Nifedipine for Severe Hypertension in Pregnancy: Emotion or Evidence?

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Abstract:

A meta-analysis of randomized controlled trials suggests that nifedipine appears to be a reasonable agent for treatment of acute severe hypertension in pregnancy. However, in a 1999 survey of Canadian practitioners, most stated that they rarely or never use nifedipine capsules for treatment of acute severe pregnancy hypertension. Also, there are case reports of adverse outcomes following use of nifedipine capsules in pregnancy, although the risks appear to have been overplayed.

We suggest that a reasonable approach is ongoing use of nifedipine capsules, with perhaps an initial dosage of 5 mg rather than 10 mg. Having women swallow the capsule without first biting it may also be a prudent approach, because there is insufficient information from most of the published clinical trials to say exactly how the nifedipine capsules were administered. Further, use of the 10 mg nifedipine prolonged action tablet may also be a reasonable approach for treatment of severe hypertension in pregnancy, although more data are needed. Such research would be particularly relevant given that nifedipine appears to be a promising treatment for spontaneous preterm labour.

We must resist the temptation to throw out of our limited therapeutic armamentarium an effective oral preparation before adequately considering the evidence.

Résumé:

Selon les résultats d'une méta-analyse portant sur des essais comparatifs randomisés, la nifédipine semble être un agent raisonnable pour la prise en charge de l'hypertension aiguë grave au cours de la grossesse. Cependant, dans le cadre d'un sondage mené en 1999 auprès de médecins canadiens, la plupart d'entre eux ont déclaré qu'ils n'avaient que rarement (ou même jamais) recours à des capsules de nifédipine pour la prise en charge de l'hypertension aiguë grave au cours de la grossesse. De plus, certains exposés de cas signalent des effets indésirables à la suite de l'administration de capsules de nifédipine au cours de la grossesse, bien que les risques semblent y avoir été surestimés.

Nous avançons que l'administration continue de capsules de nifédipine (peut-être selon une posologie initiale de 5 mg plutôt que 10 mg) constitue une approche raisonnable. Le fait de demander aux femmes de déglutir la capsule sans d'abord la croquer pourrait également s'avérer prudent, puisque la plupart des essais cliniques publiés ne recèlent pas assez de renseignements pour déterminer avec précision la façon dont les capsules de nifédipine ont été administrées. Qui plus est, le recours à des comprimés de 10 mg de nifédipine à action prolongée pourrait également s'avérer une approche raisonnable pour la prise en charge de l'hypertension grave pendant la grossesse; cependant, de plus amples données à ce sujet demeurent requises. De telles recherches seraient particulièrement pertinentes puisque la nifédipine semble constituer un traitement prometteur pour contrer le travail préterme spontané.

Nous devons résister à la tentation de priver notre arsenal thérapeutique (lequel est déjà limité) d'une telle préparation orale efficace avant de bien avoir étudier les preuves disponibles.

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According to Health Canada,[1] nifedipine capsules are not recommended for acute reduction of blood pressure (BP), based on the occurrence of serious cardiovascular events and death in older populations and those with type I diabetes mellitus who were given nifedipine 10 mg capsules. Most authors either reported that the sublingual capsule was bitten and swallowed or did not specify how the drug was delivered.[2] Does this information apply to the usually young, healthy, pregnant population? The answer is probably not.

Nifedipine appears to be a reasonable agent for treatment of acute severe hypertension in pregnancy.

This statement is based on our meta-analysis of 21 randomized controlled trials (RCTs) (1085 women) studying treatment of primarily severe hypertension (16/21 trials) in pregnancy. Hydralazine was associated with an excess of adverse maternal and perinatal outcomes when compared with other antihypertensives, including short-acting nifedipine.[3] Hydralazine was associated with an excess of maternal hypotension, Caesarean section, placental abruption, maternal oliguria, adverse effects on fetal heart rate, and low 1-minute Apgar scores. Hydralazine was also associated with a trend toward an excess of stillbirth. Although nifedipine (8 trials, 453 women, all with severe hypertension) and parenteral labetalol (5 trials, 150 women, 4 of 5 with severe hypertension) appeared to be reasonable short-acting agents for treatment of acute and usually severe hypertension in pregnancy, definitive data are needed from adequately powered RCTs.

In a 1999 survey of Canadian practitioners, most stated that they rarely or never use nifedipine capsules for treatment of acute severe hypertension in pregnancy.[4]

At that time, the 1997 pregnancy treatment guidelines, published by the Canadian Hypertension Society and endorsed by the Society of Obstetricians and Gynaecologists of Canada (SOGC), was available to practitioners.[5] These guidelines listed nifedipine capsules (along with hydralazine and labetalol) as first-line agents for treatment of severe hypertension in pregnancy. However, practitioners were also faced with the 1997 Health Canada Therapeutic Products Programme Newsletter,[1] which advised against the use of nifedipine capsules, without mentioning pregnancy.

There are also case reports of adverse outcomes following use of nifedipine capsules in pregnancy.

These consist of hypotension,[6] a cardiovascular event when high-dose nifedipine was used for preterm labour,[7] and a purported interaction with $MgSO_4$ to produce hypotension[6,8] or neuromuscular blockade.[9,10] Hypotension is a well-described complication of treatment (with any agent) of severe hypertension in pregnancy, particularly because most such women have preeclampsia and are intravascularly volume depleted.[11] The woman described to have a myocardial infarction with nifedipine for preterm labour had experienced chest pain on ritodrine, which was discontinued, to be replaced by 2 doses of nifedipine 40 mg (intermediate-acting preparation) given over 4 hours; the diagnosis of myocardial infarction was based on nonspecific, new-flipped T waves and a positive creatine kinase muscle-brain (CK-MB) fraction, which can be elevated in normal labour without myocardial ischemia.[12] That there may be an interaction of nifedipine with $MgSO_4$ has been neither established nor quantified. A recent retrospective cohort study, which reviewed RCTs that used nifedipine and $MgSO_4$ together, found no interaction with respect to hypotension or neuromuscular blockade. Such blockade was estimated, in the worst case scenario, to occur in less than 1% of women receiving nifedipine and $MgSO_4$ together.[13] One must also remember that a readily available, safe, and common antidote is available: calcium gluconate.

Should we abandon use of nifedipine capsules?

According to current available evidence,[3,13] the answer is clearly no. Nifedipine capsules represent a reasonable alternative, based on comparative RCTs.[3] Also, they are an oral preparation that can be promptly administered to women with confirmed severe elevations of BP in pregnancy, in the absence of either known coronary heart disease (which is rare in this population) or, probably, pregestational diabetes mellitus. That obstetricians are not always available to administer IV push medications (such as labetalol or hydralazine) is obvious, given their mandatory attendance at deliveries (even in teaching hospitals) and presence in the operating room (for urgent or emergent Caesarean section). That nifedipine capsules can be administered quickly and easily by nursing and resident staff is a tremendous advantage and avoids the temptation to administer IV push medications in mini-bags over 10 to 15 minutes, which will produce a different pharmacokinetic profile than will the IV push (or infusion) administration studied in RCTs.[3] In addition, the mechanism underlying the adverse cardiovascular outcomes associated with nifedipine capsules (in older or pregestationally diabetic populations) is a reflex increase in sympathetic tone. The same hemodynamic response occurs when hydralazine is administered, and an excess of cardiovascular morbidity has not been reported with this drug in pregnancy.

If practitioners are willing to use (or continue to use) nifedipine, are capsules the best preparation?

The intermediate-acting preparation of nifedipine (e.g., prolonged action [PA] in North America) may be an alternative. At the same time that the Health Canada "Dear Doctor" letter was issued, nifedipine capsules were withdrawn from the Australian marketplace, based on the same reasoning.[14] As a result, an RCT (64 women) of nifedipine PA 10 mg tablets (33 women, 55 BP studies) versus nifedipine 10 mg capsules (31 women, 74 BP studies) was conducted.[15] According to BP studies (rather than women), the 10 mg nifedipine PA tablets were found to achieve the same rate of "successful" treatment as were the 10 mg capsules (83% tablets vs. 76% capsules); "success" was defined as an in-range BP (that is, 110–169/80–109 mm Hg)

without hypotension (< 110/80 mm Hg), need for hydralazine at 90 minutes, or fetal distress on cardiotocography; a type II error cannot be excluded. The tablets had a slower onset of action because they were more frequently associated with repeat dosing at 45 minutes (28% tablets vs. 14% capsules) but had less hypotension at any time during the 90-minute study period (9% tablets vs. 35% capsules). There was no difference in fetal distress at any time during the 90-minute study period (4% tablets vs. 3% capsules).

Should those of us who are using nifedipine capsules switch to the PA preparation?

The latest version of the Advances in Labour and Risk Management (ALARM) course is considering adding the intermediate-acting nifedipine preparation (i.e., 10 mg PA tablets) to the list of acceptable drugs for treatment of severe hypertension in pregnancy.[16] However, to our knowledge, the ALARM recommendation would rely on only one published study of the use of intermediate-acting nifedipine for this indication,[15] and unlike nifedipine capsules,[17] the pharmacokinetics and pharmacodynamics of nifedipine PA in pregnancy have not been well established. In nonpregnant women, according to the product monograph, the onset of action of nifedipine PA tablets is 45 minutes to 2 hours. In the study by Brown *et al.*,[15] the peak effect of the nifedipine PA tablet might have been missed, because women were followed for only 90 minutes, and 28% had a repeat dose of the PA tablet at 45 minutes.

What should Canadian practitioners do?

We suggest that a reasonable approach is ongoing use of nifedipine capsules, with perhaps an initial dose of 5 mg instead of 10 mg. Having women swallow the capsule without first biting it may also be a prudent approach, as there is insufficient information from most of the published clinical trials to say exactly how the nifedipine capsules were administered. Further, use of the 10 mg nifedipine PA tablet may also be a reasonable approach for treatment of severe hypertension in pregnancy. More data are needed about both nifedipine preparations. Such research would be particularly relevant given that nifedipine appears to be a promising treatment for spontaneous preterm labour.[18,19] We must resist the temptation to throw out of our limited therapeutic armamentarium an effective oral preparation before adequately considering the evidence.

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