Title: Short-Acting Nifedipine for Hypertensive Emergencies in Children: A Review of the Clinical Effectiveness and Safety

Date: 27 March 2008

Context and policy issues:

Nifedipine

The disparate group of drugs known as calcium channel antagonists (CCAs) alter calcium concentration gradients across cell membranes.\(^1\) This affects the contraction and relaxation of smooth muscle cells including those in the blood vessels, thus influencing blood pressure (BP).

The CCA drugs have been classified by chemical structure, with nifedipine falling into the dihydropyridine group which is made up of potent vasodilators.\(^1\)

In Canada, nifedipine is available as an immediate release 5 mg or 10 mg capsule and a sustained-release tablet.\(^2\)\(^-\)\(^5\) Sublingual administration of the liquid within the capsule (via “bite and swallow” or transfer of the liquid to a 1cc syringe) may lead to slightly more rapid absorption of the active ingredient due to swallowing of the drug liquid although most researchers feel that negligible absorption occurs in the mouth with the majority occurring in the stomach and research in healthy subjects has shown this to be the case.\(^6\) Similar absorption rates for nifedipine administered via oral capsule or sublingual administration of the liquid from the capsule has led most researchers to merge data for all forms of oral nifedipine, calling this short-acting (SA) administration.\(^7\)

Nifedipine’s antihypertensive effect is observed within 5 to 20 minutes, reaches a peak at 30 to 60 minutes, and lasts 4 to 8 hours.\(^1\)\(^,\)\(^7\) The drug is metabolized by the liver with up to 30% being removed by first-pass metabolism. It is also affected by the hepatic cytochrome P450 system which has implications for concomitant use of other drugs or foods (e.g., grapefruit juice) influenced by this enzyme system.
Observations about nifedipine’s behavior are drawn from research conducted in adults as no pharmacokinetic studies have been carried out in children. The drug is approved by Health Canada for management of angina, not for treatment of hypertension, and has been manufactured by generic drug companies for at least a decade. Due to genericization, much more energy has been devoted to the sustained release form of the drug which is not used for hypertensive emergencies and is not considered in this report.

**Hypertensive emergencies and “urgencies” in children**

As compared with adults, “chronic” hypertension is uncommon in children affecting 1% to 3% with the most common cause being renal disease (e.g., glomerulonephritis, polycystic renal disease), distantly followed by aortic coarctation, pheochromocytoma, and neuroblastoma. It has been recommended that all children over age 3 have their BP measured annually and that all children have their BP measured when they are acutely ill. Normative BP values based on a child’s age, sex, height and weight have been established by a task force of the United States (US) National Heart, Lung and Blood Institute (NHLBI), most recently updated in 2005.

A hypertensive crisis is elevation of BP to a level severe enough to cause central nervous system, cardiovascular (CV), renal or retinal dysfunction. Fairly rapid control is required to prevent organ damage. The most common causes in children are acute glomerulonephritis, drug abuse, collagen vascular disease, renovascular hypertension, and head trauma. Crises are classified as either hypertensive emergencies or hypertensive urgencies. Emergencies include very high BP (≥ 95th percentile for age and sex), end-organ damage such as retinopathy, left ventricular hypertrophy, or encephalopathy, and symptoms such as nausea, vomiting, headache, and blurred vision. Urgencies are more common and involve very high BP without end-organ damage. Symptoms can include headache, blurred vision and nausea.

**Nifedipine use in pediatric hypertensive emergencies**

Integral to rapid lowering of BP is the concept of autoregulation where the body protects blood flow to the heart, kidneys and brain when BP decreases. Autoregulation is strained with acute BP drops > 25%. The aim of treating a hypertensive emergency is to reduce the BP by up to 25% using rapidly acting drugs, although the most recent guidelines temper this, suggesting a gradual rather than acute BP decrease to avoid hypoperfusion of vital organs with normalization over 24 to 48 hours after an initial BP drop < 25%. Unlike hypertensive emergencies, hypertensive urgencies can be treated over 24 hours using oral agents.

The first published report of nifedipine use in pediatric hypertensive emergencies was in 1983 when Dilmen and colleagues from Turkey reported 30% reductions in BP with use of nifedipine sublingually (0.25-0.5 mg/kg) in 10 children ages 9 to 16 years. Since that time, the drug has continued its role in pediatric hypertensive emergencies and acute hypertensive episodes. Latterly the experience has been published in retrospective case series, the four most recent (detailed below) appearing in 2001, 2002, 2004, and 2007. No randomized controlled trials (RCTs) or prospective case series have been published.

**Concerns related to adverse effects**

At one time, SA nifedipine was a treatment of choice for the management of hypertensive emergencies in adults due to its ease of use and rapid onset of action. However, adverse events (AEs) associated with use of the drug in adults accumulated, including hypotension, myocardial ischemia and infarction, prolonged QT interval, ventricular fibrillation and cerebral ischemia and
stroke. This led to widespread discontinuation of its use in adults in the mid- to late-1990s, in part due to Canadian and US agencies advising against its use, although no age parameters were included in this advice.

Nifedipine continued to be a popular drug for management of pediatric hypertensive emergencies as similar AEs have not generally been noted in the pediatric population, presumably due to the lack of underlying CV and cerebrovascular pathology in children. The recommended nifedipine dose has traditionally been 0.25 to 0.5 mg/kg although this has been decreased over time.

The first report of a worrisome nifedipine AE in a child was a 1998 case report provided by Swiss pediatricians. A 12-year-old girl with underlying renal disease and hypertensive urgency experienced extreme hypotension after two doses of SA nifedipine. Her initial BP of 250/165 mmHg dropped to 106/83 when a second 10 mg nifedipine capsule was administered shortly after failure of response to the first (total dose 0.7 mg/kg). The patient did not become symptomatic and recovered fully but her precipitous BP decrease caused concern. In a published response to this case report, Argentinian pediatricians acknowledged the concern but reported that they had seen good results over the previous 10 years at drug doses of only 0.1 mg/kg per dose, even when a second nifedipine dose was required. Despite the case report, they felt the drug could continue to be used safely in children with hypertensive crises.

Policy issue

Since the concerns about SA nifedipine’s safety profile have emerged there has been an ongoing debate as to the advisability of use of the drug in pediatric hypertensive emergencies. There is a division between those who believe the drug’s effectiveness and safety record along with its ease of use make it worth employing and those who believe that the benefits do not outweigh the risks and that there are safer and more effective pharmaceutical alternatives.

Research question:

What are the clinical efficacy and safety of using SA nifedipine in pediatric patients for hypertensive emergencies or unstable hypertension requiring immediate therapy?

Methods:

A limited literature search was conducted on key health technology assessment (HTA) resources, including OVID’s Pre-MedLine, MedLine, Embase, Biosis, and CINAHL, PubMed, the Cochrane Library (Issue 1, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results included articles published between 1998 and March 2008, and were limited to English language publications only. Filters were applied to limit the retrieval to health technology assessments (HTAs), systematic reviews, meta-analysis, randomized controlled trials (RCTs) and observational studies. This search was supplemented by hand searching the bibliographies of selected papers.

Summary of findings:

No HTAs, systematic reviews, meta-analysis or RCTs were identified. Four observational studies, all retrospective case series, were identified that reported on the use of SA nifedipine for hypertensive emergencies or severe hypertension in children.
Observational studies

The most recent study was a review of cases from a children’s hospital in South Africa\textsuperscript{19} and the others were a multi-site review from Canada\textsuperscript{18} and two single centre reviews from children’s hospitals in the US.\textsuperscript{16,17} The Canadian study was funded by the Children’s Hospital of Eastern Ontario Research Institute but funding for the other three studies was not reported. The four studies are presented below, beginning with the most recent.

1. \textit{Nourse & McCulloch (2007)}\textsuperscript{19}

This retrospective chart review was limited to use of SA nifedipine in children with severe or moderate hypertension secondary to acute post-streptococcal glomerulonephritis (APSGN), a disorder associated with hypertension in 80\% to 97\% of cases.\textsuperscript{19} The report authors commented that because nifedipine is widely available, inexpensive and easy to administer, it is often the only drug available to rapidly reduce BP in children presenting with hypertensive emergencies at their peripheral medical facilities.

Eligible records spanned four years (1999 to 2002) and included 57 patients who received SA nifedipine sublingually or orally. Of these, 44 were considered to have severe BP elevation (systolic BP > 30\% above 95th percentile for age and sex) and 23 had moderate BP elevation (systolic BP > 15\% above 95th percentile for age and sex); data were not reported separately for these two groups. The report was quite brief and many details were not reported (Table 1).

Only 44 of the 57 children (77\%) had BP readings carried out within 2 hours and this group provided the efficacy data. Unlike the other three studies reported below, mean changes in BP in response to nifedipine therapy were not reported. As Table 1 shows, the data were presented as proportions of patients who had decreases > 25\% and < 25\% in systolic and diastolic BPs and mean arterial pressure (MAP).

When degree of BP decrease was analyzed according to drug dose administered there was no direct relationship between drug dose and magnitude of BP drop. Only one AE was reported, a child (age not provided) who had a seizure two hours post-drug although BP was not recorded at the time. The nifedipine dose administered was quite high (0.38 mg/kg) but it was not possible to determine whether the seizure had occurred because of the drug. The patient recovered fully and was discharged with no neurological sequelae.
Table 1: Nourse & McCulloch (2007) Observational Study of SA Nifedipine in Children with Severe Hypertension

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Demographic data (n=57)</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion: Children who received SA nifedipine for acute treatment of severe or moderate HT associated with APSGN.</td>
<td><strong>Age (years):</strong> Mean ± SD, 7.4 ± 3.0 (no other demographic details provided).</td>
<td><strong>Drug &amp; dosage:</strong></td>
<td>Data only presented for 44 children (77%) who had BP measured within 2 hours of drug administration.</td>
</tr>
<tr>
<td><strong>Other:</strong> Additional pathology on presentation:</td>
<td>• Pulmonary edema: 13 patients (23%).</td>
<td>• Route of SA nifedipine administration: S/L or oral.</td>
<td><strong>Efficacy</strong> (reported as proportion of patients who experienced &gt;25% or &lt;25% reduction in SBP, DBP and MAP, and dose of nifedipine in mg/kg associated with each group):</td>
</tr>
<tr>
<td>• Additional pathology on presentation:</td>
<td>• Pulmonary edema: 13 patients (23%).</td>
<td>• Mean # of doses of SA nifedipine per patient, 3.5.</td>
<td>• SBP:</td>
</tr>
<tr>
<td>• Additional pathology on presentation:</td>
<td>• Seizures: 2 patients (4%).</td>
<td>• Mean dosage strength per administration, 0.23 mg/kg.</td>
<td>• Decreased &gt; 25%: 16% of patients; MDD, 0.26.</td>
</tr>
<tr>
<td>• Additional pathology on presentation:</td>
<td>• Pulmonary edema &amp; seizures: 3 patients (5%).</td>
<td>• 20 patients (35%) received initial nifedipine dose &gt; 0.25 mg/kg.</td>
<td>• Decreased &lt; 25%: 84% of patients; MDD, 0.23.</td>
</tr>
</tbody>
</table>

**AEs:**
- One child had a seizure 2 hours post-drug (nifedipine dose 0.38 mg/kg); recovered fully.

* MAP = DBP + [(SBP-DBP) / 3]

KEY: AEs=adverse event; APSGN=acute post-streptococcal glomerulonephritis; BP=blood pressure; HT=hypertension; MAP=mean arterial pressure; MDD=mean drug dose; SA=short-acting; SBP=systolic BP; S/L=sublingual.

The authors concluded that SA nifedipine is a safe and effective drug for the treatment of severe hypertension in children with APSGN, particularly in cases of hypertensive emergency where a rapid decrease in BP is required. They emphasized the need for prospective controlled studies.

2. **Yiu et al. (2004)***

The study was a review of four years (1995 to 1998) of medical records of all children with hypertensive emergencies who had been treated with SA nifedipine (n=182) in Canadian pediatric hospitals in Edmonton, Calgary, Winnipeg, Ottawa and Montreal (Table 2). Mean age was 8.6 years, boys formed a slight majority as did Caucasians, and 80% of the children were hypertensive due to renal disease. Not surprisingly, many co-morbidities were noted and use of over 3000 other drugs was recorded during the hospitalizations of the children. The children were treated for a mean of 2.6 episodes each with a mean of 2.44 doses at each episode, using a mean dose of 0.22 mg/kg via the sublingual, oral or bite-and-swallow route. The study outcomes are shown in Table 2.
Inclusion/exclusion criteria | Demographic data (n=182) | Intervention | Outcomes
--- | --- | --- | ---
**Inclusion:**
- Age < 18 years.
- Episode of HT* emergency/crisis treated with oral SA nifedipine.
- BP measured within 6 hours following drug administration (if multiple BP readings, lowest value was taken).

**Exclusion:**
- Received IV antihypertensive drug within 4 hours before nifedipine.

**HT emergency/crisis** defined as HT with end-organ dysfunction and/or diastolic BP > 30 mmHg above 95th percentile for child’s age and sex.

Age (years):
- Mean, 8.6.
- Median, 8.3.
- Range, 0.2-17.9.

Sex:
- Male, 63%.
- Female, 37%.

Race:
- Caucasian, 64%.
- African Canadian, 4%.
- Asian, 4%.
- Other/unknown, 28%.

Primary disease:
- Renal, 80%.
- Oncological, 10%.
- Miscellaneous, 10%.

Comorbid conditions:
- Cardiac, 37%.
- Pulmonary, 40%.
- GI, 62%.
- Dermatological, 36%.

Concomitant drugs:
- Total of 3099 other drugs administered during the 477 episodes.

HT episodes:
- Total 477.
- Mean of 2.62 episodes/patient admission (range, 1-26).
- Median, 2.

Drug & dosage:
- Route of SA nifedipine administration: S/L, 56%; also oral and bite-and-swallow.
- Mean doses of nifedipine per episode, 2.44 (range, 1-12).
- Mean dosage strength per administration, 0.22 mg/kg (range, 0.04-0.67). Median, 0.19 mg/kg.

Efficacy (hypertensive emergency resolved):
- Overall: Efficacious in 408/477 episodes (85.5%).
  - Mean SBP decrease: 17%.
  - Mean DBP decrease: 25%.
- First episodes: Efficacious in 139/182 (76.4%; 95% CI 69%-82%).
  - Mean SBP decrease: 17%.
  - Mean DBP decrease: 25%.
- Patients also assessed based on resolution experience:
  - All episodes resolved for a patient: 120/182 (66%).
  - Some resolved: 25/182 (14%).
  - None resolved: 37/182 (20%).

AEs:
- Minor AEs: 574 in 83% of patients, e.g., edema, tachycardia, nausea & vomiting, GI pain, headache.
- Relationship of minor AEs to nifedipine:
  - Probable/definite: 29/574 (5%).
  - Possible: 132/574 (23%).
  - Not related: 404/574 (70%).
  - Data missing: 9 (2%).
- Major AEs: 2 patients, both BP reductions > 40% probably related to the drug. Both were oncology patients and both recovered.

$Efficacy was defined as a reduction in SBP or DBP by 20% or to < 95th percentile for age and sex.

KEY: AE=adverse event; BP=blood pressure; CI=confidence interval; DBP=diastolic BP; GI=gastrointestinal; HT=hypertension/hypertensive; IV=intravenous; LA=long-acting; NR=not reported; SA=short-acting; SBP=systolic BP.

In addition, associations between resolution and underlying characteristics were explored:
- Primary disease renal: no association (P=0.72).
- Use of more than five concomitant medications: no association (P=0.38).
- Use of long-acting hypertensive medications: no association (P=0.06).
- Administration of more than six nifedipine doses: no association (P=0.11).
- Starting systolic BP > 140: no association (P=0.23).
- Sublingual medication: slight association (P=0.05).

The study authors prospectively defined AEs, categorized them as major or minor, and also judged the AEs as to the likelihood that they were caused by nifedipine. Among the predetermined AEs judged to be major was a decrease in systolic or diastolic BP > 40% and both major AEs fell into this group. Two boys with oncology conditions (Ewing sarcoma and neuroblastoma) experienced dramatic drops in BP after nifedipine, one after the first dose (BP dropped from 176/110 to 104/49) and the other after the second dose (BP dropped from 123/99 to 65/40) although neither became symptomatic or suffered any known consequences.

A large number of minor AEs (574 in 477 episodes) were recorded including (in decreasing order): edema, GI pain, nausea & vomiting, tachycardia, headache, skin rash/pruritis, flushing and dizziness. However, only 5% of these were considered to be probably or definitely related to the
drug and 23% possibly related. From a patient perspective, 83% of children experienced a minor AE with 12% of these experiencing AEs probably or definitely related to the drug.

Despite the AEs observed, the study authors concluded that SA nifedipine appears to be an effective and safe medication for the treatment of hypertensive crises in hospitalized children and stated that it should continue to be recommended in this setting.

3. *Egger et al. (2002)*\(^{17}\)

Researchers at Loma Linda University Children’s Hospital in California conducted a retrospective chart review of children who had received SA nifedipine for “acute hypertension” between December 1994 and June 1998 (n=166). Hypertension requiring urgent treatment was defined as BP > 95th percentile for age and sex but there was no specific discussion of hypertensive emergencies. The catalyst for the study was concern about the safety of nifedipine following AEs reported in adults. Mean age was about 8 years, males predominated slightly and the most common underlying pathology was renal (Table 3). All patients were treated using nifedipine 10 mg capsules. If the required dosage was less than 10 mg, the contents of a capsule was drawn into a 1 cc syringe by a registered nurse and the calculated dose was administered, although exact route of administration (sublingual or oral) was not reported.

With respect to outcomes, the data only reported mean and maximum changes in systolic and diastolic BP including ranges. The authors did not report how many children had successful management of their hypertension. Likewise, AE reporting was sparse. There was no prospective definition of what constituted an AE, no division into major and minor AEs, and no attempt to attribute or not attribute AEs to nifedipine use.

The report authors noted that two of the six cases of neurological AEs occurred in children who had acute CNS injury: a 16-year-old girl with new onset hemiparesis who, one hour post-nifedipine, suffered another stroke which was fatal, and a 2-year-old girl with near-drowning who was removed from life support some time after receiving nifedipine. These two represented a third of the six patients with acute CNS injury, leading the researchers to express concern about use of SA nifedipine for children in this clinical situation.
**Table 3: Egger et al. (2002) Observational Study of SA Nifedipine in Children with Acute Treatment of Hypertension**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Demographic data (n=166)</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Received SA nifedipine for acute treatment of HT.*</td>
<td></td>
<td>Drug &amp; dosage:</td>
<td>Efficacy:</td>
</tr>
<tr>
<td>• Had BP measured within 2 hours following drug administration.</td>
<td></td>
<td>• All were treated with capsules. If dose was 10 mg, capsule given, if dose was &lt; 10 mg, drug was drawn into a 1 cc syringe for exact dose.</td>
<td>• Mean effect:</td>
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<tr>
<td></td>
<td></td>
<td>Mean # of doses of SA nifedipine per patient, 10.5.</td>
<td>o SBP drop: 17%; range 1%-60%.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean dosage strength per administration, 0.30 mg/kg (range, 0.04-1.30).</td>
<td>o DBP drop: 28%; range -6%-89%.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients receiving &gt; 0.50 mg/kg: 10%.</td>
<td>• Maximum effect:</td>
</tr>
<tr>
<td>* Defined as BP &gt; 95th percentile for age, sex &amp; body size.</td>
<td></td>
<td></td>
<td>o SBP drop: mean 28%; range 1%-63% (patient with 63% decrease dropped from 147 to 54 &amp; was on dialysis).</td>
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<td></td>
<td></td>
<td></td>
<td>o DBP drop: 43%; range 8%-89% (patient with 89% decrease dropped from 120 to 13).</td>
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<td>Patients receiving dose &gt; 0.5 mg/kg (n=17 patients given 124 doses), maximum decreases:</td>
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<td></td>
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<td></td>
<td>o Mean SBP decrease: 21%; range -61%-52%.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>o Mean DBP decrease: 30%; range -21%-66%.</td>
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<td></td>
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<td></td>
<td>AEs (no relationship with drug determined):</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Neurologic: 6 patients (4%) including deaths (2), dizziness (2), seizure (1) and disorientation (1). Two of 6 (33%) occurred in patients with acute CNS injury.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Symptomatic hypotension, 2 (1%), both treated with fluid replacement.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Oxygen desaturation &lt; 90% as measured by pulse oximetry, 12/88 (14%).</td>
</tr>
</tbody>
</table>

**KEY:** AE=adverse event; BP=blood pressure; CNS=central nervous system; DBP=diastolic BP; HT=hypertension/hypertensive; SA=short-acting; SBP=systolic BP.

The authors concluded that SA nifedipine is an important and effective oral antihypertensive that can be safely used for the treatment of hypertensive emergencies in children and it is rarely associated with serious AEs. However, they noted that it can be associated with profound and unpredictable changes in systolic and diastolic BP and were uncomfortable recommending its use in children who present with hypertensive emergencies associated with acute CNS injury. They advised caution with use of the drug and had revised their management protocol to initiate therapy at a low nifedipine dose (0.1 mg/kg).

4. Blaszak et al. (2001)\(^{16}\)

This study was a retrospective review of cases at the Arkansas Children’s Hospital. The cases (n=117) occurred from January 1997 to July 1999 and included children with BP > 95th percentile for age, sex and height who received SA nifedipine, either sublingual or oral, although no data were presented as to the split between these forms (Table 4).

The results of this study showed that SA nifedipine can effectively decrease systolic and diastolic BP and MAP without AEs. Aside from reporting the magnitude of systolic and diastolic BP change in response to SA nifedipine administration, the Blaszak et al. study also noted\(^{21}\):

- SA nifedipine was effective when hypertension was associated with a variety of underlying disorders (renal, oncological, post-surgical, etc.)
- The drug’s therapeutic effect was not affected by prior and concurrent use of other antihypertensive drugs.
- Withdrawing the drug from the capsule to administer via syringe did not affect BP response.
About one third of the children experienced a “precipitous” BP decrease (> 25%), without sequelae, although patients who received doses smaller than 0.25 mg/kg did not experience these dramatic drops. This observation led the researchers to conclude that SA nifedipine for the management of severe hypertension in hospitalized children is safe, although they recommended use of drug doses ≤ 0.25 mg/kg with particular caution in the smallest patients because exact doses are not available.

### Table 4: Blaszak et al. (2001) Observational Study of SA Nifedipine in Children with Severe Hypertension

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td><strong>Inclusion:</strong></td>
<td></td>
<td><strong>Drug &amp; dosage:</strong></td>
<td><strong>Efficacy:</strong></td>
</tr>
<tr>
<td>• Age &lt; 19 years.</td>
<td>Mean ± SD, 11.6 ± 5.3.</td>
<td>Route of SA nifedipine administration: S/L or oral.</td>
<td>Overall:</td>
</tr>
<tr>
<td>• Received SA nifedipine for acute treatment of severe HT.*</td>
<td>Range, 0.1-18.9.</td>
<td>Doses of SA nifedipine administered, 520.</td>
<td>o Mean SBP drop: 17 ± 11%; range -11-56.</td>
</tr>
<tr>
<td>• Had BP measured within 2 hours following drug administration (if multiple BP readings, lowest value was taken).</td>
<td>Sex:</td>
<td>Mean # of doses of SA nifedipine per patient, 4.4.</td>
<td>o Mean DBP drop: 23 ± 15%; range -32-65.</td>
</tr>
<tr>
<td><strong>Age:</strong></td>
<td>Mean 40.1 ± 22.8 kg; range 2.8-139.2 kg.</td>
<td>Mean dosage strength per administration, 0.23 ± 0.12 mg/kg (range, 0.04-0.89).</td>
<td>o MAP*: 20 ± 12%; range -18-57.</td>
</tr>
<tr>
<td><strong>Primary disease:</strong></td>
<td>Renal, 49%.</td>
<td>Magnitude of effect:</td>
<td></td>
</tr>
<tr>
<td>• Renal disease, 49%.</td>
<td>Cardiac (mostly transplant), 14%.</td>
<td>o 35% of cases involved ≥ 25% drop in MAP.</td>
<td></td>
</tr>
<tr>
<td>• Oncological, 9%.</td>
<td>DKA, 5%</td>
<td>o Mean nifedipine doses/kg were correlated with drug dose when adjusted for patient weight.</td>
<td></td>
</tr>
<tr>
<td>• Miscellaneous, 23%.</td>
<td></td>
<td></td>
<td>o 10-mg doses versus smaller doses: No differences in changes in MAP.</td>
</tr>
<tr>
<td><strong>Drug &amp; dosage:</strong></td>
<td></td>
<td></td>
<td>o Prior exposure to other antihypertensive drugs did not alter efficacy (no actual data presented).</td>
</tr>
<tr>
<td>• Route of SA nifedipine administration: S/L or oral.</td>
<td></td>
<td></td>
<td>* MAP= DBP + [(SBP-DBP) / 3]</td>
</tr>
<tr>
<td>• Doses of SA nifedipine administered, 520.</td>
<td></td>
<td></td>
<td>AE=adverse event; BP=blood pressure; CNS=central nervous system; CVS=cardiovascular system; DBP=diastolic BP; DKA=diabetic ketoacidosis; HT=hypertension/hypertensive; MAP=mean arterial pressure; SA=short-acting; SBP=systolic BP.</td>
</tr>
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**KEY:**
- AE=adverse event; BP=blood pressure; CNS=central nervous system; CVS=cardiovascular system; DBP=diastolic BP; DKA=diabetic ketoacidosis; HT=hypertension/hypertensive; MAP=mean arterial pressure; SA=short-acting; SBP=systolic BP.

**Summary of observational studies**

The four observational studies differed in a number of ways and therefore it is not clear how similar their populations were (highlights shown in Appendix 1):
- Definitions and forms of hypertension varied, from hypertensive emergencies through to moderate hypertension associated with APSGN.
- The mix of clinical conditions varied from 100% with renal disease in the form of APSGN to populations with less than 50% renal pathology.\(^{16,17}\)
- The age ranges of children varied with two studies allowing inclusion of the charts of children less than 19, one less than 18, and one not reporting the maximum age. Also, the mean age in the earliest study\(^ {16}\) was three years older than the age in the other three studies.
- All studies observed the effect of oral SA nifedipine but this included a mix of forms of administration including capsule, bite-and-swallow, and liquid extracted from the capsule.
- Monitoring of BP varied with three studies noting the lowest BP within two hours of drug administration\(^{16,17,19}\) but the Canadian study\(^{18}\) extending this to six hours post-drug.
- BP outcomes were reported differently, most significantly by the recent South African study\(^{19}\) that did not report mean BP decreases but rather divided children into the proportions who experienced BP decreases > 25% and < 25%.
• AE reporting was dramatically different with Yiu et al.\textsuperscript{18} prospectively developing an extensive AE reporting system and then presenting AEs according to major and minor, and likelihood of association with nifedipine. In comparison, AE reporting in the other three studies was scanty.

Recent treatment guidelines and reviews

The most recent comprehensive advice for the management of severe hypertension in children was published by the US NHLBI in 2005.\textsuperscript{9} Nifedipine is not included in the list of indicated drugs for hypertensive emergencies although the guidelines state that it could have a role for hypertensive “urgencies”. The specific advice contained in the NHLBI guideline document is: \textquote{"Hypertensive emergencies should be treated by an intravenous antihypertensive that can produce a controlled reduction in BP, aiming to decrease the pressure by 25 percent or less over the first 8 hours after presentation and then gradually normalizing the BP over 26–48 hours. Hypertensive urgencies are accompanied by less serious symptoms, such as severe headache or vomiting. Hypertensive urgencies can be treated by either intravenous or oral antihypertensives, depending on the child’s symptomatology. "} Of interest, the previous version of these guidelines from 1996 do recommend up to three doses of SA nifedipine 0.25 to 0.5 mg/kg for hypertensive emergencies in children.\textsuperscript{22}

Dr. Joseph Flynn from the University of Michigan published a review of CCBs in pediatric hypertension in 2000\textsuperscript{7} in which he expressed concern about the potential for sudden unpredictable hypotension after nifedipine administration and the possibility of neurological deficits as a result. He was also critical of the uncertainty of exact dosing when the contents of a capsule must be drawn into a syringe and administered, due to possible staff errors and variable concentrations of the active ingredient within a capsule’s contents. For these reasons he stated his own institution has replaced SA nifedipine for hypertensive emergencies with alternate agents including oral minoxidil and IV labetolol, and he urged others to do the same.

Flynn also published a 2003 review of nifedipine in children with severe hypertension\textsuperscript{23} in which the studies of Egger et al.\textsuperscript{17} and Blaszak et al.\textsuperscript{16} were reviewed. A number of concerns were expressed about use of SA nifedipine in pediatric emergencies including accuracy of dosage when liquid is drawn into a syringe (and the accompanying cost if this task is shifted from nursing to pharmacy to ensure accuracy) and the potential for the drug to cause sudden and profound hypotension. Despite oral administration rendering the drug easy to use, he points out that most children who present with severe hypertension will require intravenous (IV) access anyway. Flynn concludes by saying that “there seem to be significant problems with SA nifedipine that make it a poor choice,” adding that there are groups of children in whom the drug should not be used at all including those with acute CNS injury, clinical or subclinical cardiovascular disease (including long-term dialysis patients), and history of stroke, and that viable management alternatives exist that are not complicated by significant safety concerns.\textsuperscript{23}

Another nifedipine dosage issue resulting in a significant medication error was reported in 2000 by the Institute of Safe Medical Practice (ISMP), a nonprofit organization in Pennsylvania (with a Canadian affiliate) devoted to medication error prevention and safe medication use, wherein a syringe of nifedipine drawn up to be used sublingually was injected intravenously. ISMP recommendations following this incident were to prohibit the use of nifedipine by the sublingual route, to use suitable alternatives to treat hypertensive emergencies, and to use specially designed oral syringes that do not connect to IV tubing when preparing any oral liquid medication for inpatients.\textsuperscript{24}
Additional complications with the use of SA nifedipine for acute hypertension in children were presented by Leonard et al. from Philadelphia\textsuperscript{25} who reported two cases of adverse neurological events associated with rebound hypertension following drug administration, including severe cortical visual impairment in one instance and right-sided aphasia and seizures in the other.

The controversy and a largely negative view of SA nifedipine for severe hypertension in children were presented by Italian pediatric nephrologists who stated, after reviewing the research and reported complications, that “there is no easy answer to the dilemma to use or not to use SA nifedipine in a child with severe hypertension”.\textsuperscript{26} They suggested that, if a child is asymptomatic (hypertensive urgency), the need for urgent treatment is largely driven by fears harboured by the treating physician, not the needs of the child, and that if nifedipine is used, a dose less than 0.25 mg/kg would be most appropriate. For true hypertensive emergencies they recommended use of drugs other than nifedipine and suggested IV labetolol or nitroprusside.

Despite all the preceding negative advice regarding SA nifedipine, the most recent review from Loma Linda Children’s Hospital, published in mid-2006, promotes its use.\textsuperscript{1} (The review author is one of the co-authors on the Egger et al. study presented above.\textsuperscript{17}) The author states that “\textit{based on a review of the pediatric literature, SA nifedipine is a safe and effective oral antihypertensive agent in children},”\textsuperscript{11} albeit with a number of qualifiers:

- Therapy should be initiated with a dose of 0.01 mg/kg versus the previously recommended dose of 0.25 to 0.5 mg/kg.
- The dose can be repeated if necessary but should not exceed 10 mg.
- The drug should not be used in children with acute CNS injury.
- The drug should be avoided in neonates due to difficulties accurately measuring dosage.
- The drug should only be used in children with hypertensive emergencies in hospital as initial treatment, for example in an emergency department or on the ward.
- Follow-up treatment to achieve controlled lowering of BP should involve a continuous infusion of nitroprusside, labetolol or nicardine but this requires time to transfer the child to an intensive care unit (ICU) for adequate monitoring, to establish an arterial line, and for pharmacy staff to prepare continuous infusion materials.

\textit{Limitations}

The evidence was limited in a number of ways:
- Only four studies were located that had been published in the past 10 years and all were of very weak study design being retrospective chart reviews. However, practically speaking, it is not likely that a prospective study could be performed as hypertensive emergencies in children are very rare and in addition, since nifedipine has been off patent for a number of years, it may be difficult to obtain funding for such studies.
- All studies were relatively small (57 to 182 patients), including a Canadian multi-site and multi-year review, due to the rarity of the condition.
- The studies differed from each other in a number of ways including the condition of interest (e.g., hypertensive emergencies versus severe hypertension), the patient populations (age ranges, mean ages, underlying conditions), monitoring and reporting systems, and documentation of AEs.
- Additional information is unlikely to be forthcoming for the reasons listed above, due to the controversies accompanying the drug, and due to the existence of viable alternatives.
Conclusions and implications for decision or policy making:

Four observational studies published between 1998 and 2008 met the inclusion criteria for review. All found that SA nifedipine was effective for most children with acutely elevated BP, decreasing both systolic and diastolic BP by about 17% to 25%. AEs were uncommon in three of the studies although the fourth study, which was much more particular about AE detection, reported both major and minor AEs.

SA nifedipine for the management of hypertensive emergencies is controversial. The drug is quick and easy to administer and it can be stocked and employed in small or medium sized facilities that may not have access to pediatric ICUs and their accompanying expertise and technologies (although this situation does not address how to manage a patient after acute nifedipine treatment). In Canada, the mode of administration is limited to 5 mg and 10 mg capsules so for treatment of small children, a capsule’s contents must be drawn into a syringe and administered, predisposing to medication errors. The drug can be administered via capsule or extracted liquid sublingually or orally but absorption is similar between the two forms.

The drug has been employed worldwide for this unique indication for several decades since the first report of its use in 1983. However, AEs have arisen in adults leading to discontinuation of the use of the drug for severe hypertension in those over 19. Concerns about the potential for similar AEs in children have led some experts to discontinue use of the drug, replacing it with agents that must be administered parenterally, including IV labetolol, nitroprusside and nicardine. However, other experts appear to be convinced that the drug continues to have a place in therapy and have changed their practice patterns to lower drug dosage (from 0.25 mg/kg to 0.1 mg/kg) with more intensive monitoring and more qualifiers to its use.

As with many issues in medicine, risks must be weighed against potential benefits, with particular consideration being given to the clinical settings involved and the potential to deliver urgent care and also appropriate follow-up.

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### Appendix 1: Summary of Key Characteristics & Outcomes Among Studies

<table>
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<tr>
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<tbody>
<tr>
<td>n=</td>
<td>57 (efficacy data included 44)</td>
<td>182</td>
<td>166</td>
<td>117</td>
</tr>
<tr>
<td>Maximum age of children</td>
<td>NR</td>
<td>&lt; 18</td>
<td>&lt; 19 (assumed)</td>
<td>&lt; 19</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>7.4</td>
<td>8.6</td>
<td>8.5</td>
<td>11.6</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>NR</td>
<td>63/37</td>
<td>54/46</td>
<td>65/35</td>
</tr>
<tr>
<td>Renal pathology (%)</td>
<td>100 (all had APSGN)</td>
<td>80</td>
<td>45</td>
<td>49</td>
</tr>
<tr>
<td>Window to reassess BP (hours)</td>
<td>2 for efficacy analysis</td>
<td>6</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment efficacious</td>
<td>77% of episodes</td>
<td>86% of episodes</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mean # drug doses/patient</td>
<td>3.5</td>
<td>2.4</td>
<td>10</td>
<td>4.4</td>
</tr>
<tr>
<td>Mean dose of drug (mg/kg)</td>
<td>0.23; range NR</td>
<td>0.22; range 0.04-0.67</td>
<td>0.30; range 0.04-1.30</td>
<td>0.23; range 0.04-0.69.</td>
</tr>
<tr>
<td>Decrease in SBP</td>
<td>84% had decrease &lt; 25%; 16% had decrease &gt; 25%</td>
<td>17%</td>
<td>17%</td>
<td>17%</td>
</tr>
<tr>
<td>Decrease in DBP</td>
<td>57% had decrease &lt; 25%; 43% had decrease &gt; 25%</td>
<td>25%</td>
<td>28%</td>
<td>23%</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td>None</td>
<td>83% of patients; 5% probable/definite &amp; 23% possible.</td>
<td>Not divided into major &amp; minor or attributed: 6 neurologic including 2 deaths; 2 symptomatic hypotension; 12 oxygen desaturation &lt; 90%.</td>
<td>None reported</td>
</tr>
<tr>
<td>Major</td>
<td>One child had a seizure 2 hours post-drug but recovered fully.</td>
<td>1% (2 patients) had significant BP drops but were asymptomatic.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**KEY:** APSGN=acute post-streptococcal glomerulonephritis; BP=blood pressure; DBP=diastolic BP; NR=not reported; SBP=systolic BP.