CENTER FOR DRUG EVALUATION AND RESEARCH

SPECIAL INTEREST TOPIC

TITLE: MEDICAL OFFICER REVIEW OF NDA 20-344, AMENDMENT 019, PART 1A (IPPH STUDY)

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I N T E R O F F I C E M E M O R A N D U M

DATE: 8 September 1995

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SUBJECT: NDA # 20-344/Dexfenfluramine/Interneuron Pharmaceuticals, Incorporated
Amendment #019/ Part IA/International Primary Pulmonary Hypertension Study

To: Leo Lutwak, MD, PhD
Medical Officer/Metabolism & Endocrine Group #1

This replies to your request for consultation regarding the International Primary Pulmonary Hypertension Study (IPPHS). My review is based on the IPPHS study report contained in the NDA submission cited above, and information obtained directly from the Chairman of the IPPHS Scientific Board, Professor Lucien Abenhaim, McGill University, Canada. I will first summarize the background, methods, and results of the study, then comment on the methodology and clinical interpretation, and close with conclusions and recommendations.

BACKGROUND

The IPPHS was a case-control study designed to evaluate the effect of using dexfenfluramine (DF) or other anorexigens on the occurrence of PPH. It carried out in France, Belgium, the Netherlands, and the United Kingdom, and was paid for by the Servier Pharmaceuticals. I think Servier was motivated to fund the study by the French Agence du Medicament because of adverse drug experience reports associating DF use with PPH, and that the money was managed at McGill after it left Servier, although these issues are not discussed in the NDA submission. However, it is noted in the submission that the Medical Research Council of Canada peer-reviewed the study and approved the funding under the "MRC-Industry" Program, and that the Ministry of Public Health and Environment in Belgium also expressed support for the study.

The IPPHS was largely developed, managed, and analyzed by a Coordinating Center at McGill which consisted of four persons: Professor Abenhaim, for overall direction; Dr. Yola Moride, for protocol development, coordination of field work, the interim analysis, and creation of the database; Dr. Thierry Ducruet, for performance of statistical analyses; and Dr. Jacques Benichou, a consultant from the U.S. National Cancer Institute. There were Local Research Teams in the four countries for case and control recruitment, an Expert Review Panel for judging the eligibility of PPH cases to be included in the analyses, and a Scientific Board for scientific oversight and review of the final report.

METHODS

A matched study design was used because many of the PPH cases were identified at specialized referral centers. Under these conditions, the matching of controls to each case according to the practice of the case's general practitioner (GP) is an appropriate method for ensuring that persons in the resulting case-control sets had the same general opportunity, in the past, for having been prescribed DF or other anorexigens. In addition to matching on GP, the controls were also matched to the cases for sex, age (+/- 5 years), and number of physician visits per year. Overall, four controls were sought for each case, but fewer or more controls per case were permitted depending on availability. If controls for a case could not be found at the practice of the case's GP, they were sought at the practice of another GP in the same geographic area. The basic inclusion criteria for both cases and controls were: age 18-70 years, both sexes, resident of the country for more than six months, interview possible, consented to participate, and not suffering from active chronic disease (cancer, systemic diseases, etc.)

Cases. PPH cases were defined as men or women 18-70 years of age who received a first diagnosis of PPH between 1 September 1992 and 30 September 1994. The date of diagnosis was defined as the date of first right heart catheterization, and cases were retained in the final analyses only if documentation of the diagnosis was considered definitive by the Expert Review Panel. In total, 298 possible PPH cases were identified, of which 95 (32%) were retained in the final analyses. Of the 203 (68%) possible cases that were excluded, 137 (67%) either did not meet the basic inclusion criteria for cases and controls or the specific criteria for defining cases. The remaining 66 (33%) were excluded because they died before interview (26), were found not to have definite PPH by the Expert Review Panel (23), or could not be studied within the time available, were lost to follow-up, or refused to participate (17).

Controls. Controls were matched to the cases as described above, and an "index date" was assigned to each control, corresponding to the date of diagnosis for the matching case. In total, 492 potential controls were interviewed, of which 355 (72%) were retained the final analyses. The other 137 potential controls were excluded because they were matched to possible cases that were excluded as described above.

Interviews. Cases and controls were interviewed by specially trained interviewers who were not told about the specific aims of the study, to obtain information about: (1) socio-demographic and personal characteristics, medical and surgical history, familial medical history, habits, exposure to high pressure and high altitude, and other general information; (2) a detailed history of drug use during the 3-4 years prior to interview.

This was obtained using a calendar method for recording data, and a visual display of packages and/or tablets for commonly prescribed drugs. Use of DF and other anorexigens was recorded in the same way as use of other drugs.

Analysis. Standard methods for bivariate and multivariate analysis of matched case-control data were used. The main outcome statistics are odds ratios (ORs) for the association between PPH and the use of DF or other anorexigens, with 95% confidence intervals (CIs). For a rare disease such as PPH, these odds ratios are accurate estimates of the relative risk, which is the risk of PPH in persons who used DF or other anorexigens divided by the risk in persons who did not use these drugs. Initially, bivariate analyses were done for DF or other anorexigens, and many additional variables that might be risk factors for PPH. Subsequently, multivariate analyses were done which included DF, other anorexigens, and the additional factors that were found to associated with PPH in the bivariate analyses: Quetelet Body Mass Index (BMI) $\geq$ 30 at least once in lifetime, a history of treated hypertension, a history of smoking at least four years before interview, and a history of having tried to lose weight using several methods other than DF or other anorexigens.

RESULTS

The main findings are that:

(1) Persons who had used DF or other anorexigens for longer than three months were about nine times more likely to have PPH than persons who had never used these drugs (OR= 9.1, 95% CI= 2.6-31.5). There was no significant increase in risk among persons who had used the drugs for three months or less (OR =1.9, 95% CI= 0.5-6.9).

(2) The increased risk of PPH was concentrated in persons who had used DF or other anorexigens within the year before being studied (OR= 5.9, 95% CI= 2.1-16.9). There was no significant increase in risk among persons who had stopped using the drugs more than one year before being studied (OR= 2.4, 95% CI= 0.6-8.8).

(3) Persons with BMI$\geq$ 30 at least once in their lives were about 2-4 times more likely to have PPH than persons with BMI< 30 (among never-users of DF or other anorexigens, OR= 2.1, 95% CI= 1.0-4.2; among ever-users, OR= 3.6, 95% CI= 1.3-9.8).

(4) The use of DF or other anorexigens was associated with a similar relative increase in the risk of PPH among persons with BMI≥ 30 (OR= 5.0, 95% CI= 1.5-16.2) and among persons with BMI< 30 (OR= 2.9, 95% CI= 1.1-7.4). Thus, the effect of using DF or other anorexigens was to multiply the effect of having a BMI ≥ 30, so that the effect of the two risk factors together was greater than the sum of their individual effects.

(5) The results described above pertain mainly to DF, since most use of "DF or other anorexigens" by cases and controls in the study was in fact use of DF. However, the results for other anorexigens were similar to the results for DF to the extent that separate analyses were feasible.

COMMENT

The IPPHS is an excellent study, and I think it provides the best resource we can expect to obtain for information about the effect of using DF or other anorexigens on the occurrence of PPH. I will comment on specific strengths and weaknesses of the study with regard to methodology and to clinical interpretation.

Methodology

Very careful consideration is given in the IPPHS study report to the main sources of potential error in case-control studies, which are selection bias, information bias, confounding, and chance. In this regard, I think many of this issues raised in the commentary by Dr. Gerald Faich that is included in the NDA submission are in fact adequately discussed in the IPPHS study report itself, and are not sufficient reasons to discount the findings. I do agree with Dr. Faich that it would be helpful to see a comparison of findings about the use of DF or other anorexigens for controls drawn from the practice of the matched case's GP versus controls drawn from the practice of another GP in the same geographic area, and that it would also be helpful to see ORs with BMI stratified at 27 instead of 30 (since this may be an issue with regard to proposed labeling), but I doubt that these analyses will appreciably change the overall study findings. Also, I think Dr. Faich oversimplifies a complex topic in stating that "Odds ratios below 5 in pharmacoepidemiologic studies are often only suggestive..." due to the potential for bias or confounding. In my own experience, the consistency and plausibility of findings from studies in the area of pharmaco-epidemiology have depended more on the size and quality of the studies, than on the ORs themselves.

Clinical Interpretation

The IPPHS report does not provide a tabulation of data on the use of DF or other anorexigens, by the cases and controls, according to country, sex, and age. I think this information is needed for clinical/regulatory interpretation of the IPPHS findings, and I therefore asked Professor Abenhaim, on 15 August, if he could provide me the tabulation referred to above. He was very courteous and faxed me the requested data on 30 August. These data are summarized in Tables 1-3, and are interpreted below.

Table 1 shows that:

(1) A total of 20 (21.1%) of the 95 PPH cases and 23 (6.5%) of the 355 controls in the final IPPHS analyses had used DF or other anorexigens.

(2) However, only 2 (6.9%) of the 29 male cases and 1 (1.1%) of the 90 male controls had used DF or other anorexigens, compared to 18 (27.3%) of the 66 female cases and 22 (8.3%) of the 265 female controls.

(3) Thus, the main findings from the IPPHS about the effect of using DF or other anorexigens on the occurrence of PPH are, in essence, findings about the effect in women.

Table 2 shows that:

(1) As above, 18 (27.3%) of the 66 female PPH cases and 22 (8.3%) of the 265 female controls had used DF or other anorexigens.

(2) However, only 1 (7.7%) of the 13 female cases and none of the 45 female controls in the U.K. & Netherlands had used DF or other anorexigens, compared to 15 (33.3%) of the 45 female cases and 19 (10.6%) of the 180 female controls in France, and to 2 (25.0%) of the 8 female cases and 3 (7.5%) of the 40 female controls in Belgium.

(3) Thus, the main findings from the IPPHS about the effect of using DF or other anorexigens on the occurrence of PPH are, in essence, findings about the effect for women in France and Belgium.

Table 3 shows that:

(1) A total of 17 (32.1%) of the 53 female PPH cases and 22 (10.0%) of the 220 female controls in France and Belgium had used DF or other anorexigens.

(2) The female cases and controls in France and Belgium were distributed across the entire 5-decade age interval of eligibility for cases, from 18 through 70 years.

(3) The association between PPH and the use of DF or other anorexigens appears to be concentrated in women over 40 years of age, (However, this observation is tentative, since it does not take into account the matched design of the IPPHS.)

CONCLUSIONS AND RECOMMENDATIONS

I think the IPPHS provides strong evidence that the use of DF or other anorexigens by women for over three months increases their risk of developing PPH, and that this increased risk persists for up to a year after the drugs are discontinued. I also think the IPPHS provides evidence that the effect of using DF or other anorexigens on the risk of PPH acts in a way that multiplies the effect of having a BMI $\geq$ 30, such that the combined effect of the two factors together is greater than the sum of their individual effects. These adverse effects of using DF or other anorexigens may be greater for women over 40 years of age than for younger, women, but this observation is tentative. Finally, since most of the exposure to "DF or other anorexigens" in the IPPHS was in fact exposure to DF, I think the above conclusions can be reasonably applied to decision-making about DF itself.

I recommend that Professor Abenhaim be invited to present the findings of the IPPHS to the Metabolic-Endocrine Drugs Advisory Committee meeting on 29 September, and have asked the Executive Secretary of the Advisory Committee to do this. As part of his presentation, I will ask Professor Abenhaim to:

(1) Describe the IPPHS data concerning the use of DF or other anorexigens by controls drawn from the practice of the matched case's GP versus controls drawn from the practice of another GP in the same geographic area, and discuss the implications of any differences between the two types of controls with regard to the overall validity of the study.

(2) Describe any effects on the main findings from the study if BMI is stratified at 27 instead of 30, since this may be an issue with regard to proposed labeling.

(3) Show how the PPH case and controls who had used DF or other anorexigens for longer than three months were distributed by duration of use, e.g., >3 months to $\leq$ 1 year, 1-2 years, and so on. As Dr. Troendle has pointed out, this would help to provide perspective on what is actually meant by "longer than three months" of use.

(4) If possible, use available data on the total incidence of PPH in France and/or Belgium, and data from the IPPHS, to estimate the absolute risk of PPH that is attributable to the use of DF or other anorexigens by women 18-70 years of age, according to the following definitions and method of calculation:

Definitions

I_T = Total incidence of PPH in France and/or Belgium, per 100 000 women 18-70 years of age per year, in 1993-94.

I_E = Incidence of PPH in France and/or Belgium, per 100 000 women 18-70 years of age per year, in 1993-94, for women who had used DF or other anorexigens for longer than three months within the year before diagnosis.

I_U = Incidence of PPH in France and/or Belguim, per 100 000 women 18-70 years of age per year, in 1993-94, for women who had never used DF or other anorexigens.

P = Proportion, in the IPPHS database, of female controls 18-70 years of age, in France and Belgium, who had used DF or other anorexigens for longer than three months within the year before their "index dates."

OR = Odds ratio, based upon the IPPHS data, for the association between the occurrence of PPH and the use of DF or other anorexigens for longer than three months within the year before the date of diagnosis (cases) or the "index date" (controls).

AR = Attributable risk = $I_E - I_U$

Calculations

$$I_T = I_E P + I_U (1-P)$$

$$I_T = (OR)\ (I_U)\ P + I_U\ (1-P)$$

$$I_U = I_T / (OR)\ P + (1-P)$$

Put in values of I_T, OR, and P, and solve for I_U

Then $I_E = (OR)\ I_U$, and

$$AR = I_E - I_U$$

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NDA 20-344
HFD-510/SobelS/TroendleG/StadelB
HFD-007/KleinM/KramerD

APPEARS THIS WAY
ON ORIGINAL

TABLE 1

Cases and controls
by
sex and use of DF or other anorexigens

BOTH SEXES

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	20	(21.1)	23	(6.5)
	No	75	(78.9)	332	(93.5)
		95		355	

MEN

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	2	(6.9)	1	(1.1)
	No	27	(93.1)	89	(98.9)
		29		90	

WOMEN

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	18	(27.3)	22	(8.3)
	No	48	(72.7)	243	(91.7)
		66		265	

TABLE 2

Female cases and controls
by
country and use of DF or other anorexigens

ALL FOUR COUNTRIES

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	18	(27.3)	22	(8.3)
	No	48	(72.7)	243	(91.7)
		66		265	

U.K. & NETHERLANDS

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	1	(7.7)	0	(0.0)
	No	12	(93.1)	45	(100.0)
		13		45	

FRANCE

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	15	(33.3)	19	(10.6)
	No	30	(66.7)	161	(89.4)
		45		180	

BELGIUM

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	2	(25.0)	3	(7.5)
	No	6	(75.0)	37	(92.5)
		8		40	

TABLE 3

Female cases and controls in France and Belgium
by age and percent that had used DF or other anorexigens

Age (Years)	Cases N	Cases (% users)	Controls N	Controls (% users)
≤30	9	(11.1)	35	(17.1)
31-40	10	(10.0)	47	(8.5)
41-50	17	(64.7)	65	(13.8)
51-60	11	(27.3)	37	(5.4)
>60	6	(16.7)	36	(2.8)
	53	(32.1)	220	(10.0)