

Drugs in resuscitation: an update

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ABSTRACT

Drug therapy is recommended after effective cardiopulmonary resuscitation and defibrillation in cardiac arrest. Some drugs appear to have short-term benefits, such as improved survival to hospital, e.g. vasopressor and antiarrhythmics. Hence, they have been included in the cardiac life support algorithm. However, to date, no drug (or combination of drugs) has been shown to improve long-term survival in randomised trials. Hopefully, improvements in post-arrest intensive unit care can translate improved survival in hospitals into better long-term outcomes. This review is an update on drugs during resuscitation, including the choice of agents, dosing, sequence and route. Specific drugs may have benefits in correcting identified causes of collapse. Drug usage during resuscitation is an evolving science, with the use of medications improving as results of clinical studies become available.

Keywords: antiarrhythmic agents, atrial fibrillation, bradycardia, cardiac arrest, vasopressors

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INTRODUCTION

The major rationale for drug use for Advanced Cardiac Life Support (ACLS) is that they improve coronary perfusion pressure (CPP). CPP is the difference between the aortic and right atrial pressure during the cardiac relaxation phase. A CPP > 15 mmHg is predictive of return of spontaneous circulation (ROSC).^(1,2) Increased CPP also correlates with improved 24-hour survival rates in animal studies.^(3,4) Unfortunately, pharmacological support of the circulation has not been shown to increase the rate of survival to hospital discharge. It must be stressed that drug therapy is only considered after instituting effective cardiopulmonary resuscitation (CPR), attempting defibrillation and after establishing vascular access.

MEDICATIONS FOR ARREST RHYTHM

The four rhythms that produce cardiac arrest are asystole, pulseless electrical activity (PEA), pulseless ventricular tachycardia (VT) and ventricular fibrillation (VF). None of these rhythms generate significant forward blood flow.

Vasopressors

To date, no placebo-controlled trial has shown that the administration of any vasopressor agent at any stage during the management of cardiac arrest rhythms increases the rate of neurologically intact survival to hospital discharge.

Adrenaline

For generations of doctors, the administration of adrenaline has been a staple of resuscitation in all algorithms of cardiac arrest. This is because the α -adrenergic effects of adrenaline can increase coronary and cerebral perfusion pressure,⁽⁵⁾ and coronary pressure determines myocardial blood flow. There is, however, no evidence linking adrenaline administration to improvement in human survival. Furthermore, the optimal dose, if any, of adrenaline remains uncertain. Administration of high-dose adrenaline (0.1–0.2 mg/kg) failed to yield a significant difference in survival or neurological outcome when compared to the standard 1 mg dose in multiple randomised trials and meta-analysis.^(6–11) If intravenous (IV) access was delayed and the patient was already intubated, adrenaline by the endotracheal route used to be recommended at a dose of 2–2.5 mg. Currently, the intraosseus (IO) route can be an alternative to the IV route.

Vasopressin

This is a noradrenergic peripheral vasoconstrictor that also causes coronary and renal vasoconstriction. Initial evidence for vasopressin came from small studies, which showed that administration of 40 units or more increased CPP and improved outcome when compared with 1 mg of adrenaline.^(12–14) However, two randomised controlled trials (RCTs) involving adults in cardiac arrest failed to show an increase in the rate of ROSC or survival to discharge for vasopressin when compared with adrenaline.^(15,16) A meta-analysis of five randomised out-of-hospital trials showed no difference in outcomes (ROSC, death within 24 hours or death before hospital discharge⁽¹⁷⁾) with vasopressin vs. adrenaline. Two RCTs^(18,19) also demonstrated no difference in outcomes (ROSC, survival to discharge or neurologic outcome) when comparing adrenaline in combination with vasopressin vs. adrenaline alone in cardiac arrest. Currently, vasopressin is removed from the algorithm for refractory VF, and one dose of vasopressin 40 units IV/IO may replace either the first or second dose of adrenaline in the treatment of cardiac arrest.

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Norepinephrine

Administration of this agent in cardiac arrest had not demonstrated any additional benefit.⁽⁸⁾

Endothelin

Endothelin-1 is a 21-amino acid peptide with powerful vasoconstrictor properties. Evidence from five studies of cardiac arrest in animals documented consistent improvement in CPP with endothelin-1, but this did not translate to improved myocardial blood flow.⁽²⁰⁻²⁴⁾ No published studies conducted in humans are available to date.

Treatment recommendations

Current evidence is insufficient to support or refute the routine use of any vasopressors in any sequence for cardiac arrest. Despite the lack of human data, it is reasonable to continue to use adrenaline on a routine basis. Adrenaline is administered as IV 1 mg bolus every 3–5 minutes, while CPR is ongoing.

Antiarrhythmics

Antiarrhythmic agents have been used for terminating VT or VF, and for preventing recurrences. Unfortunately, there is no evidence that administering any antiarrhythmics routinely during cardiac arrest increases the rate of survival to hospital discharge.

Amiodarone

Two RCTs in the pre-hospital setting showed that administration of amiodarone to patients with refractory VF/pulseless VT improved survival to hospital admission when compared with administration of a placebo or lignocaine.^(25,26) Additional studies documented consistent improvement in defibrillation response when amiodarone was given to patients with VF or haemodynamically unstable VT.⁽²⁷⁻²⁹⁾ Of note is the fact that conclusive scientific data supporting an improvement in survival to hospital discharge with amiodarone therapy is still lacking. Current data suggests that amiodarone use only improved survival to hospital admission and not to discharge. Currently, amiodarone may be considered for VF or pulseless VT that is unresponsive to CPR, defibrillation and vasopressor therapy. An initial dose of 300 mg may be followed by a second dose of 150 mg.

Lignocaine

Previously, lignocaine, a class Ib agent that affects automaticity and upstroke of myocardial action potential in ischaemic tissue, was advocated for use in VF. Unfortunately, the limited scientific data that addressed this issue did not suggest survival benefit from lignocaine.^(30,31) Trials comparing amiodarone and

lignocaine found lower rates of ROSC⁽²⁸⁾ and a higher incidence of asystole⁽³⁰⁾ with the use of lignocaine. Lignocaine can be considered if amiodarone is not available (class IIb, LOEB). The initial dose is 1–1.5 mg/kg IV. If VF persists, additional doses of 0.5–0.75 mg/kg IV push may be administered at 5–10 minute intervals, up to a maximum dose of 3 mg/kg.

Magnesium sulfate

Two observational studies have shown that magnesium is effective for termination of torsades de pointes associated with prolonged QT interval.^(32,33) Otherwise, empiric magnesium therapy is not helpful in inpatient cardiac arrest or refractory VF.^(34,35)

Treatment recommendations

In the setting of VF or pulseless VT unresponsive to CPR, defibrillation and vasopressor, IV amiodarone can be given at an initial dose of 300 mg, followed by 150 mg. Lignocaine can be considered as an alternative if amiodarone is not available. The initial IV dose is 1–1.5 mg/kg, followed by 0.5–0.75 mg/kg at 5–10 minute intervals; should VF or pulseless VT persists, the dose may be increased to a maximum of 3 mg/kg. 1–2 g of IV magnesium sulphate should be administered for known hypomagnesaemia or torsades de pointes. There is insufficient data to recommend for or against its routine use in cardiac arrest.

Other drugs

There is no evidence to suggest that routinely administering other drugs during cardiac arrest increases survival to hospital discharge. There are several reports on the successful use of thrombolytics during cardiac arrest when the arrest was likely due to pulmonary embolism.^(36,37)

Atropine

Atropine is a parasympathetic agent that has previously been used in cardiac arrest for bradycardic PEA and asystole, although its use had not been proven to increase survival.⁽³⁸⁾ In fact, its use in asystole was based on a case series of only eight patients.⁽³⁹⁾ Further prospective controlled non-randomised cohort studies in adults showed that treatment with atropine was not associated with any consistent benefit after in-hospital or out-of-hospital cardiac arrest.⁽⁴⁰⁻⁴³⁾ As the available evidence suggests that the routine use of atropine during PEA or asystole is unlikely to have any therapeutic benefit (class IIb, LOEB), atropine has been removed from the cardiac arrest algorithm.

Sodium bicarbonate

Sodium bicarbonate is not recommended for routine

use during cardiac arrest and/or after ROSC. It may be considered for life-threatening hyperkalaemia or cardiac arrest associated with hyperkalaemia, pre-existing bicarbonate-responsive acidosis and for treatment of tricyclic antidepressant overdose. The use of bicarbonate may be considered in intubated and ventilated patients with a long arrest interval or upon return of circulation after a long arrest interval.

MANAGEMENT OF SYMPTOMATIC BRADYCARDIA AND TACHYCARDIA

This section discusses the pharmacological options for peri-arrest rhythms, which include symptomatic bradycardia and VT (refer to the ACLS algorithms for the treatment flow charts of these arrhythmias). It is not in the interest of this section to discuss how to arrive at a diagnosis of the presenting arrhythmias. When an arrhythmia is termed unstable, it refers to a condition in which vital organ function is acutely impaired or cardiac arrest is imminent. Symptomatic implies that an arrhythmia is causing symptoms such as palpitations and lightheadedness, but the patient may not be in imminent danger. There is therefore more time to plan and decide on the most appropriate intervention.

Bradycardia

Treatment is initiated only for symptomatic or unstable bradycardia.

Atropine

In the absence of reversible causes such as heart block secondary to myocardial infarction, patients with bradycardia and hypotension can be managed with atropine and small fluid boluses. The recommended dose is 0.6 mg, repeated every 3–5 minutes to a maximum dose of 2.4 mg. Doses of atropine < 0.5 mg may cause paradoxical bradycardia and hence, should be avoided. Failure to respond will necessitate second-line drug therapy with dopamine and adrenaline, or transcutaneous pacing while the patient is prepared for emergent transvenous pacing, if required. Atropine is also indicated as an antidote in organophosphate, carbamate or nerve agent poisoning that presents with drug-induced bradycardia, as these rhythms are frequently refractory to standard ACLS protocols.

Dopamine

Dopamine is a catecholamine with both α - and β -adrenergic actions. It is considered for use when atropine fails or is contraindicated. Infusion rates are started at 5–20 $\mu\text{g}/\text{kg}/\text{min}$, and titrated to patient response.

Adrenaline

Adrenaline infusion may be used for patients with symptomatic bradycardia or hypotension after atropine or pacing fails. Begin the infusion at 2–10 $\mu\text{g}/\text{min}$ and titrate to patient response. In the setting of bradycardia secondary to calcium channel blocker⁽⁴⁴⁾ or β -blocker overdose,^(45,46) start IV calcium infusion, followed by IV glucagon.⁽⁴⁷⁾ The recommended dose of glucagon is a slow bolus of 3–10 mg administered over 3–5 minutes, followed by an infusion of 3–5 mg/hr, titrating the infusion rate to achieve adequate haemodynamic response. Hyperinsulinaemic-euglycaemia therapy should be considered.⁽⁴⁸⁾

NARROW-COMPLEX TACHYCARDIA

There are four options for the treatment of narrow-complex tachycardia: physical vagal manoeuvres, pharmacological conversion, rate control and electrical cardioversion. The choice depends on the stability of the patient and the rhythm. If a patient demonstrates rate-related cardiovascular compromise, with signs of altered mental status, ongoing ischaemic chest pain or hypotension, immediate synchronised cardioversion is indicated.

Supraventricular tachycardia (SVT)

It is important to distinguish the various forms of SVT such as, that which originates from the atrial myocardium vs. those with a re-entry circuit partly or wholly based in the atrioventricular (AV) node itself, as therapies are aimed at different conduction pathways. The majority of SVTs due to re-entry mechanism will respond to drugs that slow down or interrupt conduction through the AV node. If vital signs are stable, vagal manoeuvres, such as carotid sinus massage or Valsalva manoeuvre, may be used initially. This may successfully terminate the arrhythmia.

Adenosine

Adenosine is safe and effective, and is the drug of choice (ACC/AHA class recommendation) for conversion of paroxysmal SVT if vagal manoeuvres fail.⁽⁴⁹⁻⁵⁴⁾ It has the advantage of a short half-life (< 10 seconds) and rapid onset of action. The initial dose of adenosine is 6 mg IV push. Adenosine should be given rapidly through a large proximal (e.g. antecubital) vein, followed by a 20 ml saline flush with arm elevation (to ensure that the drug enters the central circulation before its degradation). If the rhythm persists after 1–2 minutes, a 12 mg bolus is given in the same way as above. Prior to injection, the patient should be warned about transient side effects such

as chest discomfort, dyspnoea and flushing, and given reassurance. Larger doses may be needed in the presence of theophylline and caffeine (as they attenuate the effects of adenosine), while a smaller initial dose (3 mg) should be used in patients taking dipyridamole, carbamazepine and in heart transplant patients. If a central line is available at the time of treatment, an even smaller dose of 1–3 mg may suffice. Adenosine is contraindicated in patients with atrial fibrillation (AF) with suspected Wolff-Parkinson-White (WPW) syndrome due to the fear of initiating rapid ventricular rates.

Calcium channel blockers

Calcium channel blockers are another drug of choice for patients presenting with SVT. For SVTs that do not convert with adenosine, or which recur after initial successful cardioversion with adenosine, non-dihydropyridine calcium channel blockers such as verapamil or diltiazem^(49,51,54) may also be used. Diltiazem and verapamil are longer-acting AV nodal blocking agents and act to slow conduction and increase refractoriness in the AV node, thereby interrupting reentrant circuits. Verapamil, and to a lesser extent, diltiazem, can decrease blood pressure if given in large doses. This is due to their negative inotropic effect on the myocardium at high doses. These effects are rarely seen when the drugs are given as a slow continuous infusion (verapamil at 1 mg/min and diltiazem at 2.5 mg/min),⁽⁵⁵⁾ or when pre-treatment with calcium is provided.^(56,57)

Beta-blockers

β -blockers have been used with success,⁽⁵⁴⁾ but side effects such as significant bradycardias, AV conduction delay and hypotension may occur. A variety of agents, such as atenolol, metoprolol, propranolol and esmolol, may be used. Contraindications include second- or third-degree heart block, hypotension, severe congestive heart failure and bronchospasm. Both calcium channel blockers and β -blockers are contraindicated in patients with WPW syndrome who are in AF.

Amiodarone

If the rhythm remains uncontrolled or the conversion is short-lived and the arrhythmia recurs, amiodarone may be used.⁽⁵⁸⁻⁶⁰⁾ It is useful in patients with impaired ejection fraction. Although effective in cardioverting SVTs, the higher toxicity and proarrhythmic properties of this drug make it a less desirable option compared to the other AV nodal blocking agents. Amiodarone is dosed at 150 mg IV over ten minutes, followed by 1 mg/min infusion over six hours, and then 0.5 mg/min maintenance over 18 hours.

The major adverse effects are hypotension and bradycardia, which can be prevented by slowing the rate of infusion.

ATRIAL FIBRILLATION

Treatment options for AF with rapid ventricular rate include rate control or rhythm control. Patients with AF of > 48 hours duration are at risk for cardioembolic events, and therefore, electrical or pharmacological cardioversion should not be attempted in these patients unless the patient is unstable. Although the possibility of cardioembolic phenomenon is remote in recent onset AF (duration < 48 hours), it is not impossible. An alternative strategy is to perform cardioversion after anticoagulation with heparin and conduct transoesophageal echocardiography so as to ensure the absence of left atrial thrombi. Otherwise, for the purpose of rate control, β -blockers,^(61,62) calcium channel blockers,^(62,63) magnesium⁽⁶⁴⁾ or a combination of these drugs could be used.

β -blockers are effective in controlling ventricular rate associated with new-onset AF. Its use is advocated as a first-line agent, especially in cases where there is high adrenergic output, such as thyrotoxicosis, acute hypertensive crisis and myocardial infarction. It can be used for both acute and chronic rate control. Calcium channel blockers such as diltiazem have also been efficacious and relatively safe to use. The use of both β -blockers and calcium channel blockers should be cautioned in patients with heart failure. Moreover, both drugs are contraindicated in patients with accessory pathways, as they may develop a rapid ventricular response and VF secondary to reflex sympathetic stimulation of the accessory pathway.^(66,67) Amiodarone can achieve rate control quickly,^(59,68) and conversion rates are highly variable. It is also commonly used to maintain sinus rhythm in AF patients in whom a rhythm control strategy is chosen. It is also useful in AF with severe left ventricular dysfunction; however, the potential risk of converting to sinus rhythm, and thereafter, the possibility of a cardioembolic sequel, should be considered before using this agent. For rhythm control, amiodarone, ibutilide, propafenone, flecainide or magnesium may be used. Rhythm control may be a viable option for new-onset AF of < 48 hours.

WIDE-COMPLEX TACHYCARDIA

Regular wide-complex tachycardia (QRS > 0.12 seconds) includes VT, SVT with aberrancy and those associated or mediated by accessory pathways. If the wide-complex regular tachycardia is diagnosed to be an SVT (with aberrancy or pre-existing bundle branch block), IV adenosine or slow infusion of calcium channel blocker is recommended. The dosages and methods of

injection are as discussed earlier. In patients with stable, regular, monomorphic wide-complex tachycardia that is undifferentiated, IV adenosine is a relatively safe drug to use for diagnosis and treatment. Adenosine should, however, not be given for unstable or for irregular or polymorphic wide-complex tachycardia, as it may cause degeneration of the arrhythmia to VF. If the rhythm is identified as likely VT in a stable patient, antiarrhythmic drugs may be effective. IV amiodarone may be used. Amiodarone may be more effective in terminating wide-complex tachycardia than lignocaine.⁽⁶⁹⁾ It is given as a slow IV bolus of 150 mg over ten minutes, repeated if necessary, followed by 1 mg/min infusion for the next six hours and 0.5 mg/min infusion over the next 18 hours.

Alternative drugs for wide-complex tachycardia are procainamide and sotalol (not available in IV formulation). Procainamide is dosed at 20–50 mg/min until the arrhythmia is converted, hypotension ensues, or QRS interval is prolonged by 50%, or when the total cumulative dose of 17 mg/kg is reached. Be prepared to electrically cardiovert a patient who is haemodynamically unstable. Without prompt treatment, a stable VT may quickly deteriorate to pulseless VT.

ROUTES OF DRUG ADMINISTRATION

All resuscitation drugs should be given intravenously. If IV access is delayed or cannot be achieved, IO access should be considered.⁽⁷⁰⁻⁷²⁾ Central lines provide better peak drug concentration and shorter circulation times, but are also more difficult to obtain and result in longer interruption in CPR. Studies have not shown any benefit from administering the drugs through the endotracheal route. If adrenaline or amiodarone are indicated during CPR, the shortest possible pause should be allowed for rhythm analysis prior to drug administration. The drug could subsequently be given at any part of the CPR cycle.

CONCLUSION

Only adrenaline and amiodarone are now recommended as first-line treatment during cardiac arrest. It is important to understand that a change in guideline does not imply that the old guidelines are wrong. Rather, it indicates that priorities have shifted in order to extract the highest possible survival rate for cardiac arrest patients.

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