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 fetal 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 singleton intramural 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, the response to oral treatment with 400 µg conventional oral misoprostol was also compared to the response to 400 µg SR misoprostol. SR misoprostol was found to have less effect on uterine tonus, although it was more potent in terms of inducing contractions. The pharmacokinetic profile of MPA following administration of SR misoprostol was also compared to the response to 400 µg conventional oral misoprostol. It was found that SR misoprostol was associated with higher levels of inflammatory mediators in the cervix following treatment. Treatment with misoprostol was associated with higher levels of inflammatory mediators in the cervix following treatment. Immunohistochemical analysis was performed on cervical biopsies. Treatment with misoprostol was associated with higher levels of leukocytes (CD45) and monocytes (CD68). Treatment with misoprostol was also associated with higher levels of MMP 8 and MMP 9, while TIMP 1 and 2 expression was reduced. The effect of 400 µg oral or vaginal misoprostol on inflammatory mediators in the cervix was also investigated. Immunohistochemical analysis was performed on cervical biopsies. Treatment with misoprostol was associated with higher levels of leukocytes (CD45) and monocytes (CD68). Treatment with misoprostol was also associated with higher levels of MMP 8 and MMP 9, while TIMP 1 and 2 expression was reduced. The higher levels of MPA serum levels seem to correlate with uterine contractility, while the duration of elevated MPA levels seems to correlate with the effect on uterine contractility. A certain threshold level of MPA is reached, but once this is reached, the response to misoprostol becomes more pronounced. The findings of this thesis 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