International Congress Series 1279 (2005) 358–363

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Misoprostol in the management of postpartum haemorrhage

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Abstract. Postpartum haemorrhage (PPH), mostly due to atony of the uterus, remains an important cause of maternal morbidity and mortality worldwide. Therefore, prevention and treatment of PPH with uterotonics such as prostaglandins is an important tool in perinatal management. Misoprostol is a cheap, thermostable, prostaglandin E1 derivate. It is a potent uterotonic and cervical priming agent. It is available in a tablet and can be administered orally, vaginally, rectally or sublingually, with different pharmacokinetic profiles. The oral and sublingual route result in the fastest onset of action and strongest initial uterotonic effect. Rectally, there is a prolonged uterine contraction after a slow onset of action. On the basis of available literature it can be concluded that misoprostol is not the first choice for active management of third stage of labor, when conventional uterotonics are available. Two case reports, two observational studies and a single-blinded randomised study support the use of misoprostol in the treatment of PPH. Two small randomised controlled trials combining different routes of administration could not confirm these findings. Larger trials are required to identify the best drug combinations, route, and dose, before misoprostol can be recommended for routine use in the treatment of PPH.

Keywords: Postpartum haemorrhage; Misoprostol; Uterotonics

1. Introduction

Obstetrical haemorrhage may cause acute and dramatic haemodynamic disorders and coagulopathies in young and healthy women. Life-threatening haemorrhages occur in 1:1000 pregnancies and are the leading cause of maternal mortality in developing

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0531-5131/
doi:10.1016/j.ics.2004.12.039

countries [1]. In the Netherlands it is a significant cause of maternal morbidity and the fourth direct cause of maternal mortality after preeclampsia, trombo-embolism, and infection [2].

Most of these haemorrhages are postpartum haemorrhage (PPH) due to atony of the uterus. There is evidence that active management of the third stage of labour, i.e. early umbilical cord clamping, 10 IU oxytocin, and controlled cord traction, decreases blood loss during the third stage of labour and reduces the risk of postpartum haemorrhage [3]. When PPH occurs, conventionally a number of medical and surgical interventions are used to control bleeding [4]. In addition, adequate measures such as timely fluid administration for correction of hypovolemia are necessary to prevent serious maternal morbidity. One component in the prevention and treatment of PPH is uterotonic therapy, most commonly with oxytocin. The advent of prostaglandins (F2α and prostaglandin E2 analogues) has opened new potentials for the management of the third stage of labour. However these drugs are expensive and have to be infused or injected, and may have serious side effects and are thermoinstable.

2. Misoprostol

Misoprostol (cytotec®) is a water-soluble prostaglandin E1 analogue (15-deoxy-16-hydroxy-16-methyl PG E1). Initially, it has been approved to be taken orally for the prevention and treatment of peptic ulcers associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Misoprostol appeared to be a potent uterotonic and cervical priming agent [5]. It is widely used for induction of abortion [5], cervical ripening, and induction of labour [6]. It has several advantages when compared with other available prostaglandins. Misoprostol is less expensive than other preparations of prostaglandins and does not require refrigerated storage. Other advantages of misoprostol are a non-invasive route of administration and a long half-life. These features make misoprostol suitable for use, particularly in developing countries. Common side effects of misoprostol when used in prevention or treatment of PPH include shivering, fever, diarrhoea, and abdominal pain. Shivering (up to 76%) and fever have been reported with the use of misoprostol in the third stage of labour [7–9]. As with other prostaglandins, the rate of adverse effects is related to factors such as dose and route of administration. Serious adverse effects such as coronary and bronchial spasms have not been reported thus far in relation to the use of misoprostol.

3. Pharmacokinetics

Misoprostol is rapidly absorbed after oral administration [10]. The tablet can also be administered sublingually, vaginally or rectally [9,11–13]. Orally, there is a rapid and almost complete resorption from the gastrointestinal tract, rapid first-pass metabolism (de-esterification) to form its free acid, the active metabolite of the drug, and rapid excretion [14]. The plasma concentration of misoprostol acid rises quickly after 600 mcg oral administration, is detectable in serum after 2 min with a serum peak level after 20 min, then drops steeply by 90 min and remains low. [10,11] The onset of action is as soon as 6 min (range 4–10 min) [9]. In colostrum, misoprostol acid reaches its maximum concentration 1 h after oral administration and then declines gradually [11].