

Norvasc®  
(amlodipine besylate)

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Drug Monograph- Norvasc®  
February 26,2003

Medline search terms for primary literature: amlodipine, Norvasc, poisoning, overdose, therapeutic error, toxicity

## I. Identifying Features

- A. Norvasc is a long-acting dihydropyridine calcium antagonist, or calcium channel blocker (CCB). Its generic name is amlodipine besylate, and its chemical nomenclature is (R.S.) 3-ethyl-5-methyl-2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-1,4-dihydro-6-methyl-3,5-pyridinecarboxylate benzenesulphonate. Its empirical formula is  $C_{20}H_{25}ClN_2O_5C_6H_6O_3S$ .<sup>1</sup>
- B. Norvasc was FDA approved for use in 1996, and is indicated in the treatment of essential hypertension, chronic stable angina, vasospastic angina, myocardial ischemia, congestive heart failure, and Raynaud's disease.<sup>4</sup> It has also been shown to decrease left ventricular mass in hypertensive patients with hypertrophy, decrease proteinuria in Type 2 diabetics, and increase vasodilation of the pulmonary arteries in patients with pulmonary hypertension. However, it does not have FDA approval for these latter uses.
- C. Norvasc is available from Pfizer as white tablets for oral administration in 2.5, 5, and 10 mg strengths. It is also available under the following names in foreign countries:
- Amcard, Calchek (India)
  - Amdepin (Africa)
  - Amdipin, Amlodip, Amlosyn, Norvas (Colombia)
  - Amlocar (Peru)
  - Amlodin (Japan)
  - Amlopine (Thailand)
  - Amlor (Belgium, France, Israel)
  - Norvas (Mexico, Spain)
  - Norvask (Bulgaria)
  - Norvask, Tensivask (Indonesia)

The active ingredient, amlodipine, is also found in combination with benazapril HCl in

Lotrel capsules from Novartis<sup>1</sup>

## **II. Pharmacologic Action**

A. Cardiac and vascular smooth muscle cells are dependent on calcium movement through specific ion channels for contraction. Norvasc, like other CCBs, exerts its pharmacological action by "inhibiting the transmembrane influx of calcium into myocardial fibers, cardiac pacemaker cells, and vascular smooth muscle cells" by binding to and blocking these calcium ion channels.<sup>2</sup> The dihydropyridine class of CCBs, to which Norvasc belongs, is more selective for vascular smooth muscle than for cardiac cells. As such, Norvasc tends to cause fewer incidents of cardiac depression and fewer conduction disturbances, compared to Verapamil or Diltiazem. It acts on the L-type calcium channel and binds both dihydropyridine and nondihydropyridine sites. It does not tend to produce negative inotropic or chronotropic effects. Administration of Norvasc results in "relaxation of vascular smooth muscle, producing decreased afterload, decreased systemic blood pressure and increased coronary vascular dilatation."<sup>3</sup> Norvasc has a basic amino side chain that makes it very different from all other CCBs, and creates a very interesting pharmacologic, pharmacokinetic and toxicological profile.<sup>1</sup>

## **III. Therapeutic Dosing**

- A. The recommended dose of Norvasc for adults is 5 mg/ day initially, titrated to response over 7-14 days, up to a maximum dose of 10 mg once daily. If the patient has hepatic insufficiency or if Norvasc is being started as an adjunct to existing antihypertensive therapy, the dose should be 2.5 mg/day.
- B. The initial dose in children is 0.1 mg/kg once to twice a day. This can be titrated up to doses of 0.1-0.3 mg/kg once to twice a day. The maximum dose in children is 0.6 mg/kg/ day, up to 20 mg per day.
- C. Individuals who are small, elderly or fragile should be started on 2.5 mg/day.<sup>1</sup>

#### IV. Pharmacokinetics

- A. Absorption- Norvasc has a  $pK_a$  of 8.6. At physiologic pH, its basic amino side chain is ionized and carries a positive charge. When undergoing absorption, the drug molecule orients itself between the hydrophobic and hydrophilic regions of the membrane. The ionized side chain interacts with the negatively charged region of the phospholipid head, and this slows diffusion of Norvasc through the membrane to its receptor site. This interaction accounts for several of the drug's unique pharmacokinetic parameters, including its gradual onset and offset of action. Norvasc has an onset of action of 30-50 minutes and a peak effect at 6-12 hours. Its oral bioavailability (F) ranges from 57-91%, and is not affected by food.<sup>1,2,3</sup>
- B. Distribution- Norvasc is 93% protein bound in the plasma. It has a volume of distribution of approximately 12-20 L/kg,<sup>3</sup> and thus partitions extensively into the tissues. Once at the receptor site, it exhibits relatively slow association and dissociation with receptors. In a study by Burges, et al., in vitro studies showed that, compared to other dihydropyridines, Norvasc's association and dissociation rates are up to "3 orders of magnitude slower".<sup>2</sup> This contributes to Norvasc being cleared more slowly, and having a longer duration of action. Steady-state plasma concentrations are achieved after 7-8 consecutive days of daily dosing.<sup>1</sup> Normal therapeutic serum levels are 3-15 ng/ml.<sup>4,5,6</sup>
- C. Metabolism- Norvasc has an elimination rate of 11 ml/min/kg (1/3 that of other CCBs).<sup>2</sup> This is another unique pharmacokinetic parameter that contributes to its long half-life. The majority of the drug (90%) undergoes hepatic metabolism, via CYP 3A4, to an inactive metabolite. It is an inhibitor of CYP 2B6, 2C8, 2C9, and 3A4, and thus has the potential for many drug interactions. Patients who are elderly or have hepatic insufficiency will have decreased clearance of Norvasc, and will need to be started on a lower dose.

D. Elimination- 10% of the parent compound and 60% of the inactive metabolites are excreted in the urine. The terminal elimination half-life of Norvasc ranges from 31-46 hours.<sup>3</sup>

## V. Adverse Effects

A. In controlled trials comparing placebo to therapeutic doses of Norvasc of up to 10 mg/day, the most commonly reported side effects were:<sup>1,4,7</sup>

Adverse Event	Norvasc (%)	Placebo (%)
Edema*	10.8	0.6
Headache	7.3	7.8
Fatigue	4.5	2.8
Palpitation*	4.5	0.6
Dizziness*	3.4	1.5
Nausea	2.9	1.9
Flushing*	2.6	0.0
Abdominal pain	1.6	0.3
Somnolence	1.4	0.6

\*dose related

B. Adverse effects of chronic use or exposure to Norvasc have not been reported.<sup>1</sup>

C. Allergic reactions to Norvasc have been reported in clinical trials in  $\leq 1\%$  but  $> 0.1\%$  of patients.<sup>1</sup>

D. Norvasc is contraindicated in patients with known sensitivity to amlodipine.<sup>1</sup>

## VI. Fetal Effects

A. There has been no documentation describing the transplacental transfer of amlodipine in humans. However, with a molecular weight of 567, it should be expected to cross the

placenta.<sup>8</sup>

- B. "The drug is not teratogenic or embryotoxic in rats and rabbits given doses up to 8 and 23 times, respectively, the maximum recommended human dose (MRHD) on a body surface area basis during their respective periods of major organogenesis. However, rats administered 8 times the MHRD for 14 days before mating and throughout gestation had a significant increase in intrauterine deaths (about 5-fold), and prolonged labor and gestation."<sup>8</sup>
- C. There are no well established criteria for the use of Norvasc in any semester of pregnancy. Norvasc should only be used in pregnancy when the healthcare team and patient have collaboratively decided that the benefit to the mother outweighs any risk the medication may pose to the fetus. Norvasc is classified as pregnancy category C by the FDA.

## VII. Toxicity of the Agent

The following table summarizes case reports of Norvasc toxicities

Patient Age and Gender	Amount of Norvasc	Coingestants	Time to onset of s/sx	s/sx	Treatment	Outcome	Peak level (3-15ng/ml)
63 yo female <sup>(9)</sup>	70 mg (intentional)	oxazepam (peak level of 5.25mcg/ml) toxic=3-5mcg/ml	2.5°	- hypotension (70systolic) -bradycardia (40bpm) -ectopy -↓ Glasgow  BP 99/71  (1° later) hypotension (54/34) reflex tachy (142)  (6° later) BP 131/78  (20° later) ↑Ca+ ↑glucose	-fluids -pressors lavage/AC -flumazenil -atropine -nor-epi -Ca+Gluc -cardiac massage -intubation -ventilation -epi -glucagon  -Ca+ and glucagon stopped	death due to shock and cardiac arrest at 26°	185 ng/ml at 11°

				resp. acid.  (1° later) hypotension  sinus arrest asystole	-epi Ca+boluses -NaHCO <sub>3</sub> Hypervent.		
15 yo female (10)	140 mg (intentional)	mefenamic acid (peak of 2.0 mg/L) ther= 10mg/L	2°	-hypotension (70/40) -reflex tachy (130)  (3° later) -labored breathing and cyanosis  -asystolic cardiac arrest  -BP 100/60 -P 105  -Pulmonary edema  (20 min. later) -deteriorated  (1° later) -asystole	-fluids -CaGluc.   -CPR -adrenaline -atropine -CaCl -NaHCO <sub>3</sub>  attempts to resuscitate	death due to cardiovascular collapse at 6°	2700 ng/ml at 8°
42 yo female (6)	50-100mg (intentional)	40 oz. beer level= 263mmol		-sinus tach (122 bpm) -Hypotension (84/45)  -moved to ICU  -Pulmonary edema  (10° later) -transferred to med unit  (36° later) DC home	-AC/WBI -fluids	survival with good F/U	88ng/ml at 2.5°  (2nd level at 38° was 79ng/ml)
76 yo male (11)	100 mg (unintent.)  *over 24° period	none	unknown	-shock -refractory hypotension -jaundice -ARF	-fluids -hetastarch -Ca+ -glucagon -norepi		67ng/ml on day 1  (day 8,

				-Pulmonary edema -lact. acid. -1 <sup>st</sup> deg. AV block		10 days later, A/A/O  (died 112 days later of sepsis)	still 32 ng/ml)
*2 yo male	5 mg or 0.4 mg/kg	none	3°	Low BP	Fluids AC	Observed X 12° and DC home	unknown
*2 yo male	Unknown	None	1°	Lethargy	Lavage AC	Observe x 18° and DC home	unknown
*3 yo male	Unknown	None	1.5°	Lethargy	Lavage AC	Observe x 18° and DC home	unknown
Unknown (7)	250 mg (intentional)	unknown	none	asymptomatic	Not hospitalized	Uneventful	unknown
Unknown (7)	120 mg (intentional)	unknown	none	asymptomatic	Lavage	Normotensive	unknown
Unknown (7)	105 mg	unknown	unknown	hypotensive	Plasma expansion	Normalization of BP	unknown

\*source- Belson, et al., 1999<sup>12</sup>

#### A. Historical and epidemiological factors

According to the AAPCC Annual Report, there were 9,264 exposures to CCBs in 2001. The majority of them occurred in persons >19 years of age, and were unintentional. Approximately half of them (4,825) required treatment in a health care facility. These CCB exposures resulted in 60 fatalities. Of these 60, 9 (15%) involved Norvasc and all were reported as intentional ingestions. This serves as evidence as to the serious potential for toxicity surrounding Norvasc.<sup>13</sup>

B. Evidence gathered from the case reports available in the primary literature provide little in the way of toxic and lethal doses. The following toxic and lethal doses were derived by utilizing ingested amounts from each case report, along with reported patient weights. It is important to note that weights were not provided for all patients.

### Children

Toxic= 0.4 mg/kg<sup>13</sup>

Lethal= unknown

### Adults

Toxic= 0.7 mg/kg

Lethal= 1.9 mg/kg

Toxic levels in adults are based on 3 of the case reports. The 42 year old female is estimated to have ingested 75 mg of Norvasc, and estimating her weight at between 70 kg, that results in a 1.1 mg/kg toxic dose. Likewise, the 76 year old male ingested 100 mg (over a 24 hour period), and estimating his weight at around 75 kg, that results in a toxic dose of approximately 1.3 mg/ kg. Finally, it is estimated that the 40 year old woman ingested 50-100 mg of Norvasc. Using the lower end of 50 mg and estimating her weight at 70 kg gives a toxic dose of 0.7 mg/kg. The lethal dose of Norvasc in adults is based on the case report of the 15 year old female. Her weight was reported as 73.2 kg, and she ingested 140 mg of the drug. That results in a lethal dose of 1.9 mg/kg. The toxic dose for children is an actual, definitive amount documented in a study by Belson.<sup>12</sup> There was no evidence in the literature that elucidated a lethal dose in children.

### C. Pathophysiology of Acute Intoxication

Calcium channel blockers exert their toxicity via saturation and blockade of calcium channels that are vital to heart and smooth muscle contraction. When this lack of contractility is potentiated due to toxic levels of the drug, refractory hypotension and reflex tachycardia ensue. This effect of hypodynamic shock, or “bottoming out”, is greatly exaggerated with Norvasc, due to its increased effect on vascular smooth muscle, increased binding to calcium channels via its basic amino side chain, and its extremely sluggish association and dissociation with these channels. Also, CCB toxicity produces hyperglycemia and lactic acidosis, which renders the patient even more unstable.

Hyperglycemia is thought to be caused by several mechanisms. First, “there is inhibition of calcium-mediated insulin release by pancreatic islet cells. Second, CCB toxicity produces myocardial and whole-body insulin resistance. Third, the combination of poor tissue perfusion and severe acidosis impairs carbohydrate delivery and glycolysis in shock conditions. As a result, hyperglycemia develops, and myocardial energy transfer

becomes inefficient. The cause of lactic acidosis is uncertain, but it is speculated that lacticacidemia is probably a manifestation of poor tissue perfusion. In addition, lactic acidosis may also be due to mitochondrial dehydrogenase inhibition during CCB-induced circulatory shock. In high concentrations, CCBs inhibit mitochondrial calcium entry at the sarcolemma and the mitochondrial membrane, which in turn can decrease pyruvate dehydrogenase activity. Pyruvate does not enter the Krebs's cycle and lactate accumulates, producing metabolic acidosis.”<sup>5</sup>

- D. Symptoms of acute Norvasc intoxication are the same as for other CCBs, but it is imperative to keep in mind that they may be delayed due to the delayed absorption and onset of Norvasc. Additionally, it is important to remember that symptoms of Norvasc intoxication may persist far longer than those of other CCBs, due to its slow disassociation with calcium channels and prolonged half-life. The symptoms of toxicity include severe hypotension, bradycardia with subsequent reflex tachycardia, arrhythmias, hyperglycemia, metabolic acidosis, pulmonary edema, electrolyte imbalances, and possible congestive hepatopathy. Other signs and symptoms include dizziness, lethargy, confusion and coma. It is recommended to observe the patient for at least 12 hours, since Norvasc does not reach peak plasma levels for 6-12 hours.
- E. There is no toxicological test to rapidly determine if someone has had a potentially toxic exposure to Norvasc, or to determine the severity of such an exposure. Levels can be obtained, but the peak is often so long after the exposure that they really serve no purpose other than to add to the literature. It is critical to obtain an accurate history from the patient or friends and family concerning the ingestion. It is also critical to have a good understanding of the unique pharmacokinetic parameters of Norvasc in order anticipate differences in the onset and progress of symptoms. Onset of symptoms and observation periods for patients with Norvasc intoxication will be very delayed and prolonged compared to other CCB poisonings.

## **VIII. Treatment**

A. Induced emesis with syrup of ipecac is not recommended in Norvasc overdose, as patients may rapidly deteriorate once symptoms begin, and there is the possibility of aspiration. Since Norvasc is slowly absorbed, gastric lavage with a 36-40 French tube (24-28 for pediatric patients) should be performed if the patient presents to the healthcare facility within 4-6 hours. In patients with bradycardia or heart block, lavage should not be performed, due to risk of vagal stimulation. Norvasc has been shown to be adsorbed to charcoal<sup>14</sup>, and use of activated charcoal (AC) is recommended. Multiple dose AC may also be beneficial, due to delayed absorption. Whole bowel irrigation (WBI) may be considered if the patient does not have ileus and is relatively stable.

B. Supportive care in a Norvasc overdose encompasses maintaining hemodynamic stability, glucose control, and proper acid-base balance. The use of inotropes, such as dopamine or epinephrine, to keep blood pressure up is routine. Atropine is commonly used to treat bradycardia, as well as insulin and glucagon, which both exhibit inotropic effects that can circumvent calcium channels. Also, fluids can be administered to assist in regaining hemodynamic stability, but caution should be exercised due to the risk of pulmonary edema. Additionally, Amrinone, which is a phosphodiesterase inhibitor, can be used to overcome calcium channel blockade. It works by inhibiting the breakdown of cyclic adenosine monophosphate (cAMP). "Increased levels of cAMP results in increased phosphorylation of L-type calcium channels, which increases their permeability to calcium ions."<sup>3</sup> Amrinone seems to be an attractive treatment choice in that it does not increase myocardial oxygen demand like catecholamines do. However, it does have the drawback of inducing relaxation vascular smooth muscle, which can potentiate hypotension. Given its limited use in this setting, it should only be used as an adjunct to inotrope therapy. The dose is 0.75 mg/kg IV bolus over 2-3 minutes, followed by maintenance infusion of 5-10 mcg/kg/min.<sup>15</sup> Insulin's beneficial role in Norvasc overdose was first documented in a 1999 study by Yuan. et al.<sup>5</sup> During Norvasc toxicity, there is a shift in myocardial metabolism from carbohydrate metabolism to fatty acid oxidation. In the study by Yuan, et al.<sup>5</sup>, it was shown that "euglycemia has the ability to simultaneously increase lactate oxidation while completely eliminating myocardial fatty acid oxidation during shock. This metabolic profile optimizes heart function." It has intrinsic inotropic properties, and also stimulates cellular glucose, and

possibly lactate, uptake. These actions serve not only to reduce blood glucose, but also to prevent or correct acidosis. According to a recent study in Drug Safety, " a bolus dose of insulin 1 IU/kg is given, followed by an infusion of insulin at 0.5-1 IU/kg/h titrated to clinical response. Therapeutic targets include a systolic blood pressure >100 mm Hg and a heart rate >50 beats/min. Capillary glucose is checked every 20 minutes for the first hour of the infusion and hourly thereafter. Serum potassium is checked hourly. Patients are maintained on a half normal saline solution with 10% dextrose at an infusion rate equal to 80% of maintenance. Insulin infusion is weaned as signs of toxicity resolve."<sup>3</sup>

C. "There is no known effective method for enhancing the elimination of calcium channel antagonists. Given the extensive protein binding and large volume of distribution of Norvasc and other calcium channel antagonists, neither hemodialysis or hemoperfusion is likely to be helpful."<sup>3</sup>

D. The most frequently implemented antidote in CCB overdose is calcium salts, due to their availability and ease of administration. Either calcium gluconate or calcium chloride can be used. The calcium serves to saturate the calcium channel and outcompete the antagonist for the binding site. Dosage recommendations consist of boluses 1g every 2-3 minutes until clinical effect is achieved or titrating a calcium infusion to maintain a serum calcium of 8 mg/dL.<sup>3</sup> In doing this, there is a risk of the patient developing hypercalcemia, and caution must be exercised. Also, because Norvasc binds and unbinds with the channel so slowly, it may take higher doses of calcium or calcium may simply be less effective. As stated before, insulin and glucagon have both been used as antidotes to improve patient status in Norvasc toxicity. Finally, there is a potassium-channel antagonist, 4-aminopyridine, that has been proposed to increase intracellular calcium concentrations by causing increased influx and also by increasing calcium release from the sarcoplasmic reticulum. However, its safety and efficacy have not been proven in clinical trials.<sup>3</sup>

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