



*An initiative of NSW Clinical
Pharmacologists & Pharmacists
Funded by the NSW Department of
Health*

LITERATURE REVIEW

TREATMENT OF HYPERTENSIVE CRISES

**A Critical Assessment of the NSW Therapeutic Assessment Group
Inc.**

October 1998

Authors: Ms Meredith Page, Medical Information, MSD
(Formerly RNS Hospital, Sydney)
Ms Deborah Leibbrandt, RNS Hospital, Sydney

This review was prepared by the authors in consultation with members of the NSW Therapeutic Assessment Group Inc.

This work is copyright of the NSW Therapeutic Assessment Group Inc and NSW Health Department. Apart from any use as permitted under the *Copyright Act 1968*, no part of this document may be reproduced by any process without written permission.

Whilst the information contained in this document has been presented with all due care and the information is considered to be true and correct at the date of publication, changes in circumstances after publication may impact on the accuracy of the information.

This document represents expert consensus opinion and should not be relied on as professional advice other than in this context. The information provided should not be regarded as a substitute for detailed expert advice in individual cases. NSW Therapeutic Assessment Group Inc will accept no responsibility for any loss, claim or damage suffered or caused by any person acting or refraining from action as a result of any material in this document.

1. INTRODUCTION

Although never registered for the indications, nifedipine capsules (5 and 10 mg) have been widely used and recommended for treatment of hypertensive urgencies and as an alternative to intravenous agents in hypertensive emergencies¹⁻¹³. The supply of nifedipine capsules to the Australian market was discontinued in May 1996 (10mg) and May 1997 (5mg); the reason cited by the manufacturer was to remove the potential for confusion among prescribers and patients due to the concurrent availability of Adalat[®] capsules and Adalat[®] tablets¹⁴. The Australian Drug Evaluation Committee (ADEC) also strongly recommended the withdrawal of nifedipine capsules from the Australian market. Severe hypotension had been reported in patients inadvertently receiving capsules instead of tablets¹⁵.

This document provides a summarised update of available drugs used to treat hypertensive emergencies and urgencies in Australia. It does not specifically address the management of hypertensive crises in pregnancy or childhood.

2 Brief review of Hypertensive Emergency

- Hypertensive emergency is defined as an elevation of both systolic and diastolic blood pressure (BP) with the presence of acute end organ disease²⁻¹⁰. The organs at particular risk are those that receive the greater proportion of cardiac output, that is the heart, the brain and the kidneys^{2,6,9}. Hypertensive emergencies include hypertensive encephalopathy, dissecting aortic aneurysm, cerebrovascular accidents, severe hypertension with progressive renal insufficiency and acute left ventricular heart failure. Hypertensive emergencies may also be caused by phaeochromocytoma, pre-eclampsia and eclampsia, or be drug-related (eg MAO inhibitors and tyramine ingestion, withdrawal of α 2 agonists such as clonidine, use of sympathomimetic agents) or occur post-operatively.¹⁻⁹ Hypertensive emergency is not distinguished by an arbitrarily chosen BP value^{2,5,7}.
- Hypertensive urgency (or pseudoemergency¹⁰) is described as elevated BP (diastolic >120mmHg^{3,4,8}) with an absence of acute end organ disease¹⁶. Examples of hypertensive urgencies include peri-operative hypertension, intractable nose bleed, hypertension associated with increased circulation of catecholamines and most commonly, severe diastolic hypertension without complications^{3,7}.
- Hypertensive emergency and hypertensive urgency are encompassed in the term hypertensive crisis^{2,4,8}. Hypertensive emergencies are rare and treatment must balance the risks of lowering BP too rapidly against persistent hypertension with continued end organ dysfunction.

3 Rationale of treatment

3.1 Hypertensive Emergencies

- Hypertensive emergencies require immediate reduction of BP to prevent or minimise end organ damage⁴⁻⁶. The patient should be admitted to hospital for close observation, monitoring and treatment. An Intensive Care setting and intravascular monitoring is preferred and expert help and advice should be sought urgently. Decreasing the BP too rapidly may impair organ perfusion and lead to loss of autoregulation of cerebral blood flow and subsequent cerebral ischaemia and cerebral infarction (especially in chronic hypertensive patients)^{2,4,5,10}. The goal of treatment is therefore to reduce BP to minimise end organ damage while preventing complications of a rapid BP reduction^{4,6}. Hirschl⁶ recommends reduction of BP over 60 -90 minutes to a mean BP of 120mmHg or a 20 - 30% reduction in mean arterial pressure (MAP- ie diastolic BP + 2/3 pulse pressure). McKindley and Boucher⁴ endorse lowering diastolic BP to 100-110mmHg and systolic BP to 160-170mmHg within a few minutes to 1 hour of onset. Goals should be modified (ie a more gradual reduction in BP) in those patients susceptible to loss of cerebral blood flow (CBF) eg the elderly, patients with chronic hypertension and patients with atherosclerotic cerebrovascular disease⁵.

- The ideal drug for the treatment of hypertensive emergencies should have the following characteristics⁵: 1. rapid onset (controlled not precipitous) and cessation of clinical effects; 2. predictable dose response relationship; 3. restoration of cerebral autoregulation; 4. lack of side effects; 5. convenience. Several authors argue against the use of oral agents in hypertensive emergencies^{2,3,5,6,10} for reasons including unpredictable effect on MAP, unpredictable time to peak effect, higher failure rate than with parenteral therapy and lack of ease in titrating or discontinuing oral agents. In addition there is no less need for the patient to be monitored (to detect early signs and symptoms of cerebral decompensation) with oral compared with intravenous therapy. However if IV access is impossible or impractical, alternatives include an intramuscular injection of either clonidine or hydralazine or an oral dose of antihypertensive medication. Institution of appropriate oral therapy may be required once hypertension has been controlled, and parenteral agents (if used) gradually withdrawn.

3.2 Hypertensive Urgencies

- In hypertensive urgencies, patients require a gradual reduction in BP over a period of 24 to 48 hours^{4,8,16}. While hypertensive urgencies such as perioperative hypertension, intractable nose bleed and hypertension associated with increased circulation of catecholamines are best managed with parenteral agents³, the majority of hypertensive urgencies (which do not include the conditions mentioned above) can be managed effectively with oral medications^{1,3,4,16}. Caution and vigilant monitoring should be exercised when treating a hypertensive urgency in an older person with cardiovascular risk factors or any patient with known vascular disease.
- Some authors^{8,17} assert that most patients with hypertensive urgency can be treated as outpatients (with 24 hour follow-up) but others recommend that patients with severe diastolic hypertension should be admitted for observation and treatment (or at least observed for 6 hours) since patient compliance cannot always be assured and inadequate treatment may lead to an hypertensive emergency^{4,16}.
- The initial treatment of a patient with an hypertensive urgency presenting to the emergency department should be a short period of rest in a quiet darkened room^{11,16,18}. Gales¹¹ and Hirsch¹⁸ recommend at least 30 minutes in a supine position before medication is instituted. Other studies document that between 30 minutes and 2 hours of quiet rest can decrease the diastolic BP of patients with very severe hypertension (>210/120) by 15 to 20%¹⁶.

4 Background to the withdrawal of nifedipine capsules

- Nifedipine in capsule form is the best studied rapidly acting oral antihypertensive agent for hypertensive crises^{11,17}, however it was only ever approved by the Australian TGA (Therapeutic Goods Administration) and the United States FDA (Food and Drug Administration) for the management of chronic stable or vasospastic angina pectoris (and not for the treatment of any form of hypertension)^{10,15}.
- Sublingual administration of the capsules for hypertensive emergency was commonly recommended as a means of increasing nifedipine's rate of absorption and increasing its ease of administration in patients unable to swallow^{2,6,8,11}. However, since van Harten et al.¹⁹ demonstrated that it is in fact intestinal absorption alone which accounts for nifedipine's efficacy and that sublingual absorption is negligible, the oral bite and swallow method has been recommended when rapid onset is required^{1,4,7,9}.
- In 1985, the FDA recommended that the practice of giving sublingual nifedipine for hypertensive emergencies be abandoned because "dose-response information as well as assessment of true risk of a cataclysmic complication of this form of dosing was lacking"^{10,15}.
- In 1990, a report of a serious adverse drug reaction following nifedipine administration in a 44 year old man with a hypertensive urgency resulted in criticism of its indiscriminate use in treating severe hypertension²⁰. Jaker et al²⁰ noted that although nifedipine capsules have been advocated for the treatment of hypertensive emergencies, controlled studies comparing nifedipine with nitroprusside were lacking.

In a 1995 review, Murphy⁵ commented that experience with nifedipine in adults with hypertensive emergencies is insufficient to recommend it for general use and an unknown potential exists with a drug that has a relatively long duration of action (2-6 hours). (Duration of effect after sublingual administration is 3-6 hours⁶.)

In 1996, Grossman et al¹⁰ tabled 16 cases of severe adverse drug reactions (ADRs) with “sublingual” or oral nifedipine documented in reports on Medline between 1966 and 1994. The ADRs included cerebrovascular ischaemia, severe hypotension, stroke, acute myocardial infarction, conduction disturbances, foetal distress and death. In hypertensive emergencies these serious ADRs occur with agents that precipitously lower arterial pressure. The authors argued that because velocity, magnitude and duration of decrease in arterial pressure are not predictable with nifedipine capsules, the routine use of nifedipine capsules in hypertensive emergencies and urgencies should be abandoned.

5 Drugs used to treat hypertensive crises

- Table 1 details drugs currently used to treat hypertensive crises (parenteral, sublingual and oral) including sodium nitroprusside, glyceryl trinitrate, diazoxide, hydralazine, phentolamine, esmolol, clonidine, captopril, prazosin, labetalol and nifedipine tablets. The table includes information about recommended doses, specific indications, ADRs and the advantages and disadvantages with the use of each drug. Methyldopa, a centrally acting α_2 adrenoreceptor antagonist, has not been included in Table 1 as it is of limited use due to its slow onset of action (3-6 hours after intravenous administration). Intravenous loop diuretics such as frusemide (not discussed in Table 1) are used to reduce renal sodium retention when systemic pressure is lowered.
- Table 2 lists the drug(s) of choice for specific hypertensive emergencies as well as drugs which should be avoided. The choice is dependent on properties of the drug, indication, clinical effects, advantages and contraindications.

5.1 Parenteral medications

Sodium nitroprusside

- Sodium nitroprusside is a vascular smooth muscle relaxant that works directly at cellular level. It affects arterial and venous tone equally in the systemic circulation^{2,5} Sodium nitroprusside can increase heart rate, myocardial oxygen demand and intracranial pressure (ICP), however it is still recommended for some crises associated with cerebrovascular accidents. It should not be used as initial therapy when the emergency is associated with significant increases in ICP or myocardial ischaemia, in the absence of heart failure. Potential cyanide toxicity is rare if recommended doses and duration of treatment are followed. Thiocyanate toxicity is potentially more common in patients with renal insufficiency who require an infusion for >48 hours^{2,3,5,7,8,18}. (Sodium nitroprusside is converted to cyanide by sulfhydryl groups in erythrocytes and in tissues, the cyanide is rapidly metabolised in the liver to thiocyanate which is excreted in the urine). Signs of toxicity include nausea, vomiting, headache, restlessness, delirium and toxic psychosis⁴.

Glyceryl trinitrate

- Glyceryl trinitrate is a direct vasodilator having a dominant effect on venodilation. This results in a reduction in venous return (preload) to the heart, a decrease in left ventricular diastolic volume and pressure and a subsequent decrease in myocardial oxygen demand. Glyceryl trinitrate also dilates coronary arteries and promotes a favourable redistribution of blood flow to ischaemic areas²⁻⁶.

Esmolol

- Esmolol is a short-acting β blocker with β_1 selectivity. Its effects are similar to other β blockers however it is unique due to the rapid cessation of effect with discontinuation of infusion.

Hydralazine

- Hydralazine is a direct vasodilator that produces marked arterial dilation and minimal venous dilation. It reduces the diastolic pressure more than the systolic and can induce a reflex increase in heart rate and cardiac output²⁻⁵.

Diazoxide

- Diazoxide is predominantly an arteriolar dilator^{2,4,5,6}. BP reduction is immediate and is due to a decrease in systemic vascular resistance.

Clonidine

- Clonidine is a centrally acting α_2 adrenergic agonist which diminishes sympathetic neuronal vasoconstrictor tone to the heart, kidneys and peripheral vasculature. This results in a decrease in cardiac output, total peripheral resistance and heart rate in severely hypertensive patients^{5,9}.

Phentolamine

- Phentolamine is a competitive and nonselective α_1 (post-synaptic) and α_2 (pre-synaptic) receptor blocker⁵. It has a rapid onset of action and rapid clearance.

5.2 Oral medications

Nifedipine tablets

- Although nifedipine capsules had become widely popular in the treatment of hypertensive emergency¹⁰, there is negligible information in the literature about the administration of nifedipine tablets (10 and 20mg) for this indication. Many studies do not specify the formulation of nifedipine used and it is assumed that oral administration refers to capsules^{13,21}.
- Nifedipine tablets have a slower rate of absorption compared with the liquid-filled gelatin capsules (t_{max} = 1.5 - 4.2 hours compared with t_{max} 30-60 min). The manufacturer states that the pharmacological action of nifedipine tablets persists up to 12 hours post-administration compared with up to 8 hours for the capsules. The VDUAC Cardiovascular Guidelines¹ list nifedipine tablets (10-40mg orally, twice daily) in combination with a β -blocker as treatment for "urgent reduction of BP" if myocardial ischaemia is present.

Captopril

- Captopril is an angiotensin converting enzyme (ACE) inhibitor which reduces the production of angiotensin II and the secretion of aldosterone. This results in a reduction of BP secondary to a reduction in total peripheral resistance and decreased aldosterone-mediated sodium and water retention^{5,22}. Captopril decreases both afterload and preload to the heart and increases regional blood flow. It increases coronary blood flow (CBF) in patients with congestive heart failure, yet such an effect is minimal in other patients⁵.
- Although not registered for this indication, captopril has been administered both orally and sublingually in tablet form for the treatment of hypertensive urgencies²²⁻²⁴. The optimal route of administration is unknown^{11,16}, however several studies have demonstrated a faster onset of action when the tablets are administered sublingually^{5,23}. It has yet to be established whether the absorption of captopril sublingually is connected with the swallowing of saliva (as for nifedipine) or due to absorption via the oral mucosa²³. For rapid onset, it may be useful to administer captopril oral solution 5mg/mL which is available in Australia and New Zealand for the initial dose titration of captopril where fractional doses may be required. The solution can be used for multiple patients but any remaining solution must be discarded 28 days after opening which may make it an expensive option. The oral solution is not available in the USA or the UK, and there is little specific mention of its use for the treatment of hypertensive urgencies.

- Captopril effectively reduces BP in hypertensive urgencies and is well tolerated^{1,2,4,5,25,26}. Maximum reduction in MAP after sublingual captopril 25mg averages 23% in limited studies⁵. In a randomised single blind study comparing sublingual nifedipine (10mg) with sublingual captopril (25mg) the hypotensive effect of nifedipine was more rapid than that of captopril (10 versus 20 minutes for diastolic BP and 20 versus 30 minutes for systolic BP), however no difference was observed in the time or in the magnitude of peak hypotensive effect between the two treatments²⁵.
- In general, in comparative trials, fewer adverse effects have been observed with captopril than with nifedipine administration. There are many references to support that it does not produce the compensatory tachycardia seen with many other vasodilators^{22, 24-26}. However, caution should be exercised so that BP is not lowered too rapidly due to its rapid onset of action.
- **Oral:** The onset of antihypertensive effect after oral administration is between 10-30 minutes^{5,6,16,18,23} with the time to maximal effect quoted as 30mins - 2 hours^{5,11,22}. **Sublingual:** The dissolution time of a captopril tablet sublingually administered is estimated to be 3.6 ± 1.2 minutes (25mg)²⁴ and 5 ± 1.3 minutes (50mg)²³ with a maximal effect at 30 - 60 minutes^{4,11,16,24} and duration of action is reported to be between 4 - 8 hours^{4,5,6,16}. **Chew and swallow:** After swallowing a crushed tablet, onset of effect has variously been reported to be between 5-20 minutes^{2,11,16,22-25}.

Clonidine

- An initial reduction in MAP by 20% or to a diastolic BP below 120mmHg can usually be achieved with oral clonidine⁸.
- Houston¹⁷ collated data from four studies on clonidine for hypertensive crisis. The average dose used was 0.36mg, average fall in systolic BP was 56mmHg, diastolic BP was 25mmHg and for MAP 38mmHg. Average time to maximal reduction was 2.75 hours with 92.6% of patients responding to treatment.

Prazosin

- Prazosin is a selective α_1 receptor antagonist both in the arterial and venous vasculature⁹.
- Anderson and Reed⁹ report a study of 19 moderate to severe hypertensive patients who received 5mg prazosin. Diastolic BP dropped to 100mmHg in 77% of treatment episodes by 3 - 4 hours.
- However, Wu et al²⁶ conducted a study comparing the antihypertensive effects of sublingual captopril 25mg, nifedipine 10mg and prazosin 2mg in hypertensive emergency in haemodialysis. They report response rates at 120 mins post dose to be 83% for captopril, 90% for nifedipine and 11% for prazosin.

Labetalol

- Labetalol produces selective antagonism at the postsynaptic α_1 receptors and non-selective antagonism at β receptors^{2,4,5,27}. It also has β_2 partial agonist activity. It lowers BP primarily through peripheral vasodilatation mediated by its alpha blockade²⁷. An intravenous form is not available in Australia.
- Atkin et al²⁷ administered labetalol orally to 18 patients who had severely elevated BP (mean baseline 201/132mmHg) without acute end organ dysfunction. Each patient received an initial dose of 200mg, followed by hourly doses up to 1200mg. Labetalol reduced DBP in 94% of the patients within 6 hours.

5.3 Sublingual administration

Glyceryl trinitrate

- Bussman et al²⁸ administered glyceryl trinitrate 1.2mg sublingually to 20 patients with a mean BP of 211/122. After 5 minutes the mean BP had dropped to 171/95. This was compared with 20 patients with a mean BP of 210/118 who received 10mg nifedipine (chewed and swallowed). After 5 minutes the mean BP had dropped to 185/102. After 15 - 20 minutes, a satisfactory decrease in BP was reached in both groups. The reduction in BP persisted for up to 6 hours. No information was retrieved on the use of the spray in hypertensive crises.

Captopril

- See Captopril (oral preparations)

6 Summary

Hypertensive emergencies tend to be rare, physiologically diverse and are associated with end organ dysfunction, whereas hypertensive urgencies occur more frequently and are not associated with end organ dysfunction. There are many drugs available to treat hypertensive crises with the most commonly used being parenteral sodium nitroprusside and glyceryl trinitrate. Other parenteral drugs include esmolol, hydralazine, diazoxide, clonidine and phentolamine.

Despite some criticism in the literature, oral medications have been used effectively for the treatment of both hypertensive urgencies and emergencies. Nifedipine capsules are no longer available. However, oral preparations used include prazosin, captopril, clonidine, labetalol and nifedipine tablets. Sublingual administration of glyceryl trinitrate and captopril is also effective.

Vigilant monitoring of the patient together with appropriate drug use is required. BP reduction should be performed cautiously and gradually and there are serious risks to the patient if reduction of BP is too rapid. Follow-up doses of medication should be administered only after allowing time for occurrence of the maximal effect. For oral and sublingual administration, consideration needs to be given to the difficulty in titrating doses, longer duration of effect compared to parenteral administration and the possibility of failure to produce a significant effect.

Table 1: Drugs Used in Hypertensive Crises

PARENTERAL				
Drug	Dose	Special indications	Advantages	Disadvantages
sodium nitroprusside 50mg vial (vascular smooth muscle relaxant)	Initially 0.2mcg/kg/ min as IV infusion ; increase by 0.2mcg/kg/min every 5-10 min to maximum dose of 10mcg/kg/min	All hypertensive emergencies (except in presence of raised ICP or acute ischaemia in absence of HF)	-immediate onset & rapid cessation (1-3 min) of effect -preload & afterload reduction -no sedation	-photodegradation(cover bottle) -requires infusion with constant monitoring (arterial line preferred) of volumetric pump-therefore requires specialist units -rebound hypertension on cessation
glyceryl trinitrate 50mg/10mL amp (vasodilator, especially venodilation)	5-200 mcg/min by IV infusion	-Myocardial ischaemia (especially with infarction or angina) -Post-operative -CHF -Pulmonary oedema	-coronary vasodilatation -rapid onset (2-5min) & short acting(5-15min) -no sedation -relieves coronary spasm	-binds to polyvinyl chloride glass with polyethylene adhesive sets -tolerance may develop -constant monitoring & arterial line required-therefore limited to specialist units
diazoxide 300mg/20mL amp (arteriolar dilator)	(variable in literature) Initial 25mg IV bolus . Increase by 25-50mg (bolus) every 5-10 min up to maximum dose of 300mg.	-Hypertensive encephalopathy -Malignant hypertension -Eclampsia -Post-operative hypertension	-rapid onset (1-5min) & rapid peak effect (3-5min)	-may require use of β blockers -highly protein bound results in unpredictable & long-lasting effect -painful extravasation -dose reduction in renal impairment -avoid in myocardial ischaemia, heart failure or aortic dissection
hydralazine 20mg amp (vasodilator with marked arterial dilation)	-5-10mg IV boluses every 20 min or -10-50mg IV every 4-6 hours prn -IV infusion can be given -IM route not recommended	-Eclampsia -Hypertension in renal disease -Malignant hypertension -Post-operative hypertension	-fast onset (5-15min IV or 20-30min IM), however IM route not recommended by manufacturer	-increase ICP -fine BP control not possible -can not use in angina, aortic dissection -variable duration of effect -effect of metabolism (acetylation) -reflex sympathetic stimulation increases HR, CO & oxygen consumption

Table 1: Drugs Used in Hypertensive Crises (continued)

PARENTERAL (continued)					
Drug	Dose	Special indications	Advantages	Disadvantages	Adverse effects
<p>phentolamine 10mg amp</p> <p>(competitive & non selective α_1 & α_2 receptor blocker)</p>	<p>0.5-10 mg IV bolus, repeat every 5-15 min or -infuse 5-10mcg/kg/min</p>	<p>-Phaeochromocytoma (+β antagonist) -increased circulation of catecholamines (eg MAOIs, clonidine withdrawal syndrome, cocaine)</p>	<p>-rapid onset (1-2min) -possibly no adverse CNS effects</p>	<p>-variable duration of action (30-120min) -paradoxical pressor response (very rare)</p>	<p>-diarrhoea, headache -nausea, vomiting, abdominal pain -can induce angina or MI in coronary artery disease -profound fall in BP if volume depleted</p>
<p>esmolol 100mg/10mL vial 2.5g/10mL vial</p> <p>[short acting β blocker (β_1 selective)]</p>	<p>loading dose: 500mcg/kg/min maintenance: 300mcg/kg/min for 3 min, then 100mcg/kg/min by iv infusion (& titrate)</p>	<p>-Perioperative control of BP during repair of aortic dissection -Phaeochromocytoma, (with α blockade) (plus sodium nitroprusside for both)</p>	<p>-rapid onset (1-2min) -duration of effect (20min), therefore rapid cessation of effect -easily titrated</p>	<p>-limited approval in product information (supraventricular tachycardia); limited experience with hypertensive emergencies -thrombophlebitis if small veins used & concentration greater 10mg/mL -needs to be used in combination with vasodilator / α blocker</p>	<p>-bronchospasm -bradycardia, heart block -hypotension</p>
<p>clonidine 150mcg/mL amp</p> <p>(centrally acting α adrenergic agonist)</p>	<p>IV: 150-300mcg over 5 min IM: 150-300mcg</p>	<p>-acute hypertensive crisis & alternative to oral treatment (PI) -Alternative to sodium nitroprusside (VDUAC)</p>	<p>-rapid onset (IV: 5min; IM: 5-10min) -decreases heart rate & no increase in myocardial oxygen consumption</p>	<p>-can dramatically decrease cerebral blood flow -fine BP control not possible -paradoxical increase in BP with IV admin (dilute with 10mL N/S and give slowly to minimise effect) -do not use in CHF, 2nd or 3rd degree heart block, bradycardia or sick sinus syndrome</p>	<p>-dizziness -sedation -profound hypotension -dry mouth -nausea and vomiting -bradycardia</p>

Table 1: Drugs Used in Hypertensive Crises (continued)

ORAL					
Drug	Dose	Special indications	Advantages	Disadvantages	Adverse effects
captopril 12.5mg & 25mg tabs & 5mg/mL oral solution (ACE inhibitor)	-25mg po every 30min prn -6.25-12.5mg sl initially, then 12.5-25mg prn.	-CHF complicated by severe hypertension -hypertension associated with scleroderma	-benefit on cerebral autoregulation and blood flow -reduces pre & afterload -no fluid retention -no compensatory tachycardia -easy to administer -may positively affect myocardial perfusion	-careful 1st dose observation (may experience marked hypotensive effects in high renin state, accelerated or malignant hypertension, salt or water depletion, recent use of sympathetic blockers eg prazosin, labetalol) -avoid in patients with bilateral renal artery stenosis -avoid in patients receiving immunosuppressive agents -avoid in pregnant patients	-hypotension -acute renal failure in patients with bilateral renal artery stenosis -photophobia -hyperkalaemia -rash -angioneurotic oedema -transient conjunctival congestion -marked 1st dose effect in patients with high renin levels
prazosin 1,2 & 5mg tabs (selective α_1 receptor antagonist)	-2-5mg po or -1-2mg po & repeat hourly prn	-alternative to sodium nitroprusside -hypertensive urgencies associated with circulating catecholamines (with β blockade)	-easy to administer	-onset of effect variable between patients (30-60min) due to first pass metabolism -difficult to titrate -first dose syncope	-syncope -palpitations, tachycardia -headache -orthostatic hypotension
clonidine 100 & 150 mcg tabs (centrally acting α adrenergic agonist)	-0.05-0.2mg po stat. Repeat every 2 hours prn. Maximum dose: 0.6-0.8mg	-hypertensive urgencies only -used in renal dysfunction	-decreases heart rate & no increase in myocardial oxygen consumption	-sedation (hamper neuro monitoring) -avoid in CHF, 2nd or 3rd degree heart block, bradycardia or sick sinus syndrome) -patient should remain supine or sitting for 6-12 hours	-sedation, dry mouth, dizziness -nausea & vomiting -profound hypotension -bradycardia, heart block -decreased CBF

Table 1: Drugs Used in Hypertensive Crises (continued)

ORAL (continued)					
Drug	Dose	Special indications	Advantages	Disadvantages	Adverse effects
labetalol 100 & 200mg tabs (α_1 post synaptic antagonist, non selective β antagonist, partial β_2 agonist)	-200-400mg po. Repeat every 2-3 hours	-head trauma -renal dysfunction -post-operative hypertension -phaeochromocytoma -hypertensive urgencies -eclampsia	-safe in renal impairment -safe during pregnancy	-avoid in asthma, chronic airways limitation, 2 nd & 3 rd degree heart block -onset of peak effect variable, titration of dose difficult (dosing period long) -failure to achieve target BP reduction occurs 25-50% of cases	-bronchconstriction -headache, drowsiness, dizziness -heart block -orthostatic hypotension -exacerbation of CHF
nifedipine tablets 10 & 20mg calcium antagonist	- 10-40mg bd	-presence of myocardial ischaemia		-long duration of action	-reflex tachycardia -hypotension -headache, dizziness, flushing

SUBLINGUAL ADMINISTRATION					
Drug	Dose	Special indications	Advantages	Disadvantages	Adverse effects
glyceryl trinitrate 600mcg tab, 400mcg/ metered dose spray (vasodilator)	1.2mg sl or by metered dose spray		-positive effect on LVF, pulmonary oedema, angina, infarction -easy to administer, familiarity -rapid onset (sl & spray: 4min) & rapid clearance		-headache, dizziness -facial flushing, tachycardia -hypotension, syncope

Table 2: Choice of Drugs in Hypertensive Emergencies

Hypertensive emergency	Drug(s) of choice	Drug(s) to avoid or use with caution
Cerebrovascular accident	sodium nitroprusside, labetalol	diazoxide, β antagonists
Acute renal insufficiency	sodium nitroprusside (beware of \uparrow risk of thiocyanate toxicity), hydralazine, labetalol,	ACE inhibitors (\uparrow risk of renal failure if renal artery stenosis present), β antagonists (\downarrow renal blood flow)
Acute myocardial infarction	glyceryl trinitrate, labetalol, calcium antagonists	hydralazine, diazoxide (\uparrow heart rate)
Acute left ventricular failure	glyceryl trinitrate, sodium nitroprusside	hydralazine, diazoxide (\uparrow heart rate), β antagonists (\downarrow cardiac output)
Acute pulmonary oedema	sodium nitroprusside & loop diuretics; glyceryl trinitrate & loop diuretics	β antagonists or methyldopa (both can exacerbate oedema)
Dissecting aortic aneurysm	sodium nitroprusside + β antagonists; labetalol	hydralazine, diazoxide (\uparrow heart rate)
Post-operative hypertension	labetalol, glyceryl trinitrate, sodium nitroprusside	
Phaeochromocytoma May be drug related eg MAOI interaction or clonidine withdrawal	sodium nitroprusside, labetalol, phentolamine, β antagonists (only after phentolamine)	β antagonists (in absence of alpha blockade), methyldopa (displaces noradrenaline from stores)
Pre-eclampsia & eclampsia	hydralazine, glyceryl trinitrate, sodium nitroprusside (reserved for eclampsia resistant to other agents)	diazoxide (may cause cessation of labour), diuretics (\downarrow intravascular volume), β antagonists
Hypertensive encephalopathy	sodium nitroprusside, labetalol, diazoxide	β antagonists, methyldopa, clonidine

REFERENCES:

1. Cardiovascular Drug Guidelines Sub-Committee, Victorian Drug Usage Advisory Committee. Cardiovascular Drug Guidelines, 2nd ed. Melbourne, Victorian Medical Postgraduate Foundation Inc, 1995:67-8.
2. Oh TE, editor. (Chui PT and Low JM: Acute hypertension and vasodilators) Intensive Care Manual, 4th ed. Oxford, Butterworth-Heinemann 1997:153-61.
3. Abdelwahab W, Frishman W and Landau A. Management of hypertensive urgencies and emergencies. *J Clin Pharmacol* 1995;35:747-62.
4. McKindley DS and Boucher BA. Advances in pharmacotherapy: Treatment of hypertension crisis. *J Clin Pharmacy and Therapeutics* 1994;19:163-80.
5. Murphy C. Hypertensive Emergencies. *Emergency Medicine Clinics of North America* 1995;13:973-1007.
6. Hirschl M M. Guidelines for the Drug treatment of hypertensive crisis. *Drugs* 1995;50:992-1000.
7. Gifford RW. Management of hypertensive crises. *JAMA* 1991;266:829-35.
8. Calhoun DA and Oparil S. Treatment of Hypertensive Crisis. *NEJM* 1990; 323:1177-83.
9. Anderson RJ and Reed WG. Current concepts in treatment of hypertensive urgencies. *Am Heart J* 1985:211-19.
10. Grossman E, Messerli FH, Grodzicki T and Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA* 1996;276:1328-30.
11. Gales MA. Oral Antihypertensives for hypertensive urgencies. *Ann Pharmacotherapy* 1994; 28:352-8.
12. Houston MC. Treatment of hypertensive urgencies and emergencies with nifedipine. *Am Heart J* 1986;111: 963-9.
13. Bertel O and Conen LD. Treatment of hypertensive emergencies with the calcium channel blocker nifedipine. *Am J Med* 1985;79:31-5.
14. Written communication from Bayer re: Adalat[®] capsules and tablets for the treatment of angina pectoris.
15. Adalat capsules product information. Date of TGA Approval 6 June 1989, Date of Safety Related Amendment 21 November 1995.
16. Thach AM and Schultz PJ: Nonemergent hypertension. New perspectives for the emergency medicine physician. *Emerg Med Clin North Am* 1995;13:1009-35.
17. Houston MC: Treatment of hypertensive emergencies and urgencies with oral clonidine loading and titration. A review. *Arch Intern Med* 1986;146:586-89.
18. Thomas J, editor. Australian Prescription Products Guide 1997, 26th ed. Australian Pharmaceutical Publishing Co Ltd, Hawthorn, Vic. Sodium nitroprusside for injection BP monograph 2327-31.
19. van Harten J, Burggraaf K, Danhof M, van Brummelen P and Breimer DD. Negligible sublingual absorption of nifedipine. *Lancet* 1987;2:1363-5.

20. Jaker M, Atkin S and Newark NJ. *Reply to Oral nifedipine in the treatment of hypertensive urgency: cerebrovascular accident following a single dose.* Arch Intern Med 1990;150:687.
21. Houston MC. Treatment of severe hypertension and hypertensive crises with nifedipine. Western J Med 1987;146:701-4.
22. Chan E and Visram N. Sublingual Captopril in Hypertensive Crisis. Can J Hosp Pharm 1987;40:100.
23. Di Veroli C and Pastorelli R. Orally dissolved captopril compared with captopril in standard oral administration in the treatment of hypertensive emergencies and urgencies in the elderly. Curr Ther Res 1991;50:586-90.
24. Karachalios GN, Chrisikos N, Kintziou H, Petrogiannopoulos K and Kehagioglou K. Treatment of hypertensive crisis with sublingual captopril. Curr Ther Res 1990;48:5-9.
25. Angeli P, Chiesa M, Caregaro L, Merkel C Sacerdoti D, Rondana M and Gatta A. Comparison of sublingual captopril and nifedipine in immediate treatment of hypertensive emergencies. A randomised, single-blind clinical trial. Arch Intern Med 1991;151:678-82.
26. Wu SG, Lin SL, Shiao WY, Huang HW, Lin CF, Yang YH. Comparison of sublingual captopril, nifedipine and prazosin in hypertensive emergencies during hemodialysis. Nephron 1993;65(2):284-7.
27. Atkin SH, Jaker MA, Beaty P, Quadrel M, Cuffie C, Soto-Greene ML. Oral labetalol versus oral clonidine in the emergency treatment of severe hypertension. Am J Med Sci 1992;303(1):9-15.
28. Bussman WD, Kenedi P, von Mengden HJ, Nast HP, Rachor N. Comparison of nitroglycerin with nifedipine in patients with hypertensive crisis or severe hypertension. Clin Invest 1992;70(12):1085-8.

Other references used in addition to above in compilation of tables

Thomas J, editor. Australian Prescription Products Guide 1997, 26th ed. Australian Pharmaceutical Publishing Co Ltd, Hawthorn, Vic. Catapres[®] monograph: 613-4.

Thomas J, editor. Australian Prescription Products Guide 1997, 26th ed. Australian Pharmaceutical Publishing Co Ltd, Hawthorn, Vic. Apresoline[®] monograph: 391-3.

Thomas J, editor. Australian Prescription products Guide 1997, 26th ed. Australian Pharmaceutical Publishing Co Ltd, Hawthorn, Vic . Aldomet[®] monograph 298-300.

Thomas J, editor. Australian Prescription Products Guide 1997, 26th ed. Australian Pharmaceutical Publishing Co Ltd, Hawthorn, Vic. Glyceryl nitrate for injection monograph 1193-5.

Thomas J, editor. Australian Prescription Products Guide 1997, 26th ed. Australian Pharmaceutical Publishing Co Ltd, Hawthorn, Vic. Brevibloc[®] monograph 538-41.

Written communication from Ciba-Geigy re: Apresoline ampoules. June 27, 1994.

Thomas J, editor. Australian Prescription Products Guide 1997, 26th ed. Australian Pharmaceutical Publishing Co Ltd, Hawthorn, Vic. Regitine[®] monograph 2194-2195.

Messerli FH, Kowey P and Grodzicki T. Sublingual nifedipine for hypertensive emergencies. Lancet 1991;338:881.

Adalat tablets product information. Date of TGA Approval 4 April 1995. Date of Safety Related Amendment 21 November 1995.