SHORT COMMUNICATION

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Isotretinoin Exposure during Pregnancy
Assessment of Spontaneous Reports in France

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Abstract

Background: In three previous studies, we have shown that pregnant women were still being exposed to isotretinoin and that compliance with recommendations was incomplete. The relaxation of these recommendations (summary of product characteristics 2004), combined with the release of generic brands, encouraged us to carry out a fourth study.

Objective: To assess isotretinoin exposure during pregnancy following the application of less stringent recommendations and the marketing of generic isotretinoin brands.

Methods: All cases of isotretinoin exposure during pregnancy, between 1 January 2003 and 31 December 2006, spontaneously reported to pharmacovigilance centres, the Teratogenic Agent Information Centre, and pharmaceutical companies in France were assessed. Cases were classified for analysis into the following groups: 'conception <1 month after isotretinoin discontinuation', 'conception during isotretinoin treatment' and 'patient already pregnant when isotretinoin was started'. The rate of spontaneously reported isotretinoin exposure during pregnancy was estimated by dividing the number of isotretinoin-exposed pregnancies by the number of women of childbearing age treated with isotretinoin.

Results: Over 4 years, 147 cases of isotretinoin exposure during the teratogenic risk period were spontaneously reported, i.e. 'conception <1 month after isotretinoin discontinuation' (23%), 'conception during isotretinoin treatment' (61%), and 'patient already pregnant when isotretinoin was started' (16%). Nineteen percent of the patients did not use any form of contraception. In 23% of the patients, the method of contraception used did not comply with recommendations, while in 86% of the cases, isotretinoin was prescribed by a dermatologist. Among the 44 pregnancies with available data on fetuses or neonates, there were two (4.5%) malformations compatible with the time

of exposure and with isotretinoin embryopathy. The rate of spontaneously reported isotretinoin exposure during pregnancy has increased by approximately 30%, from 0.32 (95% CI 0.26, 0.38) to 0.41 (95% CI 0.34, 0.49) per 1000 women of childbearing age treated since 1999–2002.

Conclusions: We suggest that recommendations be tightened, with specific information regarding the most effective contraceptive method combined with compulsory monthly pregnancy testing during treatment. The French Drug Agency has informed the European Medicines Agency of the need for measures aimed at improving compliance.

Background

Isotretinoin is a very effective drug for treating severe recalcitrant nodular acne. Because of its high risk of fetal malformations,[1,2] risk management efforts have been taken to avoid exposure to the drug during pregnancy through a variety of methods. These methods include physician and patient education to promote the use of birth control, and frequent pregnancy tests throughout the course of treatment. Isotretinoin is contraindicated during pregnancy and in women of childbearing age, unless all criteria of the pregnancy prevention programme, as outlined in the summary of product characteristics (SPC), are satisfied. Roaccutane® (Hoffman-La Roche) was the first brand of isotretinoin marketed in France (1984) for the treatment of acne. Between December 2001 and February 2002, seven generic brands of isotretinoin were approved, three of which have been marketed in France: Curacne® and Procuta® both since 2002, and Contracne® since 2005.

Two previous studies[3,4] conducted by our team have highlighted the persistent risk associated with isotretinoin exposure during pregnancy and the failure of healthcare professionals and patients to comply with recommendations. Based on these findings, recommendations regarding treatment procedures were tightened in France in 1997 and again in 2001. In a third study,[5] a reduction in the incidence of isotretinoin exposure during pregnancy was observed in response to the changes made to the recommendations.

Because of major objections persistently raised in France regarding contraception in women of childbearing age, the French Drugs Agency (AFSSAPS) launched a European arbitration procedure for harmonization of the SPC for all generic versions of the drug. A European amendment was introduced in September 2004 for Roaccutane®, Curacne® and Procuta®. This amendment was published in the French VIDAL Drug Compendium[6] in 2005 for Roaccutane®, 2006 for Curacne® and Procuta®, and the 2007 version for Contracne®. The main changes were as follows: less stringent recommendations for the need for contraception (exclusion of the recommendation for women for whom the prescriber ''believes that there are convincing reasons to suggest the lack of any pregnancy-related risk''); less precise recommendations for the method of contraception (''at least one effective form of contraception, preferably two additional methods including one local method''); and suppression of the obligation to carry out a monthly pregnancy test (''during treatment: the need to carry out a monthly pregnancy test should be determined on the basis of local practices and must take into account the patient's sexual activity and menstrual cycles'').[6]

The aim of our study was to assess isotretinoin exposure during pregnancy following the application of less stringent recommendations and the marketing of generic isotretinoin brands.

Methods

As in previous studies,[3-5] all cases of isotretinoin exposure during pregnancy spontaneously reported in France to the 31 pharmacovigilance

centres, the Teratogenic Agent Information Centre, and Roche (Roaccutane®), Pierre Fabre (Curacné®), Biorga (Contracné®) and Expanscience (Procuta®) were assessed.

Duplicate reports were checked and considered as one single report. To limit heterogeneity of data quality, selection and duplicate reports, all cases were reviewed by the same researcher (APJB). Included in the study were all women who had conceived between 1 January 2003 (end of our third study)[5] and 31 December 2006, and who underwent isotretinoin exposure during the teratogenic risk period, i.e. women who had conceived during treatment or during the first month following treatment discontinuation, or those who were already pregnant (between 1 January 2003 and 31 December 2006) at the start of treatment. Pregnancies conceived more than 1 month after stopping treatment, as well as cases of paternal exposure, were excluded from the analysis. Cases were classified into the following groups for analysis: 'conception <1 month after isotretinoin discontinuation', 'conception during isotretinoin treatment', and 'patient already pregnant when isotretinoin was started'.

The rate of reported isotretinoin exposure during pregnancy was estimated by dividing the number of isotretinoin-exposed pregnancies during the teratogenic risk period reported in this study by the number of women of childbearing age treated with isotretinoin during the study period in France. This last figure was estimated by taking into account isotretinoin sales obtained from the manufacturers of the drugs included in the study, rate of childbearing women among all isotretinoin treated women and recommended dose, according to the French SPC, for a woman weighing 55 kg (3.355 g/course of treatment [minimum daily dose of 0.5 mg/kg for 4 months] and 10.065 g/course of treatment [maximum daily dose of 1 mg/kg for 6 months]).

Results

During the 4-year study period, 147 cases of isotretinoin (Roaccutane® 54%, Curacne® 31%, Procuta® 12%, Contracne® 1% and unknown 2%) exposure during the teratogenic risk period were spontaneously reported. The mean patient age was 27.3 ± 6.4 years (range 16–44 years). Eighty-nine patients (61%) conceived during isotretinoin treatment, 34 (23%) conceived <1 month after stopping isotretinoin and 24 (16%) women were already pregnant at the time of starting isotretinoin treatment.

Contraception was used at the time of conception in 60 (41%) patients, no contraception was used in 28 (19%) patients and contraception was unknown in 59 (40%) patients (table I). Among the 60 patients with known contraceptive use, 70% used oral contraception, 17% used an intra-uterine device (IUD), 12% used cyproterone and 5% used local forms of contraception. Finally, for 11 (23%) of the 48 women for whom this information was available, the contraceptive method (local contraceptive methods, microprogestative pills or cyproterone) was not in compliance with recommendations. Among the 28 patients who did not use contraception, the reasons given were as follows: unknown (19 cases), oral contraception prescribed but not taken (4 cases), woman infertility (2 cases), partner infertility

Table I. Contraceptive status and period of isotretinoin exposure

Contraception status	Conception <1 month after isotretinoin discontinuation (n = 34)	Conception during isotretinoin treatment (n = 89)	Patient already pregnant when isotretinoin was started (n = 24)	Total (n = 147)
Pregnancies with contraceptive status documented	15	64	9	88
Contraception used [n (%)]	9	48	3	60
failure of contraception	6 (40)	33 (52)	3 (33)	42 (48)
poor compliance	1 (7)	14 (22)	0	15 (17)
contraception discontinued	2 (13)	1 (1)	0	3 (3)
No contraception [n (%)]	6 (40)	16 (25)	6 (66)	28 (32)

Table II. Rate of isotretinoin exposure during pregnancy per 1000 women

Drug	Total	Minimum rate[a] (95% CI)	Maximum rate (95% CI)[a,b]
Total	147	0.41 (0.34, 0.49)	1.24 (1.04, 1.46)
Roaccutane®	79	6.53 (5.17, 8.13)	19.59 (15.54, 24.36)
Curacne®	45	0.22 (0.16, 0.29)	0.66 (0.48, 0.89)
Procuta®	19	0.14 (0.08, 0.22)	0.41 (0.25, 0.65)
Contracne®	1	0.22 (0.006, 1.27)	0.69 (0.017, 3.82)

a Minimum rate corresponds to the maximum daily dose (1 mg/kg/day for 6 months).

b Maximum rate corresponds to the minimum daily dose (0.5 mg/kg/day for 4 months).

(1 case), poor compliance (1 case) and suicide attempt (1 case).

Among the 64 patients for whom information was provided, 49 (77%) had a prescription for isotretinoin (general practitioner 10%, dermatologist 86% and other physician 4%) and 15 (23%) reported self-medication with isotretinoin.

The outcome of pregnancy (known in 70% of cases [103/147]) was a live birth in 23 cases (22%), a miscarriage in seven cases (7%) and a terminated pregnancy in 73 cases (71%), using voluntary (41) or medical (32) termination. Among the 44 pregnancies with available data on fetuses or neonates, there were five malformations. In two fetuses, an agenesis of the vermis, following isotretinoin exposure up to the fifth and seventh weeks of the pregnancy, respectively, was the reason for medical termination. In three neonates, minor malformations were diagnosed or confirmed during the first days of life, i.e. two cases of interventricular septal defects, with isotretinoin discontinued 30 days before conception, and one case of genital anomalies (protruding clitoris and abnormal labia majora) following isotretinoin exposure during the first 3 weeks of pregnancy. In another case of isotretinoin exposure during the first 6 weeks of pregnancy, speech disorders and learning difficulties were observed in the child when enrolled in primary school. Considering only the two cases of agenesis of the vermis compatible with the time of exposure and with retinoic acid embryopathy,[1] the incidence of malformations associated with isotretinoin exposure was estimated at 4.5% (2/44).

The rate of pregnancies exposed to isotretinoin was estimated to range from 0.41 (95% CI 0.34, 0.49) to 1.24 (95% CI 1.04, 1.46) per 1000 women of childbearing age treated, depending on the doses used. This rate also varied depending on the isotretinoin brands used, the highest incidence being recorded with Roaccutane® (table II). Since our previous study, carried out between 1999 and 2002, pregnancy rates following isotretinoin exposure during the teratogenic period have increased by about 30% (table III). This may mainly be accounted for by the increased rate of women who have conceived during isotretinoin treatment.

Discussion

Compared with our previous study carried out between 1999 and 2002 (table III), the latest study showed that there were no changes in exposure incidence in patients who had conceived <1 month after stopping isotretinoin, and in patients who were already pregnant at the time of treatment initiation. For this reason, an increase in the overall incidence cannot be explained simply by a higher declaration rate. The estimation of pregnancy rates during isotretinoin exposure varies depending on authors and methodologies, and our data are likely to be at the lower limit as they are based on spontaneous reporting. In a retrospective cohort study in southern California using electronic capture of all isotretinoin prescriptions, the rate of fetal exposure to isotretinoin was 2.1/1000 before 2002 and 2.3/1000 after 2002.[7] In a trial comparing two formulations of isotretinoin,[8] one pregnancy occurred in 244 women exposed to the drug, corresponding to 4.1/1000 treatment courses (95% CI 1.0, 22.6). In an isotretinoin survey conducted between 1989

Table III. Rate of isotretinoin exposure during pregnancy per 1000 women since 1987

Study and date	Duration of study (mo)	No. of pregnant women exposed to isotretinoin	Sales of isotretinoin (kg)	Minimum[a]/maximum[b] rate (95% CI)			
				total	conception <1 mo after isotretinoin discontinuation	conception during treatment with isotretinoin	patient already pregnant when isotretinoin was started
Study 1[3] Jan 1987 to Jun 1995	102	318	5104	0.20 (0.18, 0.21)/ 0.80 (0.70, 0.90)	0.06 (0.04, 0.08)/ 0.30 (0.23, 0.33)	0.10 (0.03, 0.11)/ 0.40 (0.33, 0.49)	0.03 (0.02, 0.04)/ 0.10 (0.03, 0.17)
Study 2[4] Mar 1997 to Dec 1998	22	37	1176	0.31 (0.21, 0.42)/ 0.93 (0.63, 1.25)	0.07 (0.03, 0.13)/ 0.20 (0.09, 0.40)	0.15 (0.08, 0.23)/ 0.45 (0.24, 0.69)	0.09 (0.05, 0.16)/ 0.1 (0.13, 0.31)
Study 3[5] Jan 1999 to Dec 2002	48	103	3000	0.32 (0.26, 0.38)/ 0.96 (0.77, 1.15)	0.12 (0.08, 0.16)/ 0.35 (0.24, 0.48)	0.13 (0.10, 0.18)/ 0.41 (0.29, 0.54)	0.06 (0.03, 0.09)/ 0.17 (0.06, 0.37)
Study 4 Jan 2003 to Dec 2006	48	147	2755	0.41 (0.34, 0.49)/ 1.24 (1.04, 1.46)	0.09 (0.06, 0.13)/ 0.28 (0.19, 0.40)	0.25 (0.20, 0.30)/ 0.75 (0.60, 0.92)	0.06 (0.04, 0.10)/ 0.20 (0.12, 0.30)

a Minimum rate corresponding to the maximum daily dose (1 mg/kg/day for 6 months).

b Maximum rate corresponding to the minimum daily dose (0.5 mg/kg/day for 4 months).

and 1993, there were 402 pregnancies in women enrolled by their physician and followed up by telephone or mail. This corresponds to a rate of 3.4/1000 isotretinoin treatment courses.[9-11] A non-interventional, population-based study conducted from 1984 to 2002 using the RAMQ (Régie de l'Assurance Maladie du Québec) database[12] revealed that the pregnancy rate was 32.7/1000 (95% CI 26.6, 40.1). This rate is higher than previously published rates.

The isotretinoin exposure rate during pregnancy for the different brands could not be compared with our previous study results regarding Procuta® and Contracne® because of the small number of women exposed to these products. Exposure rate during pregnancy did not change for Curacne® (0.22–0.66/1000 vs 0.17–0.50/1000 in the previous study). Surprisingly, for Roaccutane®, there was a substantially increased exposure rate (6.53–19.59/1000 vs 0.33–0.99/1000).[5] This increased rate may be accounted for by Roaccutane® exposure being over-reported or the other formulations being under-reported, in the absence of any precise information of the brand used.[13] The rate of pregnancy termination (73% vs 86% in our previous study) was similar for all isotretinoin formulations. Therefore, this observation does not support the possibility that less information regarding teratogenic risk was provided to patients taking generic drugs.

Exposures during pregnancy are often the result of poor compliance with the contraceptive methods stipulated by the SPC recommendations drawn up before 2004. The removal of certain restrictions stipulated in the initial product licence in 2004 may account for the significant number of women using inadequate contraception methods. In fact, SPC recommendations no longer include advice on the contraceptive methods to be used. In our study, the proportion of women not using contraception remained high (28/88 [32%]). When used, contraception did not conform to pre-2004 SPC recommendations in 23% of cases (11/48 women with known contraception use). However, the requirement to continue contraception for 1 month after stopping isotretinoin was better adhered to. This is illustrated

by the substantial decrease in exposure rates due to stopping contraception too early after isotretinoin discontinuation (2 of 9 [22%] vs 12 of 20 [60%]) in our previous study.[5] The higher proportion of patients who conceived during treatment (61% vs 43% in the previous study) could not be explained by the non-use of contraception (25% vs 35%) or poor compliance (22% vs 36%). This may result from contraception failures, which were more frequently reported in the current study (52% vs 32%). In line with our previous studies,[3-5] the high rate of contraception failures in patients using an IUD (24% of the cases of contraception failure) suggests a decrease in IUD effectiveness in women treated with isotretinoin.

As our study provides no pregnancy test data, we cannot evaluate to what extent the decision to leave the need for a monthly pregnancy test up to the prescriber's judgement has influenced the study results. However, in a study in southern California, pregnancy tests that met the 7-day criteria improved dramatically after implementing the Kaiser Permanente programme without reducing the pregnancy rate.[7] The Kaiser Permanente isotretinoin risk management programme focused on three areas: verification of a negative pregnancy test by the pharmacist before the patient received the prescription, utilization of the laboratory for pregnancy testing and quality improvement measurements that are rapidly reported back to pharmacies and providers.[7]

Many studies demonstrated that voluntary pregnancy prevention programmes were not consistently followed, resulting in fetal exposure.[7,14-18] A new iPLEDGE™ management programme, including mandatory registration of patients, healthcare providers, pharmacies and wholesalers, was implemented in March 2006.[19] This programme allows for real-time linkage of pregnancy test results for verification prior to dispensing isotretinoin.[19,20] It has recently been suggested that contraception failure could be decreased by combining oral contraception with a barrier method. However, only parenterally administered progestin-only contraceptives could circumvent poor compliance, which remains the major problem in isotretinoin treatment.[21]

Limitations of our study, such as heterogeneity of data quality, selection and under-reporting, are inherent to spontaneous reporting from different sources. These limitations have been lessened as the same researcher (APJB) from our team reviewed all cases.

Based on our results, the AFSSAPS has reiterated to the European Medicines Agency (in September 2009) the need for measures to improve compliance, particularly a booklet for patients containing information about teratogenic risk, contraceptive methods and pregnancy tests, as well as a patient consent form. Thereby, the prescriber will ensure that the patient has been informed on the teratogenic risk and that the consent form has been signed. Moreover, the pharmacist can ensure that everything is in order before distributing isotretinoin.

Conclusions

Compared with the results of a previous study using the same methodology, isotretinoin exposure rate during pregnancy has increased, mainly due to an increased conception rate during treatment. This may be partially accounted for by the removal of certain restrictions specified in the initial product licence in 2004, such as the need for contraception and the type of methods used. Therefore, the AFSSAPS suggested the need for better information about effective contraceptive methods and monthly pregnancy testing during treatment. If the European Medicines Agency follows the AFSSAPS propositions, the benefits of stronger recommendations should be evaluated again.

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