Diuretic, opiate and nitrate use in severe acidotic acute cardiogenic pulmonary oedema: analysis from the 3CPO trial

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Summary

Background: Drug treatments for acute cardiogenic pulmonary oedema (ACPO) have not been rigorously evaluated and recent observational data suggests some agents are related to poorer outcome.

Aim: We aimed to examine the effect of treatment with diuretics, nitrates and opiates on 7-day mortality, acidosis and respiratory distress in UK Emergency Department (ED) patients with severe acidotic pulmonary oedema.

Design: Analysis of data from the 3CPO trial; a multicentre randomized controlled trial.

Methods: Data were analysed from patients recruited with severe acidotic pulmonary oedema to the 3CPO trial in 26 UK EDs between 2003 and 2007. The effects of these treatments on 7-day mortality, improvement in acidosis (pH change between baseline and 1 h) and improvement in respiratory distress (patient measured breathlessness using a Visual Analogue Score between baseline and 1 h) were tested using univariate logistic regression analysis, and a regression model used to adjust for confounding baseline differences.

Results: Nitrates were given to 947/1048 (90.4%) patients, diuretics to 934/1049 (89.0%) patients and opiates to 541/1052 patients (51.4%). Adjusted analysis showed that opiate treatment was associated with less improvement in acidosis [difference in improvement in pH –0.022, 95% confidence interval (CI) –0.014 to –0.030, P < 0.001], but no difference in mortality or improvement in respiratory distress. We found no evidence that nitrate or diuretic use were associated with any difference in mortality, improvement in acidosis or respiratory distress.

Conclusions: Opiate use is associated with less improvement in acidosis during initial treatment and may attenuate effective treatment of severe acidotic ACPO.

Introduction

Acute cardiogenic pulmonary oedema (ACPO) is a common medical emergency with in-hospital mortality reported to be 10–20%.1,2 Principal early therapies include loop diuretics, nitrates and opiates despite a paucity of evidence to support the benefit or otherwise of these therapeutic agents.3,4 There is an increasing understanding that ACPO is one
presentation of a spectrum of disease processes that constitute acute heart failure syndromes (AHFS) that may require differing management regimes\textsuperscript{5–7} and have varying outcomes. Recent data from observational studies have challenged the benefit of both loop diuretics and opiates reporting an association between these agents and a poorer clinical outcome.\textsuperscript{8–11}

We aimed, using data from the 3CPO trial, to examine the association between the administration of diuretics, nitrates and opiates and the outcomes of 7-day mortality, acidosis and respiratory distress in patients presenting to UK EDs with severe acidotic ACPO.

Materials and methods

This is an analysis of data from the previously reported 3CPO trial,\textsuperscript{12,13} a multicentre trial comparing CPAP, NIPPV or standard oxygen therapy alone in patients with severe acidotic ACPO presenting to 26 UK EDs between July 2003 and April 2007.

Inclusion criteria included age (16 years or older), clinical diagnosis of ACPO, chest radiograph with typical features of interstitial oedema, arterial blood gas analysis with a pH < 7.35 ([H\textsuperscript{+}] > 45 nmol/l) and a respiratory rate of more than 20 breaths per minute. Any patient requiring an immediate lifesaving intervention (such as cardiopulmonary resuscitation, inotropic support, intubation or percutaneous coronary intervention), a clear alternative primary diagnosis, inability to provide consent, or previous recruitment in the 3CPO trial was excluded from this study.

Depending on the severity of the illness, informed written consent was obtained at entry into the study followed by telephone randomization and allocation on a 1:1:1 basis. Written consent for continued participation in the trial was obtained from the patient as soon as possible after recruitment.

Regardless of the allocated trial intervention (CPAP, NIPPV or standard oxygen therapy), the treating physician could administer other therapies, if appropriate, although a simple trial management algorithm was promoted as illustrated in Figure 1.

The primary outcome for the comparison of non-invasive ventilation (CPAP or NIPPV) to standard oxygen therapy was 7-day mortality and for the comparison of CPAP to NIPPV it was the combined measure of 7-day mortality and endotracheal intubation. Secondary outcomes included physiological variables, intubation, myocardial infarction rates, critical care admission and length of stay.

The recruiting physician recorded physiological variables and breathlessness at baseline and 1 and 2 h and arterial blood gas analysis at baseline and 1 h after initiation of treatment.

The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the United Kingdom Medical Research Council and compliant with the United Kingdom Data Protection Act 1998. It was approved by a Multicentre Research Ethics Committee (MREC/02/0/074, U.K.) and registered (ISCRN:07448447).

Data analysis

We investigated whether administration of nitrates, loop diuretics and opiates were associated with differences in 7-day mortality, acidosis and respiratory distress. These outcomes were chosen to reflect the effect of treatment upon an important objective outcome (mortality), an important physiological measure (pH) and the main patient reported symptom (respiratory distress). Acidosis was measured by the change in pH between baseline and 1 h. This parameter was chosen in preference to other physiological measures because it was independently associated with 7-day mortality and least likely to be directly influenced by treatment in a way that may not correlate with treatment benefit. For example, pulse rate, respiratory rate and blood pressure may all be directly influenced by drug treatments without this necessarily conferring a treatment benefit. Similar SaO\textsubscript{2}, pO\textsubscript{2} and pCO\textsubscript{2} may all be directly influenced by oxygen therapy or respiratory support without this necessarily conferring benefit. Respiratory distress was measured by the change between baseline and 1 h in patient perceived breathlessness measured by a visual analogue scale (VAS) ranging from 0 (no breathlessness) to 10 (maximum breathlessness).

We used univariate logistic (mortality) or linear (pH and respiratory distress) regression to determine whether there was an association between each treatment and each outcome. When treatments are not randomized, as in this analysis, an association between treatment and outcome may be due to selective administration of the treatment to patients with more (or less) severe illness. To address this potential confounding by illness severity, we undertook multivariable regression analysis to identify patient characteristics that predicted each outcome and then used these characteristics to produce adjusted estimates of the effect of each treatment on each outcome. We undertook stepwise linear regression to identify which of the following covariates were independent ($P<0.05$) predictors of change in pH and change in respiratory distress:
age, gender, past medical history and baseline characteristics (Supplementary Data). A previous analysis\(^{14}\) showed that age, systolic blood pressure and the ability to obey commands were independent predictors of 7-day mortality. We then undertook multivariable logistic or linear regression to estimate the effect of each treatment on outcome, adjusted for confounding by baseline characteristics that were independent predictors of outcome. The data were analysed using the SPSS Version-15 software package (SPSS, Chicago, Illinois).

### Results

Patient characteristics and flow through the 3CPO trial have been reported elsewhere\(^ {12,13}\) and are summarized in Figure 2. Of the 1069 recruited patients, 1062 were randomized and allocated to a trial intervention. Nitrates were administered to 947/1048 patients (90.4%): 766 intravenous, 139 sublingual, 7 via both routes and 35 not recorded. Diuretics were given to 934/1049 patients (89.0%): 914 intravenous, 3 oral and 17 not recorded. Opiates were given to 541/1052 patients (51.4%), all via the intravenous route. Table 1 shows the baseline characteristics of patients who received each of the three treatments.

### Mortality (7-day)

Table 2 compares 7-day mortality of patients receiving each of the three agents to those not receiving each agent. Patients given nitrates had lower mortality, while those given opiates or diuretics had higher mortality, although only the results for nitrates approached statistical significance. These differences in mortality may be explained by nitrates being administered to patients with less severe illness, while diuretics and opiates were given to those

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**Figure 1.** 3CPO standard therapy algorithm.
with more severe illness. We therefore adjusted the analysis for potential confounding by baseline age, systolic blood pressure and the ability to obey commands. After adjustment there was no evidence of any association between treatment with nitrates \[\text{adjusted odds ratio (OR) 1.05, 95\% confidence interval (CI) 0.52 to 2.12, } P = 0.897\] , diuretics \[\text{adjusted OR 1.48, 95\% CI 0.62 to 3.51, } P = 0.337\] or opiates \[\text{OR 1.27, 95\% CI 0.80 to 2.02, } P = 0.304\] and 7-day mortality. Hence it appears that the lower mortality seen in patients given nitrates was probably due to nitrates being administered to

### Table 1 Baseline characteristics of patients at presentation

<table>
<thead>
<tr>
<th>Number</th>
<th>Given nitrate</th>
<th>Given diuretic</th>
<th>Given opiate</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean±SD</td>
<td>77.6 (9.8)</td>
<td>77.6 (9.7)</td>
<td>77.6 (9.6)</td>
<td>77.8 (9.7)</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>413 (43.6)</td>
<td>405 (43.4)</td>
<td>243 (44.9)</td>
<td>459 (43.2)</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemic heart disease (%)</td>
<td>587 (62.0)</td>
<td>578 (61.9)</td>
<td>359 (66.4)</td>
<td>653 (61.5)</td>
</tr>
<tr>
<td>Congestive heart failure (%)</td>
<td>412 (43.5)</td>
<td>411 (44.0)</td>
<td>238 (44.0)</td>
<td>463 (43.6)</td>
</tr>
<tr>
<td>Valvular heart disease (%)</td>
<td>95 (10.0)</td>
<td>108 (11.6)</td>
<td>60 (11.1)</td>
<td>110 (10.4)</td>
</tr>
<tr>
<td>COPD (%)</td>
<td>171 (18.1)</td>
<td>176 (18.8)</td>
<td>92 (17.0)</td>
<td>190 (17.9)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>522 (55.1)</td>
<td>508 (54.4)</td>
<td>281 (51.9)</td>
<td>578 (54.4)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>287 (30.3)</td>
<td>283 (30.3)</td>
<td>159 (29.4)</td>
<td>326 (30.7)</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>163 (17.2)</td>
<td>166 (17.8)</td>
<td>88 (16.3)</td>
<td>184 (17.3)</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>95 (10.0)</td>
<td>93 (10.0)</td>
<td>51 (9.4)</td>
<td>105 (9.9)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>157 (16.6)</td>
<td>155 (16.6)</td>
<td>91 (16.8)</td>
<td>177 (16.7)</td>
</tr>
<tr>
<td>Baseline physiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse (beats per minute)</td>
<td>113 (22)</td>
<td>113 (22)</td>
<td>115 (22)</td>
<td>113 (22)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>164 (36)</td>
<td>161 (37)</td>
<td>163 (37)</td>
<td>162 (36)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>89 (24)</td>
<td>88 (24)</td>
<td>89 (24)</td>
<td>88 (24)</td>
</tr>
<tr>
<td>Respiratory rate (breaths per minute)</td>
<td>32 (7)</td>
<td>32 (7)</td>
<td>32 (7)</td>
<td>32 (7)</td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>90 (8)</td>
<td>90 (8)</td>
<td>90 (8)</td>
<td>90 (8)</td>
</tr>
<tr>
<td>Arterial pH</td>
<td>7.21 (0.09)</td>
<td>7.22 (0.09)</td>
<td>7.21 (0.09)</td>
<td>7.21 (0.09)</td>
</tr>
<tr>
<td>Arterial pO2 (kPa)</td>
<td>13.2 (7.9)</td>
<td>13.3 (8.1)</td>
<td>13.4 (8.1)</td>
<td>13.3 (8.0)</td>
</tr>
<tr>
<td>Arterial pCO2 (kPa)</td>
<td>7.6 (2.3)</td>
<td>7.6 (2.2)</td>
<td>7.6 (2.3)</td>
<td>7.6 (2.3)</td>
</tr>
<tr>
<td>Arterial bicarbonate</td>
<td>20.5 (4.4)</td>
<td>20.6 (4.4)</td>
<td>20.3 (4.2)</td>
<td>20.6 (4.4)</td>
</tr>
<tr>
<td>Breathlessness VAS (0 to 10)</td>
<td>8.9 (1.6)</td>
<td>8.9 (1.6)</td>
<td>9.0 (1.4)</td>
<td>8.9 (1.6)</td>
</tr>
</tbody>
</table>

COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease.
those with a better prognosis. This probably reflects nitrates being avoided in those with low blood pressure.

**Metabolic status (pH change between baseline and 1 h)**

Table 3 shows that patients receiving nitrates had greater improvement in pH over the following hour than those who did not, patients receiving opiates had less improvement, and patients receiving diuretics had the same improvement as those who did not. Stepwise linear regression showed that baseline arterial pH (coefficient $-0.489$, 95% CI $-0.556$ to $-0.422$, $P < 0.001$), systolic blood pressure (coefficient $0$, 95% CI $0$ to $0.001$, $P < 0.001$), normal Glasgow Coma Scale verbal response (coefficient $0.035$, 95% CI $0.012$ to $0.058$, $P = 0.003$), known chronic obstructive pulmonary disease (coefficient $-0.019$, 95% CI $-0.033$ to $-0.05$, $P = 0.010$) and baseline arterial pO2 (coefficient $-0.001$, 95% CI $-0.001$ to $0$, $P = 0.046$) were independent predictors of change in pH. This means that patients tended to have a greater improvement in their metabolic status if they had a lower baseline pH, higher systolic blood pressure, normal Glasgow Coma Scale verbal response, lower baseline arterial pO2 or no history of chronic obstructive pulmonary disease. After adjustment for potential confounding by these covariates, opiate administration was still associated with less improvement in arterial pH (coefficient $-0.022$, 95% CI $-0.014$ to $-0.030$, $P < 0.001$), nitrate administration was no longer associated with any difference in improvement (coefficient $0.005$, 95% CI $-0.010$ to $0.020$, $P = 0.537$) and there remained no association between diuretic administration and improvement in pH (coefficient $-0.009$, 95% CI $-0.022$ to $0.005$, $P = 0.201$). So patients receiving opiates had less improvement in their metabolic status, even after accounting for illness severity, while the greater improvement seen in patients receiving nitrates was probably due to preferential administration of these agents to patients with a better prognosis.

**Respiratory distress (VAS change between baseline and 1 h)**

Table 4 shows that there was no evidence that administration of any of the agents were
associated with greater improvement in breathlessness. Nevertheless, we still undertook linear regression to identify predictors of greater improvement in breathlessness. This showed that baseline breathlessness VAS (coefficient 0.543, 95% CI 0.378 to 0.708, \( P < 0.001 \)), valvular heart disease (coefficient 1.298, 95% CI 0.519 to 2.076, \( P = 0.001 \)), normal GCS verbal score (coefficient 1.697, 95% CI 0.634 to 2.760, \( P = 0.002 \)), hypertension (coefficient 0.647, 95% CI 0.133 to 1.160, \( P = 0.014 \)) and baseline peripheral oxygen saturation (coefficient 0.036, 95% CI 0.003 to 0.069, \( P = 0.032 \)) were independent predictors of change in breathlessness VAS. This means that patients tended to have a greater improvement in breathlessness if they were more breathless at presentation, or if they had valvular heart disease, hypertension or a normal GCS verbal score. After adjustment for potential confounding there remained no association between nitrate administration (coefficient –0.006, 95% CI –0.020 to 0.007, \( P = 0.359 \)), opiate administration (coefficient 0.009, 95% CI –0.025 to 0.043, \( P = 0.591 \)) or diuretic administration (coefficient 0.003, 95% CI –0.013 to 0.018, 0.744) and improvement in breathlessness VAS.

**Discussion**

This analysis of data from the 3CPO trial is the first observational data from the UK and Europe investigating the relationship between key emergency therapies (nitrates, opiates and diuretics) in AHFS management and important early clinical outcomes such as mortality, patient physiology and breathlessness. These data show no clear association between the chosen outcomes and nitrate or diuretic administration. There was a clear association between opiate administration and change in pH at 1 h after administration, with those patients receiving opiates improving less than those patients not receiving them. There was no clear relationship between opiate administration and mortality or patient breathlessness.

The use of nitrates was associated with lower mortality and a greater improvement in pH on univariate analysis, but this finding was lost after adjustment for age, ability to obey commands and baseline systolic blood pressure. These findings are likely to reflect the relationship between clinician judgement, nitrate administration and clinical outcome. Nitrates were correctly prescribed to patients with AHFS and hypertension who are known to have a better outcome than those patients with AHFS and low blood pressure.\(^5\)\(^7\) There is a paucity of evidence to support the use of nitrates in AHFS despite mechanistic reasons to confer benefit and widespread use and recommendation in clinical practice.\(^8\)\(^9\)\(^15\)\(^16\)

Data from the UK suggested an association between ED nitrate administration (OR = 3) and improved mortality\(^17\) and randomized trials suggest that high dose bolus nitrate and low dose diuretic is more effective than high dose diuretic and low dose nitrates.\(^18\)

Intravenous loop diuretics remain the commonest agent administered to patients with AHFS with and without pulmonary oedema. The majority of patients in a UK ED study received furosemide whilst \(<70\% \) received nitrates.\(^17\) According to the Acute Decompensated Heart Failure National Registry (ADHERE) study in the United States, 88% of patients with acutely decompensated heart failure (ADHF) receive intravenous loop diuretics, and in two-thirds of these patients no vasoactive drugs were used in conjunction.\(^19\)\(^20\) There is some associative evidence from ADHERE and other research showing that patients receiving diuretics in particular higher doses had poorer outcomes.\(^21\) This may be a relationship between severity of illness and dosing regimes or due to underlying pathophysiological processes worsening renal function after diuretic use.\(^22\) There was no evidence of a relationship in this analysis between diuretic administration and outcomes.

Analysis of the ADHERE database, containing nearly 150,000 patients, found that morphine therapy in acute decompensated heart failure was associated with increased mortality (OR = 5) despite extensive risk adjustment.\(^8\) This is corroborated by a review by Graham\(^4\) who found no evidence supporting the use of morphine, and two smaller retrospective studies suggesting an association with harm.\(^9\)\(^10\) In the 3CPO trial, patients given opiates showed less improvement in pH over the following hour when compared with those not given opiates. This effect was not explained by adjustment for baseline confounding and suggests that opiates may attenuate metabolic improvement in ACPO but in these data, this did not result in an increase in mortality. Opiates play an important role due to central analgesic and sedative effects. This and earlier data may only show that sicker and more distressed patients were more likely to receive opiates rather than opiates directly implicated in poorer outcomes.

There are a number of considerations in interpretation of these data from the 3CPO trial. First, the patient cohort was sick with severe acidotic ACPO and therefore the results may not be generalizable to other populations. Secondly, as previously
described, these patients were recruited if they had ACPO and therefore the findings may not apply to other groups of patients with AHFS. Previous data have looked at diuretic dosage throughout hospital stay and therefore it may be unlikely that a single dose at presentation will significantly influence important outcomes. Finally, nitrates and diuretics were prescribed in 90% of patients and it is possible that this cohort was underpowered to detect a difference in outcome even if it is actually present. This means that the negative findings in this study do not exclude a potentially worthwhile or harmful effect from treatment with nitrates or diuretics.

There are clearly increasing concerns that the blind continuation of administration of these agents to all patients with AHFS is inappropriate and there should be research evidence to support the more thoughtful use of these agents depending on presenting physiology, presence of pulmonary oedema, likely volume status, renal function, presence of acute coronary syndrome and likely underlying aetiology. The time is now right for randomized controlled trials of these agents in the early management of AHFS.1,5,13

In conclusion, in this analysis of data from patients with severe acidic ACPO from the 3CPO trial, the only clear relationship between emergency drug (nitrates, diuretics and opiates) administration and important early clinical outcomes (7-day mortality, pH change and respiratory distress) was a slower improvement in pH at 1 h in those patients receiving opiates.

Supplementary Data

Supplementary Data is available at QIMED Online.

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Conflict of interest: None declared.

References

16. The task force on Acute Heart Failure of the European Society of Cardiology. Executive summary of the guidelines


Appendix 1

Trial Management Group

Alasdair Gray (Chief Investigator), Reader and Consultant in Emergency Medicine, Royal Infirmary of Edinburgh; David Newby, Professor of Cardiology and Consultant Cardiologist, Royal Infirmary of Edinburgh; Steve Goodacre, Consultant in Emergency Medicine, Northern General Hospital, Sheffield and Professor of Emergency Medicine, University of Sheffield; Jon Nicholl, Professor, Health Service Research, ScHARR, University of Sheffield; Catherine Kelly, Consultant Physician in Acute Medicine, Royal Infirmary of Edinburgh; Steven Crane, Consultant in Emergency Medicine, York Hospital; Mark Elliott, Consultant Respiratory & General Physician, St James University Hospital, Leeds; Neil Douglas, Professor of Sleep Medicine, Royal Infirmary of Edinburgh; Taj Hassan, Consultant in Emergency Medicine, Leeds General Infirmary; Paul Plant, Consultant in Respiratory Medicine, St James University Hospital, Leeds; Fiona Sampson, Research Fellow, University of Sheffield; Kathryn Paulucy, Clerical Officer, University of Sheffield; Moyra Masson, Trial Manager, Royal Infirmary of Edinburgh; Yemi Oluboyede, Research Associate, University of Sheffield; Katherine Stevens, Health Economist, University of Sheffield.

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Data Monitoring Committee

Robin Prescott (Chairperson), Director of Medical Statistics & Professor of Health Technology Assessment, University of Edinburgh; Allister Hargreaves, Consultant Cardiologist, Falkirk and District Royal Infirmary; Colin Selby, Consultant Respiratory Physician, Queen Margaret Hospital, Dunfermline; Ursula MacIntosh, Consultant in Emergency Medicine, Stirling Royal Infirmary.

Recruiting sites, clinical leads and patients recruited

Royal Infirmary of Edinburgh, Alasdair Gray (n=161); Southern General Hospital, Glasgow, Phil Munro (n=23); Ninewells Hospital, Dundee,
Neil Nichol (n=21); Crosshouse Hospital, Crawford
McGuffie (n=50); Hairmyres Hospital, Kilmarnock,
John Keaney (n=28); Northern General Hospital,
Sheffield, Steve Goodacre (n=136); York Hospital,
Steve Crane (n=63); St James University Hospital,
Leeds, Steve Bush (n=56); Leeds General Hospital,
Taj Hassan (n=37); Barnsley Hospital, Jane
Brenchley (n=54); Harrogate Hospital, Helen Law
(n=19); Pinderfields Hospital, Wakefield, Matt
Shepherd (n=8); Frenchay Hospital, Bristol, Jason
Kendall (n=68); Royal United Hospital, Bath,
Dominic Williamson (n=60); Bristol Royal
Infirmary, Jonathan Benger (n=32); Royal Devon
& Exeter Hospital, Gavin Lloyd (n=39); Torbay
Hospital, Torquay, Simon Cope (n=31); Hope
Hospital, Salford, Carole Gavin (n=29),
Manchester Royal Infirmary, John Butler (n=28);
Whiston Hospital, Prescot, Francis Andrews
(n=29); Wythenshawe Hospital, Manchester,
Darren Walter (n=21); Warrington Hospital, Mary
Higgins (n=11); Birmingham Heartlands Hospital,
Anthony Bleetman (n=19); Selly Oak Hospital,
Birmingham, Peter Doyle (n=30); James Cook
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Dissmann (n=11); Princess Royal University
Hospital, Farnborough, Ian Stell (n=5).