Abstract

Drug therapies are usually contraindicated in specific patient populations where evidence suggests that administration may result in a serious reaction or may seriously and negatively alter the risk benefit of treatment. There are few absolute contraindications to licensed regimens of mifepristone and prostaglandin for termination of pregnancy. However, those that are specified on “summary of product characteristics” [product labeling (PL)] differ from country to country. Differences reflect the dynamic environment of emerging scientific evidence, local experience and guidelines, and local regulatory processes, which all influence the resultant PL. The reasons and rationale for specific contraindications for mifepristone and prostaglandin for the termination of pregnancy are detailed, and the reasons for the differences between PL in different countries are explained.

Keywords: Mifepristone; Prostaglandin; Termination of pregnancy; Contraindications

1. Introduction

Mifepristone is a potent antagonist of progesterone and glucocorticoid receptors, and the vast literature characterizes the pharmacokinetics and dynamics of this interesting drug [1,2].

In this paper, contraindications to the use of mifepristone, in association with prostaglandin, for the termination of pregnancy — as specified on the summary of product characteristics (SmPC) for Mifegyne (Exelgyn, France) or on the product labeling (PL) for Mifeprex (Danco, USA) — will be discussed. The contraindications for mifepristone and the medical reasons for their inclusion will be summarized.

2. Definition and evolution of contraindications

In general, a drug may be contraindicated for use in specific patient populations if evidence indicates that giving the drug may, in the most extreme situation, result in life-threatening reactions or, more generally, would shift the risk benefit ratio of treatment versus no treatment or alternative treatment to the negative in that population. Usually, preexisting morbidity with or without concomitant drug therapy is the main consideration. In strict definitions given for marketing authorizations, contraindications to the use of a drug are considered absolute (i.e., under no circumstances should the drug be given to a member of the specific population described). If a sound rationale can be made for administration in certain circumstances, then the contraindication may not be absolute and may more correctly be included under warnings and precautions.

From the above definition, it can be seen that, due to emerging information and the development of new indications for a drug, existing contraindications may become inappropriate or incomplete. Changes to the SmPC or PL over time will reflect such developments.

In the case of commercially available mifepristone, scrutiny of the respective marketing authorizations granted by different regulatory authorities at different times will show that the stated contraindications differ in a number of cases. To understand how these differences came about, it is necessary to provide a brief history of mifepristone in the market place and the regulatory processes that resulted in the current disparity.
3. Regulatory history of mifepristone

Roussel UCLAF first achieved marketing authorization for mifepristone in France in 1988. This first product license authorized the sale of Mifegyne — in association with the prostaglandin E1 analogues, sulprostone (intramuscular) and gemeprost (per vaginal) — for the termination of pregnancy of up to 49 days’ gestation.

Sulprostone (intramuscular) was withdrawn from the world market in 1992 as incidences of severe cardiovascular reactions associated with its use with mifepristone were recorded [3,4]. French trials then demonstrated that the orally active prostaglandin, misoprostol, offered an effective and relatively safe alternative to sulprostone for use with mifepristone for the termination of pregnancy of up to 49 days’ gestation [5]. Marketing authorization was subsequently achieved for this combination in France in 1992.

Sulprostone was never licensed for use in the UK, and parallel to the development of the mifepristone/sulprostone association in France, UK and Scandinavian research concentrated on the association of mifepristone and the potent prostaglandin E1 analogue, gemeprost. Gemeprost was available as a pessary and was licensed for use for the induction of second-trimester termination of pregnancy. Drawing on the benefit of the experience in France, the UK studies pushed the limits of experience further and investigated the use of mifepristone and gemeprost for the termination of pregnancy of up to 63 days’ gestation [6]. Marketing authorization was granted for this indication in the UK in 1991 and in Sweden in 1992.

Between 1991 and 1997, further marketing authorizations were obtained in France, UK and Sweden, which extended the use of mifepristone for other indications: (a) in association with prostaglandin for the induction of second-trimester termination of pregnancy (France, UK and Sweden); (b) without prostaglandin for cervical preparation prior to surgical termination of pregnancy (France and UK); and (c) for induction of labor for fetal death in utero (France). By 1997, the rights for mifepristone had been transferred to Exelgyn in Europe and to the Population Council in the United States. Both Exelgyn and the Population Council have since then separately achieved marketing authorization held by Danco are as follows:

4. Contraindications to mifepristone and prostaglandin

4.1. List of contraindications

The contraindications listed in the current marketing authorization held by Exelgyn are as follows (for termination of pregnancy of up to 49 days’ gestation):

- Chronic adrenal failure
- Known allergy to mifepristone or to any component of the product
- Severe asthma uncontrolled by therapy (Exelgyn SmPC only)
- Inherited porphyria
- Pregnancy not confirmed by ultrasound scan or biological tests
- Pregnancy of 50 days’ amenorrhea and beyond
- Suspected extrauterine pregnancy
- Contraindication to the prostaglandin analogue selected.

The contraindications listed in the current marketing authorization held by Danco are as follows:

- Confirmed or suspected ectopic pregnancy or undiagnosed adnexal mass
- Intrauterine device (IUD) in place
- Chronic adrenal failure
- Concurrent long-term corticosteroid therapy (Danco PL only)
- History of allergy to mifepristone, misoprostol or other prostaglandins
- Hemorrhagic disorders or concurrent anticoagulant therapy
- Inherited porphyria.

The differences are highlighted in italics.

4.2. Rationale for contraindications

4.2.1. Indications for inclusion

Pregnancy not confirmed by ultrasound scan or biological tests and pregnancy of 50 days’ amenorrhea and beyond, strictly speaking, are not true contraindications; their inclusion only adds to further emphasize the patient selection criteria for the listed indication, especially because mifepristone and prostaglandin are also indicated for the medical termination of second-trimester pregnancy.

Suspected extrauterine pregnancy is listed as a contraindication to indicate that the treatment combination is not authorized for use in the management of extrauterine pregnancy and to stress the need to ensure that ectopic pregnancies are not missed; a missed diagnosis can result in a life-threatening condition.

At the time of the first introduction of mifepristone, studies had been performed to assess its efficacy in the treatment of ectopic pregnancy, and results were mixed [7,8]. It was not clear if administration of mifepristone would help or exacerbate the condition, or merely delay the onset of effective treatment and, hence, increase the risk associated with continuing ectopic pregnancy.
Since the first marketing authorization for mifepristone, more controlled studies have been performed to investigate the potential usage of mifepristone for the management of ectopic pregnancy. The use of mifepristone in association with methotrexate has been shown to be beneficial [9,10]. Despite some promising results, a clear treatment protocol for the use of mifepristone is yet to be defined, and it would be premature and inappropriate to recommend its use for the management of ectopic pregnancy.

4.2.3.1. Inherited porphyria. This contraindication was added to the SmPc for Mifegyne in 2001 following review of the results of a study in a recognized animal model for the detection of risk associated with drug administration [15].

4.2.3.2. Allergy to mifepristone or any component of the product. Hypersensitivity and allergic reactions have been reported after the administration of mifepristone (data on file; Exelgyn [16]) and misoprostol [17]. Reactions have included facial and general edema, urticarial and macropapular rashes, erythemas, wheezing and others. All reported reactions were treated conventionally, and the women recovered. It is obviously not possible to know if a potential patient may have an allergic reaction to treatment; however, a previous reaction in a patient presenting for the second time should represent a contraindication to further use.

4.2.3.3. Hemorrhagic disorders or concurrent anticoagulant therapy. These conditions represent a contraindication to treatment in the Danco PL but not on the Exelgyn SmPC, although disorders of hemostasis were included on previous versions and, in the current version, are included among warnings and precautions. There is no evidence that mifepristone and prostaglandin administration affects hemostasis other than as a result of blood loss following abortion induced by treatment. Bleeding is a normal part of the abortion process, and blood loss is usually no greater than that after surgical abortion at similar gestations [18]. However, hemorrhage is a recognized adverse effect of medical abortion, and although no formal studies have been performed, it is logical to expect that women treated with anticoagulants may be at a greater risk for hemorrhage and that the adverse consequences of hemorrhage in women with anemia would be greater. It can be argued that these risks would be similar with all methods of abortion, and, in the case of spontaneous miscarriage and incidences, can be managed with transfusion. Hence, specifically contraindicating medical abortion with mifepristone in all these women is unwarranted.

The difference between the PL of Danco and the SmPC of Exelgyn may reflect both the difference in experience within the two markets and the broader application of mifepristone and prostaglandin in the license held by Exelgyn.

4.2.3.4. Contraindications to the prostaglandin analogue selected. Relevant contraindications to both gemeprost and misoprostol are limited to hypersensitivity or allergy, which are discussed above. It should, however, be noted that misoprostol was not developed as a drug for use in pregnant women; indeed, the SmPC/PL for misoprostol contraindicates its use in pregnant women.

4.2.3.5. IUD in situ (Danco PL only). IUDs should be removed prior to abortion to avoid the risks of uterine perforation and infection. It is difficult to imagine a situation where mifepristone and prostaglandin would be given
knowingly to a woman with an IUD in situ, and every effort should be made to remove the IUD before proceeding with medical abortion. Due to lack of clinical experience, it is not known if administration of mifepristone and prostaglandin to a pregnant woman with an IUD in situ would result in a high risk of serious adverse events. Natural miscarriage with an IUD in situ is probably quite common and is not necessarily life-threatening. Strictly speaking, IUD in situ does not qualify as a contraindication; however, including it as such is useful and conveys an appropriate message to prescribers.

5. Contraindications and risks of cardiovascular events

Some confusion may exist as to the recommendations associated with the use of mifepristone and prostaglandin in women with a history of cardiovascular disease or with risk factors for cardiovascular disease (e.g., women who smoke). Although mifepristone and prostaglandin are not currently contraindicated in such women, this has not always been the case; it may, therefore, be useful to discuss how and why the recommendations have changed over time.

When mifepristone was first introduced in France, the contraindications listed did not include cardiovascular risk or smoking.

In 1991, subsequent to the occurrence of a fatal cardiovascular event in a 30-year-old multiparous woman who smoked heavily and who received mifepristone and sulprostone for termination of early pregnancy [3], the following contraindications were added:

- Women who smoke regularly or who have given up smoking for less than 2 years
- Women aged over 35 years of age.

It is important that patients abstain from all tobacco in the days following administration and on the day of prostaglandin administration.

In 1992, sulprostone was replaced by misoprostol as a prostaglandin for use in association with Mifegyne, and the wording of the contraindication section was amended as follows:

In previous years and with [the] use of another analogue of prostaglandin (sulprostone), rare and serious cardiovascular events (myocardial infarction, ventricular fibrillation, coronary spasm) were reported in women who were over 30 years of age and who smoked more than 10 cigarettes per day. To date, no similar events have been observed with the use of gemeprost or misoprostol; however, experience with these two prostaglandins is limited (about 10,000 cases with gemeprost and 1000 with misoprostol).

Until more experience is achieved and as a precautionary measure, it is therefore recommended that this method is not used in women who are over 35 years of age and who smoke regularly or who have stopped smoking within the last 2 years.

This method is therefore contraindicated in:

- Women smokers who are more than 35 years of age
- Women with cardiovascular risk factors (angina, Raynaud’s syndrome, arrhythmia, cardiac insufficiency, severe arterial hypertension).

In 1998, the above section was modified and removed from “contraindications” and added to “precautions.” The wording of this section states that the method is not recommended in women who are over 35 years of age and who smoke more than 10 cigarettes per day.

The Danco PL suggests that, due to the absence of adequate clinical studies in women with chronic diseases, including cardiovascular and hypertensive diseases or heavy smoking, women who are over 35 years of age and who also smoke 10 or more cigarettes per day should be treated with caution. A similar but less specific advice is given in the “warnings and precautions” section of the SmPC for gemprogest.

The cardiovascular effects of prostaglandin administration are known [19], and cardiovascular adverse events have been reported in association with the clinical use of gemprogest [20] and misoprostol [17]. Although no cardiovascular effects of misoprostol administration were found in a specially targeted study in pregnant women [21], it should be noted that this study was small and was performed in otherwise healthy women.

The state of pregnancy, in itself, increases the risk associated with a history of cardiovascular disease and/or risk factors, and smoking is additionally harmful (nicotine is a stimulant with direct cardiovascular action). In women with a history of cardiovascular disease or risk factors, any method of abortion will not be without additional risk; contraindicating the use of one particular method would reduce the options available to the clinician and to the women, and would force them to adopt another method that may be associated with even greater risk. All methods of abortion should be used with special care in such women, and it is therefore appropriate that the PL for mifepristone and prostaglandin, while not contraindicating use, advise caution in such circumstances.

6. Conclusions

The medical termination of pregnancy with mifepristone and prostaglandin has been used in clinical practice for 15 years. Since the introduction of the method, the listed contraindications for use have changed according to emerging science and increased experience with the method in larger numbers of women in more countries. Differences exist between the contraindications listed on the respective SmPC and PL of Exelgyn and Danco, possibly reflecting the different experiences and breadth of use of mifepristone with or without prostaglandin. There are relatively few absolute contraindications to the use of mifepristone and prostaglandin.
for the termination of pregnancy, and those that do exist are mostly justifiable. However, in the case of some of the contraindications listed, their inclusion as such is arguable, and they may be better considered as precautionary advice.

References