Special feature: Lung injury

Review

The injured lung: clinical issues and experimental models

B. J. A. Jugg*, A. J. Smith, S. J. Rudall and P. Rice

Biomedical Sciences Department, Dstl Porton Down, Salisbury SP4 0JQ, UK

Exposure of military and civilian populations to inhaled toxic chemicals can take place as a result of deliberate release (warfare, terrorism) or following accidental releases from industrial concerns or transported chemicals. Exposure to inhaled toxic chemicals can result in an acute lung injury, and in severe cases acute respiratory distress syndrome, for which there is currently no specific medical therapy, treatment remaining largely supportive. This treatment often requires intensive care facilities that may become overwhelmed in mass casualty events and may be of limited benefit in severe cases. There remains, therefore, a need for evidence-based treatment to inform both military and civilian medical response teams on the most appropriate treatment for chemically induced lung injury. This article reviews data used to derive potential clinical management strategies for chemically induced lung injury.

Keywords: acute lung injury; acute respiratory distress syndrome; toxic chemicals; treatment strategies; porcine

Gas! GAS! Quick, boys! - An ecstasy of fumbling,
Fitting the clumsy helmets just in time;
But someone still was yelling out and stumbling,
And flound'ring like a man in fire or lime ...
Dim, through the misty panes and thick green light,
As under a green sea, I saw him drowning.
In all my dreams, before my helpless sight,
He plunges at me, guttering, choking, drowning.
(Wilfred Owen 1917)

1. THE ISSUE

Exposure of military and civilian populations to inhaled toxic chemicals can take place as a result of deliberate release (warfare, terrorism) or following accidental releases from industrial concerns or transported chemicals. Exposure to inhaled toxic chemicals can result in an acute lung injury (ALI), and in severe cases acute respiratory distress syndrome (ARDS), for which there is currently no specific medical therapy, treatment remaining largely supportive. This treatment often requires intensive care facilities that may become overwhelmed in mass casualty events and may be of limited benefit in severe cases [1]. There remains, therefore, a need for evidence-based treatment to inform both military and civilian medical response teams on the most appropriate treatment for chemically induced lung injury. Following exposure to such chemicals, there is often a latent period that may last several hours during which time signs and symptoms may not

be evident. Early transient symptoms of irritation and cough may not reflect the final clinical outcome, and even at high challenge concentrations, there may be a delay in signs and symptoms such that medical intervention is not triggered.

Chemical warfare (CW) has been widely condemned since it was first used on a massive scale during World War 1 (WW1) [2]. Chlorine (Cl_2) was the first lethal chemical to be released and continues to present a threat, most recently being employed in attacks with vehicle-borne improvised explosive devices in Iraq [3]. In an attack on 28 January 2007, nine patients were admitted to a United States Combat Support hospital following exposure to Cl_2 . All casualties developed ARDS, eight of these requiring airway pressure release ventilation. Phosgene (CG) was also widely used in WW1 and was responsible for the majority of the fatalities resulting from chemical exposures [1]. The clinical picture resulting from CG exposure has been described in detail [4,5]. Briefly, initial exposure is followed by an asymptomatic period that varies in duration with dose (6–12 h); this is followed by non-cardiogenic pulmonary oedema leading to respiratory failure and death. A number of similarities exist between the injury produced by CG exposure and that reported in patients with ALI or ARDS [6,7]. Other agents employed during WW1 included sulphur mustard (HD), which was first used at Ypres in 1917. HD was responsible for more than 125 000 British gas casualties, most of whom had some degree of associated pulmonary involvement [8]. HD was also widely used as a CW agent during the 1980s in the Iran–Iraq conflict where it resulted in over 100 000 medical casualties [9,10].

The psychological impact of CW agents on society makes them ideal for terrorism [2], as shown by the

* Author for correspondence.

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coordinated release of the nerve gas sarin in the Tokyo subway system in 1995 by Aum Shinrikyo. The attack was directed against trains passing through Kasumigaseki and Nagatachō stations, close to the seat of the Japanese Government. There were nine fatalities, 50 seriously injured and over 5000 people requiring hospital treatment for temporary visual problems [11]. Most of those reporting to hospitals had not been exposed but presented diagnostic difficulties that soon overwhelmed the medical care system.

Both Cl_2 and CG are commonly used toxic industrial chemicals (TICs). CG is produced directly or as a chemical intermediate for the synthesis of a number of industrial compounds in the manufacture of paints and plastics [1]. Large amounts of Cl_2 are produced each year (10 million tonnes per annum in Europe; [12]) for use in many processes including water purification [13]. Accidental release of TICs can cause large numbers of casualties. At 02.40 h on the morning of 6 January 2005 in Graniteville (USA), the collision and derailment of a train carrying Cl_2 resulted in up to 90 tonnes of gas being released over the town. Eight people died before reaching medical care and of the 71 hospitalized, one died some three months later. Of the survivors, many developed significant pulmonary signs and severe inflammation of the airways. Fifty eight per cent of the hospitalized met the criteria (in terms of mean partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FiO_2) ratio) for ALI or ARDS [14]. Had the accident occurred later in the day, the numbers of casualties would have been much higher.

Members of the Armed Forces are, therefore, at risk of exposure to a wide range of chemicals and environmental materials during war fighting, operations other than war, and while providing aid to civil authorities. Military personnel must be properly prepared and equipped to operate in a military environment where chemical or biological agents may be deployed. While this has been true since WW1, more recently, the chemical threat has extended to include the civilian environment.

It is not always possible to possess advance intelligence of the chemicals likely to be encountered in war, so appropriate pre-treatments, even if these were available, may not be in place. In the civilian situation, advance warning is even less probable and pre-treatment would not be possible. Therefore, it is essential to develop post-exposure therapeutic strategies to minimize casualty rates and increase survival in individuals poisoned by lung-damaging chemicals [15]. Since the nature of the exposure may not be known immediately, this requirement extends to developing generic countermeasures that may be effective against a range of chemical agents. Prognostic indicators are also not yet available and effective triage must be based on clinical symptoms, which can be slow to develop. In the military setting, most battlefield deaths occur within the first 10 min of wounding and the military now refer to the time immediately after injury as the 'platinum 10 minutes', rather than the 'golden hour' that used to be talked about [16]. However, following a chemical incident, these timelines are unrealistic since the delayed symptomology and lack of

effective medical countermeasures mean the only option currently available is evacuation to a medical facility for ventilatory support.

2. THE MODEL

Chemically induced lung injury has a complex aetiology involving a number of cellular targets. Moreover, the results of the initial challenge may cause an inflammatory reaction, which can contribute to the injury and which involves a coordinated response from many cell types both in the lung and other body systems. Interactions with other organ systems, particularly the heart and circulation, may be involved in the development of ALI/ARDS and may provide novel treatment opportunities. The complex response of the organism to lung injury is, therefore, difficult to recreate *in vitro* and must be studied *in vivo* if a complete assessment of the injury mechanism and response is to be considered. Single cell type monolayer cultures have been used to investigate aspects of cellular injury. While such models can be used to investigate specific mechanisms, they cannot model the complex interactions that occur *in vivo* during the injury and repair phases of chemically induced lung injury. However, *in vitro* models have utility as a screening tool to investigate mechanistic interactions and to down-select potential treatment options.

In vivo small animal models provide preliminary evaluation of drug treatment effectiveness [17,18], but there can be inherent issues with these models. Owing to their small body size and variations in physiology, small animals are not always the best models to extrapolate to man in the evaluation of lung injury. In comparison, large animal models, such as the pig, offer significant advantages over smaller animals. The lung physiology of the pig is more comparable to man than that of rodents [19,20] and their large size means that human intensive care unit (ICU) equipment can be used owing to similarities in the tracheobronchial tree and vascular architectures. Thus, there is greater confidence in the extrapolation of the data to man than would be possible from a small animal model.

The terminally anaesthetized large white pig model has been extensively and successfully used at Dstl Porton Down over the last 10 years. The model was established in sham exposed animals that were conventionally ventilated over 24 h. The model was then validated using CG (10 min exposure) and a concentration identified to produce a consistent ALI [21]. We have used this model to assess the efficacy of single commercial off the shelf (COTS) treatments, which may be available for use by emergency first responders or by buddy aid prior to medical evacuation. These therapies were chosen to act on biochemical pathways known to be affected by CG exposure [4,5]. These have included intravenous and inhaled steroids [22], inhaled salbutamol [15] and inhaled furosemide. The administration of single treatments for CG-induced lung injury did not improve survival or arterial blood oxygenation, the primary outcome measures in these studies. We have also used this model to assess current strategies available in

the field hospital or ICU, investigating the optimal time for delivering these treatments e.g. when to give supplemental oxygen (early versus late). We demonstrated the benefits of a protective ventilation strategy (low tidal volume, high positive end expiratory pressure—acute respiratory distress network [7,23]) and supplemental inspired oxygen therapy against CG injury [24].

The protective ventilation strategy significantly improved survival, arterial blood oxygenation and pathology at 24 h [7]. Oxygen supplementation also significantly improved survival and arterial blood oxygenation at 24 h even when given at low flow (40% versus 80%) and delayed onset (started 12 h post-exposure) [24]. Use of a protective ventilation strategy and oxygen therapy is currently recommended to treat CG-induced lung injury.

More recently we have adapted the model to investigate the toxicological effects of inhaled HD vapour using a novel exposure generation system [25]. These 12 h studies have used spontaneously breathing animals. An inhaled dose of HD vapour that produces a consistent injury has been identified against which treatment strategies will be investigated. The findings from this study emphasize how the pathology in this model better reflects the pathology seen in humans exposed to inhaled HD and provide further evidence of the importance of species selection to aid extrapolation to man [26,27].

3. FINDINGS AND FUTURE DIRECTIONS

Currently, treatment for CG-induced lung injury remains supportive, with the administration of single treatments not improving survival. Combined therapies are likely to be the most effective treatment strategy and should be investigated. The present terminally anaesthetized pig model is limited in its application since it cannot easily be taken beyond 24 h post-exposure. Thus, any beneficial effects in terms of survival, physiological and pathological parameters cannot be determined beyond 24 h and no assessment made as to whether the clinical benefits are real or simply delaying the outcome. This limitation of the terminally anaesthetized model would be overcome by the development of a long-term recovery pig model.

Taking the experiments beyond 24 h and recovering the pigs from anaesthesia would allow the effects of inhaled toxic chemicals and any treatment strategies successful in the short term (above) to be investigated further. It would also ensure that any beneficial treatment strategy from the anaesthetized studies is truly effective and not merely delaying the onset of injury. Identified effective treatment strategies will inform military and civilian doctrine on the best practice for the treatment of casualties following exposure to lung-damaging chemicals. From current research, treatments that clearly need to be investigated further include, but are not limited to:

- Combined pharmacological therapies including steroids, non-steroidal anti-inflammatory drugs, β -agonists—potential for buddy aid to ameliorate lung injury prior to medical evacuation.

- Pharmacological therapies combined with intensive care strategies—to determine longer term patient benefit.
- Extra-corporeal membrane oxygenation or Nova-lung (iLA)—for the evacuation phase where maintenance of oxygenation is essential.
- LiDCO (continuous real time cardiovascular monitoring)—assessment of the degree of lung injury (leakiness of lungs), is this prognostic of outcome?

A recovery model using pigs would be ideal to investigate these treatments and could be used to investigate the long-term health effects following exposure to inhaled toxic chemicals, which for obvious reasons is not feasible with a terminally anaesthetized model.

The requirement for further research into evidence-based medical countermeasures to delay, ameliorate or treat the injury from lung-damaging chemicals continues. The issues of delayed symptomology and lack of prognostic or diagnostic indicators mean that current military and civilian protocols for effective triage may well be ineffective. The potential for mass casualties following a chemical incident is likely to overwhelm local healthcare systems, with the 'worried well' increasing the burden.

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