Pharmacogenomics of misoprostol for the treatment of postpartum haemorrhage

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Objective Misoprostol, a synthetic E1 prostagladin analogue, represents a safe and effective treatment option for postpartum haemorrhage (PPH) when oxytocin is not available. However, misoprostol use has been associated with fever greater than 40 °C in some but not all populations. For example, 35% of women from Ecuador had fever ≥40 °C after receiving sublingual misoprostol (800 mcgs), while much lower rates of fever (0–9%) were recorded in other populations. Environmental factors, clinical practices and patient characteristics that could possibly contribute to the increased rate of high fevers have been previously explored. Our aim was to investigate whether genetic variability contributes to misoprostol-induced fever.

Methods Fifty women from Quito, Ecuador on 600 mcgs sublingual misoprostol for PPH were included in the study and their body temperature was measured. DNA was extracted from whole blood and genotyping for 33 single nucleotide polymorphisms (SNPs) was performed using mass spectrometry (Sequenom). Our gene selection was based on mechanisms involved in prostaglandin induced fever. We included genes that encode misoprostol pharmacological targets, enzymes involved in prostaglandin metabolism and proteins involved in transport across body membranes. Statistical analysis was performed using analysis of variance (ANOVA). Genetic findings were validated in vitro using the hCMEC/D3 cell line and different ABCC4 inhibitors (MK571, indoprofen and indomethacin) to measure transport and intracellular accumulation of an active metabolite of misoprostol, [^{3}H], labelled misoprostol acid (4 μCi/mL).

Results 8/50 women (16%) developed fever >40 °C. Using body temperature in continuous data analysis, we found an association between misoprostol-induced fever and SNPs in genes encoding drug transporters including an ABC-binding cassette efflux transporter ABCC4 and two organic anion influx transporters SLCO2A1 and SLCO1B1. In vitro experiments using the hCMEC/ D3 cell line as a model of the blood–brain barrier demonstrated that misoprostol is actively transported by ABCC4.

Conclusions We demonstrated that genetic variability in misoprostol transporters may be a contributing factor in misoprostol-induced fever. In addition, this is the first study to demonstrate that misoprostol acid is a substrate for ABCC4, which is expressed at the blood–brain barrier. Further studies are needed to replicate our findings in a larger number of participants.