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COMMENTARY

Misoprostol and the debate over off-label drug use

Introduction

Many readers will be surprised to learn that antenatal betamethasone is not licensed by the UK Medicines and Healthcare products Regulatory Agency (MHRA, formally the Medicines Control Agency) to prevent neonatal respiratory distress syndrome in pregnancy. Nor is oxytocin 10 units im licensed to prevent postpartum haemorrhage. However, oxytocin 5 units iv is licensed to treat a missed miscarriage and norethisterone (days 19–26) is licensed to treat menorrhagia despite now being considered ineffective and outdated (Table 1).

Clearly, drug licensing is not proof of effectiveness and many drugs of proven efficacy are not licensed. It is also clear that, although drug companies have a responsibility to re-apply for their licence every five years, the scrutiny of these repeat applications by the MHRA is inadequate. This article will examine the role of drug licensing, especially with regard to the controversy over the use of misoprostol.

Misoprostol

Important new developments in obstetrics and gynaecology are usually rapidly integrated into clinical practice. Misoprostol is an exception. Despite extensive research evidence, it is only slowly being incorporated into practice. This is largely because it has no licence for use in reproductive health. However, the US Food and Drug Administration (FDA) has recently licensed mifepristone to be used with misoprostol for the termination of pregnancy,[1] even though misoprostol itself is not licensed for use in pregnancy. This decision has fuelled debate over drug licensing and left many doctors unsure of their legal and professional position regarding the prescription of off-label drugs. The example of misoprostol provides some insight in the role of drug licensing; the reasons why companies choose to apply for a licence and the consequences of a missing licence for the health of potential patients.

Misoprostol is a prostaglandin E_1 analogue licensed for the prevention and treatment of gastroduodenal ulcers. It has been on the market since 1985 and is approved for ulcer treatment in more than 80 countries under the brand name of Cytotec. It has several advantages over other prostaglandins on the market: (i) being an E_1 analogue, it has no effect on the bronchi or blood vessels; (ii) it can be stored at room temperature for many years; (iii) it can be used orally, vaginally, sublingually or rectally; (iv) it is cheap; and (v) the only side effects of note are diarrhoea and shivering, both of which are dose dependent and self-limiting. Misoprostol has been extensively studied in reproductive health[2,3] and is widely recommended for the treatment of missed and incomplete miscarriages, the induction of abortion, and cervical preparation before uterine instrumentation. It also has potential in late pregnancy for induction of labour and postpartum haemorrhage prophylaxis and treatment.

Bizarrely, however, the major obstacle to widespread use of this drug in obstetrics and gynaecology has been its manufacturer and patent holder, Searle (now incorporated into Pfizer). The US-based company has not applied for licences for any reproductive health indications, despite the abundant literature on its safe and effective use. The reason is probably an effort to avoid potentially damaging discussions about the drug's use for inducing abortion, the outcome is the denial of access to a potentially life-saving treatment to millions of women around the world. This is especially true in Africa where three of the biggest causes of maternal mortality—haemorrhage, septic abortion and pre-eclampsia—could each be reduced with easy access to a stable and cheap prostaglandin.

The fight over misoprostol has at times become intense with obstetricians and reproductive health campaigners squaring up against the pharmaceutical industry and anti-abortion lobby. At the heart of the debate is the question of the role of drug licensing.[4] Many obstetricians are wary of using drugs for unlicensed indications for fear of litigation and this has been seized upon by those who wish to restrict the use of misoprostol to its gastrointestinal indications.[5] The manufacturer has also been quick to remind obstetricians that the drug is not licensed for reproductive health uses.[6] On the other side, proponents of wider use point out the potentially important public health implications and the current widespread use of other off-label medications in both paediatrics and obstetrics. Conroy *et al.*,[7] for example, found in a survey of paediatric wards across Europe that 46% of all drug prescriptions were off-label.

Drug licensing

So what is a 'drug licence'? If it does not demonstrate that the drug is currently thought to be effective for the indication, and if many useful and proven treatments are

Table 1. Summary of the status of six drugs for particular clinical indications. Licensing information is taken from Medicines Compendium 2003 (ABPI). In the 'BNF' column, drugs get a tick if mentioned as a management option under that drugs entry in the British National Formulary.[11] In the 'RCOG' column, a tick is obtained if the drug is mentioned as an option in Royal College of Obstetricians and Gynaecologists guidelines (or that of an approved affiliate in the case of PPH).

Drug and indication	Licensed?	BNF	RCOG
1. Oxytocin 10 im to prevent PPH	X	✓	✓[21]
2. Misoprostol for termination of pregnancy before 24 weeks	X	✓	✓[10]
3. Antenatal betamethasone to prevent neonatal respiratory distress syndrome in premature deliveries	X	X	✓[22]
4. Clindamycin to treat β haemolytic streptococci in pregnancy	X	X	✓[23]
5. Oxytocin 5 iv to treat missed miscarriage	✓	X	X
6. Norethisterone (days 19–26) to treat menorrhagia	✓	✓	X

not licensed, then what is its purpose? The MHRA says that it demonstrates that the drug submitted to the agency passed a stringent risk–benefit analysis for that indication. But they are not proactive in seeking licences. It remains the manufacturer's decision whether to apply for a licence and they need to do that as a hard-headed commercial decision. So a drug licence means that the drug has not only passed a risk–benefit analysis, but also a stringent profit–loss analysis. Obtaining a drug licence for a new medication is an expensive and laborious process, costing on average US$ 897 million and taking 7–15 years.[8] The high cost of trials and the company's hurry to get results (and thereby get the drug on the market) mean that these trials are usually just big enough to show the drug's safety and efficacy over placebo. Thus, the trials are often small and consequently unpublishable. Indeed, the drug companies have no responsibility to make the data from their trials public. This is in marked contrast to some of the large high quality randomised controlled trials that have led to the evidence on which the professional colleges guidelines are based. These trials could be used by the manufacturer to licence the drug, but this is only worth the cost to the company if a license would lead to increased sales. The use of antenatal betamethasone for the prevention of respiratory distress syndrome is a case in point. The drug is cheap and the professional bodies are already pressurising doctors to prescribe it. The potential additional benefit for the company of a licence is minimal and they have not therefore applied for a licence for this indication.

What evidence to trust?

Doctors around the world are receiving conflicting opinions about misoprostol. Understandably, many are unsure which recommendation to accept, bearing in mind the costs, legality and safety. Should it be the manufacturer, the MHRA, the World Health Organization (WHO), the Royal Colleges, the Cochrane Collaboration or government regulators? To illustrate the variety of advice available, the recommendations from various organisations regarding vaginal misoprostol for abortion and for the induction of labour, the most contentious of the misoprostol indications, are presented below.

Misoprostol for abortion

There is now overwhelming evidence for the benefits of using misoprostol as the prostaglandin of choice following mifepristone for medical abortion in the first and second trimesters.[2] However, the advice of the manufacturer is that misoprostol is not licensed for use in pregnancy and should therefore not be used. Despite this, the FDA has recently granted a licence for the anti-progesterone agent mifepristone and the recommended abortion regimen has misoprostol as the prostaglandin of choice.[1] This has resulted in the unique situation where misoprostol is FDA-approved as part of an abortion regimen but not in its own right. To reflect this, the FDA has recently changed the labelling so that misoprostol is no longer 'contra-indicated in pregnancy' but rather that it 'should not be taken by pregnant women to reduce the risk of ulcers induced by non-steroidal anti-inflammatory drugs'.[9] This move followed the French registration of misoprostol, which lists pregnancy as a contraindication except in the case of an induced termination.

In the UK, the Royal College of Obstetricians and Gynaecologists (RCOG) recommends misoprostol for the induction of abortion along with mifepristone[10] and the British National Formulary has added a paragraph stating 'misoprostol is given by mouth or by vaginal administration to induce medical abortion [unlicensed indication]'.[11]

Misoprostol for induction of labour

Misoprostol is increasingly being used in the USA and elsewhere for the induction of labour. The Cochrane review concludes that for vaginal administration, 'doses not exceeding 25 μg four-hourly appeared to have similar effectiveness and risk of uterine hyperstimulation to conventional labour inducing methods',[12] although there have been disturbing reports of uterine hyperstimulation if higher doses are used. It is contraindicated in women with a previous caesarean section scar, as the risk of uterine rupture appears to be around 10%.[13,14]

In the light of this evidence, the recent WHO manual 'Managing Complications in Pregnancy and Childbirth'[15] recommends the use of misoprostol for induction of labour and places it in its list of 'essential drugs', even though it is absent from the official WHO list of essential drugs.[16]

(In fact, WHO's list of essential drugs does not contain a single prostaglandin.) The American College of Obstetrics and Gynecology agrees: 'if misoprostol is to be used for cervical ripening...25 μg should be considered the initial dose'.[9] The RCOG/National Institute for Clinical Excellence (NICE) guideline on labour induction is more cautious, stating that although 'vaginal misoprostol appears to be a more effective agent than intravaginal or intracervical PGE_2 or oxytocin', the safety issues surrounding its use are 'unclear' and that its use should be 'restricted to RCTs'.[17]

To many this debate may appear to be primarily of academic interest. In Africa, however, where there is minimal access to alternatives, it is crucial in the fight against maternal mortality.

The importance of misoprostol in Africa

Maternal mortality is a major problem in Africa with an estimated 270,000 deaths per year. Overall, one in every 16 women dies in her reproductive years from a pregnancy-related cause. WHO estimates that for every 100,000 live births in Africa there are about 1000 maternal deaths compared with 276 for Asia, 190 for Latin America and 10 for Europe.[18] Clearly, these shocking figures call for a concerted and interdisciplinary approach to save mothers and their children. Progress is hindered, however, by the lack of access to an approved prostaglandin for obstetric use. Misoprostol is currently approved in only three countries in Africa, South Africa, Ghana and Uganda. The only drugs approved to induce contractions of the uterus in most parts of Africa are oxytocin and ergometrine. Use of these two drugs is limited by a number of factors. Firstly, they have a number of contraindications and potentially serious side effects. Secondly, they need to be given intravenously (through a regulated infusion system) or intramuscularly, and both are ideally stored in a refrigerator. All of these conditions are difficult to fulfil in low resource settings. Finally, these two drugs are not always effective because of their site of action. While they are effective at stimulating uterine contractions, they do not have any direct effect on the cervix. This is in contrast to the prostaglandins that are effective in both sites by inducing contractions and ripening the cervix. This detail is important where a uterine evacuation or delivery is needed despite a closed cervix. In this situation, the clinician may need to use high doses of oxytocin over long periods, which can lead to fetal hypoxia, ruptured uterus or water intoxication. The lack of effectiveness of oxytocin may also result in the need to perform caesarean sections in women who have an intrauterine fetal death. This adds not only a psychological burden to women in a situation that is already difficult, but also unnecessarily increases the risk of morbidity and mortality.

Misoprostol, on the other hand, is effective at inducing contractions throughout pregnancy.[3] Although there is consensus on its usefulness, the lack of a licence for reproductive health indications has led to other problems. Firstly, there remains confusion among doctors as to which dosage and route to use. The drug manufacturer usually provides such guidance, but the absence of a formal drug insert or advertising has led to wide variations in practice.[19] This has potentially contributed to many fetal deaths from uterine rupture due to the use of excessive doses for induction of labour in the third trimester of pregnancy. The problem is exacerbated by the fact that misoprostol is only available in 200 or 100 μg tablets. This tablet size is made with the ulcer indication in mind and is excessive for labour induction where 25 or 50 μg tablets are needed. Difficulty in accurately delivering small doses may also have contributed to the use of excessive doses. The second problem is that many governments in the developing world look to the formal licensing of a drug in the UK or USA, or to inclusion on the WHO's list of essential drugs before they will agree to its local registration. This in turn is necessary before local hospitals and clinics can use it, even if it is life-saving.

Conversely, the decision of the manufacturer to market the drug only for ulcer use has also has some positive consequences. Because continuous use is needed for the prevention of gastric ulcers, misoprostol was priced by the manufacturer at a price that would allow its continued administration at a dose of 800 μg (four tablets) daily. As less than one tablet is needed for induction, this has led to it being a very affordable treatment for induction of labour.

Conclusions

It is clear that the drug licence alone is not the appropriate determinant of whether a drug is effective for any given indication. The MHRA was set up to regulate the pharmaceutical industry and not the medical profession, and its advice should always be seen in this context. Furthermore, the current licensing system is inadequate in a situation where the patent holder decides not to apply for an indication because there is no economic interest, even when the drug would be of huge potential benefit to patients. No other company can take the initiative when the patent rights are still valid and national health authorities have remained silent on this issue. The pharmaceutical industry's refusal to apply for a licence in this situation raises serious ethical questions.

In legal terms, the onus is for doctors to follow the practice that would be accepted by a reputable group of peers. But who are the reputable group of peers? Given the data in Table 1, this is probably not the MRHA: the professional colleges' statements of 'good practice' would be seen as superior to that of the drug license in the courtroom. The UK's NICE was set up in 1999 to provide 'authoritative, robust and reliable guidance on current best practice'[20] and has started producing authoritative guidelines. In due

course, NICE will provide advice on drug use in most areas of clinical practice, and they will become the final arbiter of 'best practice' in the UK. Hopefully, they will also work with the colleges and MHRA to streamline the advice that doctors receive. Currently, however, in those areas not yet covered by NICE, practitioners will need to rely on recommendations from the professional organisations.

Misoprostol has huge potential in obstetric and gynaecological practice and the low rate of side effects is currently not sufficiently acknowledged. The lack of approved indications should not deter us from using it where there is sufficient evidence for its safe and effective use. The good news is that the patent rights have run out in a number of countries and generics are already starting to arrive on the market. A dedicated misoprostol product approved for several reproductive health indications should be approved in France in the months to come.

Conflict of interest

The authors all worked as obstetricians in Africa between 2000 and 2003 without access to prostaglandins. In 2002, ADW and CF helped introduce misoprostol into Ugandan clinical practice.

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