Originales

Risk of pulmonary embolism associated to the use of hormonal contraceptives: a series of eight cases

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SUMMARY
Objetive: To describe and analyze the suspected Pulmonary Embolisms (PEs) as adverse drug reaction (ADR) attributed to the use of Hormonal Contraceptives (HCs), identified in the Hospital Pharmacy Unit of a second level hospital, regarding the informative note issued by the AEMPS.
Methods: A retrospective observational study analyzing suspected PE in women using HCs wich were detected in the Hospital Pharmacy Unit through the pharmaceutical validation of treatment for hospitalized patients in a hospital during a two-year period. The cause-effect relationship between drug administration and the ADR is classified according to the Karch-Lasagna algorithm.
Results: Eight cases of PE were detected in the Hospital Pharmacy Unit, in women using HCs, with a mean age of 22.9 years (SD: 2.67) and a mean Risk Factor (RF) of 2.3 (SD: 0.9) per patient, the most frequent being smoking and obesity. In none of the eight cases described, the HC involved was second generation.
Conclusions: HCs are drugs which have demonstrated having a higher benefit than the risks associated with their use. However, it is necessary to assess each patient's RFs at initiation of treatment with HCs and during said treatment, in order to select the most adequate HC and reduce the risk of PE. It is also important to conduct an adequate healthcare education for patients, which will help to detect and prevent RFs, as well as to identify the signs and symptoms of PE.

Key Words: **Pulmonary embolism, venous thrombosis, contraceptive agents.**

Riesgo de tromboembolismo pulmonar asociado al uso de anticonceptivos hormonales: una serie de ocho casos

RESUMEN
Objetivo: Describir y analizar las sospechas de tromboembolismo pulmonar (TEP) como reacción adversa a medicamentos (RAM) atribuidas al consumo de anticonceptivos hormonales (ACH), identificadas en el Servicio de Farmacia Hospitalaria de un hospital de segundo nivel, a propósito de la nota informativa emitida por la AEMPS.
Métodos: Estudio observacional retrospectivo en el que se analizan las sospechas de TEP que fueron identificadas en el Servicio de Farmacia Hospitalaria a través de la validación farmacoterapéutica de los tratamientos de pacientes ingresados en el hospital durante un período de dos años. La relación causa-efecto entre la administración del fármaco y la RAM se catalogó en base al algoritmo de Karch-Lasagna.
Resultados: Se detectaron ocho casos de TEP en el Servicio de Farmacia en mujeres usuarias de ACH, con una edad media de 22,9 años (DE: 2,67) y una media de factor de riesgo (FR) de 2,3 (DE: 0,9) por paciente, siendo los más frecuentes el tabaco y la obesidad. En ninguno de los ocho casos descritos, el ACH implicado era de segunda generación.
Conclusiones: Los ACH son fármacos que han demostrado tener un beneficio mayor a los riesgos asociados a su uso. No obstante, es necesario evaluar los FR de cada paciente al inicio del tratamiento con ACH y durante el mismo con el fin de seleccionar el ACH más apropiado y reducir el riesgo de TEP. También es importante realizar una correcta educación sanitaria a las pacientes que ayude a detectar y evitar los FR, así como a identificar los signos y síntomas de TEP.

Palabras clave: **Tromboembolismo pulmonar, trombosis venosa, agentes anticonceptivos.**

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INTRODUCTION

Venous Thromboembolism (VTE) is a clinical term which includes two closely associated conditions: Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)[1,2]. There are various risk factors (RFs) associated with an increase in the incidence of PE, and this will be higher when there is a higher number of concomitant RFs[3-5]. Table 1 shows a classification of RFs for VTE based on their etiology[2].

Hormonal contraceptives (HCs) are indicated to prevent pregnancy through a pharmacological method, and they contain combined oestrogens and progestagens. HCs with oral, vaginal or transdermal administration present a high contraceptive efficacy, and an adequate safety profile[6]. HCs can be classified into different generations, based on the quantity of oestrogens and the type of progestagen they contain (Table 2)[7].

First generation HCs are associated with many adverse effects, such as vascular disorders. Second generation HCs cause fewer side effects, though they are also associated with an increased risk of VTE (5-7 cases per each 10,000 woman-years)[8]. Third generation HCs present a better lipid profile and lower risk of acute myocardial infarction[9] than second generation HCs, though the risk of VTE is higher[10,11] (6-12 cases per each 10,000 woman-years). Finally, fourth generation HCs present a risk of VTE similar to third generation HCs (9-12 cases per each 10,000 woman-years)[8].

HCs containing cyproterone (derived of progesterone) have a high antiandrogenic potency, and a risk of VTE similar to the rest of HCs[12]. These are only indicated for the treatment of acne, androgenic alopecia, and mild forms of hirsutism, and their use is contraindicated for contraception only. Likewise, chlormadinone is also a derivative of progesterone with a marked antiandrogenic activity[13].

The risk of thrombosis associated to the use of HCs seems to be linked with the concentration of oestrogen, with the androgenic potency of the gestagen associated, and the thrombophilic burden of patients, because it has been observed that the pharmacological modulation of oestrogens causes an increase in the concentrations of coagulation factors, and a reduction of the factors inhibiting coagulation[9], and these alterations will be higher with third and fourth generation HCs[14].

On January, 2013, the Spanish Agency of Medicines and Medical Devices (AEMPS) informed about the initiation of a review of third and fourth generation HCs by the Pharmacovigilance Risk Assessment Committee (PRAC) to assess if the information provided in product specifications and leaflets was enough to make the best treatment decision by healthcare professionals and patients[15]. Medications containing cyproterone were also evaluated by the PRAC from January, 2013[16]. These reviews ended on October, 2013, and May, 2013, respectively, and the conclusion was that the benefit of using HCs is higher than its risks, though there are slight differences among the different combinations of HCs; the likelihood of VTE is higher during the first year, at treatment re-initiation after an interruption of at least 4 weeks, and in women who present concomitant RFs[8]. Medications containing cyproterone in combination with ethinyl estradiol are exclusively indicated for the treatment of women with hirsutism

Table 1
Classification of risk factors for VTE[2]

Type of risk	Risk factors
General	Age, prolonged immobilization, previous VTE, institutionalization, oestrogen treatment, pregnancy or postpartum, varicose veins, superficial thrombophlebitis, prolonged travels, obesity and smoking
Surgery	General major surgery, major trauma surgery, fractures, pacemakers, central venous catheter
Genetic	Prothrombin gene 20210A mutation, factor V-Leiden mutation, antithrombin deficiency, protein C deficiency, protein S deficiency, dysfibrinogenemias, hyperhomocysteinemia, plasminogen deficiency, or increase in coagulation factors (VIII, IX…)
Medical conditions	Neurological lesions, neoplasias, decompensated COPD, nephrotic syndrome, severe infection, myocardial infarction, respiratory failure, heart failure, bowel inflammatory disease, acquired antiphospholipid syndrome, chronic renal failure, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, antipsychotic treatment, burns, treatment with tamoxifen or raloxifene, diabetes mellitus

COPD: chronic obstructive pulmonary disease.

Table 2
Classification of hormonal contraceptives (HCs)[7]

Contraceptive generations	Oestrogens	Progestagens
First generation	>50 ethinylestradiol μg	
Second generation	30-50 ethinylestradiol μg	Levonorgestrel, norgestimate, norethindrone
Third generation	20-30 ethinylestradiol μg	Desogestrel, gestodene
Fourth generation	20-30 ethinylestradiol μg	Drospirenone

and/or androgen dependent acne moderate or severe and/or hirsutism, which do not respond to topical treatment and systemic antibiotic therapy. They should not be taken with other hormonal contraceptives as this would increase the risk of VTE[17].

The objective of the present study is to describe and analyze the suspected PEs as adverse drug reaction (ADR), attributed to the use of HCs identified in the Hospital Pharmacy Unit of a second level hospital during a two-year period, regarding the informative note issued by the AEMPS.

MATERIAL AND METHODS

An observational retrospective study, analyzing the suspected PEs secondary to the use of HCs in a second-level hospital from the Community of Madrid, during the period between July, 2012 and July, 2014.

Suspected PEs associated with the use of HCs were detected in the Hospital Pharmacy through the pharmaceutical validation of treatment for hospitalized patients, and were recorded in the Pharmacy Unit database. The electronic clinical record application (Selene®) was used for clinical data collection, as well as the Primary Care prescription viewer (HORUS®) and the manager of clinical requests available at the hospital (GPC®).

The following variables were collected:

- Demographic variables: Age, HC involved, and in case of using cyproterone, its indication.
- Concomitant RFs: Smoking, lack of mobility in the four weeks before the PE, previous VTE, obesity, family history of VTE, and results of thrombophilia testing.
- PE symptoms and signs at admission: Pleuritic pain, dyspnea, haemoptysis, pain or inflammation in lower limbs, tachycardia (>100 beats per minute), tachypnea (>20 breaths per minute) and desaturation (Sat. O2 <95%).
- Lab test data: Partial pressure of oxygen in arterial blood and D-dimer value.
- Diagnostic tests: Electrocardiogram, chest X-ray, computed tomography angiography (CTA), pulmonary scan, transthoracic ultrasound test, and eco-doppler.
- Clinical management: Hospitalization or not in the Intensive Care Unit (ICU), treatment of the acute stage, treatment at hospital discharge, contraindication for HC and other measures and recommendations.

The cause-effect relationship between drug administration and the ADR is classified according to the Karch-Lasagna criteria[18], from dubious to proven, as appears in table 3.

All suspected PEs associated to the use of HC were notified with the on-line Yellow Card system to the Pharmacovigilance Centre (PC) of the Autonomous Community of Madrid. The PVS was consulted about the number of suspected PEs associated to the use of HC during the same period of the study at national level.

RESULTS

During the period between July, 2012 and July, 2014, eight suspected PEs were detected in the Hospital Pharmacy Unit among patients using HCs who were admitted to hospital. The mean age of patients was 22.9 years (SD: 2.67) and the mean number of RFs was 2.3 per patient (SD: 0.9); seven patients had >2 associated RFs, five patients were smokers, and five patients were obese. The HC involved was: oral ethinylestradiol/cyproterone (derived of progesterone) in three patients, etonogestrel/ethinylestradiol vaginal ring (3rd generation) in two patients; oral ethinylestradiol/drosperidone (4th generation) in two patients, and oral ethinylestradiol/chlormadinone (derived of progesterone) in one patient. Those data collected appear on table 4. Currently, all eight patients have recovered from their thromboembolic event.

According to data provided by the PC, in the same period of two years, 46 suspected PEs associated to the use of HC were registered in Spain, including those reported from our hospital (17%).

Table 3
Karch-Lasagna algorithm improved by Naranjo[18]

	Yes	No	Score
1. There are previous conclusive reports about the ADR	+1	0	
2. The adverse event appeared when the suspected medication was administered	+2	-1	
3. The ADR improved at discontinuation or with the administration of a specific antagonist	+1	0	
4. The ADR reappeared when the medication was administered	+2	-1	
5. There are alternative causes which may cause this reaction	-1	+2	
6. The ADR occurred after placebo administration	-1	+1	
7. The drug was detected in blood or other liquids in toxic concentrations	+1	0	
8. The severity of the ADR was higher at higher doses, or lower at lower doses	+1	0	
9. The patient has had similar reactions with the medication in the past	+1	0	
10. The ADR was confirmed with some objective evidence	+1	0	
Total			
*When the information is not available, a score equal to 0 will be assigned	≥9		Proven ADR
	5-8		Probable ADR
	1-4		Possible ADR
	0		Dubious ADR

Table 4
Data summary

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8
Demographics	Age	24	17	26	24	25	24	22	21
	HC used	Oral ethinyles-tradiol/ cyprote-rone	Oral ethinyles-tradiol/ cyprote-rone + cyprote-rone	Oral ethinyles-tradiol/ cyprote-rone	Vaginal ring etonoges-trel/ ethinyl estradiol	Vaginal ring etonoges-trel/ethinyl estradiol	Oral ethinyles-tradiol/ drosperi-done	Oral ethinyles-tradiol/ drosperi-done	Oral ethinyles-tradiol/ chlormadi-none
	Cyproterone indication	--	Hirsutism	Hirsutism					
Risk factors	Number of risk factors	3	2	2	2	4	2	1	3
	Smoking	No	No	Yes	Yes	No	Yes	Yes	Yes
	Previous immobilization	No	No	No	No	Yes	No	No	Yes
	Previous VTE	No	No	No	No	No	No	No	Yes
	Obesity	Yes	Yes	Yes	No	Yes	Yes	No	No
	Family history 1st degree VTE	Yes	No	No	Yes	Yes	No	No	No
	Thrombophyllia testing	20210A mutation heterozy-gous carrier	Free antigenic Protein S 19% (>54%)	Normal	Normal	Global Protein C/ Factor V: 0.59 (0-79-1-10)	Normal	Normal	Normal
Symptoms	Pleuritic pain	Yes	Yes	No	Yes	Yes	Yes	No	Yes
	Dyspnea	No	Yes	Yes	No	Yes	No	Yes	Yes
	Hemoptysis	Yes	No	No	Yes	Yes	No	No	No
	Lower limb pain	Yes	Yes	No	No	No	No	No	No
	Tachycardia (>100 bpm)	No	No	Yes	Yes	Yes	No	Yes	Yes
	Tachypnea (>20 bpm)	No	No	Yes	No	No	No	Yes	No
	O2 desaturation (<95%)	No	--	Yes	No	Yes	No	Yes	Yes
Lab test data	Arterial blood gas	No	No	Yes	No	Yes	Yes	Yes	Yes
	Arterial PO2 <75 mmHg	--	--	Yes	..	Yes	No	Yes	Yes
	D-dimer (ng/ml)	8187	9958	13268	4487	4227	970.4	732.3	392
Diagnostic tests	Electrocardiogram	Normal	Normal	Image of incom-plete right branch block and S1Q3T3 pattern	Normal	Inverted T in III	McQuinn and White Pattern	Normal	Normal
	Chest X-ray	Normal	Normal	Normal	Blunting of the right costophre-nic angle	Normal	Normal	Normal	Normal
	CTA[a]	Bilateral acute PE	Bilateral massive PE	Bilateral massive PE	Right acute PE	--	Acute PE in RLL[b]	Left PE	"
	Pulmonary scan	--	--	--	--	Right PE	--	--	Bilateral PE
	Transthoracic ultrasound	--	Pulmonary artery thrombus	RV[c] dilation	Normal	Mild RV dilation	--	Normal	Normal
	Eco-doppler	Normal	--	Popliteal thrombosis	Normal	--	--	--	--

Table 4 *(cont.)*

Clinical management	**ICU admission**	No	Yes	Yes	No	No	No	No	No
	Acute treatment	Nadroparine forte 0-6 ml/24h	Enoxaparin 1 mg/kg/ 12h	Enoxaparin 1mg/kg/ 12h Alteplase	Enoxaparin 1 mg/kg/ 12h	Enoxaparin 1 mg/kg/ 12h	Nadroparine forte 0-6 ml/ 24h	Enoxaparin 1 mg/kg/ 12h	Enoxaparin 1 mg/kg/ 12h
	Outpatient treatment	Acenocoumarol	Acenocoumarol	Acenocoumarol	LMWHd	Acenocoumarol	LMWH	Acenocoumarol	Acenocoumarol
	HC interrupted	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	Other measures	Rest	--	Support stockings. Quit smoking	Quit smoking	Rest.	Quit smoking	Rest. Quit smoking	Rest. Quit smoking
	Karch-Lasagna Algorithm	Probable	Probable	Probable	Probable	Probable	Probable	Probable	Probable

[a] CTA: computerized tomographic angiography; [b] RLL: right lower lobe; [c] RV: right ventricle.

DISCUSSION

Despite the fact that the risk of PE associated to taking HC is very low, this is a severe ADR which requires hospital admission, and can endanger patients' lives. A series of eight PE cases in young women has been described, which were detected in the Hospital Pharmacy Unit though the pharmaceutical validation of treatments in hospitalized patients, with a probable association with the use of HC according to the Karch-Lasagna algorithm applied.

In none of the eight cases described, the HC involved was second generation; these are associated with a lower risk of PE. All patients also presented concomitant RFs. These data demonstrate the importance of conducting an adequate anamnesis, evaluating all RFs associated to each patient before initiating treatment with HC and during said treatment, because RFs can vary over time. Likewise, it is necessary to select the most adequate HC for each patient, with the aim of reducing the risk of VTE.

According to the indications by the AEMPS after reviewing the safety of HCs use, it is recommended to use second generation HCs in all patients about to initiate contraceptive treatment; the use of third or fourth generation HCs could be considered in search of a better lipid profile and the lower risk of acute myocardial infarction for those patients who had previously presented situations of high thrombotic risk (such as pregnancy or surgery), and have not suffered VTE.

An adequate health education must be conducted for patients, informing about the potential risks of taking HCs and which RFs will favour PEs, with the aim of reducing as much as possible those already present (such as smoking or excess weight), and preventing or detecting the potential RFs which can appear in the future (such as immobilization). Patients should also be informed about the signs and symptoms of VTE for an early identification.

HCs are drugs which have demonstrated having a benefit in terms of preventing non-desired pregnancies superior to the potential risks associated with their use. Conducting coagulation tests in all patients using HCs would not be justified, because the incidence of VTE associated with the use of HCs is still low, but it could become relevant in the case of patients who have had previous episodes of VTE or a family history of VTE.

The limitations of our study are its retrospective nature, where the indication of ethinylestradiol-cyproterone could not be determined in one of the patients, the arterial blood gas tests were not available for all patients, and the duration of treatment with HCs until the thrombotic event could not be established, in order to determine whether the PE occurred within the first year of treatment.

Competing interests: The authors declare no conflicts of interest.

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