9 Hypertensive Emergencies in Children After Stem Cell Transplantation: Care in Selecting Hypotensive Drugs

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Abstract

Hypertensive emergencies in children are rare, but associated with a significant risk of morbidity and mortality. These situations make an immediate, and especially a controlled reduction of blood pressure necessary. In children after stem cell transplantation hypertension is usually secondary to a renal impairment caused by the treatment with cyclosporine and tacrolimus. Due to the lack of adequate published experience with the used hypotensive drugs, and the lack of corresponding guidelines for an effective management of these situations, the actual treatment options in children only vary slightly from those in adults, and are primarily based on small retrospective clinical trials, and case reports.

All drugs have their strengths and weaknesses, which should be taken into consideration by the prescriber, and be balanced against the personal experience. Because of their mechanism of action and a potential nephroprotective effect the calcium channel blockers may be particularly suitable in hypertensive emergencies with a renal etiology. Especially nicardipine appears to be the hypotensive agent of first choice, but for an evaluation about its safety in paediatric use the published studies and case reports are not sufficient. Clevidipine may play a major role in the future because of its promising pharmacokinetic and safety profile, but there is a need for further trials concerning its use in children.

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Introduction

Today one of the most serious late complications of allogeneic stem cell transplantation remains to be the graft versus host disease (GVHD). Up to a minimum of 100 days following stem cell transplantation, approximately 50% of patients will experience some degree of chronic GVHD. An optimized immunosuppression is one important part of successful stem cell transplantation to prevent GVHD.

The calcineurin inhibitors cyclosporine and tacrolimus have become standard agents for immunosuppression and the treatment of GVHD. Cyclosporine and tacrolimus cause vasoconstriction of the afferent and efferent glomerular arterioles, leading to a reduction in renal blood flow and glomerular filtration rate (GFR), and often result in hypertension (Chandar and Zilleruelo 2011). Up to now, the exact mechanism inducing vasoconstriction is unexplained, but some possible reasons are discussed in recent publications, including a reduced production of prostaglandins, an increased sympathetic tonus, a transformation of growth factor beta-1, and an upregulation of oxidative stress, resulting in endothelial dysfunction. In some rare cases, hypertension can manifest as a hypertensive emergency.

Severe elevations in blood pressure can be classified as hypertensive urgencies, which are associated with elevations in blood pressure, but excludes the symptoms of end-organ injury, and hypertensive emergencies. A hypertensive emergency has been defined as elevation of both systolic and diastolic blood pressure with acute end-organ damage. The height of blood pressure in hypertensive emergencies is the subject of controversial discussion in the published literature, including blood pressure greater than the 99th percentile for age and sex, and blood pressure increase greater than 15 or 30 mmHg above the 95th percentile for age and sex. Independent of absolute blood pressure values, the common factor in all reports that determines the need for immediate therapy is the evidence of impending or progressive end-organ damage. The organs most likely to sustain damage in these situations are the central nervous system, the heart, the eyes, and the kidneys (Hari and Sinha 2011).

In children, hypertensive emergencies most commonly present with signs and symptoms of hypertensive encephalopathy, which may manifest as an onset of headache, nausea, and vomiting followed by severe headache, confusion, visual changes, stupor, somnolence, seizure, focal neurologic deficits, and coma. Hypertensive encephalopathy can result in cerebral infarction or hemorrhage in children. However, this appears with a higher occurrence in adults. Further examples of end-organ damages are acute myocardial infarction, acute left ventricular failure with pulmonary edema, unstable angina pectoris, dissecting aortic aneurysma, or eclampsia.

The differentiation between hypertensive emergencies and hypertensive urgencies is extremely important in the clinical setting, as the presence or lack of end-organ damage will dictate the urgency and aggressiveness of treatment. The rapid reduction and control of blood pressure is essential in hypertensive emergencies to avoid further end-organ damage or even death, while in hypertensive urgencies the target pressure can be achieved in up to 48 h after its first presentation, with minimal or no change in outcome. The need to lower the blood pressure rapidly to avoid end-organ damage must be balanced against a too rapid reduction in blood pressure with organ hypoperfusion leading to further end-organ damage (Chandar and Zilleruelo 2011). A constant cerebral blood flow during changes in blood pressure is ensured by an autoregulatory arteriolar constriction or dilatation of cerebral vessels, a mechanism with upper limits. In profound hypertension, the loss of this autoregulatory mechanism by the cerebral vasculature makes rapid blood pressure reduction even more harmful as the blood vessels in the brain are not capable of adjusting to too rapid changes in blood flood. The greatest risk thereby is cerebral ischemia, as well as myocardial infarction or blindness.

In current publications, there are different opinions about how fast blood pressure should be lowered in a hypertensive emergency. Some publications recommend a reduction of blood pressure by 10–15% over a period of 30–90 min, others suggest

a decrease of more than 25% over a period of 1 h up to a greater timeframe of 2–3 h or 8 h, followed by a further gradual reduction in blood pressure over the next 26–48 h (Horn et al. 2011).

Although cases of hypertensive emergencies are rare, it is necessary to scrutinize the treatment options, and the available drugs in the forefront. For an optimal adjustment of variable blood pressure levels, children with hypertensive emergencies should be treated inside the monitored setting of a paediatric intensive care unit to prevent steep declines of blood pressure that may have significant morbidity or mortality. The used drugs should be titratable, intravenously applicable, hypotensive, and well tolerated.

The drugs commonly used in hypertensive emergencies are listed below. Furthermore, some key properties of the drugs and a short overview of today's available literature a tentative appraisal about their suitability in hypertensive emergencies in children after stem cell transplantation is made. The recommended paediatric doses, important adverse effects, and contraindications are summarized in two tables.

Sodium Nitroprusside

The most commonly used intravenous agent in hypertensive emergencies is sodium nitroprusside. After being metabolized to nitric oxide it causes direct arterial and venous dilatation. It decreases both afterload and preload and increases cardiac output. Sodium nitroprusside acts within seconds of administration. The duration of action is 1–2 min and it possesses a very short plasma half-life of about 2–4 min, making it easy to adjust treatment if blood pressure is thought to be too low. Due to its potency, blood pressure should be monitored constantly with an arterial line when using this agent.

Erythrocytes metabolize sodium nitroprusside to toxic cyanide. The rhodanase in the liver converts cyanide into thiocyanate, which is excreted renally. Infusions at high doses and over a long duration of up to 48 h and above may cause the accumulation of cyanide and/or thiocyanate. An additional impairment of liver or kidney function increases the risk of accumulation and intoxication. High levels of cyanide or thiocyanate may result in metabolic acidosis, altered mental status, and clinical deterioration. In some cases monitoring of thiocyanate blood levels may be necessary (treatment with high doses and/or for more than 48 h or renal impairment), but monitoring still remains controversial. The range of cyanide levels associated with signs and symptoms of toxicity (>0.5 mg/L) has never been validated in paediatrics and other adverse effects can occur in the absence of elevated cyanide or thiocyanate levels (Thomas et al. 2009). Sodium nitroprusside doses of 5 μg/kg/min or more should be avoided. If the use of sodium nitroprusside is unavoidable, a simultaneous infusion of thiosulfate can provide sulphur necessary to prevent cyanide accumulation, provided that liver function is not impaired.

The important side effects of sodium nitroprusside are shown in Table 9.1. Because of the decrease of cerebral blood flow with increase of intracranial pressure at the same time, sodium nitroprusside is contraindicated in patients with reduced cerebral perfusion. It should be avoided in patients with coarctation of the aorta and atrioventricular shunts.

The rapid onset of action and its short half-life makes sodium nitroprusside a valuable drug in most cases of hypertensive emergencies, but in those with a renal etiology it appears less adequate. The risk of an additional deterioration of renal function can not be compensated by a simultaneous infusion of thiosulfate, because children after stem cell transplantation tend to ascites and fluid overload. In those patients, sodium nitroprusside is the last resort in treatment. It should be used only for short periods of time and be limited to situations where no other suitable drugs are available.

Beta-Adrenergic Receptor Antagonists

Labetalol hydrochloride is a widely used selective alpha$_1$- and non selective beta-adrenergic receptor antagonist. It can be administered either

Table 9.1 Important adverse effects, and contra indications of the drugs (Adapted from Horn et al. 2011)

Drug	Important adverse effects/contra indications
Sodium nitroprusside	Hypotension, reflex tachycardia, metabolic acidosis, weakness, psychosis, headache, thyroid suppression, nausea, sweating, cyanide and thiocyanate toxicity
	Infusions at high doses and over a long duration, up to 48 or 72 h, may cause accumulation of toxic cyanide and/or thiocyanate (which may in metabolic acidosis, altered mental status, and clinical deterioration), and should be avoided
	An additional impairment of liver or kidney increases the risk of accumulation and intoxication, and necessitates dose adjustment.
	Contraindicated in patients with reduced cerebral perfusion
	Should be avoided in patients with coarction of the aorta and atrioventricular shunts
Labetalol hydrochloride	Bradycardia, bronchospasm, atrioventricular block, worsening of heart failure, ventricular arrhythmia, prolonged hypotension, increased risk of hyperkalaemia, worsening of renal function, hepatocellular necrosis, and chronic active hepatitis;
	Should be avoided in patients with asthma, chronic obstructive lung disease, heart failure, bradycardia, or greater than first-degree heart block
Esmolol	Hypoglycemia, hypotension, nausea, vomiting, depression, phlebitis, bronchospasm, heart block, bradycardia, and negative inotropic effect;
	Contraindicated in patients with cardiogenic shock, heart block, severe asthma, or chronic obstructive lung disease
Metoprolol	Conformable to those of labetalol
Urapidil	Severe hypotension, dizziness, nausea, giddiness, headache, fatigue, and palpitations
Hydralazine	Reflex tachycardia, increase in cardiac contractility, sodium and water retention, headache, elevation of intracranial pressure, lupus erythematosus, vasculitis, glomerulonephritis, and aggravation of angina;
	Contraindicated in patients with coronary artery disease, dissecting aortic aneurysm, cerebral vascular accidents, cerebral edema and encephalopathy
Diazoxide	Tachycardia, heart failure, pulmonary hypertension, respiratory failure, fluid retention, hyperglycemia, hirsutism, seizure
Enalapril	Prolonged hypotension, renal failure (especially in neonates), neutropenia, hyperkalaemia, hypoglycaemia, febrile convulsion, bronchopneumonia, bronchial obstruction, and exacerbation of asthma;
	Contraindicated in patients with bilateral renal artery stenosis
Clonidine	Orthostasis, bradycardia, atrioventricular block, significant sedation, dizziness, fatigue, constipation, anorexia, and arrhythmia
Fenoldopam	Hypotension, tachycardia, t-wave flattening, angina, arterial fibrillation, flatter;
	Should be avoided in patients at risk for intraocular hypertension and intracranial hypertension
Nifedipine	Symptomatic hypotension, reflex tachycardia, arrhythmias, bone marrow suppression, alteration in mental status, and oxygen desaturation;
	The combination of cyclosporine and nifedipine may increase the incidence as well as the severity of gingival overgrowth
	Should be avoided in patients with acute CNS injury
Nicardipine	Conformable to those of nifedipine
Clevidipine	Conformable to those of nifedipine

orally, as a continuous infusion or as an intravenous bolus injection. Due to its antagonistic effects on alpha$_1$-receptors, it leads to vasodilatation and the beta-adrenoceptor effects result in a decreased myocardial contractility. Labetalol hydrochloride has approximately no effect on cardiac output. It reduces the systemic vascular resistance without reducing peripheral blood flow. The heart rate is either maintained or slightly reduced. Intracranial pressure is unaffected.

The inactive metabolites are excreted in urine, feces, and bile. The lipohilic drug labetalol is metabolized via glucuronidation. As glucuronidation pathways are not fully matured in infants and small children (Benedetti and Baltes 2003), labetalol achieve sufficient concentrations at lower doses in this population. As metabolism is the main route of excretion of labetalol, renal failure has no significant effect on plasma half-life, clearance, or apparent volume of distribution. Labetalol hydrochloride has a relatively slow onset of action and reaches its peak effect of hypotension in about 10 min. Hypotension can last for up to 4 h. Besides the most common side effects, labetalol hydrochloride may increase the risk of hyperkalaemia and acute renal failure may occur in cases associated with overdoses. Recent literature report partially fatal hepatocellular necrosis and chronic active hepatitis associated with the use of labetalol. It led to its withdrawal from sale in Germany in the early 1990s.

Published information about the administration of labetalol hydrochloride in paediatrics is scant, although it is widely used. In one retrospective chart review (Thomas et al. 2011) continuous infusions of labetalol hydrochloride, nicardipine and sodium nitroprusside were compared in 27 paediatric patients aged less than 24 months concerning their efficacy and safety. Fifeteen patients received labetalol, six received nicardipine, and four received nitroprusside. They found no significant difference of a continuous infusion of labetalol in efficacy and adverse effects compared with nicardipine and nitroprusside. Labetalol produced a mean blood pressure lowering effect of at least 20% in all blood pressure measurements within 8 h. Blood pressure reduction was sufficient up to doses of 0.59 mg/kg/h, with a little benefit a higher doses. Despite the wide use of labetalol hydrochloride in paediatrics, actual publications could not rule out the possibility of worsening renal function and an additional injury of the liver by this drug. Due to this risk, it appears not suitable to apply labetalol in critically ill children.

Esmolol is a pure cardioselective $beta_1$-blocker. It decreases blood pressure by reducing heart rate and myocardial contractility, and thus cardiac output. It has no direct vasodilatory effect, and is particularly beneficial when there is associated tachycardia (Chandar and Zilleruelo 2011). The important traits of esmolol are the very short onset of action after intravenous application and its short half-life making therapy easy to control. It acts within 60 s or less and due to its fast metabolism, hypotension can last only for 10–20 min. Up to now, no clear dose-effect relationship has been published. Esmolol metabolism does not depend on renal or hepatic function and is based on intracytoplasmic red blood cell esterases via rapid hydrolysis of ester linkage. This makes the drug potentially well-suited for critically ill patients with multiorgan failure (Flynn and Tullus 2009), but particular care is necessary in any prerequisite that causes anaemia, because a prolonged half-life of esmolol can occur. Esmolol can cause congestive heart failure, bradycardia, and bronchospasm. Its contraindications are those expected from a beta-adrenergic blocker. The data on paediatric use of esmolol are mainly based on small clinical trials and case reports. In the US, a paediatric trial was completed, but no paediatric labelling has been approved by the FDA (Flynn and Tullus 2009). This still induces some doubts about its suitability.

Like esmolol, metoprolol is a selective $beta_1$-blocker decreasing heart rate, myocardial contractility, and cardiac output without any direct venous dilation. The peak effect after intravenous application occurs within 10 min after administration. Compared to esmolol it has a longer half-life of about 3–5 h and undergoes an extensive hepatic metabolism via cytochrome P450 isoenzyme 2D6, entailing the capability of essential drug-drug interactions. The side effects of metoprolol are similar to those observed with of labetalol and esmolol.

In current publications, there is only one case report about the paediatric use of metoprolol in a hypertensive emergency in a 12-year old female (Liesemer and Mullen 2009). The girl received intravenous metoprolol 2.5 mg 3 times at intervals of 5 min, resulting in a decline in heart rate and blood pressure, and subsequent resolution of electrocardiogram changes. Apart from this, no

further published experiences with paediatric use of intravenous metoprolol can be found. The tenuous data on paediatric use of intravenous metoprolol, its long half-life and its metabolism through CYP 2D6 makes its use in hypertensive emergencies at least questionable. Other drugs should be preferred in this indication.

Urapidil

Urapidil reduces blood pressure by decreasing vascular resistance, mainly due to its postsynaptic $alpha_1$-adrenoceptor antagonism. It inhibits the vasoconstrictive action of catecholamines and has an antagonistic effect on central 5-hydroxytryptamine $(5\text{-HT})_{1A}$-receptors. This explains the absence of a sympathetic nervous system response like reflex tachycardia. Urapidil has no effect on intracranial pressure. It acts in about 3–10 min. The hypotensive effect lasts for a minimum of 30 min up to 6 h. Urapidil has a half-life of about 5 h and undergoes an extensive hepatic metabolism. It does not affect lipid or glucose metabolism, nor does it impair renal function.

Despite the wide use of urapidil both in adults and children, the published facts about the paediatric use are extremely limited. Only one clinical trial concerning its use for the treatment of acute hypertensive crises in 19 infants and children can be found (Schöber et al. 1984). In all cases, a prompt decrease in systolic, mean and diastolic blood pressure was achieved within the first 15 min and the effect lasted throughout the whole time of continuous venous infusion of urapidil. The authors report a slow increase in serum potassium and a decrease in serum sodium being significant only after at least of 12 h of therapy. There was no change in heart rate and urine volume.

The wide use of urapidil especially in Germany seems to be based on its good tolerance and the experiences of the attending physicians. The long half-life of 5 h, and especially the scarce published data about the paediatric use still raises questions about its suitability. Without further publications about its controllability and safety in children no recommendation can be made.

Direct-Acting Vasodilators

Hydralazine is a direct vasodilator of arteriolar smooth muscle that decreases systemic blood pressure. It can be administered either as intravenous bolus or intramuscular injection. The mechanism of action is still unexplained, but consists most likely in an alteration of intracellular calcium metabolism, leading to an interference with the calcium movements within the vascular smooth muscle that are responsible for initiating or maintaining the contractility. Hydralazine has an onset of action that occurs within 5–30 min after intravenous administration. Hypotension can last for up to 12 h. The use of hydralazine is accompanied by potential side effects. It stimulates the central nervous system which causes reflex tachycardia and an increase in cardiac contractility. Besides others the activation of the renin-angiotensin-aldosteron system, sodium and water retention, elevation of intracranial pressure and drug-induced lupus erythematosus, vasculitis and glomerulonephritis has been reported.

The published data about the use of hydralazine in children is scant, most likely because the drug is used primarily in pregnant woman with preeclampsia. The extremely long half-life can result in an unpredictable effect on blood pressure, limiting its controllability. This fact and also the possibility of significant adverse effects make its use in critical ill children doubtful at any rate.

Diazoxide is another direct-acting vasodilator. It is not only used in the treatment of hypertension, but also in the treatment of hypoglycaemia. It acts by increasing the permeability of the vascular smooth muscle cell membrane to potassium ions. Diazoxide is structurally similar to thiazide diuretics but the drug possesses no diuretic properties. With multiple doses it is even more likely to increase plasma volume by sodium and water retention resulting from increased reabsorption at the proximal tubules. Diazoxide acts within 10 min after intravenous application and reaches its peak of hypotensive effect after approximately 30 min. As well as with hydralazine, reduction of blood pressure can maintain for up to 12 h.

Plasma half-life of diazoxide ranges within 20–30 h and is explained by extensive renal tubular reabsorption and high plasma protein binding of about 90%. In patients with renal impairment, an adjustment of doses is required. Severe adverse effects are related to the use of diazoxide (Table 9.2). Until now, the mechanism of the potentially occurring heart failure remains uncertain, but it may be caused by direct toxic effect on the myocardium. Thus far, no correlation between the dosage of diazoxide and the severity of fluid retention or heart failure has been proved.

Few clinical trials and case reports on the paediatric use of diazoxide in hypertensive emergencies have been published, because diazoxide is mainly used as a hypotensive agent in pregnant woman or in the treatment of hyperinsulinaemic hypoglycaemia.

Regarding to its long half-life, which limits its controllability, and the risk of the occurrence of potentially life-threatening adverse effects, the use of diazoxide in hypertensive emergencies can not be recommended.

Enalapril

The angiotensin-converting enzyme (ACE) inhibitor enalapril is a prodrug that is metabolized *in vivo* to the active form enalaprilat by various esterases. Enalaprilat produces vasodilation, and decreases vascular resistance. Excretion of enalaprilat is primarily renal. Therefore, renal impairment results in a significant accumulation of enalaprilat and necessitates dose reduction. Enalapril has a slow onset of action, which may limit its use during a hypertensive emergency. A hypotensive effect can be seen in 10–60 min after injection and lasts for up to 12 h. Apart from other adverse effects, especially in neonates enalapril may cause acute renal failure (Flynn and Tullus 2009). Some clinical trials and case reports on the paediatric use of enalapril can be found. In most of the publications patients were treated due to of chronic hypertension, without any sign of end-organ damage, resulting in the use of tablets or capsules of enalapril, rather than the use of the intravenous form. Therefore, the facts about the use of intravenous enalapril in hypertensive emergencies are limited. The paediatric use of enalapril in hypertensive emergencies can not be recommended, because the hypotensive effect is unpredictable and comparatively uncontrollable, especially in cases with a renal aetiology.

Clonidine

The lipid-soluble imidazolidine derivate clonidine is an alpha$_2$-adrenergic receptor agonist. It lowers blood pressure, and has also sedative properties. The exact mechanism of action of clonidine is complex and unexplained. It may act on the central nervous system by direct stimulation of the alpha neuronal adrenergic receptors, and another role may play endothelial-derived nitric oxide (NO). The sedative effects of clonidine may be explained by the stimulation of alpha$_2$-adrenergic receptors in the locus coerulens, by augmented release of gamma-aminobutyric acid (GABA), and by interaction with serotonergic and opioid receptor systems. Clonidine metabolism does not depend on hepatic function or the cytochrome P 450 enzyme system, and instead follows minor pathways. Approximately 50% of the intravenous administered clonidine is excreted unchanged in urine without prior metabolism.

Clonidine has an onset of action of about 5 min after injection, and about 15–30 min after oral application. The hypotensive effect can last for up to 8 h. Based on actual publications, no clear recommendation on dose of intravenous clonidine can be made. Some authors report no effect on blood pressure with doses between 0.2 and 2.0 μg/kg/h, while other report on doses between 0.625 and 1.25 μg/kg/h that are already able to induce a reduction in blood pressure. So far, a plasma concentration dependent blood pressure effect has not been proven. 18–36 h after discontinuation of oral, intravenous, and transdermal use of clonidine signs of sympathetic hyperactivity may occur which may lead to withdrawal effects, including tachycardia, tremors, sweating, and rebound hypertension. The sudden withdrawal of the drug can result in severe

Table 9.2 Recommended paediatric doses of the drugs used in hypertensive emergencies (Modified from Horn et al. 2011)

Drug	Recommended paediatric dose	Need for dosage adjustment
Sodium nitroprusside	Starting dose 0.3–0.5 μg/kg/min	Renal failure: (+)
	Can be titrated up to 8–10 μg/kg/min	Hepatic insufficiency: (+)
		During dialysis: (–)
Labetalol hydrochloride	Bolus dose 0.2–1.0 mg/kg/dose (with a maximum of 40 mg/dose)	Renal failure: (–)
	Followed by continuous infusion of 0.25–4.0 mg/kg/h	Hepatic insufficiency: (+)
		During dialysis: (–)
Esmolol	Loading dose of 500–700 μg/kg/min over 1 min	Renal failure: (–)
	Maintenance dose of 20–1,000 μg/kg/min	Hepatic insufficiency: (–)
		During dialysis: (–)
Metoprolol	Bolus 0.1 mg/kg (maximum dose of 5.0 mg) administered up to 3 times at 5 min intervals	Renal failure: (–)
	Followed by a continuous infusion of 1–5 μg/kg/min	Hepatic insufficiency: (+)
		During dialysis: (–)
Urapidil	Starting dose of 1–14 mg/kg/h (2 mg/kg/h in children up to 6 years of age)	Renal failure: (+)
	Can be reduced to maintenance dose of 0.2–3.3 mg/kg/h (1 mg/kg/h in children up to 6 years of age)	Hepatic insufficiency: (+)
		During dialysis: no information
Hydralazine	0.1–0.2 mg/kg/dose (with a maximum of 20 mg/dose) every 4–6 h	Renal failure: (+)
		Hepatic insufficiency: (–)
		During dialysis: (–)
Diazoxide	1–3 mg/kg/dose (with a maximum of 150 mg/dose), repeated at intervals of 5–10 min	Renal failure: (+)
		Hepatic insufficiency: (–)
		During dialysis: (–)
Enalapril	5–10 μg/kg/dose every 8–24 h (with a maximum of 1.25 mg/day)	Renal failure: (+) (p.o.)
		Hepatic insufficiency: (+)
		During dialysis: (+)
Clonidine	1–2 μg/kg every 6 h (with a maximum of 0.8 mg/day) (p.o.)	Renal failure: (–)
		Hepatic insufficiency: (–)
	0.2–2.0 μg/kg/h (i.v.)	During dialysis: (–)
Fenoldopam	0.2–0.8 μg/kg/min	Renal failure: (–)
		Hepatic insufficiency: (–)
		During dialysis: (–)
Nifedipine	0.1–0.6 mg/kg (with a maximum of 20 mg/dose) every 4–6 h (p.o.)	Renal failure: (–)
		Hepatic insufficiency: (+)
	0.2–1.0 μg/kg/min (i.v.)	During dialysis: (–)
Nicardipine	0.5–5.0 μg/kg/min	Renal failure: (+)
		Hepatic insufficiency: (+)
		During dialysis: (–)
Clevidipine	Starting dose of 0.5–1 μg/kg/min	Renal failure: no information
	Followed by continuous infusion of 0.5–3 μg/kg/min (Towe and Tobias 2010)	Hepatic insufficiency: no information During dialysis: no information

rebound hypertension. It has to be reduced gradually. The concomitant use of a beta-blocker can increase the susceptibility of withdrawal effects and should be avoided.

The few publications about the use of intravenous clonidine for the treatment of hypertensive emergencies report its use only in adults. Attributable to its relative long half-life, and its unclear Pk/PD relationship, the hypotensive effect of clonidine is unpredictable and entails the risk of unnecessary overdoses.

Fenoldopam

A newer agent is the vasodilator and selective dopamine$_1$ receptor agonist fenoldopam. It is a dopamine D_1-like receptor agonist that also binds to α_2-adrenoceptors, but not to other vascular receptor. It lowers peripheral vascular resistance and has no direct effect on cardiac contractility, but cardiac output may increase because of a decrease in afterload. Fenoldopam increases renal blood flow and urinary flow and induces natriuresis. The drug causes no significant change in glomerular filtration rate. It undergoes a fast and extensive metabolism by the liver, independent of the cytochrome P450 enzymes. The nontoxic metabolites are mainly excreted in the urine and partially in the feces. The hypotensive effect occurs within 5 min after intravenous application, and can last for up to 60 min. It has an elimination half-life of approximately 10 min. After continuous infusion of fenoldopam for greater than 48 h, tolerance can occur which may lead to a reduced effectiveness. Compared to the potency in adults, fenoldopam showed a relatively poor efficacy in children. Fenoldopam can cause a dose-dependent increases in intraocular pressure. It should be avoided in patients at risk for intraocular and intracranial hypertension. The intravenous application form of fenoldopam contains sodium metabisulfate that may cause acute allergic reactions in patients with potential sulfite sensitivity.

Published experience about its use in children is limited. By now, there is only one published clinical trial and few case reports. Hammer et al. (2008) reported on 77 children aged 1 month to 12 years of age undergoing surgical procedures requiring controlled hypotension. The authors noticed that fenoldopam at doses 0.8–1.2 μg/kg/min is able to reduce blood pressure significantly, and doses between 1.0 and 1.2 μg/kg/min resulted in continued control of blood pressure. Furthermore, it is noteworthy that the effective dose range was significantly higher in children undergoing anaesthesia and surgery than labelled in adults, while pharmacokinetic and side effect profiles were similar in children and adults.

The short elimination half-life makes fenoldopam good controllable, but concerning its efficacy in children there are still some open questions. And the determining disadvantage of fenoldopam may be the appearance of a tolerance after infusions for a period of longer than 48 h, because in some cases of hypertensive emergencies continuous infusions over days are necessary to control blood pressure. Fenoldopam may be a promising alternative to other drugs for short-term therapy. Based on actual publications a recommendation can not be made. Additional experiences on its use in children are warranted.

Calcium Channel Blockers

Calcium channel blockers (CCB) primarily cause dilatation of the afferent arteriole in the glomerulus, and also have a small effect on the efferent arteriole. As a result, the glomerular filtration rate (GFR), and the renal blood flow increases. Due to the decrease of renal vascular resistance, the excretion of sodium and water is increased. Hereby the renal perfusion and function are maintained. In addition to their hemodynamic effects CCB may be able to suppress mesangial cell proliferation and attenuate mesangial entrapment of macromolecules. They may modulate gene transcriptions involved in proinflammatory changes (Cuschieri et al. 2002). They may also have a moderate antiproteinuric effect during profound blood pressure decreases (Kloke et al. 1998).

CCB are metabolized in the liver by the cytochrome P450 3A4, and could affect the clearance

of drugs like cyclosporine or tacrolimus, which also share this system for their metabolism.

A protective effect of CCB on graft survival in renal transplant patients treated with cyclosporine or tacrolimus has been suggested by some authors. For example, Harper et al. (1996) reported a significant improvement of initial graft function, rejection frequency and long term graft survival in 147 patients using the combination of oral nifedipine and cyclosporine. Nifedipine may minimise vasoconstrictive cyclosporine nephrotoxicity, allowing a higher maintenance dose of cyclosporine to be used, and reducing the incidence of rejection. On the one hand, Feehally et al. (1987) reported a better renal function in renal transplant patients receiving nifedipine compared with hypertensive patients receiving other hypotensive agents, but on the other hand they found a shorter mean graft survival in those patients treated with nifedipine. They suggested that nifedipine may have a potential value as a cyclosporine nephroprotective agent. No author was able to clarify the exact mechanism of this possible protective effect. Further, it appears to be independent to blood pressure lowering. Other publications did not confirm the beneficial influence of CCB on graft function or survival.

Nifedipine is a first-generation dihydropyridine calcium channel blocker that is indicated for the use in adults with vasospastic and chronic stable angina. In addition it is widely used for the treatment of hypertensive emergencies both in adults and in children. Nifedipine is a potent vasodilator that produces reflex sympathetic stimulation of the heart with an increase in heart rate and cardiac output. It may have a more powerful effect on diastolic than on systolic pressure. Like other CCB's, nifedipine undergoes an extensive hepatic metabolism via the cytochrome P450 3A4 enzyme system, but it appears not to interact with cyclosporine and tacrolimus. Nevertheless rises and falls in drug levels have been seen in some patients. All metabolites are inactive and excreted in the urine within the first 24 h. In addition, to other adverse effects (Table 9.2), the combination of cyclosporine and nifedipine may increase the incidence as well as the severity of gingival overgrowth. Nifedipine can be administered orally (short-acting-nifedipine) or intravenously.

Short-acting nifedipine acts within 5–10 min following oral administration. The peak effect occurs within 30–60 min and can last for up to 8 h. In adults, short-acting nifedipine has been associated with cases of stroke, an increased risk of myocardial infarction, cerebrovascular ischemia, syncope, conduction disturbances, fetal distress, and death. This has lead to a wide abandonment of the use in hypertensive emergencies in adults. Some authors still advocate short-acting nifedipine as a safe agent for use in children with severe hypertension. As an explanation, it is mentioned that the frequency of severe adverse events may be greater in adults because severe hypertension in adults may be associated with a higher incidence of generalized cardiovascular disease. Until now, a common reason for the severe adverse events in adults has not been found. Strong short-term drops in blood pressure followed by increased levels may have a negative impact on the cardiovascular system. Castaneda et al. (2005) noted that the high concentration of nifedipine in the available preparations for oral administration make it difficult to accurately apply small doses of nifedipine. This may increase the risk of incorrect dosage. Consequently, rapid drop in blood pressure could be greater than desired. As a result of this unpredictable magnitude of the antihypertensive effect the risk of severe adverse effects can also increase and may produce end-organ damage from hypoperfusion. They suggested that it may be more appropriate to treat hypertensive emergencies with intravenous agents that can be titrated for a better control of reduction in blood pressure. Flynn (2003) also noted that short-acting nifedipine may be safe in some hypertensive children, but alternative agents that produce more controlled reductions in blood pressure, and that are easier to administer and accurately dose, should probably be chosen for the majority of children with severe hypertension.

Especially in Germany, a continuous infusion of nifedipine is still used in the treatment of hypertensive emergencies both in adults and in children. This may derive from the fact that the

intravenous application of nifedipine acts within 1 min and may compensate the difficulties of accurate dosage. Because of its insolubility in water, the available preparations for intravenous nifedipine contain 18% [V/V] ethanol which implies an additional and above all a preventable risk for critically ill children (Horn et al. 2011). This is aggravated by absolutely no published original data concerning the suitability and safety of intravenous nifedipine in children.

The hypotensive effect of orally applied short-acting nifedipine is unpredictable which is based on the inexactness of dosage. This could be amended with an intravenous application and perhaps the experience of the attending physicians outweigh the missing published experiences about its paediatric use, but the serious adverse effects observed in adults still raise the suspicion about its suitability in critically ill children. The use of nifedipine should be more scrutinized because there may be alternative drugs with a better safety profile.

Nicardipine is a second-generation dihydropyridine calcium channel antagonist. It is structurally related to nifedipine but it differs from nifedipine by having a tertiary amine structure added to the ester side chain at position three of the hydropyridine ring and a nitro group moved to the meta position of the phenyl ring. Therefore, nicardipine is about 100 times more water soluble and more stable towards light than nifedipine (Curran et al. 2006). Compared to nifedipine, nicardipine has a higher selectivity for L-type calcium channels in vascular smooth muscle than in cardiac myocytes and possesses a strong cerebral and coronary vasodilatory activity. Nicardipine has minimal inotropic cardiac effects and shows no significant venodilatory action. Its hypotensive effect appears to be greater in hypertensive patients than in healthy normotensive volunteers (Curran et al. 2006). Nicardipine is primarily metabolized in the liver through the cytochrome P450 enzyme system. Oxidation is mainly mediated by human CYP3A4, CYP2C8, and CYP2D6. Thus nicardipine can be a relatively potent competitive inhibitor of these CYP enzymes. Nicardipine can cause a higher increase in cyclosporine and tacrolimus blood levels than nifedipine, and raises the risks for toxicity. Hooper et al. (2011) reported on the interaction between tacrolimus and intravenous nicardipine in the treatment of post-kidney transplant in two cases and in an analysis of 2,068 kidney transplantations. Adverse effects of tacrolimus were threefold more likely in paediatric patients treated with intravenous nicardipine than in those treated with other continuous intravenous antihypertensive drugs. A close monitoring of cylclosporine and tacrolimus blood levels is recommended to avoid overdose and toxicity. Nicardipine may also interact with many clinically used drugs reported as a specific substrate for CYP2D6. Despite the fact that it is principally metabolized by the liver, a lower clearance has been reported in patients with renal impairment.

Nicardipine has a rapid onset of action. The hypotensive effect occurs within 1 min after application and can last for up to 3 h. In addition to its side effects, nicardipine is able to produce a statistically significant increase in intracranial pressure and should be used with caution in patients with space-occupying brain lesions. An abrupt withdrawal of the drug may cause rebound angina and hypertension.

The use of intravenous nicardipine in severe hypertension in adults is based on a wide range of publications, but there are only some case reports and small clinical trials about the use of nicardipine in the treatment of hypertensive emergencies in children (Horn et al. 2011). In these publications the number of reported cases is low and the clinical trials have either a small number of patients or they are retrospective. Treluyer et al. (1993) reported about the use of intravenous nicardipine in 14 children with severe hypertension. In all patients, nicardipine was effective and save. No side effects were seen with the mean cardiac frequencies not varying significantly. Gouyon et al. (1997) came to similar results. They reported about the use of intravenous nicardipine in eight hypertensive preterm infants. In all cases nicardipine was effective without hypotension or other clinical side effects. Levene et al. (1990) reported on their experience with intravenous nicardipine in four severely asphyxiated fullterm infants at high risk for adverse outcome

and had abnormal cerebral Doppler haemodynamic studies. In all patients, the heart rate increased. In two infants, they noticed a sudden and marked fall in mean arterial blood pressure (MAP), together with severe impairment of skin blood-flow and a concurrent fall in cerebral blood-flow velocity. In these cases of collapse, the serum levels of nicardipine were ≤40 ng/ml, so apparently this reaction was not due to toxic levels. The authors supposed that it may be possible that a negative inotropic effect together with peripheral vasodilatation, have caused sudden failure of peripheral blood-flow, and underlined that infants suffering from severe birth asphyxia may have compromised myocardial function, which may be an additional factor in the acute failure of cardiac output in the presence of drug-induced vasodilatation. In their opinion, the use of nicardipine, and possibly other calcium channel antagonists, in asphyxiated newborn infants should be only attempted if blood pressure is carefully monitored. Milou et al. (2000) reported on the use of intravenous nicardipine in 20 neonates (15 preterm) with systemic hypertension. In all patients the systolic blood pressure significantly decreased after 3–48 h of nicardipine treatment. They noticed no hypotension. Heart rate, water urinary excretion and plasma levels of sodium, potassium, urea and creatinine did not vary significantly through the first 2 days of treatment. Other clinical side effects like edema, flushing or seizures were not observed. Flynn et al. (2001) reviewed retrospectively the medical records of 29 children with hypertensive emergencies treated with intravenous nicardipine. In all patients nicardipine effectively lowered blood pressure. Only a small number of adverse effects were seen during the treatment (including tachycardia, flushing, palpitations, and hypotension), most of them were relatively minimal and had no adverse impact on the patients 'clinical status'. They also turned out that smaller patients required higher doses of nicardipine on a per-kilogram body weight basis than larger ones. An additional antihypertensive effect has not been seen above 4 μg/kg/min. In their opinion nicardipine appeared to be a safe and effective agent for the management of severe hypertension.

There are also some retrospective clinical trials and case reports about the use of nicardipine for controlled hypotension during some surgical interventions. In all reported circumstances nicardipine was effective for the control of perioperative hypotension, and the given dosages between 1 and 10 μg/kg/min were also well tolerated. The noticed side effects (including limited increase of heart rate, prolonged duration of action, and hypotension) had no outcome on the patients' clinical courses.

Clevidipine is an ultrashort-acting dihydropyridine calcium channel antagonist for intravenous control of blood pressure. It possesses selectivity for arteriolar dilatation without changing heart rate, central venous pressure, pulmonary artery occlusion pressure or cardiac index even with increasing doses. The volume of distribution is small, the clearance is high, and because of the additional ester link of the structure, there is a rapid hydrolysis by esterases in arterial blood and extravascular tissues to inactive metabolites. Clevidipine has an onset of effect within 2–3 min after continuous infusion. The possibility of a quick hydrolysis of the ester link results in an extremely short half life of approximately 1 min.

The pharmacokinetics of clevidipine may be similar to those of sodium nitroprusside. A comparative study of clevidipine and sodium nitroprusside in adults following coronary artery bypass has shown no significant difference between these two agents in controlling the mean arterial pressure (Powroznyk et al. 2003). The only difference found by the authors was the haemodynamic changes including tachycardia that were less pronounced with clevidipine than with sodium nitroprusside. Aronson et al. (2008) found a significantly higher ($p=0.004$) mortality for sodium nitroprusside-treated patients compared to clevidipine-treated patients. The potential of clinically significant drug-drug interactions of clevidipine or its metabolites via induction and inhibitation of cytochrome P450 is small. Clevidipine and its major metabolite H152/81 have shown a moderate induction of CYP 3A4, but only at concentrations that greatly exceed anticipated therapeutic levels. Beyond that, both clevidipine and H152/81, moderately decrease CYP 2C9 activity (Zhang et al. 2006).

Almost all published studies and case reports are dealing with its use only in adults. Until today, just one retrospective review by Towe and Tobias (2010) concerns the use of clevidipine in ten paediatric patients. The described indications were the control of perioperative hypertension, to provide controlled hypotension during orthopedic surgical procedures, and in one patient to improve distal perfusion during a toe-to-finger implant. The target blood pressure was achieved between 5 and 10 min in all patients, two patients required intermittent doses of metoprolol to control reflex tachycardia. They noted no adverse effects such as excessive hypotension. In three patients receiving clevidipine with propofol the triglyceride levels were obtained.

The fast onset of action, and the short half-life are suitable attributes of clevidipine making it a promising drug for the management of hypertensive emergencies. It appears that it also has a low drug-drug interaction potential, and a good safety profile. For a better evaluation of this promising new agent, further studies about the potential and safety of this agent especially in the management of hypertensive emergencies, and about its use in children are desirable.

In conclusion, all drugs used in hypertensive emergencies have their assets and drawbacks. And all of them may cause serious adverse effects, which are able to further deteriorate the critical state of the paediatric patient. Not surprisingly, the published facts about paediatric use of all drugs are scare and often based on case reports and small, mainly retrospective, clinical trials. In a few of them no data at all on their paediatric use can be found. Corresponding guidelines are lacking. This is aggravated by the fact that the underlying cases regularly have a different clinical history and can barely be compared with one another. In all-probability this unsatisfactory status will remain unchanged in the foreseeable future. And it should not to be forgotten that the experience of the attending physicians is of particular importance in choosing the right drug for the actual situation. For this reason, an evidence-based recommendation can not be made. Hypertensive emergencies in children after stem cell transplantation usually have a renal etiology and for the stated reasons, the calcium channel blocker nicardipine appears to be the drug of first choice. Clevidipine may play a major role in the future, because of its promising pharmacokinetic and safety profile, but there is the need for further studies concerning its use in children. It is essential for the attending paediatrician to evaluate the properties, side effects, possible drug-drug interactions, the barely adequate published data and the personal experiences with the drugs already in the forefront of a hypertensive emergency.

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