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Which inotrope?

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Summary A variety of inotropes are used to support the failing heart and improve arterial pressure. There is debate over the competing merits of the various agents available and a lack of good evidence on which to base clinical practice, particularly in paediatrics. Studies comparing the various agents have usually been performed on a small number of patients, and some have produced contradictory results. Recommendations are made based on the best evidence available and on the beliefs and personal experience of the authors.

PRACTICE POINTS

- 'Low-dose' dopamine is ineffective in the treatment or prevention of renal failure and is potentially harmful
- Adrenergic receptor downregulation may cause a poor response to exogenous catecholamines
- The administration of glucagon or steroids may help to restore responsiveness to catecholamines when acute tolerance has occurred
- Adrenaline has a favourable spectrum of activity and is the cheapest and also the most effective inotrope available
- Phosphodiesterase inhibitors act synergistically with adrenaline

INTRODUCTION

Inotropes are drugs that alter myocardial contractility, the term is usually reserved for those drugs which improve contractility. Inotropic drugs are used to increase blood pressure and cardiac output. Cardiac output is determined by the interactions between heart rate, preload, afterload and contractility; the manipulation of all these variables is necessary to optimize cardiac function in the sick infant.

It is difficult to measure the contractile state of the myocardium directly so the effects of inotropic drugs are usually monitored by their effect on blood pressure and on indirect measures of cardiac output such as urinary output and metabolic status. All of the commonly used inotropic drugs have effects not just on myocardial contractility, but also on vascular resistance and to some extent on preload. It is often difficult to distinguish the actions of inotropes in supporting the heart from those affecting the peripheral circulation.

The use of inotropic drugs in paediatric clinical practice is determined mainly by personal preference and prejudice, and is a subject of controversy. There are few randomized, blinded, controlled studies of inotropic drugs in adults, and even fewer have been performed in infants and children. In any event, information from studies involving adults cannot necessarily be applied to infants because of the marked differences in cardiovascular physiology and pathophysiology. The few randomized controlled studies that exist have mostly been performed on premature babies with hypotension and in infants and children during and after cardiac surgery. In addition, there are of course animal studies, but their applicability to the immature human is uncertain. Experimental results obtained from animals or normal humans may not be relevant in the septic state or in patients with congenital or acquired heart disease.

This article aims briefly to review the commonly used drugs and their pharmacological actions and to suggest a therapeutic approach based partly on the evidence available and mostly on the beliefs and personal experience of the authors.

Indications for the use of inotropic drugs

Inotropic drugs are indicated for:

1. *Hypotension*, i.e. inadequate vital organ perfusion pressure.
2. *Acute heart failure*. Inotropic drugs are harmful in chronic heart failure; afterload reduction is the only

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approach to have consistently shown benefit. This implies that inotropes should be used for the shortest possible time in acute heart failure.

3. *Impaired vascular tone*. A variety of conditions exist in which there is a failure of the peripheral vascular tone with or without myocardial depression, for example septic shock.

PHARMACOLOGY OF INOTROPIC DRUGS

Inotropes can be divided into two main classes: those acting via cyclic adenine monophosphate (cAMP) and those which are cAMP independent. The first group includes adrenergic agonists, dopaminergic agonists, cyclic nucleotide phosphodiesterase (PDE III) inhibitors, thyroid hormone and glucagon. These drugs produce their clinical effects either by stimulating cAMP production (adrenergic agonists) or by inhibiting cAMP degradation (PDE III inhibitors). The cAMP-independent drugs are digoxin and calcium salts.

cAMP-dependent drugs

Beta-adrenergic receptor agonists

Comparisons of adrenergic agonists traditionally depict the relative affinity that these agents have for each receptor (alpha, beta, dopaminergic, etc). These comparisons are, however, misleading since there are three subtypes of alpha-1 and alpha-2 receptors and two types of dopaminergic receptors. It is probably better to look at a simple division of drugs into those which are predominantly beta-agonists (isoprenaline, dobutamine and dopexamine), those which have mixed alpha and beta effects (adrenaline, noradrenaline and dopamine) and those with pure alpha effects (phenylephrine). Only by comparing the drugs when they are administered to patients is it possible to determine which agent most efficiently improves cardiac function with the fewest side-effects.

Dopamine

Dopamine, a naturally occurring endogenous catecholamine, has complex cardiovascular effects: inotropy is largely caused by an indirect action whereby dopamine causes noradrenaline release from the cardiac sympathetic nerves. Reduced myocardial noradrenaline stores in neonates may be a cause of relative dopamine resistance in this age group. Dopamine has traditionally been perceived as a drug with varying effects according to dosage. This view is simplistic since the plasma dopamine concentration varies widely between individuals. In children under the age of 2 years, dopamine clearance appears to be double that of adults. In critically ill adults and in children with renal and hepatic failure, clearance is reduced, so that the plasma concentrations resulting from infusion may be impossible to predict.[1]

At low doses, dopaminergic effects are held to predominate. Doses of 5–10 $\mu g/kg\ min^{-1}$ are said to produce beta-1 receptor agonist effects, with further increases causing alpha effects, which are said to predominate at doses of more than 20 $\mu g/kg\ min^{-1}$. Even at doses of less than 3 $\mu g/kg\ min^{-1}$, dopamine has, however, substantial systemic haemodynamic effects. It has also traditionally been viewed, at least at low doses, as a drug devoid of harmful effects. Again, this is untrue; among its undesirable effects are a reduction in growth hormone secretion and thyrotropin release, decreased T-cell function, thus potentially impairing resistance to infection, reduced splanchnic perfusion, a depression of respiratory drive, increased intrapulmonary shunting, increased pulmonary vascular resistance and arrhythmogenesis.[2,3]

The longstanding and widespread use of low-dose dopamine (less than 5 $\mu g/kg\ min^{-1}$) for improving renal function and urinary volume in critically ill patients has been discredited in adults in a high-quality, multicentre, randomized, double-blind placebo-controlled trial.[4] This study demonstrated that low doses of dopamine had no effects on serum creatinine level, the need for renal replacement therapy, the duration of intensive care stay or mortality in critically ill patients. Evidence to support its use either as a reno-protective agent or as a therapeutic intervention for the attenuation of acute renal failure in critically ill neonates and children is also non-existent,[5] and this use should be abandoned.[6]

Dopamine is (despite the lack of consensus among neonatologists on the acceptable lower limit for systemic blood pressure) commonly used in preterm infants to treat systemic hypotension.[7] Evidence that the use of sympathetic amines improves outcome in hypotensive neonates is generally lacking, and there is a need for well-designed randomized clinical trials. It is generally accepted that the vasoconstrictor and inotropic effects of dopamine predominate in the newborn period. The optimal dose of dopamine is uncertain, some studies suggesting the need for high doses (more than 10 $\mu g/kg\ min^{-1}$), others proposing that lower doses may be effective. The dopamine clearance rate may be decreased in sick preterm infants so that the beneficial effects of low-dose dopamine in these patients may be related to decreased drug metabolism and excretion.

When using dopamine, it seems reasonable to start treatment at a low dose and assess the response, the necessary dose being that required to achieve the desired effect without excessive side-effects. A meta-analysis of the results of randomized, blinded comparative studies with dobutamine concluded that dopamine was more effective than dobutamine for the short-term treatment of hypotension in preterm infants, although there are no

data confirming the long-term benefit and safety of dopamine.[8] It is not clear from these studies whether the primary effect of dopamine in these circumstances is as an inotrope improving poor myocardial contractility, as a vasoconstrictor increasing low systemic vascular resistance or as a combination of the two.

Dobutamine

Dobutamine is a synthetic catecholamine with a structure similar to that of isoprenaline. It has no dopaminergic effects and does not stimulate the release of endogenous catecholamines. Dobutamine has been in use for about 20 years, and studies have compared its action with dopamine.[8,9] It has a theoretically attractive spectrum of actions but in clinical practice causes tachycardia even in modest doses. In animal studies, prolonged infusions of dobutamine significantly reduce the systemic to pulmonary arterial pressure ratio—a potentially undesirable effect in the critically ill neonate.[10] In septic shock, dobutamine frequently fails to meet the goal of adequate perfusion pressure, which is not surprising in view of its miniscule alpha-agonist effect and predominant vasodilatory properties.

Dopexamine

Dopexamine is a newer synthetic catecholamine. When compared with dobutamine in adult patients with heart failure, the two agents produced similar effects on heart rate, stroke volume and mean arterial pressure. However, the majority of patients receiving dopexamine developed sustained tachycardia, necessitating treatment with esmolol, despite reduction of the drug dose to minimal levels. Dopexamine would appear to have a similar profile to that of dobutamine with no evident advantage. Its use in paediatrics cannot currently be recommended.

Adrenaline

Adrenaline (epinephrine) is the catecholamine released from the adrenal medulla in times of stress and has complex effects. When used in low doses, it increases myocardial contractility, and heightens muscle blood flow through its beta-1 and beta-2 effects, without vasoconstriction. At higher doses, it continues to stimulate the myocardium, but alpha effects in the peripheral vascular system cause the afterload to increase. Adrenaline-induced improvements in cardiac output may, however, increase renal and splanchnic blood flow despite the vasoconstrictor effects. The development of tachycardia and dysrhythmias may limit the usefulness of adrenaline as an inotrope at high doses, although the incidence of dysrhythmias is less with adrenaline than with high-dose dobutamine, dopamine or dopexamine. Adrenaline is frequently used to improve blood pressure and cardiac output in patients who are unresponsive to dopamine.

There appear to be no studies comparing its use with that of other inotropes in premature infants, and few in adults. Animal studies suggest that adrenaline is more effective than dopamine at increasing cardiac output and that dopamine produces preferential pulmonary vasoconstriction, decreasing the ratio of systemic arterial pressure to pulmonary artery pressure.[11] In adults recovering from aortocoronary bypass surgery, adrenaline (10 and 30 ng/kg min^{-1}) produced increases in stroke volume comparable to those seen with dobutamine (2.5 and 5 μg/kg min^{-1}) but with a lower increase in heart rate.[12]

Adrenaline has the advantage of being by far the cheapest inotrope available and is the drug of choice in acute resuscitation from cardiac arrest. It is commonly used when dopamine has failed to produce an adequate response, but it is hard to understand the enthusiasm for other drugs, especially dopamine, over adrenaline. It is surprising that adrenaline is not used more frequently outside the acute resuscitative situation and it is, in our view, the catecholamine of choice.

Noradrenaline

Noradrenaline (norepinephrine) is the principal chemical transmitter released from the peripheral adrenergic nerve endings. Its vasoconstrictor (alpha) effects predominate, although it also has direct actions on cardiac beta-receptors. Because it causes profound vasoconstriction, it may be expected to increase myocardial workload and oxygen demand in proportion to the elevation in afterload, and it may even precipitate left ventricular failure. Noradrenaline tends to be used infrequently because of its renal vasoconstrictor effect. Its vasoconstrictor effects may, however, be used to advantage when hypotension is caused mainly by profound vasodilatation, for example in sepsis when hypotension fails to respond to appropriate fluid loading.

Isoprenaline

Isoprenaline has only beta-1 and beta-2 agonist effects, although the beta-2 effects predominate. In practice, this means that it is very effective in increasing the heart rate and lowering the systemic and pulmonary vascular resistance, but it is poorly inotropic. The pulse pressure widens because of an increase in systolic pressure and a decrease in diastolic pressure, but the overall mean arterial pressure may fall. Isoprenaline may be useful for increasing the ventricular rate in heart block and may be used in the treatment of pulmonary hypertension, although the decrease in systemic pressure may limit its use in these conditions.

Beta–adrenergic downregulation

The number and affinity of cell surface receptors appear to be subject to both acute and chronic change. Adrenergic receptor density is significantly affected by physiological catecholamine levels and by clinical status. Chronic heart failure and ventricular dysfunction are associated with a downregulation of beta-1 adrenergic receptor density, probably because of chronic hyperstimulation by endogenous noradrenaline. Downregulation is in most cases predominantly beta-1 subtype selective, but in critically ill infants there is additional significant beta-2 subtype downregulation. In animal myocardium, chronic hypoxia also leads to beta receptor downregulation,[13,14] which implies a potential problem in the use of adrenergic agonists in children with cyanotic congenital heart disease.

Acute changes in beta receptor density have been detected following cardiac surgery and cardiopulmonary bypass. This phenomenon may render patients refractory to infused catecholamines and lead to difficulties in clinical management. There is emerging evidence that the use of corticosteroids may help to restore beta receptor density and decrease the need for pressor support in critically ill newborns with pressor-resistant hypotension.[15] The long-term use of beta-blockers may help to reduce receptor downregulation in chronic heart failure.

Inhibitors of cAMP degradation

PDE III inhibitors are non-glycosidic, non-sympathomimetic agents that produce both positive inotropic effects and vasodilatation by inhibiting cAMP degradation. It is thought that the PDE III inhibitors compete with the phosphate function of cAMP for binding to the esteratic site of PDE III, thereby causing a competitive inhibition of this enzyme and an accumulation of cAMP, and thus increasing the intracellular calcium level. These drugs have the ability to augment beta-adrenergic stimulation at a level beyond the beta receptor, potentiating the action of catecholamines. All of these drugs are pulmonary and systemic vasodilators. Because of their attractive mode of action and pharmacological profile, many PDE III inhibitors with a variety of dissimilar structures have been synthesized.

Amrinone

Amrinone, the first PDE III inhibitor to be used clinically, acts mainly as a vasodilator. The ratio of the inotropic action to the vasodilatation produced is 1:30. When compared with adrenaline, amrinone causes a similar increase in cardiac output but is, not surprisingly, less effective than adrenaline in raising the mean arterial pressure.[16] When the two drugs are combined, they have a greater effect on cardiac output than either drug alone. Thrombocytopenia has, however, been reported to be a problem in up to 1 in 40 of the patients treated.

Limited studies of the pharmacokinetics of amrinone in infants and children indicate a dramatically larger volume of distribution and a decreased elimination half-life compared with the values seen in adults.

Enoximone

Enoximone was the next PDE III to become available in the UK but has few, if any, advantages over amrinone. It needs refrigeration, has a bright green colour and has largely been supplanted by milrinone.

Milrinone

Milrinone is the most recently available PDE III inhibitor and has some advantages over its predecessors. Like its less potent forerunner, amrinone, it is a pyridinone derivative. It can be stored at room temperature, is easy to administer and appears to have haemodynamic effects very similar to those of other PDE III inhibitors. Milrinone has been shown to be especially useful in patients with a mild depression of cardiac systolic function. The half-life is such that a single dose, when given to cardiac surgical patients on bypass, will produce an inotropic action that lasts for several hours post-operatively.

Many case reports and series support the idea that milrinone, especially in combination with catecholamines, is effective in the management of low cardiac output. Good, reliable, double-blind, randomized studies with other inotropic agents have yet to be published. Milrinone currently appears to be the PDE III inhibitor of choice for moderate left ventricular dysfunction and may reduce the dose requirement of adrenaline.

Thyroid hormone

Thyroid hormone has been used for many years as an inotropic agent and certainly has a role to play in the hypothyroid patient. After cardiac surgery, transient reductions in thyroid hormone level and impaired cardiac function resemble the endocrine and cardiovascular alterations that are associated with hypothyroidism. A randomized, double-blind trial in children who had undergone cardiac surgery found that tri-iodothyronine improved myocardial function, especially in those with a low cardiac output following a prolonged operations.[17] In adults after coronary artery surgery, the infusion of tri-iodothyronine increases the cardiac index and lowers the systemic vascular resistance but can induce severe myocardial ischaemia. It is used in hormone replacement therapy in donor heart preparations prior to transplantation, but its place in the management of patients with poor ventricular function is uncertain.

Glucagon

Glucagon activates protein kinase, which acts via the same pathway as adrenaline. When adrenergic receptors are downregulated, glucagon receptors may still be intact; in such circumstances, glucagon injection may improve the response to adrenaline. On its own, however, it is not effective as an inotrope for more than a few minutes.

cAMP-independent drugs

Digoxin

Digoxin slows atrioventricular conduction and is a mild inotrope. Unlike catecholamines, digoxin has an important role to play in the treatment of chronic heart failure, even for patients in sinus rhythm. Its role in acute heart failure is, however, limited. The pharmacokinetics of digoxin have been extensively studied in infants and children; children beyond the neonatal period have increased digoxin clearance.

Calcium salts

Numerous studies of isolated heart muscle have shown that increasing the concentration of extracellular calcium ions leads to an increase in myocardial contractility. In vivo studies comparing calcium chloride with placebo have shown an increase in mean arterial blood pressure but no increase in cardiac index with calcium chloride. Calcium chloride may also blunt the response to adrenaline and dobutamine in some patients and in experimental animals. Hypocalcaemia is common in infants and young children, and in these circumstances, calcium salts may act as an inotrope. When the ionized calcium level is normal, in vivo studies show, however, that the major effect of intravenous calcium salts is an increase in vascular resistance and blood pressure with no increase in cardiac output. This increase is transitory as any calcium administered rapidly equilibrates with bone.

In conclusion, small doses of calcium chloride may be useful to increase the systemic vascular resistance or to treat hypocalcaemia, but this agent is not recommended as an inotrope.

Alpha-adrenergic agonists

There is no evidence that this group of drugs has any inotropic activity, but they may usefully increase vascular resistance.

CONCLUSIONS

The use of inotropes in paediatrics has been based largely on experience in adults, but children are not, in physiological terms, small adults, and their response to drugs may be quite different. Animal and human studies have demonstrated developmental changes in sympathetic innervation, receptor density and responsiveness that may affect the reaction to inotropic drugs.

There is no current ideal inotropic drug. Both beta-adrenergic agonists and PDE III inhibitors have advantages and disadvantages related to their pharmacology, method of administration and cost. New classes of inotrope that work via different mechanisms may emerge in the future; agents that could reduce the damaging overexpression of nitric oxide synthase in the systemic circulation might, for example, be helpful in the treatment of septic shock.

In our opinion, adrenaline should be the first-line inotrope of choice. It is the drug of choice in cardiac arrest and has been shown to provide inotropy with the fewest side-effects. There is no evidence that dopamine or dobutamine is, in any way, superior to adrenaline, and both are certainly more expensive and less potent. In patients with moderate-to-poor ventricular function in which afterload reduction is beneficial, the combination of milrinone and adrenaline is attractive. Noradrenaline may be indicated if systemic vascular resistance is low, and calcium should be administered only when there is a deficiency of the ion. Glucagon may possibly have a place if escalating doses of adrenaline are required and an acute downregulation of the beta-receptors has occurred.

Good-quality evidence on the relative merits of these drugs is sadly lacking, and further randomized controlled studies are urgently needed so that clinicians can make sensible and rational decisions on which inotrope to use.

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