgen steroids

Testosterone is a hormone with multiple physiologic, especially reproductive and metabolic, functions. It is the primary sex hormone in males, with androgenic and anabolic effects. Androstenedione and dehydroepiandrosterone have effects similar to those of testosterone. These hormones are mutually called AAS (8). These are relatively small molecules, and by passive diffusion, they reach all the cells in an organism, where they encourage gene transcription and lead to iRNK production. The enzyme 5 α -reductase has a significant role in the conversion of androgens and in the production of female sex hormones in males (9). Supraphysiological doses of AAS lead to a gain in muscular mass and strength, even with only occasional training. The anabolic effect is achieved by the binding of glyco-corticoid receptors and the prevention of the glyco-corticoid catabolic effect (10).

The most common case of abuse is the use of AAS in cycles of several weeks with short pauses in between. The effect of such AAS use is a decrease in the concentrations of

thyroxin, cortisol, sex hormones and growth hormones (11). Overall, the use of AAS in supraphysiological doses leads to an increase in muscular mass and the strength of the muscles, a reduction in muscle damage, an increase in protein synthesis, an increase in lipolysis, a decrease in the percentage of body fat, an increase in bone density, an increase in the process of erythropoiesis, increases in the values of haemoglobin and haematocrit and an increase in glycogen reserves (12). Adverse effects of abuse are present in numerous organic systems. In the cardiovascular system, they intensify the occurrence of the prothrombotic state, cause vasospasm in the blood vessels and have direct toxic effects on the myocardium. Frequent findings of AAS abuse are also eccentric hypertrophy of the left ventricle with diastolic dysfunction, arrhythmia and the frequent occurrence of ischemic events (13, 14). The most frequently observed types of liver damage are cholestasis, hepatitis and a disorder of the synthesis of coagulation factors (15, 16). Supraphysiological doses of AAS are hazardous to the endocrine and reproductive systems. Long-term use leads to the decreased production of testosterone, sex hormones, and proteins that bind sex hormones, as well as decreases in testicle size, sperm cell mobility disorders, decreases in fertility, changes in libido and the occurrence of gynaecomastia. The effects can sometimes be reversible. Gynaecomastia often develops with AAS abuse, and occurs as a consequence of the increased concentration of oestrogen that is produced by the endogen conversion of AAS and leads to breast enlargement in men (17). Changes in muscular-skeletal system are characterized by short periods of growth, frequent tearing of the ligaments and tendons, muscle damage and rhabdomyolysis. The adverse effects on the CNS can be various, from increased aggression towards others, behavioural disorders, manic behaviour, an inclination to violence, and the occurrence of psychoses, paranoia and hallucinations as well as depression and sleep disorders (17,18).

Blockage of 5 α -reductase

One of the additional ways by which the additional leap in testosterone concentration is achieved is by the induction of high concentrations of gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) secretion.



Direct stimulation, via the administration of LH, is typically very complicated and carries huge risks of decreased testosterone secretion due to irregular use of the preparations; hence, many bodybuilders resort to an indirect stimulation of LH and testosterone production (19), which can be achieved in several ways: by applying neurotransmitters, neuropeptides, blockers of negative feedback mechanisms or blockers of oestrogen. The use of these medications leads to the increased production of endogenous LH via the manipulation of the physiological regulatory systems that are responsible for pulsatile hypothalamic GnRH secretion (19, 20). The aromatization of testosterone represents an irreversible process, and the blockage of this process leads to the blockage of the effect of oestrogen on an organism. With the blockage of oestrogen receptors in the hypothalamus by medication, the activation of the feedback mechanism occurs, increasing the secretion of sex hormones of the pituitary gland and consequently testosterone up to as much as 40% (21, 22). More efficient medications that act via this mechanism can lead to significant increases in muscular mass and strength. There are no significant clinical indications for the use of these medications, except in the treatment of gynaecomastia and older men with prostate carcinoma (23). Bodybuilders primarily use the effect of these medications to restart the secretion of sex hormones of the pituitary gland, which was suppressed by extremely high values of testosterone during the training cycle.

Growth hormones and Insulin-like Growth Factor 1

The abuse of growth hormones presents another health problem. GH acts synergistically with other hormones in an anabolic manner and leads to an increase in muscle mass (24). The main effect is achieved by the increased entry of amino acids into the cells and the increased synthesis of proteins. For the full effect of GH, a certain concentration of oestrogen is necessary, which is produced by peripheral conversion (25). The use of aromatization inhibitors leads to the increase of GnRH, LH, follicular stimulating hormone (FSH) and testosterone concentrations but also results in the decreased effect of insulin-like growth factor 1; hence, inhibitors are primarily used to start the secretion of sex hormones of the pituitary gland.

Insulin

The effects that insulin has on cells have led to it being abused by sportsmen. Insulin enables the easier entry of glucose into the cells, so a larger amount of glucose enters the cells than is currently necessary for the process of cell respiration, along with the formation of an energy depot in the form of glycogen. The increase in the energy depot has an important role in muscle recovery after a load. There are opinions that insulin also increases the size of the muscle itself. It is considered that this effect is primarily attributed to fast-acting insulin, which prevents the degradation

of the existing proteins in the muscle itself, whereas GH is primarily responsible for the synthesis of new proteins in the muscle (26).

Physical activity presents a risk of hypoglycaemia when administering fast-acting insulin before training, which additionally increases the probability of the occurrence of hypoglycaemic episodes. Severe hypoglycaemic episodes, almost as a rule, are followed by the loss of consciousness. Injuries caused by the loss of consciousness can also be very serious for the patient. Hypoglycaemic episodes can lead to serious brain damage and increase patient mortality, especially if they last for an extended period of time. The administration of insulin to people who are not educated carries a high risk for the development of severe complications, and the abuse of this medication can be life threatening (27, 28).

CONCLUSION

The abuse of medications in sport represents a very serious health problem. Large numbers of amateur athletes use prohibited means to achieve better results. The adverse effects of medications that are used can be very dangerous for the health of patients. Hypoglycaemic coma, iatrogenically caused by the abuse of insulin, represents a very serious complication, which can be followed by confusion, a slowed thinking process, loss of cognitive function, and also death. It is important to invest significant effort into the prevention of the purchase of medications for the purpose of the abuse via Internet, on the black market or in gyms in order to prevent these serious, life-threatening complications.

REFERENCES

1. Pope HG Jr, Kanayama G, Hudson JI. Risk factors for illicit anabolic-androgenic steroid use in male weightlifters: a cross-sectional cohort study. *Biol Psychiatry*. 2012 Feb 1;71(3):254-61.
2. Rane A, Rosén T, Skårberg K, Heine L, Ljungdahl S. Steroids are a growing problem at gyms. *Lakartidningen*. 2013 Sep 25-Oct 8;110(39-40):1741-6.
3. Papadopoulos FC, Skalkidis I, Parkkari J, Petridou E. Doping use among tertiary education students in six developed countries. *Eur J Epidemiol*. 2006;21(4):307-13.
4. Donovan RJ, Egger G, Kapernick V, Mendoza J. A conceptual framework for achieving performance enhancing drug compliance in sport. *Sports Med*. 2002;32(4):269-84.
5. Komoroski EM, Rickert VI. Adolescent body image and attitudes to anabolic steroid use. *Am J Dis Child*. 1992 Jul;146(7):823-8.
6. Ritsch M, Musshoff F. Dangers and risks of black market anabolic steroid abuse in sports --gas chromatography-mass spectrometry analyses. *Sportverletz Sportschaden*. 2000 Mar;14(1):1-11.



7. Wilson JD. Androgen abuse by athletes. *Endocr Rev.* 1988 May;9(2):181-99.
8. Bahrke MS, Yesalis CE. Abuse of anabolic androgenic steroids and related substances in sport and exercise. *Curr Opin Pharmacol.* 2004 Dec;4(6):614-20.
9. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med.* 2004;34(8):513-54.
10. Kicman AT. Pharmacology of anabolic steroids. *Br J Pharmacol.* 2008 Jun;154(3):502-21.
11. Parkinson AB, Evans NA. Anabolic androgenic steroids: a survey of 500 users. *Med Sci Sports Exerc.* 2006 Apr;38(4):644-51.
12. Hoffman JR, Ratamess NA. Medical issues associated with anabolic steroid use: are they exaggerated? *J Sports Sci Med.* 2006 Jun 1;5(2):182-93.
13. Deligiannis AP, Kouidi EI. Cardiovascular adverse effects of doping in sports. *Hellenic J Cardiol.* 2012 Nov-Dec;53(6):447-57.
14. Karila, T. (2003). Adverse effects of anabolic androgenic steroids on the cardiovascular, metabolic and reproductive systems of anabolic substance abusers (Doctoral dissertation, University of Helsinki).
15. Hoffmann U. Anabolic steroids—a problem in popular sports. *Toxicchem Krimtech.* 2002; 69 (3):136-42.
16. Sørø KL, Sørø M, Gluud C. Liver pathology associated with the use of anabolic-androgenic steroids. *Liver.* 1992 Apr;12(2):73-9.
17. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. *Sports Med.* 2004;34(8):513-54.
18. Hall RC, Hall RC, Chapman MJ. Psychiatric complications of anabolic steroid abuse. *Psychosomatics.* 2005 Jul-Aug;46(4):285-90.
19. Handelsman DJ. Clinical review: The rationale for banning human chorionic gonadotropin and estrogen blockers in sport. *J Clin Endocrinol Metab.* 2006 May;91(5):1646-53.
20. Mendelson JH, Ellingboe J, Kuehnle JC, Mello NK. Heroin and naltrexone effects on pituitary-gonadal hormones in man: interaction of steroid feedback effects, tolerance and supersensitivity. *J Pharmacol Exp Ther.* 1980 Sep;214(3):503-6.
21. Schnorr JA, Bray MJ, Veldhuis JD. Aromatization mediates testosterone's short-term feedback restraint of 24-hour endogenously driven and acute exogenous gonadotropin-releasing hormone-stimulated luteinizing hormone and follicle-stimulating hormone secretion in young men. *J Clin Endocrinol Metab.* 2001 Jun;86(6):2600-6.
22. Hayes FJ, Seminara SB, Decruz S, Boepple PA, Crowley WF Jr. Aromatase inhibition in the human male reveals a hypothalamic site of estrogen feedback. *J Clin Endocrinol Metab.* 2000 Sep;85(9):3027-35.
23. Fradet Y, Egerdie B, Andersen M, Tammela TL, Nachabe M, et al. Tamoxifen as prophylaxis for prevention of gynaecomastia and breast pain associated with bicalutamide 150 mg monotherapy in patients with prostate cancer: a randomised, placebo-controlled, dose-response study. *Eur Urol.* 2007 Jul;52(1):106-14.
24. Meinhardt U, Nelson AE, Hansen JL, Birzniece V, Clifford D, et al. The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized trial. *Ann Intern Med.* 2010 May 4;152(9):568-77.
25. Riggs BL, Hartmann LC. Selective estrogen-receptor modulators - mechanisms of action and application to clinical practice. *N Engl J Med.* 2003 Feb 13;348(7):618-29.
26. Sinha A, Formica C, Tsalamandris C, Panagiotopoulos S, Hendrich E, et al. Effects of insulin on body composition in patients with insulin-dependent and non-insulin-dependent diabetes. *Diabet Med.* 1996 Jan;13(1):40-6.
27. MacLeod KM, Hepburn DA, Frier BM. Frequency and morbidity of severe hypoglycaemia in insulin-treated diabetic patients. *Diabet Med.* 1993 Apr;10(3):238-45.
28. Graveling AJ, Frier BM. Hypoglycaemia: an overview. *Prim Care Diabetes.* 2009 Aug;3(3):131-9.