Department of Woman and Child Health

Misoprostol - pharmacokinetics and effects on uterine contractility and cervical ripening in early pregnancy

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ABSTRACT

Misoprostol is an orally active synthetic PGE1 analogue which has become an important drug in obstetric and gynaecological practice because of its uterotonic and cervical priming actions. It is safe, cheap, widely available and stable at room temperature. Misoprostol has been found to be useful for medical abortion, cervical priming prior to surgical abortion, evacuation of the uterus in cases of incomplete abortion, missed abortion and intrauterine foetal death, induction of labour and treatment and prevention of post-partum haemorrhage. It was discovered in clinical studies that the misoprostol tablets licensed for oral use could be administered by other routes and that this could influence efficacy. A better understanding of the impact of the route of administration would thus help to further improve misoprostol regimens for several indications. The aims of this thesis were therefore to evaluate the effect of different administration routes and doses of conventional misoprostol and a new slow release (SR) formulation of misoprostol, focusing on its effects on uterine contractility and the pharmacokinetic profile of misoprostol free acid (MPA). In addition, the effect of misoprostol on inflammatory mediators in the cervix was investigated. Healthy women with a normal intrauterine pregnancy in the first trimester who requested vacuum aspiration for termination of pregnancy were recruited for the studies.

Uterine contractility was studied after treatment with oral (400 µg), vaginal (400 µg) or sublingual misoprostol (200 or 400 µg). Regardless of the dose and route of administration, the first effect of misoprostol to be observed was a rise in tonus which was more pronounced after oral or sublingual administration. Following sublingual and vaginal administration, regular uterine contractions developed, while oral treatment had only a minor effect on uterine contractions. The response to oral treatment with 400 and 800 µg SR misoprostol was also compared to the response to 400 µg conventional oral misoprostol. SR misoprostol was found to have less effect on uterine tonus, although it was more potent in terms of inducing uterine contractions. The pharmacokinetic profile of MPA following administration of SR misoprostol compared to conventional vaginal and sublingual misoprostol revealed lower peak plasma levels but a longer lasting elevation of these plasma levels.

The effect of 400 µg oral or vaginal misoprostol on inflammatory mediators in the cervical tissue was compared with an untreated control group. Immunohistochemical analysis was performed on cervical biopsies. Treatment with misoprostol was associated with higher levels of leukocytes (CD45), and monocytes (CD68) in the cervix compared to untreated controls. A greater staining of MMP 8 and MMP 9 was found following treatment, while TIMP 1 and 2 expression did not differ between the treatment and control groups.

Taken together, the results indicate that the peak MPA serum levels seem to correlate with uterine tonus, while the duration of elevated serum levels seems to correlate with the effect on uterine contractility. A certain threshold level of MPA is needed, but once this is reached; the duration of elevated MPA over this critical threshold seems to be the most important parameter in terms of inducing contractions. The findings relating to the pharmacokinetic properties and the effect on uterine contractility of different routes of administration will enable clinicians to design optimal regimens for various clinical applications.

Key words: misoprostol/ induced abortion/ pregnancy/sublingual administration/cervical ripening/slow-release/uterine contractility/ pharmacokinetics

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