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Risk of meningioma among users of high doses of cyproterone acetate as compared with the general population: evidence from a population-based cohort study

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WHAT IS ALREADY KNOWN ON THIS SUBJECT

- Information from the spontaneous reporting system raised the hypothesis of an increased risk of meningioma in patients treated with high doses of cyproterone acetate (CPA).
- Meningiomas are known to be hormone-sensitive tumours and express progesterone receptors and CPA has an anti-androgenic, progestagenic and antigonadotropic effect.
- More formal evidence from epidemiological studies is lacking.

WHAT THIS STUDY ADDS

- This population-based cohort study supports the hypothesis that the exposure to high dose CPA increases the risk of meningioma
- The increased risk was observed both in men and women and was only relevant for exposures longer than 1 year.

AIM

Information from the spontaneous reporting system raised the hypothesis of an increased risk of meningioma in patients treated with high doses of cyproterone acetate (CPA). The objective of this study was to test the hypothesis of an increased risk of meningioma among users of high dose CPA as compared with non-users in a medical records computerized database.

METHODS

A retrospective cohort study was performed in a Spanish primary care database (BIFAP). Meningioma incidence rates were compared in patients exposed to high dose CPA (users) with those non-exposed and with those exposed to low dose CPA. Poisson regression analysis was used to estimate the incidence rate ratios after adjusting for age and gender.

RESULTS

Among 2474 users of high dose cyproterone (6663 person-years) four meningioma cases were identified, resulting in an incidence rate (IR) of 60.0 (95% CI 16.4, 153.7) per 100 000 person-years, which was significantly higher than that observed among the non-users (IR 6.6; 95% CI 6.0, 7.3) and among women users of low dose cyproterone (IR 0.0, 95% CI upper limit 5.5). After adjusting for age and gender, patients exposed to high dose CPA showed an increased risk of meningioma of 11.4 (95% CI 4.3, 30.8) as compared with non-users.

CONCLUSIONS

The results of this study support the hypothesis that the exposure to high dose CPA increases the risk of meningioma.

Introduction

Meningiomas are mostly benign, slow growing tumours originating from the arachnoid cap cells. Meningiomas have an annual incidence ranging from 3 to 8 per 100 000 person-years in the different series, occur more frequently in women and its incidence increases with age [1, 2]. Ionizing radiation is the only unequivocal risk factor identified for meningeal neoplasm although others have been suggested [1].

Information from the spontaneous reporting system raised the hypothesis of an increased risk of meningioma in patients treated with high doses of cyproterone acetate (CPA) [3]. The review by the European Pharmacovigilance Working Party (PhVWP) [4] concluded that the available evidence supported a causal relationship between high dose CPA (≥25 mg) and the occurrence of meningioma. The summary of product characteristics was modified accordingly including a formal contraindication of these formulations in patients with meningioma or a history of meningioma [4].

The main objective of this study was to estimate the incidence rates of meningioma in the general population and to test the hypothesis of an increased risk of meningioma among users of high dose CPA as compared with non-users in a computerized medical records database.

Methods

Setting

The study was performed using the information from the Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria (BIFAP) database. This is a longitudinal population-based database kept by the Spanish Agency for Medicines and Medical Devices that collates, from 2001 onwards, the computerized medical records of 1883 general practitioners (GPs) throughout Spain [5]. The research database includes anonymized information on 3 274 302 persons, totalling 13 718 431 person-years of follow-up. Data recorded in BIFAP include demographic information, prescription details, clinical events, specialist referrals and laboratory test results [5].

Study design

We performed a retrospective cohort study with three groups: those who have recorded at least one prescription of high dose CPA, those with at least one recorded prescription of low dose CPA and those with no recorded prescriptions of CPA.

Study population

The study period comprised from January 1, 2001 to December 31, 2007. The study population included all individuals aged younger than 100 years who were enrolled for at least 1 year with the GP. Patients with a recorded diagnosis of meningioma before the start to follow-up were excluded.

For the CPA cohorts, the date of the first recorded prescription was considered to be the start of follow-up date whilst for the general population cohort the start to follow-up date was 1 year after the enrolment date with the GP. All patients were then followed up until the earliest date of the following end points: recorded diagnosis of meningioma, death, date of 101st birthday, end of patient's registration in BIFAP or the end of the study period.

Exposure definition

In Spain there is only one high dose CPA product on the market with a strength of 50 mg. All patients receiving at least one high dose CPA prescription during their follow-up in the study period were included among the 'high dose user' cohort, while those with no recorded prescription of high dose CPA were included among the 'non user' cohort. Those women receiving CPA at low dose were included in a separate cohort of 'low dose users'. Those patients who happened to be exposed to both high and low dose CPA were included in the 'high dose user' cohort.

Outcome definition and case ascertainment

There is not a specific code identifying meningioma in the ICPC-2 dictionary. To identify all potential cases of meningioma, the string text 'meningioma' was searched as free text in the different sections of the medical records.

Through a computer algorithms search we identified 668 potential meningioma cases. The clinical profiles of all these cases were reviewed by trained physicians and were classified as valid cases (n = 456), possible cases (n = 140) and non-cases (n = 72).

The main analysis included only valid cases. Sensitivity analyses were performed by including valid and possible cases in the case definition.

Statistical methods

Crude and age-standardized incidence rates and 95% CI were calculated. Multivariate Poisson regression analysis was used to estimate the incidence rate ratios (IRR) of patients exposed to high dose CPA as compared with those non-exposed after adjusting for age and gender.

Results

Incidence rates of meningioma in the general population

During the study period, a total of 456 valid meningioma cases were identified in 2 137 191 people (6 881 155 person-years of follow-up) yielding a crude incidence rate of 6.6 (95% CI 6.0, 7.3) per 100 000 person-years and an

age-standardized incidence rate of 4.1 (95% CI 3.7, 4.5). The incidence of meningioma was higher in women (crude 8.9, 95% CI 8.0, 9.9; age-standardized 5.4 95% CI 4.7, 6.0) compared with men (crude 4.0, 95% CI 3.4, 4.8; age-standardized 2.6, 95% CI 2.1, 3.1) and increased with age.

Risk of meningioma in patients exposed to cyproterone acetate

During the study period, 2474 people (6663 person-years of follow-up) had, at least, one high dose CPA prescription registered in BIFAP in the study period (high dose CPA cohort). Of them, 70% were female, with a mean age at cohort entry of 27.1 (SD 11.8) years in females and 72.6 (SD 15.7) years in males. Among this cohort we identified four meningioma cases (Table 1), resulting in an incidence rate of 60.0 (95% CI 16.4, 153.7) per 100 000 person-years. All cases exposed to high dose CPA had a treatment duration longer than 1 year. When the analysis was restricted to patients with such long duration the incidence rate increased to 117.1 (95% CI 31.9, 299.9).

The cohort of low dose CPA users comprised 22 238 people, all of them women (67 272 person-years of follow-up). Among them no meningioma cases were identified (Incidence rate 0.0, 95% upper CI limit 5.5 per 100 000 person-years).

After adjusting for age and gender, patients in the high dose CPA cohort showed a rate ratio compared with the non-users cohort of 11.4 (95% CI 4.3, 30.8) (Table 2). When valid and possible cases were included in the case definition the adjusted rate ratio in the high dose CPA cohort was 9.1 (95% CI 3.4, 24.5).

Discussion

The first signal of an association of high dose CPA with meningioma was raised by the analysis of a case series published by Froelich *et al*. in 2008 [3]. Meningiomas are known to be hormone-sensitive tumours and express progesterone receptors and CPA has an anti-androgenic, progestagenic and antigonadotropic effect providing a biological plausibility to those findings [1].

Results using the BIFAP database support the hypothesis of an increased risk of meningioma in patients on high dose CPA. This increased risk was only observed in patients with exposures longer than 1 year. We did not find an increased risk among women on low doses. All these findings give support to the PhVWP conclusions and risk minimization actions [4].

The main limitations of the study are related to the low number of events observed in the high dose CPA cohort (four cases) and a limited follow-up time (mean follow up 3.2 years). Besides, we cannot be certain that the meningioma did not exist before the start of CPA use, but all CPA exposed cases had a recorded exposure of at least 2 years

Table 1

Characteristics of meningioma cases in patients exposed to high dose cyproterone acetate (CPA)

Case number	Age (years)	Gender	First CPA prescription registered (Date)	Last CPA prescription registered before diagnosis (Date)	Meningioma diagnosis date	Time from first prescription to diagnosis (years)	Indication	Localization of tumour
1	83	M	23/09/2003	17/03/2005	09/01/2006	2.3 years	Prostate cancer	Cavernous sinus
2	71	M	24//07/2002	18/01/2005	08/03/2005	2.6 years	Prostate cancer	Olfactory groove
3	66	F	03/03/2003	13/05/2005	26/09/2005	2.6 years	Not specified	Olfactory groove
4*	43	F	09/09/2004	11/07/2006	18/01/2007	2.3 years	Androgenic alopecia	Left cerebral hemisphere

*Patient also on treatment with low doses of CPA.

Table 2

Meningioma risk in patients on high doses of cyproterone acetate (CPA). Results of adjusted Poisson regression analysis

Variable	Categories	Cases	Person-years	Rate ratio (95% CI)	*P* value
CPA use	Non-users	452	6 807 220	1	
	Low dose	0	67 272	*	*
	High dose	4	6 663	11.4 (4.3, 30.8)	<0.0001
Age (years)	0–44	53	4 012 449	1	
	45–64	162	1 705 155	7.1 (5.2, 9.7)	<0.0001
	65+	241	1 163 551	14.7 (10.9, 19.8)	<0.0001
Gender	Male	130	3 228 899	1	
	Female	326	3 652 256	2.0 (1.6, 2.4)	<0.0001

*Not calculable.

before the diagnosis, which makes this unlikely. On the other hand, multivariate analysis includes only age and gender as confounding factors. Information on other suggested meningioma risk factors [1] (i.e ionizing radiation, hereditary syndromes, exogenous hormones) are not routinely registered in BIFAP, but there is no reason to think that such risk factors are associated with CPA use which makes it improbable that they actually behave as confounders. Moreover, none of the four meningiomas cases exposed to high dose CPA reported any of these risk factors in its clinical profile. Finally, asymptomatic meningiomas cases were not considered leading to an underestimation of the real incidence of meningioma. However, we do not expect that this underascertainment affects CPA exposed patients in a differential way compared with those non-exposed given that the study period ended before the signal was published and the meningioma incidence rates were rather stable during the study period.

The main strengths of the study are first, that BIFAP is a population-based database that includes prospective information of patients attending different levels of the public health care system. Thus, all potential meningioma cases are likely to be registered in the database, although a certain level of under-recording could be expected because of the lack of systematic registration in the BIFAP database of cause of death and autopsy information, when performed. Second, clinical profiles of potential cases were reviewed by trained physicians and results were not sensitive to the inclusion of possible cases. Third, the study period ended before the signal was published, minimizing the possibility that physicians selectively searched for meningioma in CPA users and fourth, the possibility that the underlying disease itself rather than the exposure to CPA can explain the association is improbable given the variety of indications.

The results of this study provide additional evidence to support the research hypothesis, although this cannot be considered a definitive proof and further research is needed.

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Competing Interests

There are no competing interests to declare.

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