Education and Background Notes

GTN - Mechanism of Action

- Mechanisms are not entirely understood but thought likely at the cellular level to involve:
  - GTN → metabolised to nitric oxide (NO) in smooth muscle cells →
  - Activation of guanylate cyclase →
  - Increased production of cyclic guanosine monophosphate (cGMP) →
  - Relaxation of smooth muscle (Riley 1996)
- Clinically, the use of GTN produces a **perceptible reduction** in uterine tone readily appreciated by the obstetrician as has been reported widely in case series and clinical practice.
- Interestingly, studies in pregnant women and animals using intrauterine pressure catheters have not been able to demonstrate a reduction in uterine **tone** after GTN (Buhimshci 2002, Langevin 2000).
- However, a **measurable reduction in uterine muscle compliance** in the presence of GTN compared to neutral buffer has been demonstrated in vitro studies and is probably the mechanism of action (Langevin 2000).

GTN – Neonatal Effects

Neonatal serum levels of GTN

- Administration of GTN to the mother a few minutes before birth results in extremely low neonatal GTN levels as measured in umbilical cord vessels. The median umbilical vein (travelling from placenta to the baby) to maternal vein plasma levels ratios were:
  - 1:400 after IV GTN 250 microgram stat
  - 1:160 after IV GTN 500 microgram stat
  - Umbilical artery concentrations (coming back from the baby to the placenta) were 10 x lower again than the umbilical vein levels
  - These levels are 10 – 100 fold lower than for neonates undergoing cardiac surgery (David 1998)

Neonatal Measures of Wellbeing

- Neonatal heart rate, blood pressure, Apgars and cord gases were no different in the GTN group compared to the placebo group after IV GTN (David 1998; David 2000). There did not appear to be any neonatal adverse effects after Sublingual / Lingual SPRAY GTN.
- A retrospective observational study of birth outcomes where IV and Sublingual / Lingual GTN were used by obstetricians as rescue medications when struggling with fetal entrapment, found an increase in low 5-minute Apgar and admission to NICU with Spray GTN but not IV GTN compared to cases where GTN was not needed. The numbers were small. In addition, since IV requires the anaesthetist to dilute the GTN, the authors felt that Spray GTN was more likely to be utilised by the obstetrician in desperate situations when time was very short and that it was the indication for the GTN, rather than the GTN itself, that was responsible for the neonatal condition (Isquick 2017).

Preterm Breech Head Entrapment in Cervix / Uterus

- This can occur during both vaginal and caesarean breech birth, especially < 32 weeks, because the head is much larger than that of the body. In vaginal birth, the body can deliver before full dilatation of the cervix with the head then being trapped above or in the cervix. Similarly, at CS, the head can be trapped by the contracted upper uterine segment.
- In one review of preterm breech births (26 – 29+6 weeks), the rate of overall head entrapment at birth (combined vaginal and caesarean birth) was 10% (16 / 169) and 13 cases required either incision of the cervix or extension of the uterine incision. Four babies died after head entrapment (Kayem 2008).
- In our own local experience, incision of the cervix possibly condemns women to future recurrent second trimester pregnancy loss. In addition to fetal and neonatal deaths from head entrapment, neonatal quadriplegia can occur secondary to the desperate manoeuvres undertaken by birth attendants to release the baby's head.
- Clinical experience suggests that **GTN IV or SPRAY** relaxation of the cervix can avoid some of these outcomes.
- An alternative for fetal entrapment situations is **terbutaline IV** (UTD Hofmeyr 2019).
  - This can be given in 50 microgram boluses (usual dose 50 – 100 microgram, maximum 250 microgram)
  - Prepare the solution **before** the birth so it is ready if needed (see below).

Intravenous (IV) *TERBUTALINE* for Fetal Entrapment

- **Terbutaline Intravenous (IV)** is an alternative tocolytic which:
  - Acts as fast as GTN IV.
  - Has a duration of action (up to 4 - 5 hours (MIMS 2019) or 1.5 – 4 hours (AHFS 2019)) that is considerably longer than GTN IV (3 minutes). This can lead to uterine atony and can increase the risk of postpartum blood loss when used at the time of delivery.
    - Terbutaline IV infusion was given to 13 women (and IV placebo to 12 women) shortly before elective CS to see if it improved neonatal lung function (it did).
      - The total dose of terbutaline was about 800 microgram (usual tocolytic dose is up to 250 microgram).
      - The amount of perioperative **blood loss** was nearly double in the terbutaline group compared to placebo (600 v 325 mL), which is unsurprising given its duration of uterine relaxation action (Eisler 1999).
    - However, in a labour RCT where IV terbutaline 250 microgram versus IV GTN 400 microgram were given to remediate fetal distress in labour, there were said to be no differences in **blood loss** between the groups (Pullen 2007).
- **Terbutaline subcutaneous (SC) is slower in onset than IV,** reaching maximum effect at 30 minutes. It is therefore not as useful for fetal entrapment. Its duration of action is also up to 4 – 5 hours.

- Terbutaline's long duration of uterine relaxation action and its increased risk of atony means that terbutaline:
  - **Is not** advisable in a **uterine inversion or retained placenta** situation. Use GTN.
  - **May** be advisable in **fetal entrapment** situation (GTN and terbutaline have not been directly compared). Obstetric staff may use either, especially for preterm breech head entrapment at vaginal birth.
  - **Is advisable** in situations of:
    - Acute fetal distress where there is delay in getting to the operating theatre.
    - External cephalic version (ECV) of the term breech.

      (note, these latter two are outside the scope of the current document)

- **Contraindications to Terbutaline**
  - Cardiac disease
  - Uncontrolled hyperthyroidism
  - Baseline maternal heart rate > 120 - 140

- **Adverse effects with terbutaline**
  - Tachycardia, palpitations, tremor, flushing, sweating
  - Headache
  - Dizziness, nervousness, anxiety
  - Nausea, vomiting
  - Cardiac arrhythmia, myocardial infarction and pulmonary oedema have rarely been reported almost always with prolonged usage

Dilution and Administration of IV Terbutaline

INTRAVENOUS TERBUTALINE Dilution & Administration

- Draw up 250 microgram / 0.5 mL of terbutaline in a 1 mL syringe (i.e. half of a 500 microgram / 1 mL ampoule)
- Transfer terbutaline 250 microg / 0.5 mL to a 10mL syringe and add 9.5 mL of 0.9% normal saline to **make up 10 mL**
- This dilution is now **25 microg per mL**
- When required, administer **50 microg / 2 mL over 1 minute**.
- **Repeat** if response inadequate (at rate of 50 microg / minute).
- **100 microgram (4 mL)** is often **sufficient**
- **250 microgram (10 mL) is Maximal Dosage** for Terbutaline IV
- **Do not administer if maternal HR is above 120 - 140 / minute**

  (South Australia 2014)

(MIMS 2019, AHFS 2019, others as mentioned)