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Clomiphene misuse and risk of severe cardiovascular events

Céline Eiden¹ • Véronique Pinzani¹ • Marion Laureau² • Nicolas Chapet³ • Juline Beringer² • François Roubille^{3,4} • Mustapha Sebbane² • Hélène Peyrière¹

Dear Editor,

Clomiphene is a selective oestrogen receptor modulator usually used to treat subfertility in women. However, misuse of clomiphene was recently reported in men by bodybuilders, and to treat infertility [1]. Here, we present the case of 2 subjects with severe cardiovascular complications due to clomiphene misuse in a performance-enhancing drug context that occurred in 2019 in a French area.

Case 1

A 24-year-old man presented at 2:00 p.m. to the emergency unit for tachycardia and palpitations. The patient reported intense strength activity using anabolic-androgenic steroids periodically (2 or 3 months ago) for several months and was currently on clomiphene. On admission, the physical examination revealed a heart rate of 108 beats/min and elevated blood pressure of 183/99 mmHg. Cardiac examination revealed a regular rate and rhythm, and electrocardiography revealed sinus tachycardia. Cardiac biomarkers and chest radiography were normal. Troponin value was 5 ng/ml (normal value < 14) and creatinine-kinase was 330 U/ml. Electrolyte levels and renal function were normal. No other medical

history was noted. The last clomiphene intake was in the morning at 8 a.m. (one 50-mg tablet). His symptoms improved without treatment a few hours later, and he was discharged at 6:00 p.m. with the recommendation to stop clomiphene use.

Case 2

A 30-year-old man was hospitalized for acute myocardial infarction (MI) complicated by recovered cardiac arrest. Coronary angiography showed a suspended thrombus into the inter-anterior ventricular with no sign of atheromatous coronary artery disease. A bolus of eptifibatide (Integrelin®) was administered followed by a thromboaspiration, and a stent was placed. Aspirin, ticagrelor, heparin, and bisoprolol were started. The patient had a history of testosterone injections as doping substances. He recognized tobacco and cannabis smoking (10 pack-year and 3–4 cannabis uses/day). Except for being overweight (body mass index 29.3), no other conventional risk factor for MI was detected in this very young patient. The day before, he had taken 2 pills of 50 mg of clomiphene and one the day of the event. Urine toxicological analyses were positive for cannabinoids, and negative for amphetamines, cocaine, and ethanol. After 1 day in the intensive care unit (ICU), the patient was transferred to cardiac inpatient services. Intracardiac echocardiography showed a left ventricle ejection fraction at 45%. At day 4, the patient was discharged against medical advice.

Both cases were reported anonymously according to national law to the French medicines regulatory authorities (ANSM) via the Pharmacovigilance and Addictovigilance centres as serious adverse drug reactions resulting from a drug misuse [2]. Clomiphene is misused in male bodybuilders to counteract hypogonadism induced by exogenous testosterone [1]. Clomiphene increases endogenous oestrogens in women and testosterone production levels in men, via an increased release of gonadotropins, which results in a thrombogenic effect.

✉ Céline Eiden
c-eiden@chu-montpellier.fr

¹ Department of Medical Pharmacology and Toxicology, Montpellier University Hospital, 34295 Montpellier Cedex 5, France

² Department of Emergency, Montpellier University Hospital, 34295 Montpellier Cedex 5, France

³ Department of Cardiology, Montpellier University Hospital, 34295 Montpellier Cedex 5, France

⁴ PhyMedExp, University of Montpellier, INSERM U1046, CNRS UMR 9214, 34295 Montpellier Cedex 5, France

A total of 10 other reports of clomiphene misuse by men (median age 30 years old) was collected in the French Pharmacovigilance and Addictovigilance database, 4 in a context of doping, 3 to treat subfertility (2 unknown). Cardiovascular effects reported in 5/10 cases (2 tachycardia/palpitation, 1 hypertension, 1 chest pain, and 1 pulmonary embolism). In the worldwide Pharmacovigilance database (VigiBase®), since 2012, 17 other cases have been reported (research criteria: “men” and “cardiac disorder”) with a recent increase of reports (4 in 2018, 6 in 2019), with fatal issue in 7 cases (in association with anabolic steroids in 6). In the literature, cases of acute cardiovascular complications after the initiation of clomiphene in the context of ovulatory dysfunction have been reported [3–6], as well as cases of deep venous thrombosis in the context of male hypogonadism and infertility [7].

The use of appearance- and performance-enhancing drugs is increasing and exposes patients to potential life-threatening complications. Clomiphene is usually associated with other drugs to enhance androgen production that could also predispose patients to cardiovascular risk.

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