NSW TAG NSW Therapeutic Advisory Group Inc. | Advancing quality use of medicines in NSW

Group Discussion: Use of Nifedipine in Hypertensive Disorders of Pregnancy

Date: November 2018

Background:

The NSW Ministry of Health is in the process of reviewing the Management of Hypertensive Disorders of Pregnancy Guideline/PD in which the use of oral nifedipine is discussed. Use of nifedipine for treatment of hypertension in pregnancy is off-label. The use of oral nifedipine in urgent severe hypertension in pregnancy has been predicated on its quick onset of action which is predicated on the formulation used and/or how the formulation is ingested. Nifedipine is one of a number of oral treatment options for severe hypertension in pregnancy (e.g. may be useful when a beta-blocker such as labetalol is contra-indicated).

Multiple oral formulations of nifedipine are available: a liquid capsule (only available via the SAS; recommended dosing was three times a day when it was a registered product); a 'conventional'[1] tablet (a twice-a-day formulation; soon to be discontinued); and a controlled release (CR) tablet (a once-a-day formulation). It should be noted that a 20mg dosage form is available in the conventional and CR formulations, which risks occurrence of medication errors. The liquid capsules became unavailable in Australia after concerns were raised regarding the potential for a very rapid drop in blood pressure with adverse reflex cardiac effects and increased risk of myocardial infarction. The Product Information for both tablet formulations (conventional and CR) recommend that the tablets are not crushed or chewed, albeit for different reasons: the CR formulation contains layered components which require 'activation' for drug release. The advice to abstain from crushing/chewing of conventional tablets appears to arise due to an increased rate of absorption. As of November 2018, although there may still be some short term supply of the 'conventional tablets, sponsors have announced their discontinuation in the near future.

Oral nifedipine is recommended as a treatment option for treating severe hypertension in the Management of Hypertensive Disorders of Pregnancy Guideline/PD as well as several other resources (including the Society of Obstetric Medicine of Australia and New Zealand). However, NSW TAG notes there appears to be a lack of clarity in some guidelines about which formulation should be used and how it should be used.

Table 1: Pharmacokinetics of nifedipine formulations when swallowed whole[2]

Formulation	**Time to maximum plasma concentration (t_{max}), hours**	**Half-life ($t_{1/2}$), hours**
Liquid capsule	0.5 - 2.17	1.7-3.4
Conventional (twice daily) tablet	1.5 - 4.2	6-12

There is little information about the pharmacokinetics of these formulations when the capsules are bitten or the tablets are crushed or chewed (as at October 2018). However, crushing the conventional tablet appears to increase the rate of absorption resulting in a higher maximum concentration (C_{max}) and quicker onset of action but a similar area under the curve (AUC).

[1] AMH refers to this formulation as the' conventional' formulation

2 MIMs online

The liquid capsule formulation appears to be the only immediate release (IR) formulation available in the UK and US (Up To Date and Micromedex) and hence US advice for nifedipine use in management of severe hypertension in pregnancy is based on the capsule formulation.

Currently the Australian Medicines Handbook (AMH) provides a protocol for threatened pre-term labour where the conventional tablets can be crushed/chewed to increase rate of absorption. It is recommended that repeat doses be given after 30 minutes if uterine contractions persist.

In reviewing the literature, NSW TAG has noted multiple naming of and references to nifedipine formulations that could be misleading. In order to ensure clinicians know which formulation is being referred to, we advise clinicians to check recommended dose frequency: once daily, twice daily or three time daily). This may become even more important if non-registered products are required. If nifedipine is to be used, initial and repeat uses of nifedipine formulations for acute intervention need to take into account the pharmacokinetics of these formulations in their 'whole' and 'crushed' forms.

NSW TAG and TAGNet members were asked to provide answers to the questions outlined below.

Responses:
Four responses were received from John Hunter Hospital (JHH), Maitland Hospital, Royal Hospital for Women (RHW), Randwick and Hunter Drug Information Service (HDIS).

1. **Does your site use immediate release nifedipine tablets for any urgent clinical indications?** (Such as threatened pre-term labour/tocolysis, hypertensive disorders of pregnancy to urgently reduce a woman's blood pressure or as part of general severe hypertension management?)
   - Threatened Preterm Labour/Tocolysis: Maitland, RHW, JHH
   - Hypertensive disorders of pregnancy to urgently reduce a women's blood pressure: RHW

   a) If so, are patients instructed to chew or crush the IR nifedipine tablets for quicker absorption?
   Yes (for the first 2 doses): Maitland, JHH
   No: RHW (procedures state that nifedipine should be swallowed whole as crushing, chewing may result in medication instability)

   i. And if so, have there been any cases of precipitous drops in blood pressure or adverse reflex cardiac effects such as MI?
   Yes: nil responses
   No: JHH

2. **If your site does not use oral nifedipine for hypertensive disorders of pregnancy, what oral antihypertensive(s) do you use?**
   Nil direct responses to this question. See also below in other comments.

3. **Other comments:**

JHH: Not routinely used for hypertension in pregnancy. It is not in any local guideline for hypertension in pregnancy that I can find.

Maitland Hospital: provided an area document: Drug Prescribing Guideline – Nifedipine for treatment of threatened premature labour.

Crushing is recommended in this document (also recommendation for repeat dose in 30 minutes). We do use nifedipine but rarely. We seem to use labetalol.

RHW: provided Local Operating Procedures (LOPs) for:
- Nifedipine for Tocolysis Protocol
    - Nifedipine 20mg stat, then if contractions persist repeat in 30 minute intervals for a further 2 doses
- Administration of IV Hydralazine
- Hypertension Management in Pregnancy
- Severe and/or Urgent Hypertension in Pregnancy Guideline
    - In urgent hypertensive disorders where BP ≥ 170 systolic, ≥ 110 mmHg diastolic, oral nifedipine (conventional tablet), IV hydralazine and IV labetalol are treatment options. The onset of action for 20mg tablet dose is stated to be 30-45 minutes and repeat dosing can occur after 45 minutes.
    - Other oral hypertensive drug treatments for severe hypertension in pregnancy would include (as per LOP) methyldopa, clonidine, labetalol, oxprenolol, nifedipine, prazosin and hydralazine.

4. Hunter Drug Information Service (HDIS)

Summarised response to an enquiry to HDIS- provided to NSW TAG:

Question: Are nifedipine tablets (Adefin®/Adalat®) used for preterm labour 'true' immediate release? Should the dose be repeated at 30 minutes?

Response: It is important to note that a number of different dosages and dosage forms of nifedipine have been used in relevant studies, and an optimal dosage regimen for the drug as a tocolytic has not been determined. Some clinicians recommend that when a relatively rapid response is desired the drug should be administered as a conventional liquid-filled capsule that is bitten and then swallowed.

The local (HNE) Drug Prescribing Guideline: NIFEDIPINE for treatment of Threatened Premature Labour includes dosage recommendations in accordance with the current AMH. Various guidelines from other states refer to this same dosage recommendation, but differ in their advice re crushing/chewing:

DON'T CRUSH OR NO MENTION OF CRUSHING/CHEWING
- RHW – Nifedipine for Tocolysis Protocol
    - Of interest one of the references used in this document (Tocolysis for Women in Preterm Labour. RCOG Green TOP Guideline February 2011) has been superseded with NICE NG25 which recommends the dose from the British National Formulary i.e., "The suggested dosage of nifedipine is a loading dose of 20 mg orally, followed by 10-20 mg 3 to 4 times daily adjusted according to uterine activity."
    - However, advises not to crush
- Queensland Maternity and Neonatal Clinical Guideline: Preterm labour and birth
    - No mention of swallowing whole or to chew or crush

CRUSH/CHEW

- South Australian Perinatal Practice Guideline: Nifedipine for preterm labour
  - Advises chew or crush tablet to aid rapid absorption (as per AMH)
- South Australia King Edward Memorial Hospital (KEMH) Obstetrics & Gynaecology - Adult Nifedipine Guideline
  - Advises chew or crush tablet to aid rapid absorption like in AMH

It would appear that the pharmacokinetics of the conventional nifedipine tablet available in Australia would not require repeat dosing at 30 minutes. This has been confirmed by a Clinical Pharmacologist. It also seems that UK and US recommendations vary to Australian guidance.

The editors at the AMH were also contacted in regards what references were used to support the dosing recommendations and in particular the "repeat after 30 minutes" and if the original advice applied to the liquid filled capsules which had a different PK profile.
AMH response:

- When the AMH was first published in 1998, nifedipine capsules were already unavailable in Australia. The guidance materials already developed at that time, which are still maintained by this specialty in Australia, are based on existing published studies and a reasonable degree of consensus and can logically only suggest using tablets. Therefore, the AMH dosage, including the advice to 'repeat after 30 minutes if uterine contractions persist', applies to nifedipine tablets.
- The two systematic reviews cited below (and a Cochrane review) demonstrate that the dose form of nifedipine used in studies varied (i.e. capsules only, both capsules and tablets, or tablets only). You will also notice that the dosing approach (dose size and frequency) is variable across the studies, which is why we use the introductory phrases 'The following dose has been used' and 'Refer to local protocols for dosage'.
- Comments provided to us by a Women's and Children's Hospital (WCH) Adelaide pharmacy staff expert in this area (below) may also be of interest and relevant to this enquiry. Be aware that AMH does not provide details about use of nifedipine for maintenance tocolysis, which is less well supported.
  Some relevant references:
  1. King JF, Flenady V et al Calcium channel blockers for inhibiting preterm labour; a systematic review of the evidence and a protocol for administration of nifedipine. Aust NZ J Obs Gyn 200343192-98
  2. Magee LA, Miremade S et al. Therapy with both magnesium sulfate and nifedipine does not increase the risk of serious magnesium-related maternal side effects in women with preeclampsia. Am J Obstet Gynecol 2005; 193: 153-63.
  3. South Australian Perinatal Practice Guideline. Accessed online at www.health.sa.gov.au/ppg/
  4. Conde-Agudela A, Romero R, Kusanovic JP Nifedipine in the management of preterm labor: a systematic review and metaanalysis. Am J Obstet Gynecol 2011 204134.e1-20 (doi: 10.1016/jaog.2010.11.038
  5. Caritis S. Metaanalysis and labor inhibition therapy. Am J Obstet Gynecol 2011 (doi: 10.1016/ajog.2010.11.041)
- Comments received from WCH Adelaide: The content of the Perinatal Practice Guideline is due for review in September 2018 and currently advises to crush/chew the tablets to

increase the rate of absorption, thus it is likely the t_{max} would occur before the 1.5 - 4.2 hours quoted in the PI. Additionally, the onset of effect may occur before t_{max} is reached. The dosing recommendation in the WCH Guideline is line with other publicly available Australian maternity guidelines e.g. RWH (NSW), QLD and KEMH.

Protocols/guidelines received from this email discussion are available upon request by emailing NSW TAG.

Addendum 5th November 2018:
NSW TAG has been advised that both nifedipine conventional tablets 10 mg and 20 mg strengths (Adefin®, Adalat®) will be discontinued. Those sites/LHDs familiar with and currently using nifedipine conventional tablets should review their local guidelines and consider therapeutic options. There is potential for access to SAS nifedipine; however, this is likely to be costly, may be difficult to access in a timely manner and unsustainable in the long term. Sites may wish to reserve remaining nifedipine conventional tablets for use in obstetric patients when labetalol is contra-indicated.

Responses received as at 30th October 2018