Pharmacological therapy of acute cardiogenic pulmonary oedema in the emergency department

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Abstract

This paper critically reviews the major drug types that are currently used in the management of acute cardiogenic pulmonary oedema. As decompensated heart failure becomes an increasingly common problem in emergency departments in the developed world, optimization of emergency drug therapy for these critically ill patients is essential. The evidence base for ‘routine therapy’ in the ED is considered. The review also briefly considers emerging pharmacological therapies that may have an impact on future management of cardiogenic pulmonary oedema.

Key words: acute, cardiogenic pulmonary oedema, drug therapy, emergency department.

Introduction

Acute cardiogenic pulmonary oedema is a common problem in the ED, with a reported in-hospital mortality of 15–20%. Historically, it was commonly described as ‘cardiac asthma’ and was described in patients with diaphoresis, sweating, shortness of breath and pallor. Clinical findings included widespread wheeze and moist crepitations throughout both lung fields, often associated with a gallop rhythm of the heart. Treatments before the mid twentieth century were limited, consisting simply of opiates, in the form of opium, and digitalis therapy.

Major advances in cardiovascular physiology and specifically the pathophysiology of heart failure have allowed a more detailed understanding of the mechanisms involved in heart failure to be elucidated. Many drugs are now used in the ED treatment of acute cardiogenic pulmonary oedema. These include oxygen, morphine or diamorphine, frusemide, sublingual or intravenous nitrates and sublingual or oral angiotensin converting enzyme (ACE) inhibitors. Further advances include the development of newer agents focused on atrial natriuretic peptide (ANP) and the use of non-invasive ventilation techniques, such as CPAP (continuous positive airway pressure) or BiPAP (bilevel positive airway pressure). If standard treatment fails or is insufficient, emergency intubation and ventilation may be required.

Objective

This paper will provide an update on the pathophysiology of acute cardiogenic pulmonary oedema and review the rationale and evidence for the use of...
current standard drug treatments used in EDs for the management of acute cardiogenic pulmonary oedema. It will briefly mention newer therapies that are currently being developed for use for this group of patients. Specifically, it will not cover the use of invasive or non-invasive ventilatory techniques in the ED.

Methods


In addition, manual searches of the bibliographies of relevant papers identified as a result of these searches were undertaken and any further relevant papers were retrieved. The Web of Science database (previously the Science Citation Index) was searched using an article produced by Cotter et al. to identify any further papers relevant to the topic. The Cochrane Database of Systematic Reviews was also searched.

Results

Ninety articles were identified by the above search strategy. A search of the Cochrane Database of Systematic Reviews did not yield any useful reviews. The Web of Science search yielded a further 17 papers. Further relevant papers were identified from reference lists on the original 107 identified papers.

Discussion

Pathophysiology

Cardiogenic pulmonary oedema can occur as a complication of a recent myocardial incident, such as a myocardial infarction, or it can be an exacerbation of pre-existing cardiac disease such as hypertensive or valvular heart disease (frequently associated with left ventricular hypertrophy). As the decompensating left ventricle fails, the left ventricular end diastolic pressure increases, thus increasing the pulmonary venous pressure. This in turn exerts a back pressure on the pulmonary capillary beds and when capillary pressure exceeds a certain threshold, typically around 18 mmHg in normal subjects, capillary pressure exceeds plasma oncotic pressure and a leak of extracellular fluid occurs from the capillaries into the alveoli.

In the early stages of pulmonary oedema this is characterized by interstitial oedema, where the lung lymphatics are able to compensate for the increase in alveolar water by increasing absorption and returning fluid to the circulation. This is manifested radiologically as ‘Kerley B’ lines and upper lobe venous diversion.

As pulmonary oedema worsens however, the lymphatics are unable to cope with the increasing demands made on them and extrinsic lung water collects in the alveoli. The alveoli are effectively flooded, impairing gas exchange significantly, and increasing the work of breathing for the individual.

Radiologically this produces the typical ‘bats wing’ distribution of alveolar oedema, which is often associated with cardiomegaly if the heart disease is of long standing. However, heart size can appear normal radiologically in the context of an acute myocardial infarction.

It is rare for the electrocardiogram (ECG) to be normal in patients with heart failure. Typical abnormalities include left axis deviation, left bundle branch block, left ventricular hypertrophy with or without a strain pattern, or sign of a recent or evolving myocardial infarction. It is accepted that the presence of a normal ECG effectively excludes a diagnosis of heart failure in the majority of patients.

Oxygen

Oxygen is widely accepted as an essential treatment for acute pulmonary oedema. In areas where interstitial oedema has developed, the alveolar wall is
considerably thickened by engorged lymphatics, and this also increases the diffusion distance for oxygen and therefore increases the alveolar–arteriolar oxygen gradient.4,4

The pathophysiology of acute cardiogenic pulmonary oedema suggests that there is a greatly increased barrier to oxygen diffusion in areas of the lung where alveolar oedema has developed. It follows from all of these factors that the inspired oxygen concentration should be maximized in all cases of cardiogenic pulmonary oedema, in order to maximize oxygen delivery to the less badly affected areas of the lung. Severe hypoxia is a common feature of acute cardiogenic pulmonary oedema and should be excluded in all patients with significant pulmonary oedema by arterial blood gas analysis.13

Pulse oximetry, while generally very useful, can be misleading in patients with acute pulmonary oedema as they are often peripherally vasoconstricted and a poor quality trace may result.

Arterial blood gas analysis will also allow concurrent estimation of PaCO₂ (arterial partial pressure of carbon dioxide) and acid base balance. The presence of severe metabolic acidosis often accompanies acute pulmonary oedema.17,18 This is a combination of tissue hypoxia resulting from poor pulmonary oxygen uptake with associated severe systemic vasoconstriction in order to maintain perfusion to the heart, brain and kidneys. An acute respiratory acidosis is often also present, as evidence by a raised PaCO₂. The PaCO₂ often rises as the patient tires, preceding respiratory arrest.

Many clinicians are naturally concerned that a high PaCO₂ may reflect chronic obstructive pulmonary disease (COPD), with a consequent risk of exacerbating the hypercarbia further by the administration of high flow oxygen. However the pathophysiology suggests that hypercarbia results from impaired CO₂ exchange across the thickened alveolar wall in exactly the same way as hypoxaemia develops secondary to oxygen diffusion difficulties as described above. In addition, patients with hypercarbic COPD tend to have chronically elevated serum bicarbonates, typically around 35–40 mmol/L.

The observation of a low or normal bicarbonate with the clinical picture of the acute pulmonary oedema in the presence of hypoxia and hypercarbia should confirm the picture of acute pulmonary oedema to the clinician and all these patients should be given high flow oxygen at the earliest opportunity.

This is best administered by a tight fitting partial re-breathing mask (i.e. a trauma mask) running at 15 L per minute of oxygen. If oxygenation remains poor, the PaCO₂ continues to rise or the patient is tiring, consideration should be given to the use of non-invasive ventilatory techniques or intubation and ventilation.

**Opioids: Morphine and diamorphine**

Opioids have been used for the management of congestive cardiac failure and acute pulmonary oedema for centuries. Its continuing use is uncritically encouraged by many authors.18 It is principally thought to operate in two ways. First, it has a central sedative action, which is said to reduce anxiety, stress and panic during the acute phase of extreme shortness of breath. It is also reported to have a venodilatory effect, which is reported to reduce preload on the failing heart and thereby improves cardiac output. There is, however, little evidence that morphine or diamorphine improves morbidity or mortality in this group of patients.19,20

Vismara showed in 1976 that morphine sulphate did not cause a major pooling of blood in the limbs and therefore, peripheral vasodilatation was not a mechanism of action for morphine in patients with mild pulmonary oedema.21 They postulated that any vasodilatory effect may be caused by other mechanisms such as splanchnic pooling, afterload reduction or reduced breathing efforts.

Grossmann studied morphine-induced venodilatation in humans in 1996.22 They studied healthy volunteers and it is unclear whether these results will be valid in patients with severe cardiogenic pulmonary oedema. However, their work suggested that the venodilatory effect of morphine is mediated solely through histamine release and the mu opiate receptors have very little or no involvement in the process of venodilatation. This interesting hypothesis suggests that other therapeutic pathways, that induce venodilatation without depressing the central nervous system, may be more useful for the treatment of pulmonary oedema than opiates.

In 1987 Hoffman reported a study on the prehospital management of acute pulmonary oedema, comparing various treatment protocols for acute pulmonary oedema in 57 patients.19 This study was conducted in a prehospital arena in the United States, but the drug regimes are broadly similar to those used in the UK, Europe and Australasia, and, given that it represents the first treatment given to this group of patients, the study is relevant to this review. Morphine was not found to contribute any beneficial effects in
these patients and it was postulated that it may indeed be potentially deleterious in some patients.

Chambers and Baggoley reported three cases of elderly patients with pulmonary oedema who had been given excessive doses of opioids in the prehospital arena. All required naloxone to regain consciousness and increase blood pressure. They advised caution in the use of opioids in acute pulmonary oedema.

Sacchetti reported the influence of ED management on intensive care use in 1999 for this group of patients. They used a retrospective case note review to look at 181 patients, although it is not clear how these patients were selected. A total of 2466 records were screened, all of whom had a diagnosis of congestive heart failure or pulmonary oedema. Their inclusion criteria would indicate that they only included patients who had clinical evidence of severe pulmonary oedema, but this would have to be considered very subjective, especially in the context of a retrospective case note review.

However, within these limitations, they utilized a regression analysis technique to show that the use of morphine sulphate was associated with an increased ICU admission rate (odds ratio 3.1) and an increased rate for endotracheal intubation (odds ratio 5.0). Both these results were statistically significant ($P < 0.002$ for ICU admission and $P < 0.001$ for endotracheal intubation). These findings, as well as being statistically significant are also clinically significant. It seems difficult to justify continuing to use morphine in acute pulmonary oedema when it is associated with higher intubation and intensive care admissions rates. It seems illogical to administer drugs that depress the central nervous system (e.g. opiates) if other drugs are available that produce the desired therapeutic effect, for example, nitrates for vasodilatation. Further prospective work is required in the ED setting to further clarify the role, if any, for opiates for acute pulmonary oedema.

**Frusemide**

Frusemide is a loop diuretic, which was introduced in the 1950s and revolutionized the treatment of congestive cardiac failure at the time. Prior to this time there was no effective means of clearing the fluid retention brought about by secondary hyperaldosteronism as a result of activation of the renin-angiotensin system in congestive heart failure. The development of loop diuretics allowed some of this excess fluid to be removed, although further improvements in therapy came with the development of angiotensin converting enzyme inhibitors in the 1970s and 1980s.

Frusemide, and its sister compound bumetanide, have been used extensively in the management of acute pulmonary oedema since its introduction. It is also thought to work in two distinct ways. Its principal use is to induce a significant diuresis in the kidney, thus reducing intravascular volume which is thought to allow extravascular lung water to return to the circulation and thereafter be excreted by the kidney.

However, this simplistic mechanism of action has long since been shown to be inadequate. Its second effect is to produce a decrease in vascular resistance that has been attributed to a constrictor inhibitory effect independent of its diuretic properties. Recent work by Stanke suggests that this is due in part at least to inhibition of angiotensin II induced vasoconstriction in human vascular smooth muscle.

It is likely that the vasodilatory effects of frusemide have a greater clinical impact in the early management of pulmonary oedema than the diuretic effect. Many patients with mild pulmonary oedema have clinically improved long before any significant diuresis has occurred. Sacchetti showed that administration of a loop diuretic had no beneficial or detrimental effect on ICU admission (odds ratio 1.6, 95% confidence interval 0.46–2.39) or on endotracheal intubation rate (odds ratio 0.9, 95% confidence interval 0.36–2.27).

This would suggest that although frusemide does not make matters worse acutely for patients with pulmonary oedema its diuretic effects do not make any immediate difference to outcome. They may of course have a greater difference as therapy is continued over a number of days. In the scenario of a vasoconstricted, hypotensive individual, it would seem illogical to administer large doses of loop diuretic as they are unlikely to reach their site of action in the presence of reduced renal blood flow.

It would seem more logical to give normal therapeutic doses of diuretic and to optimize cardiovascular status by the use of vasodilators in the hypertensive and inotropes in the hypotensive. Diuretic resistance can be a clinical problem in patients with acutely decompensated heart failure who have presented with increasing dyspnoea, and diuretic doses sometimes need to be increased for this reason.

**Nitrates**

Nitrates therapy has revolutionized the management of acute pulmonary oedema. The realization that acute
cardiogenic pulmonary oedema was associated with a state of severe vasoconstriction, mediated by the hyperactivation of the adrenergic system along with the deleterious effects of secondary hyperaldosteronism on the renin-angiotensin system, suggested to clinicians that an effective method to induce controlled vasodilatation rapidly may be a useful therapeutic option for these patients.25

However, nitrates are not suitable for all patients with acute cardiogenic pulmonary oedema. Caution with nitrates should be exercised in patients with a fixed cardiac output (aortic stenosis, hypertrophic obstructive cardiomyopathy, etc.) as they can be exquisitely sensitive to the effects of parenteral nitrates. A recent small study has shown the safety of nitroprusside therapy for patients with severe aortic stenosis and heart failure,29 but caution with IV nitrates should be exercised until further data are available to confirm this finding. Nitrates should also be avoided for 24 h after sildenafil therapy (for erectile dysfunction) as this combination leads to profound vasodilatation and potentially severe decreases in blood pressure.30,31

Forrester and Waters in 1978 commented on these issues when reviewing the management of congestive heart failure.32 They suggested that management should be tailored to patients’ clinical presentations, by assessing cardiac output, blood pressure and myocardial ischaemia.

Over the next few years nitrates became increasingly accepted as a useful therapy for these patients, and Hoffman’s work in 1987 suggested that nitrates were beneficial in the management of prehospital pulmonary oedema.19 Further studies have confirmed these findings.10,13,14,16,33,34

Sacchetti did not show any beneficial effect for nitrates in his series.20 However, he acknowledges that it was used in 81% of his patient in one form or another (sublingual, transcutaneous, intravenous, etc.) and it therefore would have been difficult to detect any significant difference in the data analysis. They did perform a subgroup analysis, which showed that patients who received nitrates in more than one form, and therefore a greater amount, were less likely to be intubated. However, the numbers in this sub group analysis are small and no firm conclusions should be drawn from these data.

However Cotter’s 1998 study confirms that the use of high does intravenous nitrate, administered as frequent small boluses, plus low dose frusemide is a significantly better combination than low dose nitrate by infusion with high dose frusemide in severe pulmonary oedema.10 This would lend argument to the suggestion that nitrates are an effective first line treatment for acute cardiogenic pulmonary oedema.

Given that a large proportion of patients with acute pulmonary oedema are also suffering from ischaemic heart disease, the administration of nitrates will improve coronary blood flow in the majority of patients which may improve myocardial pump performance. However, nitrate therapy is recognized to have limitations, with the rapid development of tolerance to nitrates in any form and the requirement for a nitrate free period after only a few days treatment. However, these concerns are not relevant to the acute ED setting and nitrates can therefore be recommended as a first line treatment for acute cardiogenic pulmonary oedema of all severities in the ED.

**Angiotensin converting enzyme inhibitors**

The improvements in the understanding of the pathophysiology of heart failure, and especially the neurohumoral compensatory mechanisms that are activated in cardiac failure, have allowed the development of specific drugs to target the inappropriate activation of the renin–angiotensin system in patients with heart failure. This has been seen most often in patients with established congestive cardiac failure,35 but has recently been studied in a limited fashion in patients with acute heart failure in the ED.15,36,37

Hamilton in 1996 reported a small study of ED patients in whom there was more rapid improvement of the symptoms of oedema utilizing sublingual captopril as compared to normal therapeutic regimes.37 There was a trend towards less respiratory failure requiring mechanical ventilation, although this did not achieve statistical significance.

A further small Nigerian study from 1998 compared intravenous hydralazine and oral isosorbide with captopril and prazosin in patients with severe acute left ventricular failure.38 While this is not directly relevant to an ED setting, their findings suggested that the captopril/prazosin combination may be a better vasodilator therapy to hydralazine/isosorbide.

A further German study from 1999 compared sublingual nitroglycerin and intravenous enalapril (enalaprilat) in a prehospital trial of acute pulmonary oedema.39 They did not find any significant difference between the two, but this trial is not particularly useful as it did not compare two intravenous therapies which would have seemed the logical comparison to do.
Sacchetti’s study of 1999 showed a significant decrease in both intubation rates and ICU admission rate with the use of sublingual captopril.\textsuperscript{20} When captopril was combined with morphine, it seemed to protect patients from the deleterious effects of morphine. All the ED based studies of ACE inhibitors for acute pulmonary oedema have involved very small numbers of patients and more prospective work is required.

Future drug therapies

Nesiritide

Nesiritide is recombinant human brain natriuretic peptide that can be infused intravenously. It has venous and arterial vasodilatory effects that reduce preload and afterload and it suppresses the neuroendocrine response to acute heart failure and promotes natriuresis. The VMAC (vasodilatation in the management of acute CHF [congestive heart failure]) study\textsuperscript{40} was a randomized controlled trial of intravenous nesiritide with intravenous nitroglycerin in patients with compensated acute heart failure, included on the basis of dyspnoea that was severe enough to warrant admission to hospital. It concluded that nesiritide was comparable to nitroglycerin in terms of reducing dyspnoea and had comparable 6-month mortality outcomes. It should be noted, however, that the VMAC study was sponsored by the manufacturers of nesiritide. Although it demonstrated a statistically significant improvement with nesiritide compared to placebo, there was no such difference compared to nitroglycerin, which was administered in modest doses (1–2 mg/h IV initially).\textsuperscript{40}

Care should be taken to avoid hypotension by using a low infusion rate of nesiritide after administering a loading dose. Hypotension is likely to persist longer than that seen during nitrate therapy due to nesiritide’s longer elimination half-life (18 min, compared to 2.5 min for nitroglycerin).\textsuperscript{40,41} If hypotension occurs, it will improve spontaneously or in response to an intravenous fluid challenge of up to 250 mL.\textsuperscript{41}

While it is encouraging to note the use of a novel therapeutic mechanism of action in heart failure, it is unclear as to whether nesiritide will have a place in the acute management of acute pulmonary oedema when intravenous nitrate therapy is well established in many EDs.

Levosimendan

Levosimendan is an intravenous inotropic and vasodilator agent that has been found to have symptomatic benefits in association with haemodynamic improvements and a reduction in morbidity and mortality in patients with cardiac failure.\textsuperscript{42} The inotropic effect comes from its ability to keep troponin C stabilized longer in a conformation that maintains contraction in the presence of calcium.\textsuperscript{43} Arteriolar and venous dilatation occurs due to the opening of adenosine triphosphate (ATP)-sensitive potassium channels on vascular smooth muscle. These cardiovascular effects are ideal properties in the treatment of acute heart failure, although levosimendan causes a tachycardia, which may increase myocardial oxygen demands. This agent may prove to be very useful in the ED management of acute cardiogenic pulmonary oedema.

Tezosentan

Tezosentan is an intravenous non-selective endothelin-1 antagonist, which decreases systemic vascular resistance and increases cardiac output in patients with cardiac failure.\textsuperscript{44} This drug has been studied in the setting of acute cardiogenic pulmonary oedema in the RITZ-5 study,\textsuperscript{45} which showed that high doses of tezosentan were associated with a higher mortality. Further work is clearly required to identify the exact role that tezosentan has to play in this setting.

Conclusion

High flow oxygen can be recommended for all patients with acute cardiogenic pulmonary oedema as a first line treatment. In the absence of a fixed cardiac output, nitrates can be strongly recommended. Ideally they should be given as repeated small intravenous boluses with close haemodynamic monitoring. If boluses are impractical, an intravenous infusion should be administered. Low dose frusemide should be considered if there are signs of significant fluid overload (uncommon), but there is no advantage to giving high dose frusemide routinely.

ACE inhibitors have promise for use in the ED management of acute cardiogenic pulmonary oedema but there is not enough good evidence available in the ED setting yet to allow a firm recommendation to be made. Further well powered studies are required in this area.
The time-honoured use of opiates, in the form of morphine or diamorphine, is not supported by the data available and a well-powered, randomized double blind trial should now be undertaken in the setting of the ED to clarify this debate definitively. Further experimental work on novel therapies may lead to new developments in ED management of acute cardiogenic pulmonary oedema within the next decade.

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References


