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Off-label use of misoprostol in gynaecology

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Abstract

Clinical use of drugs is approved for specified clinical indication, route of administration, dose and population group. Off-label prescribing of a registered medicine occurs outside of these parameters and may be justified by pharmacology and physiology, as well as sufficient evidence from published clinical trials and reviews.
Misoprostol and mifepristone in combination have recently been registered in Australia for medical termination of pregnancy in women of child-bearing age. There is good clinical evidence for efficacy and safety of misoprostol in uterine evacuation in both miscarriage and termination of pregnancy. The pharmacological effects of misoprostol on the uterus and clinical outcomes in both early miscarriage and abortion are comparable.
Medical management of miscarriage with misoprostol in Australia is performed off-label. A woman presenting with first trimester miscarriage must be clearly informed that use of misoprostol in her case is for a non-approved indication. This raises the issue of inequity in her management compared with that of first trimester medical abortion, including being treated off-label and the potential cost of non-subsidised medication. The clinician must also be careful to use an evidence-based protocol that would withstand medicolegal challenge in the case of an adverse outcome.

Key words: **Miscarriage, medical termination of pregnancy, MTOP, abortion, mifepristone, equity.**

Introduction

Drug product information (PI) provides details on the approved clinical use of drugs listed by the Therapeutic Goods Administration (TGA) in Australia. This includes clinical indication, route of administration, dose and population group. Information included in PIs is derived from clinical trials that support the use of a drug in each of these areas. Based on the pharmacology of a drug in relation to its approved indication, however, treatment of other medical conditions not listed on the PI may also be rationalised. Off-label prescribing occurs when a drug is prescribed for one or more criteria that are not included in the PI and, as such, information regarding appropriate dose for the condition or population group, pharmacokinetics/pharmacodynamics, and potential adverse effects may not be available in the PI or Consumer Medicines Information (CMI). Nevertheless, off-label prescribing may be justified by good quality evidence from clinical trials or systematic reviews of the literature, and a number of examples have been accepted in general and specialist clinical practice.

For example, until recently misoprostol was only approved by the TGA for treatment and prevention of upper gastrointestinal (GI) ulceration. It is commonly used off-label in obstetrics for treatment of post-partum haemorrhage as part of a management algorithm since it has demonstrated effective haemorrhage prevention and control in combination with oxytocin (Tuncalp et al., 2012). Regimes for use of misoprostol in gynaecology to evacuate the

contents of a gravid uterus, in both miscarriage and abortion have also been described (Gomez Ponce de Leon et al., 2007) and evaluated (Dodd and Crowther, 2010). Recently, misoprostol has also been approved in Australia for use in combination with mifepristone to terminate pregnancy in women of child-bearing age.

Pharmacology

Misoprostol (15-deoxy-16-hydroxy-16-methyl PGE1) is an orally active synthetic prostaglandin E1 (PGE1) methyl ester analogue. After oral administration, misoprostol rapidly de-esterifies to its biologically active form, misoprostolic acid. It has four major effects: gastrointestinal cytoprotection (approved therapeutic indication), uterotonicity, and diarrhoea and abdominal pain which are regarded as adverse effects. Cytoprotective effect is mainly by topical contact, with inhibition of gastric acid secretion and induction of oedema of the mucosa and submucosa, increasing the thickness of both layers. Uterotonicity requires binding to receptors in uterine smooth muscle and are mediated systemically after oral dosing. Abdominal pain, diarrhoea and flatulence are probably the result of exposure to the released misoprostolic acid and correlate well with the timing and magnitude of the misoprostolic acid peak plasma concentration (Davies et al., 2001).

Mifepristone (also known as RU-486) is a synthetic antiprogestin steroid with high affinity for the glucocorticoid and progesterone receptors and a weak affinity for the androgen receptor. Mifepristone acts by binding to the human uterine progesterone receptor with twice the affinity of that of progesterone, thus competitively inhibiting the endometrial and myometrial effects effect of progesterone. Under some circumstances, in the absence of progesterone, mifepristone may also act as a progesterone agonist (Robbins and Spitz, 1996). Its mechanism of action at the cellular level is highly complex and a variety of hypotheses have been proposed. During pregnancy mifepristone sensitises the myometrium to the contraction inducing action of prostaglandins (Swahn and Bygeeman, 1988). Administration of mifepristone in early pregnancy results in regular uterine contractility and increased sensitivity to prostaglandins. Moreover, with high concentrations of progesterone, blockage of decidual progesterone receptors by mifepristone results in withdrawal of progesterone support to the endometrium, leading to uterine bleeding and disruption of placental function. First trimester actions also include reduced cervical resistance, dilatation and opening of the cervix.

Registration of mifepristone

Mifepristone was first registered for medical abortion in Europe in 1988 and now has registration in many countries worldwide. From 1996 to 2005 in Australia mifepristone was classified as a "restricted good" which could only be imported with written approval of the federal Minister for Health. In 2006 the Therapeutic Goods Amendment (Repeal of Ministerial responsibility for approval of RU486) Bill 2005 was passed in Parliament which enabled the TGA to assess the efficacy, safety and quality of mifepristone should any application for registration be made.

No drug sponsor made immediate application for registration to the TGA so mifepristone remained an unapproved drug in Australia. It was, however, available to Authorised Prescribers under provisions of the Therapeutic Goods Act 1989 which permitted importation and use of drugs recognised and used overseas but that were currently unavailable in Australia.

In 2012, mifepristone (Therapeutic Goods Administration, 2014) was approved for use in combination with misoprostol (Therapeutic Goods Administration, 2012) for medical abortion in women of child-bearing age. Prescription is restricted to clinicians who have undertaken defined women's health training administered by the drug sponsor, and who have registered on the specific prescribing program. Indications for use are 1. Medical termination of a developing intra- uterine pregnancy up to 63 days of gestation, in sequential combination with a prostaglandin analogue; and 2. preparation for the action of registered prostaglandin analogues that are indicated for the termination of pregnancy for medical reasons beyond the first trimester.

Clinical use and guidelines

Combined mifepristone and misoprostol has reported widespread use for early first trimester abortions and has been the subject of a number of reviews (Kulier et al., 2011; Raymond et al., 2013).

The combination has an acceptable safety profile in clinical practice (Goldstone et al., 2012; Cleland et al.,2013) and controlled administration for abortion in outpatient and home settings has also been successfully performed even prior to formal registration of these drugs in Australia (de Costa et al., 2007; Mulligan and Messenger, 2011). Nevertheless, significant adverse events including incomplete abortion, sepsis and death have all been reported (Murray and Wooltorton, 2005; Goldstone et al., 2012). The recommendation from the Royal

Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG, 2012) is that "Medical termination should not be performed in an isolated or an inaccessible setting which lacks ready access to suitable emergency care (in a service accepting this responsibility) from administration of mifepristone until termination of pregnancy is complete."

There is still debate as to the appropriate regime for medical abortion in using mifepristone and misoprostol. According to the PI misoprostol tablets are to be administered orally. One large systematic review has found better clinical outcomes with vaginal versus oral administration, and reduced adverse effects for vaginally versus sublingual or buccal misoprostol (Kulier et al., 2011). The current approved dose of mifepristone is 200 mg in Australia whereas a dose of 600 mg of mifepristone is approved by the Food and Drug Administration (FDA) for use in the USA (Creinin et al., 2006). The International Federation of Gynecology and Obstetrics (FIGO) guidelines recommend only 200 mg of mifepristone (Faúndes, 2011) which is also supported by recent evidence (Raymond et al., 2013). It is likely that dosing regimens will continue to be researched and further evidence will be obtained that will shape recommended dosage, frequency and route of administration at different gestations.

Off-label use of misoprostol for miscarriage

Medical management of both early (miscarriage) and late pregnancy loss may be achieved with misoprostol. Its widespread use for management of first trimester miscarriage is well-supported by good quality evidence worldwide (Gomez Ponce de Leon et al., 2007; Neilson et al., 2013). Misoprostol is well tolerated and has an acceptable adverse effect and safety profile. Unfortunately there is still little uniformity in recommended treatment regimens although there is increasing evidence that lower doses may yield good results both clinically and psychologically (Barcelo et al., 2012; Petersen et al., 2013).

Misoprostol is clinically effective in management of miscarriage, has cost-benefits over other methods, and is versatile from the point of view of storage, dosing regimen and route of administration. Yet, there is a clear disparity between its approved use for abortion and its off-label use for management of miscarriage. The physiological and pharmacological mechanisms involved in both these circumstances can be assumed to be directly comparable but for the purpose of approved use of misoprostol they are viewed differently.

This raises a number of issues when dealing with women presenting with first trimester miscarriage for whom medical management is a preferred option. Off-label prescribing requires the clinician to inform the woman that her prescription is not for an approved indication as listed on the PI/CMI. The rationale for treatment with misoprostol should be explained with reference to the evidence available to reassure her of the safety and applicability of this treatment modality (Gazarian et al., 2006). Adverse effects and further information from the PI/CMI for misoprostol may be discussed, noting that that information is specifically applicable to termination of pregnancy but being inferred for her situation.

This properly informed woman might then question the reason she may incur a non- subsidised fee for misoprostol whereas someone seeking a termination need not. She may also become hesitant to undertake medical management due to this personal cost and questions about something called "off-label" treatment. Instigation of management with misoprostol should commence as soon as reasonable given the clinical and emotional circumstances surrounding the miscarriage. A delay in medical management has been shown to result in significantly increased emergency department presentations and need for emergency surgical management (Torre et al., 2012). She may also decide not to undergo medical management at all and instead opt for surgical management. The may place an increased burden on the healthcare system given the lower cost of medical versus surgical management in circumstances such as incomplete or inevitable miscarriage (Rausch et al., 2012), as well as an increased risk of preterm birth in subsequent pregnancies (Lemmers et al., 2016).

Clinicians, too, should be cautious when managing first trimester miscarriage with misoprostol. Since there are no formal guidelines in place, care must be taken when prescribing off-label to select a robust protocol that is supported with good evidence (Creinin et al., 2006). Public hospitals should have in place protocols approved at local and district levels, if not by state-wide policy if possible. Private clinicians or organisations should also have a credible system available that would withstand peer-review and legal challenge. Deviation from evidence-based regimens may leave the clinician and institution open to medicolegal challenge in the case of an adverse outcome or event.

The utility of misoprostol is not being questioned since it has great applicability in gynaecology in the Australian setting (Krishnan et al., 2014). The subtleties regarding indicated versus off-label use of misoprostol, however, must be given due attention given the transparency and evidence-

based requirements in modern obstetrics and gynaecology.

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