

Evaluation of the safety of short-acting nifedipine use in children with severe hypertension secondary to acute post-streptococcal glomerulonephritis

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Hypertension occurs in about 80 - 97% of hospitalised children who present with acute post-streptococcal glomerulonephritis (APSGN).^{1,2} The hypertension develops rapidly over a few days. In the majority of cases the hypertension resolves with diuretic therapy within the first week of admission to hospital.¹

Nifedipine is widely available in South Africa, and is relatively cheap and easy to administer. It is often the only drug available to reduce blood pressure (BP) rapidly in children presenting with hypertensive emergencies at peripheral medical facilities. In our setting this is almost always in the context of APSGN. Previous studies³⁻⁸ have shown nifedipine to be effective and safe in reducing BP in severe hypertension in children.

In adult patients, there have been concerns regarding the safety of short-acting nifedipine because of the increased risk of myocardial infarct and cerebral ischaemia⁹⁻¹³ As a result of this, government agencies in some countries have advised against the use of short-acting nifedipine for hypertension.¹⁴⁻¹⁶ Some authors in the paediatric literature^{17,18} have also advised against the use of short-acting nifedipine in severe hypertension. We review our experience with the use of short-acting nifedipine in the treatment of severe or moderate hypertension secondary to APSGN, with particular relevance to the primary health care setting.

Methods

A retrospective chart review was done. Information was obtained from the medical records of all patients admitted between January 1999 and December 2002 with the diagnosis of APSGN. Confidentiality was ensured as identifying details such as name or hospital number were kept in a separate, password-protected file and only the researchers had access to this information. These patients were admitted mainly to short-stay facilities. We reviewed both the doctors' and nurses' notes and charts and recorded the following information: age, weight, dose administered, and any adverse events (irrespective of whether or not we considered the adverse events to be secondary to nifedipine) up to 6 hours post nifedipine dose. We also recorded the systolic, diastolic and mean drop in BP after those doses where the BP was recorded again within 2 hours of the nifedipine dose. Severe

hypertension was defined as a systolic blood pressure (SBP) of 30% more than the 95th percentile for age and sex. Moderate hypertension was defined as BP of more than 15% of the SBP for age and sex, but less than 31%. Other concurrent medications and clinically relevant information, e.g. fluid overload renal failure, were also documented. Medication effectiveness was defined as a reduction in SBP or diastolic blood pressure DBP of more than 20%.^{3,5,19} The recommended starting dose for nifedipine is 0.25 mg/kg. This dose is generally administered either orally or sublingually. Either way the capsule is broken and in reality no absorption of the drug occurs in the mouth itself;²⁰ rather it is likely that all absorption of the drug occurs in the gastrointestinal tract. The initial response to this dose occurs within 20 minutes, with a duration of 4 - 8 hours. Peak concentration is reached within 20 - 45 minutes.²¹

Statistical analysis

A Student's *t*-test was used to compare the mean dose of nifedipine given when the BP dropped by more than 25% with the mean dose when the BP dropped by less than 25%.

Results

One hundred and twenty-nine patients with APSGN were identified in this time, with 198 doses of nifedipine administered to 57 patients. The nifedipine was administered either sublingually or orally. Mean age was 7.4 years (+/- 3 years). Forty-four of the patients treated with nifedipine had severe hypertension and 13 had moderate hypertension. Only 1 adverse event (a seizure) was noted 2 hours after a nifedipine dose. Twenty patients (35%) received an initial dose greater than the recommended 0.25 mg/kg. In 44 cases BP was only measured within 2 hours of administering nifedipine. Table I shows the mean dose of nifedipine in those cases (of the 44) where the BP dropped by more than 25% versus those where the BP dropped by less than 25% for SBP, DBP and mean BP. As can be seen from the table, although the doses causing a greater than 25% drop are higher, we could not find a statistical difference in the groups ($p < 0.05$). Seventy-seven per cent of doses (where the BP was measured within 2 hours) were effective in reducing BP. Unfortunately the blood pressure at 2 hours post nifedipine dose was recorded in only 4 patients



TABLE I. NIFEDIPINE DOSE AND BLOOD PRESSURE REDUCTION

% reduction in blood pressure	Patients (%)	Dose/body weight (mg/kg) (SD)
Systolic BP		
>25	16	0.257 (0.058)
<25	84	0.225 (0.079)
Diastolic BP		
>25	57	0.239 (0.07)
<25	43	0.218 (0.08)
Mean arterial pressure		
>25	34	0.254 (0.049)
<25	66	0.217 (0.085)

SD=standard deviation

with moderate hypertension. This number was considered too small to make comparisons with the severe hypertension group. Thirteen patients had fluid overload with pulmonary oedema on presentation, 2 had seizures and 3 had both.

Discussion

The rationale for regarding the use of nifedipine with caution is due to reduced organ perfusion. It has been shown that all complications of hypertension treatment occur with a 25% reduction in mean arterial pressure (MAP) and most occur with reductions in MAP > 30%.²² This is the level at which perfusion falls off the 'autoregulatory plateau'²³ and this results in a passive relationship between pressure and flow. The main concern with nifedipine is that there is sometimes a large and unpredictable fall in BP, which may lead to decreased organ perfusion.^{17,24-26} Other postulated toxic effects of nifedipine include pro-arrhythmic and pro-haemorrhagic effects,^{27,28} none of which have been proven.

As in other studies,^{6,8} our patients tolerated nifedipine well despite a sometimes large and unpredictable fall in BP. Unlike the adult population, children with hypertension have a low incidence of co-existing cardiovascular and cerebrovascular disease, which probably accounts for the better tolerance. The even lower incidence of adverse events observed in our patient group compared with other studies of children,^{6,8} may be related to the presumed rapid rise in BP in APSGN. Generally the faster the BP rises, the faster it can and should come down. With a rapid rise in BP the autoregulatory plateau has not yet shifted to the right, so that an even a greater than 25% drop in BP is still within the autoregulatory range. A rapid rise in BP without a protective shift in the autoregulatory plateau will result in transmission of systemic BP to the microcirculation, causing damage. BP should therefore be brought down rapidly.

The 1 patient who had a seizure 2 hours post nifedipine dosing unfortunately did not have his BP recorded on the nursing chart or in the doctor's notes at the time. The next entry was at 4 hours post dose and by this time the BP was again at the pre-nifedipine dose level. This patient did receive quite a high dose of nifedipine (0.38 mg/kg); however it cannot be established for certain if a too-rapid drop in BP precipitated the seizure or whether the BP stayed high despite the dose of nifedipine. Despite this the patient made a full recovery and was discharged home without any neurological sequelae.

Acute nephritis is a low renin-state hypertension, with the underlying mechanism probably mainly due to fluid overload.^{2,29} Like other authors¹ we have found that with use of diuretics the hypertension in APSGN usually resolves within

the first week, and ongoing use of other antihypertensive agents is not necessary. Nifedipine is very useful to control the worst of the hypertension until an effective diuresis is established. Nifedipine is also cheaper than most other drugs and ease of administration (no intravenous access or infusion pumps) and wide availability make it appealing in secondary and primary hospitals in our setting.

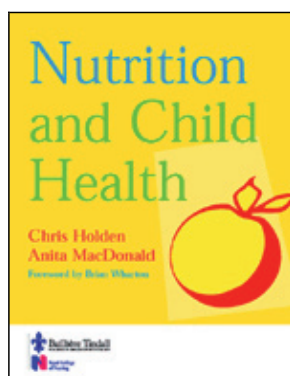
It could be argued that patients with no target organ damage (i.e. hypertensive urgency) could be managed with an oral agent causing a more gradual decline in BP. However, for the 18 patients in this study with hypertensive emergencies, where it would generally be accepted that immediate lowering of BP is necessary,²⁹ nifedipine remains a very useful medication especially in settings where the capacity to administer intravenous drugs does not exist. We however recommend an initial dose of not more than 0.1 mg/kg/dose. In patients with more persistent hypertension, a longer-acting agent should be introduced.

In conclusion, short-acting nifedipine is a safe and effective drug for the treatment of severe hypertension in APSGN. This pertains particularly in the setting of hypertensive emergency where a rapid reduction in BP is required. However these results need confirmation in prospective controlled studies.

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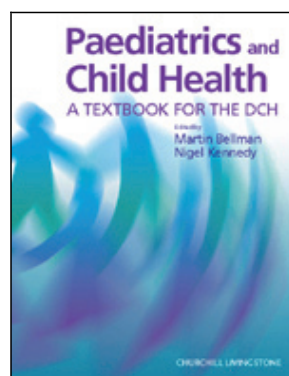
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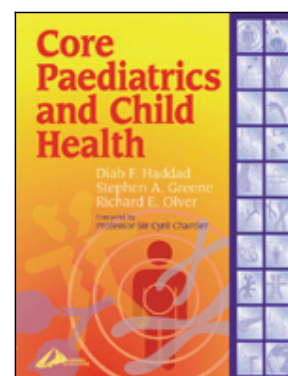


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