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ПНЕВМОНИТ, ВЫЗВАННЫЙ ПРИМЕНЕНИЕМ НАРКОТИКА, СВЯЗАННЫЙ С CYP И VKORC1 ВАРИАНТАМИ ГЕНОТИПА

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Реферат. Наличие *CYP*-варианта генотипа считается существенным фактором, повышающим вероятность развития лекарственных побочных реакций со стороны легких. Мы предположили, что у некоторых пациентов эти серьезные осложнения могут быть связаны с наличием этого варианта аллелей в сочетании с употреблением наркотиков. Мы наблюдали двух пациентов, у которых развился гриппоподобный синдром с диффузной интерстициальной инфильтрацией в легких после применения наркотика, связанный, вероятно, с наличием вариантов аллелей цитохрома Р450 (*CYP*) и комплекса 1-эпоксидредуктазы витамина К (*VKORC1*). Оба случая были гетерозиготны по *VKORC1* и имели *CYP*-полиморфизмы (*CYP2C19* *1/*2 и *CYP2C9* *1/*3 соответственно). В приведенных случаях высоковероятной была связь между наличием *CYP* и *VKORC1* вариантов аллелей и интерстициального поражения легких, вызванного приемом кокаина. Более того, это проливает свет на значимость внедрения генетического тестирования в обследование пациентов с предполагаемой токсической реакцией на наркотик.
Ключевые слова: генотип, генетическое тестирование, наркотики, токсическая реакция.

'DRUG'-INDUCED PNEUMONITIS ASSOCIATED WITH CYP AND VKORC1 VARIANTS

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Abstract. The presence of *CYP* variant genotypes appears to be a substantial susceptibility risk factor in the development of drug-induced pulmonary adverse events. We hypothesized that in some patients these serious complications may be associated with the presence of variant alleles in combination with illicit drug use. We present two patients who developed a flu-like syndrome with diffuse interstitial infiltrates after 'drug' abuse probably associated with the presence of cytochrome P450 (*CYP*) and vitamin K epoxide reductase complex 1 (*VKORC1*) allelic variants. Both cases were heterozygote for *VKORC1* and possessed *CYP* polymorphisms (*CYP2C19* *1/*2 and *CYP2C9* *1/*3, respectively). In the described cases an association between the presence of *CYP* and *VKORC1* allelic variants and interstitial lung damage caused by cocaine use was highly likely. Moreover, it highlights the increasing importance of introducing genetic testing into the work-up of patients with suspected 'drug'-induced toxicity.
Key words: genotype, genetic testing, drugs, toxic reaction.

Introduction. Cocaine abuse represents one of the most serious medical and social problems of our time. Cocaine is the most commonly used illicit drug among patients seen in emergency departments and the most frequent cause of drug-related deaths reported by medical examiners [1]. Cocaine and marijuana are very popular illicit drugs acting as stimulants of the central nervous system. Beside heart rhythm disturbances, acute and chronic parenchymal lung injuries as a result of the inhalation of these drugs are not uncommon complications in habitual drug users [1]. A variety of interstitial lung damage due to cocaine or marijuana inhalation, including acute pulmonary hemorrhage, diffuse alveolar infiltrates, and eosinophilic infiltrates have been described [2, 3]. Many inhaled chemicals are not hazardous as such, but are biotransformed to reactive intermediates [2]. To date, the mechanism of the caused lung injury is not fully understood but a direct toxic effect in a dose-dependent pattern of the inhaled agent is the most suspected [1]. To the best of our knowledge no underlying mechanisms responsible for all reported side effects are reported till now. We present two patients who developed a flu-like syndrome with diffuse interstitial infiltrates after 'drug' abuse probably associated with the presence of cytochrome P450 (CYP) and vitamin K epoxide reductase complex 1 (VKORC1) allelic variants.

Case 1. A 22-year-old male presented with dyspnea, non-productive cough, myalgia and fever since 4 days. His medical and family history was unremarkable. He smoked tobacco for a few years. Moreover, he admitted alcohol abuse, heavy marijuana and cocaine smoking during the last months. He was a little tachypnoeic (20 breaths/min). He had a moderate hypoxemia (pO_2 8,7 kPa, breathing room air), high serum C-reactive protein (254 mg/L), a white blood cell count of 16,3 10^9/L and a normal number of eosinophils. His chest X-ray showed diffuse infiltrates at presentation *(figura a)* and the high resolution CT scan a diffuse reticulonodular pattern. His diffusing capacity was slightly decreased (81% of predicted). Bronchoalveolar lavage fluid cell differentiation revealed a high number of polymorphonuclear neutrophils (32,4% of total cell count) with 53,8% alveolar macrophages, 11,2% lymphocytes, 2,0% eosinophils and 0,2% mast cells. Moreover, some 'foamy' alveolar macrophages and a few reactive pneumocytes type II cells were found. No intracellular micro-organisms were seen, cultures remained sterile. Serology was negative. No underlying immunosuppressive condition was evident. Additionally, relevant *CYP* polymorphisms and *VKORC1* G-1639A and G1173T single nucleotide polymorphisms (SNPs) were profiled. He appeared to be a *CYP2C19* intermediate metabolizer (*1/*2) and heterozygote *VKORC1* (GA/CT). Because of

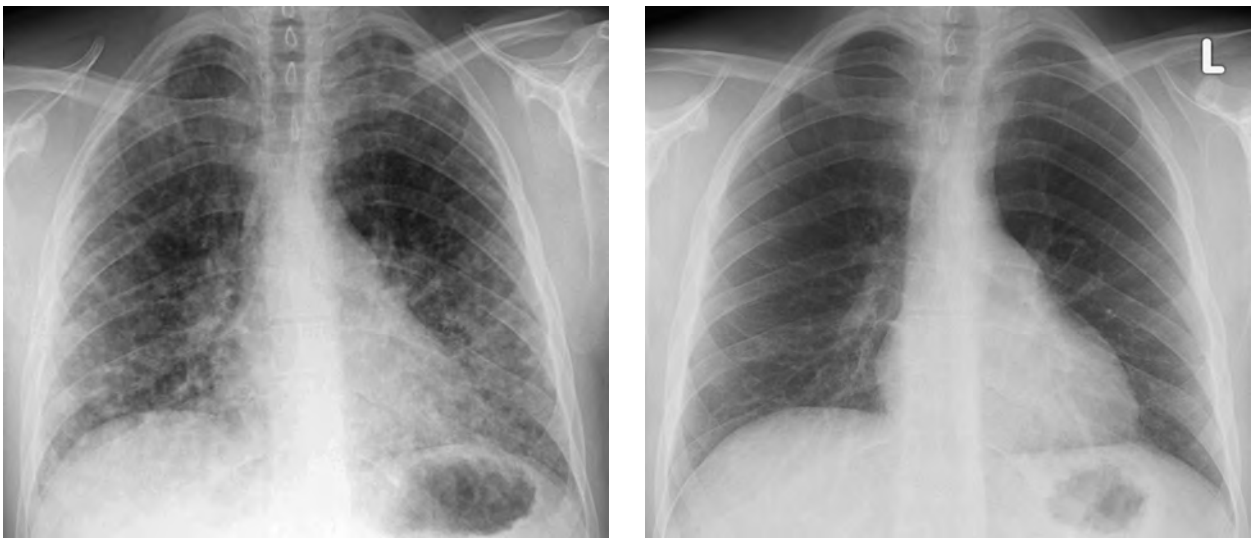
high suspicion of a 'drug'-induced pneumonitis and the absence of features of any infectious cause, corticosteroids were started (40 mg daily) and continued for two weeks. Thereafter, the corticosteroids were tapered gradually. His clinical condition improved within 2 weeks. Dyspnea and cough disappeared, follow-up chest radiograph abnormalities cleared *(figura b)* and the pO_2 became within normal limits (11,9 kPa).

Case 2. A 34-year-old woman was admitted to our hospital. She was suffering from dyspnea, malaise, hypoxia, coughing with episodes of a little hemopysis and exacerbation of asthma. Her chest X-ray showed a discreet diffuse interstitial damage. She was an irregular cocaine user (again two weeks before the last admission). Physical examination revealed some crackles at auscultation, she was tachypnoeic (25 breaths/min) and her body temperature was 37,8°C. She had a hypoxemia (pO_2 7,2 kPa, breathing room air), a serum C-reactive protein of 12 mg/L, a white blood cell count of 7,4 10^9/L and a normal number of eosinophils. The urinary test for Legionella pneumonia and Streptococcus pneumoniae was negative as well as the serology for common viruses, Mycoplasma, Ricketsiae and Chlamydia. She has been HIV positive for three years now. She was diagnosed with cardiac failure and had a myocardial infarct (MI) due to cocaine-associated ischemic injury one month before this admission. After the MI she was prescribed aspirin in order to prevent clot or thrombocyte aggregation forming and methadone to control her addiction, both these drugs are known to influence the coagulation. In addition, relevant polymorphisms were profiled. This revealed that she appeared to be a *CYP2C9* intermediate metabolizer (*1/*3) and *VKORC1* heterozygote (GA/CT). She was treated with corticosteroids and her clinical condition improved within a few days, her hypoxia normalized as well as the chest X-ray.

Discussion. Diagnosing drug-induced pulmonary and cardiovascular diseases remains a challenge for clinicians. Cocaine is a naturally occurring alkaloid that can be extracted from leafs of the Erythroxylon coca plant and is available in four forms: hydrochloride salt, «freebase», crack, and «bazuco». Crack cocaine is obtained by dissolving cocaine hydrochloride in water with sodium bicarbonate (baking soda) to extract the hydrochloride and make the substrate heat stable. The cocaine base precipitates, forming hard masses or rocks that melt when dry, vaporize at high temperatures (98°C) and can be smoked. Crack is considered to be the most potent and addictive form of cocaine and smoking is the preferred method for many drug users. Adulterants are found in street samples of cocaine and result in additional toxicity. Among the most common adulterants are local anesthetics (lidocaine, benzocaine), sugars (mannitol, lactose, sucrose), stimulants (caffeine, ephedrine), toxins (quinine, strychnine), and inert compounds (inositol, talc, cornstarch) as well as other substances (e.g. flour, aspirin, plaster) [1]. Smoking of cocaine exposes the lung directly to the volatilized drug as well as to the other combustion products of the smoked mixture, thereby increasing the risk of adverse pulmonary effects.

Pulmonary complications of cocaine are influenced by administration method, dose size, and the presence of associated substances. These complications include e.g. acute respiratory symptoms, pulmonary edema, asthma, pulmonary hemorrhage, «crack lung», talcosis, and interstitial lung disease [1]. Moreover, chronic inhalative cocaine abuse can cause foreign body associated granulomatosis mimicking sarcoidosis of the lung and other organs. It is important to establish this differential diagnosis by confidential interview and systematic polarisation microscopy to detect foreign material in tissues.

A growing body of evidence suggests that several different xenobiotic-metabolizing CYP and phase II enzymes (i.e. conjugation enzymes, including several transferases) are present in the human lung, possibly contributing to in situ activation and inactivation of toxicants [4]. Although metabolism of foreign substances is usually beneficial in eliminating potential toxins from the body, in some instances the metabolic process can transform harmless substances into toxic chemicals through a process called metabolic bioactivation. Recently, Wijnen et al. indicated that drug-induced interstitial lung diseases may be attributable to a reduced metabolic capacity by CYP enzymes [5]. The presence of *CYP* variant genotypes appeared to be a substantial susceptibility risk factor in the development of drug-induced pulmonary adverse events [5].



a ***b***

Chest X-ray ***(a)*** shows a widespread nodular pattern with a mid and lower zone predominance.
Chest X-ray ***(b)*** two weeks after presentation demonstrates no abnormalities

CYP2C9 and CYP2C19 belong to the largest CYP450 family and together with other members like CYP2D6 metabolize, to varying amounts, more than half of all frequently prescribed drugs [6]. CYP2C19 has a significant role in the detoxification of many xenobiotica such as cocaine, marijuana and its metabolites [7]. The two presented patients had either a heterozygote *CYP2C9* or *CYP2C19* variant allele. This implicates that they are an intermediate metabolizer for marijuana and cocaine (or its substitute methadone).

Diffuse alveolar hemorrhage with hemoptysis (reported in up to 26% of crack users) secondary to freebase cocaine smoking can be life threatening, with massive bleeding that may require surgery [8]. Smoking of laced cocaine or marijuana can have similar effects as was described by previous studies in which rodenticide (a so-called superwarfarin) was added to the cocaine or marijuana in order to enhance its effect [9]. The association of alveolar hemorrhage with hypersensitivity pneumonitis has been considered in the pathophysiology of this acute syndrome, which usually responds to corticosteroids. The presented cases also responded quite well to corticosteroids. Interestingly, both patients displayed a variant allele for the VKORC1 enzyme, which in turn can cause so-called coumarins sensitivity and has a profound influence on the vitamin K cycle and on vitamin K dependent clotting factors. When triggered by warfarin, so-called superwarfarins, or in these two cases (illicit) drugs, an over-anticoagulation can occur. This over-anticoagulation can cause diffuse alveolar damage, which in turn can explain some of their symptoms like the diffuse alveolar damage, as was seen in the female patient (case 2). Moreover, as both cases also possessed an allelic variant in the *CYP2C* this influence on anticoagulation was strengthened, for CYP2C9 as well as CYP2C19, play a role in metabolism of the vitamin K cycle [10].

In conclusion, these cases show a probable association between the presence of *CYP* and *VKORC1* allelic variants and interstitial lung damage caused by cocaine use. Moreover, it highlights the increasing importance of introducing pharmacogenomics into the work-up of patients with suspected 'drug'-induced toxicity. Interindividual differences in the expression of CYP enzymes are assumed to contribute to the risk of developing interstitial lung and other diseases initiated by agents that require metabolic activation or detoxification. *CYP* polymorphisms, especially in combination with *VKORC1* involvement, should be considered as one of the factors associated with the development of adverse pulmonary drug reactions including alveolar hemorrhage and other toxic effects.

Conflict of interest. The authors report no conflict of interest. The study was performed without funding.

REFERENCES

1. *Restrepo, C.S.* Pulmonary complications from cocaine and cocaine-based substances: imaging manifestations / C.S. Restrepo, J.A. Carrillo, S. Martinez [et al.] // Radiographics. — 2007. — Vol. 27(4). — P. 941—956.
2. *Tashkin, D.P.* Airway effects of marijuana, cocaine, and other inhaled illicit agents / D.P. Tashkin // Curr. Opin. Pulm. Med. — 2001. — Vol. 7(2). — P. 43—61.
3. *Gotway, M.B.* Thoracic complications of illicit drug use: an organ system approach / M.B. Gotway, S.R. Marder, D.K. Hanks [et al.] // Radiographics. — 2002. — № 22 (Spec. No). — S. 119—135.
4. *Ben-Zaken Cohen, S.* The growing burden of chronic obstructive pulmonary disease and lung cancer in women: examining sex differences in cigarette smoke metabolism / S. Ben-Zaken Cohen, P.D. Pare, S.F. Man, D.D. Sin // Am. J. Respir. Crit. Care Med. — 2007. — Vol. 176 (2). — P. 113—120.
5. *Wijnen, P.A.* Role of cytochrome P450 polymorphisms in the development of pulmonary drug toxicity: a case-control study in the Netherlands / P.A. Wijnen, M. Drent, P.J. Nelemans [et al.] // Drug Saf. — 2008. — Vol. 31 (12). — P. 1125—1134.
6. *Nebert, D.W.* Clinical importance of the cytochromes P450 / D.W. Nebert, D.W. Russell // Lancet. — 2002. — Vol. 360 (9340). — P. 1155—1162.
7. *Bland, T.M.* CYP2C-catalyzed delta9-tetrahydrocannabinol metabolism: kinetics, pharmacogenetics and interaction with phenytoin / T.M. Bland, R.L. Haining, T.S. Tracy, P.S. Callery // Biochem Pharmacol. — 2005. — Vol. 70(7). — P. 1096—1103.
8. *Tashkin, D.P.* Pulmonary status of habitual cocaine smokers / D.P. Tashkin, M.E. Khalsa, D. Gorelick [et al.] // Am. Rev. Respir. Dis. — 1992. — Vol. 145(1). — P. 92—100.
9. *Waien, S.A.* Severe coagulopathy as a consequence of smoking crack cocaine laced with rodenticide / S.A. Waien, D.Jr. Hayes, J.M. Leonardo // N. Engl. J. Med. — 2001. — Vol. 345(9). — P. 700—701.
10. *Wijnen, P.A.* Variant VKORC1 and CYP2C9 Alleles in Patients with Diffuse Alveolar Hemorrhage Caused by Oral Anticoagulants / P.A. Wijnen, C.F. Linssen, G.R. Haenen [et al.] // Mol. Diagn. Ther. — 2010. — Vol. 14(1). — P. 23—30.

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ПРИЧИНЫ КРОВОХАРКАНЬЯ И ЛЕГОЧНОГО КРОВОТЕЧЕНИЯ У БОЛЬНЫХ САРКОИДОЗОМ ЛЕГКИХ

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Реферат. С помощью современных методов лучевой диагностики (КТ, ВРКТ, КТ-ангиография, ОФЭКТ, допплер-ЭхоКГ) и фибробронхоскопии были установлены причины кровохарканья и легочного кровотечения у 26 из 290 больных саркоидозом легких, наблюдаемых в НИИ пульмонологии в течение последних 5 лет. Основными