

Misoprostol

Misoprostol, sold under the brandname **Cytotec** among others, is a medication used to prevent and treat stomach ulcers, start labor, cause an abortion, and treat postpartum bleeding due to poor contraction of the uterus.^{[1][2]} For abortions it is used by itself and with mifepristone or methotrexate.^[3] By itself, effectiveness for abortion is between 66% and 90%.^{[4][5]} Misoprostol is taken by mouth when used to prevent gastric ulcers in persons taking NSAIDs.^[2] For labor induction or abortion, it is taken by mouth, dissolved in the mouth, or placed in the vagina.^{[3][6][7]} For postpartum bleeding it may also be used rectally.^[8]

Common side effects include diarrhea and abdominal pain.^[2] It is pregnancy category X meaning that it is known to result in negative outcomes for the baby if taken during pregnancy.^[2] In rare cases, uterine rupture may occur.^[2] It is a prostaglandin analogue — specifically, a synthetic prostaglandin E₁ (PGE₁).^[2]

Misoprostol was developed in 1973.^[9] It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system.^[10] It is available as a generic medication.^[2] The wholesale cost in the developing world is about 0.36 to 2.00 USD a dose.^[11] A month's supply to treat stomach ulcers in the United States is between 100 and 200 USD.^[12] The same costs between 30 and 55 EUR in Europe.^[13]

Contents

Medical uses

- Ulcer prevention
- Labor induction
- Abortion
- Failed miscarriage
- Postpartum bleeding
- Other

Adverse effects

Contraindications

Pharmacology

- Mechanism of action

Society and culture

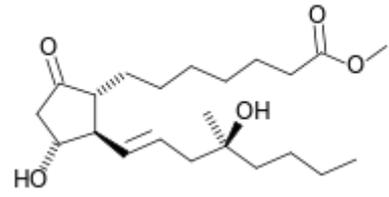
- Black market

References

External links

Medical uses

Misoprostol



Clinical data

Trade names	Cytotec, Misodel, other
AHFS/Drugs.com	Monograph (https://www.drugs.com/monograph/misoprostol.html)
MedlinePlus	a689009 (https://medlineplus.gov/druginfo/meds/a689009.html)
Pregnancy category	AU: X (High risk) US: X (Contraindicated) Used for terminating pregnancy
Routes of administration	By mouth, vaginal, under the tongue
ATC code	A02BB01 (WHO (https://www.who.cc/no/atc_ddd_index/?code=A02BB01)) G02AD06 (WHO (https://www.whocc.no/atc_ddd_index/?code=G02AD06))
Legal status	
Legal status	AU: S4 (Prescription)

Ulcer prevention

Misoprostol is used for the prevention of NSAID-induced gastric ulcers. It acts upon gastric parietal cells, inhibiting the secretion of gastric acid by G-protein coupled receptor-mediated inhibition of adenylyate cyclase, which leads to decreased intracellular cyclic AMP levels and decreased proton pump activity at the apical surface of the parietal cell. Because other classes of drugs, especially H2-receptor antagonists and proton pump inhibitors, are more effective for the treatment of acute peptic ulcers, misoprostol is only indicated for use by people who are both taking NSAIDs and are at high risk for NSAID-induced ulcers, including the elderly and people with ulcer complications. Misoprostol is sometimes coprescribed with NSAIDs to prevent their common adverse effect of gastric ulceration (e.g. with diclofenac in Arthrotec).

However, even in the treatment of NSAID-induced ulcers, omeprazole proved to be at least as effective as misoprostol,^[14] but was significantly better tolerated, so misoprostol should not be considered a first-line treatment. Misoprostol-induced diarrhea and the need for multiple daily doses (typically four) are the main issues impairing compliance with therapy.

Labor induction

Misoprostol is commonly used for labor induction. It causes uterine contractions and the ripening (effacement or thinning) of the cervix.^[15] It can be less expensive than the other commonly used ripening agent, dinoprostone.^[16]

Oxytocin has long been used as the standard agent for labor induction, but does not work well when the cervix is not yet ripe. Misoprostol also may be used in conjunction with oxytocin.^[16]

Between 2002 and 2012, a misoprostol vaginal insert was studied, and was approved in the EU.^{[17][18]} It was not approved for use in the USA, and the US FDA still considers cervical ripening and labor induction to be outside of the approved uses for misoprostol.^[19]

Abortion

Misoprostol is used either alone or in conjunction with another medication (mifepristone or methotrexate) for medical abortions as an alternative to surgical abortion.^[20] Medical abortion has the advantage of being less invasive, and more autonomous, self-directed, and discreet. It is preferable to some users because it feels more "natural," as the drugs induce a miscarriage.^[21] It is also more easily accessible in places where abortion is illegal.^[22] The World Health Organization provides clear guidelines on the use, benefits and risks of misoprostol for abortions.^[23]

Misoprostol is most effective when it is used with methotrexate or mifepristone (RU-486).^[24] Misoprostol alone is less effective (typically 88% up to eight-weeks gestation). It is not inherently unsafe if medically supervised, but 1% of

	only) <u>CA</u> : Rx-only <u>UK</u> : POM (Prescription only) <u>US</u> : Rx-only
Pharmacokinetic data	
Bioavailability	extensively absorbed
Protein binding	80-90% (active metabolite, misoprostol acid)
Metabolism	Liver (extensive to misoprostic acid)
Elimination half-life	20–40 minutes
Excretion	Urine (80%)
Identifiers	
IUPAC name	Methyl 7-((1 <i>R</i> ,2 <i>R</i> ,3 <i>R</i>)-3-hydroxy-2-((<i>S</i> , <i>E</i>)-4-hydroxy-4-methyloct-1-enyl)-5-oxocyclopentyl)heptanoate
CAS Number	59122-46-2 (http://www.commonchemistry.org/ChemicalDetail.aspx?ref=59122-46-2) ✓
PubChem CID	5282381 (https://pubchem.ncbi.nlm.nih.gov/compound/5282381)
IUPHAR/BPS	1936 (http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=1936)
DrugBank	DB00929 (https://www.drugbank.ca/drugs/DB00929) ✓

Misoprostol is also used to prevent and treat post-partum bleeding. Orally administered misoprostol was marginally less effective than oxytocin.^[33] The use of rectally administered misoprostol is optimal in cases of bleeding; it was shown to be associated with lower rates of side effects compared to other routes. Rectally administered misoprostol was reported in a variety of case reports and randomised controlled trials.^{[34][35]} However, it is inexpensive and thermostable (thus does not require refrigeration like oxytocin), making it a cost-effective and valuable drug to use in the developing world.^[36] A randomised control trial of misoprostol use found a 38% reduction in maternal deaths due to *post partum* haemorrhage in resource-poor communities.^[37] Misoprostol is recommended due to its cost, effectiveness, stability, and low rate of side effects.^[38] Oxytocin must also be given by injection, while misoprostol can be given orally or rectally for this use, making it much more useful in areas where nurses and physicians are less available.^[39]

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Other

For cervical ripening in advance of endometrial biopsy to reduce the need for use of a tenaculum or cervical dilator.

Adverse effects

The most commonly reported adverse effect of taking a misoprostol by mouth for the prevention of stomach ulcers is diarrhea. In clinical trials, an average 13% of people reported diarrhea, which was dose-related and usually developed early in the course of therapy (after 13 days) and was usually self-limiting (often resolving within 8 days), but sometimes (in 2% of people) required discontinuation of misoprostol.^[40]

The next most commonly reported adverse effects of taking misoprostol by mouth for the prevention of gastric ulcers are: abdominal pain, nausea, flatulence, headache, dyspepsia, vomiting, and constipation, but none of these adverse effects occurred more often than when taking placebos.^[40] In practice, fever is almost universal when multiple doses are given every 4 to 6 hours.

There are increased side effects with sublingual or oral misoprostol, compared to a low dose (400 ug) vaginal misoprostol. However, low dose vaginal misoprostol was linked with low complete abortion rate.^[29] The study concluded that sublingually administered misoprostol dosed at 600 ug or 400 ug had greater instances of fever and diarrhea due to its quicker onset of action, higher peak concentration and bioavailability in comparison to vaginal or oral misoprostol.^[29]

For the indication of medical abortion, bleeding and cramping is commonly experienced after administration of misoprostol. Bleeding and cramping is likely to be greater than that experienced with menses, however, emergency care is advised if bleeding is excessive.^[31]

Misoprostol should not be taken by pregnant women with wanted pregnancies to reduce the risk of NSAID-induced gastric ulcers because it increases uterine tone and contractions in pregnancy, which may cause partial or complete abortions, and because its use in pregnancy has been associated with birth defects.^{[40][41]}

All cervical ripening and induction agents can cause uterine hyperstimulation, which can negatively affect the blood supply to the fetus and increases the risk of complications such as uterine rupture.^[42] Concern has been raised that uterine hyperstimulation that occurs during a misoprostol-induced labor is more difficult to treat than hyperstimulation during labors induced by other drugs.^[43] Because the complications are rare, it is difficult to determine if misoprostol causes a higher risk than do other cervical ripening agents. One estimate is that it would require around 61,000 people enrolled in randomized controlled trials to detect a difference in serious fetal complications and about 155,000 people to detect a difference in serious maternal complications.^[44]

Contraindications

It is recommended that medical treatment for missed abortion with misoprostol should only be considered in people without the following contraindications: suspected ectopic pregnancy, use of non-steroidal drugs, signs of pelvic infections or sepsis, unstable hemodynamics, known allergy to misoprostol, previous caesarean section, mitral stenosis, hypertension, glaucoma, bronchial asthma, and remote areas without a hospital nearby.^[29]

Pharmacology

Mechanism of action

Misoprostol, a prostaglandin analogue, binds to myometrial cells to cause strong myometrial contractions leading to expulsion of tissue. This agent also causes cervical ripening with softening and dilation of the cervix. Misoprostol binds to and stimulates prostaglandin EP2 receptors, prostaglandin EP3 receptor and prostaglandin EP4 receptor but not Prostaglandin EP1 receptor and therefore is expected to have a more restricted range of physiological and potentially toxic actions than prostaglandin E2 or other analogs which activate all four prostaglandin receptors.^[45]

Society and culture

A letter from Searle generated some controversy over the use of misoprostol in labor inductions.^[46] The American College of Obstetricians and Gynecologists holds that substantial evidence supports the use of misoprostol for induction of labor, a position it reaffirmed in 2000 in response to the Searle letter.^[47] Misoprostol is also on the WHO essential drug list for labor induction.^[48]

The largest medical malpractice award of nearly \$70 million was awarded due to the use of misoprostol to induce labor in a California hospital.^[49]

A vaginal form of the medication is sold in the EU under the names Misodel and Mysodelle for use in labor induction.

Black market

Misoprostol is used for self-induced abortions in Brazil, where black market prices exceed US\$100 per dose. Illegal medically unsupervised misoprostol abortions in Brazil are associated with a lower complication rate than other forms of illegal self-induced abortion, but are still associated with a higher complication rate than legal, medically supervised surgical and medical abortions. Failed misoprostol abortions are associated with birth defects in some cases.^{[50][51][52][53][54]} Low-income and immigrant populations in New York City have also been observed to use self-administered misoprostol to induce abortions, as this method is much cheaper than a surgical abortion (about \$2 per dose).^[55] The drug is readily available in Mexico.^[56] Use of misoprostol has also increased in Texas in response to increased regulation of abortion providers.^[57]

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External links

- [Misoprostol.org](http://www.misoprostol.org) (<http://www.misoprostol.org>) an independent website containing dosage guidelines and advice on misoprostol use.
 - [The Mechanism of Action and Pharmacology of Mifepristone, Misoprostol, and Methotrexate](http://www.medscape.com/viewarticle/429755_3) (http://www.medscape.com/viewarticle/429755_3)
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