Pharmaco-management of inhalation injuries for burn survivors

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Background: Burn injury is exacerbated by inhalation injury, causing higher morbidity and mortality rates compared to those with a comparable burn injury alone. The complex pathophysiology of inhalation injury is well described, but analysis of treatment is a mammoth task and requires individual focus on a number of components of management. In this case, the focus of the review is treatment of inhalation injury using pharmacological means. It provides a concise overview of the disease process and a summary of the evidence for specific manipulation of various disease pathways.

Methods: A literature search through PubMed was completed and all links and bibliography reference articles were explored.

Results: A total of 47 papers matched the search terms. Of these, one was a comparative study with historical controls, 2 were retrospective case series, 2 studies reported a single human case series, 34 were examinations in animals, and 8 were expert opinion or reviews.

Conclusion: The literature illustrates the complicated immuno-biochemical pathways that have conflicting roles and importance, complicating integrated understanding. Secondly, there is an almost complete absence of high quality data from humans. Clinical use of pharmaco-therapies for inhalation injuries is further limited by the lack of commercial availability.

Keywords: inhalation injury, smoke, burns, inhalation, medication

Introduction
In the United States, of the estimated 2 million burns per year, 100,000 require hospitalization, and 5000 result in death (Herndon and Spies 2001). Burns are exacerbated by inhalation injury, and associated pulmonary complications (Murakami and Traber 2003). Prevalence rates vary but authors concur that those with combined burn and inhalation injury have higher morbidity and mortality rates than those with comparable burn injury alone (Tasaki et al 2002; Cox et al 2003; Endorf and Gamelli 2007). Data from the Royal Perth Hospital (RPH) Western Australia, confirms that inhalation injury causes more deaths and increased bed days and resource usage than burns alone (Table 1). Further, it is proposed that acute lung injury (ALI) and resultant acute respiratory distress syndrome (ARDS) account for up to 75% of the deaths related to fire (PatientPlus 2007).

The patho-physiology of inhalation injury is well described in the literature, though the vast majority of studies have been completed in the animal model (Table 2) (Enkhbaatar and Traber 2004; Lee and Mellins 2006; Cancio et al 2007). In brief, inhalation injury is the result of thermal or chemical injury to the airways and alveoli from exposure to superheated gases, steam, hot liquids and, or toxic products of incomplete combustion (Herndon et al 1986). Dry heat does not easily penetrate to the lower respiratory tract, and hence true thermal damage of the lung parenchyma is rare (Cox et al 2003). Tissue damage above the vocal cords is often the result of direct thermal exposure while below the cords, injury is generally caused by chemical toxins.
and particulate matter (Mlcak et al 2007). The by products of combustion; namely hydrogen cyanide, aldehydes, hydrochloric acid, acrolein, ammonia, chlorine, sulphur dioxide, and nitrogen dioxide, that are chiefly responsible for initial pulmonary tissue insult (Haponik et al 1988).

Armed with the data and the knowledge of acute lung injury patho-physiology (Figure 1), the multi-disciplinary burns team (MBT) wished to examine ways of improving outcomes in the inhalation injury group. The first step towards implementing evidenced-based practice is to review the relevant literature (Eccles and Grimshaw 2004).

**Aims**

Due to the complexity of the body’s response to inhalation injury, the RPH MBT decided to focus initially on pharmacological management. The aims of this review are therefore to:

- Determine the pharmacological options for management of inhalation injury; and
- Examine the levels of evidence to support various pharmacological interventions.

**Methods**

An on-line literature search through PubMed was completed using the following search terms: “inhalation injury”, “burn”, “pharmacomanipulation”, and “medication”. Where possible, all links and bibliography reference articles were explored.

**Results**

A total of 47 papers including 1 internet citation matched the search terms. Of the papers, one was a human case series with historical controls (n = 90), 2 were retrospective descriptive case series (n = 80, n = 98), 2 studies reported an overlapping human case series (n = 6), 34 were examinations in animals, 8 were expert opinion or reviews and the remainder were from non-reliable or public relations sources.

![Flow diagram describing the patho-physiological pathways involved in the body's response to inhalation injury (and burns).](image-url)

**Figure 1** Flow diagram describing the patho-physiological pathways involved in the body's response to inhalation injury (and burns).
Table 3 presents the results of the review according to the etiology of the negative effects of inhalation injury.

Discussion
PubMed is a well recognized first contact database for high profile journals and high impact medical literature. Warranted, this paper does not provide an exhaustive literature search. but the likelihood is that the results represent the current medical practice in pharmaco-management of inhalation injury.

The primary aim of this study was to determine the level of evidence in order to determine best practice. In summary, according to the Australian National Health and Medical Research Council (NH&MRC) guidelines (1999), at best this review suggests, level III-3 evidence (comparative study, historical controls) for the clinical use of alternating nebulized heparin alternating with the mucolytic agent, acetylcystine. Secondly, the review reveals level IV (case series) evidence promotes short term positive effects from aerosolized surfactant and negative outcomes associated with prophylactic antibiotics and corticosteroid use to ameliorate acute inhalation injury.

The first aim of this review was to examine the options for manipulation of the inflammatory pathways using medication. The findings are discussed in detail below with reference to the patho-physiological pathways in Table 2.

Table 2 Pathophysiological processes that have been linked to the etiology acute lung injury post smoke inhalation

<table>
<thead>
<tr>
<th>Pathophysiological processes</th>
<th>Inhalation injury</th>
<th>Significant burns (n=79) (&gt;20%TBSA*)</th>
<th>All burns admitted (n=717)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airways oxidative stress</td>
<td>Beta 2 – agonists</td>
<td>Nitric oxide</td>
<td></td>
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<tr>
<td>Airways cast formation</td>
<td>Nitric oxide</td>
<td>Eicosanoids – Prostaglandins</td>
<td></td>
</tr>
<tr>
<td>Loss of pulmonary surfactants</td>
<td>Eicosanoids – Thromboxane</td>
<td>Neutrophil activation/chemotaxis</td>
<td></td>
</tr>
<tr>
<td>Airways bronchoconstriction</td>
<td>Leukotrienes</td>
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**Nitric oxide (NO)**
Increased inducible nitric oxide synthase (iNOS) and resultant NO levels have been isolated in lung tissue as a result of inhalation injury (Enkhbaatar et al 2003). Up-regulation of cytokines, primarily interleukin-1, and endotoxin release are implicated as causes for NO presence as both are found in increased amounts after burn and inhalation injury. Increased levels of NO lead to loss of hypoxic vasoconstriction. Murakami and Traber (2003) reported the ensuing vasodilation leads to an increase in bronchial blood flow by up to 800%. Additionally, loss of hypoxic vasoconstriction allows poorly ventilated lung segments to receive increased blood flow (Enkhbaatar and Traber 2004). This creates ventilation/perfusion mismatch, increases the pulmonary shunt fraction, and overall results in lower oxygen saturations in the blood.

Furthermore, Enkhbaatar and Traber (2004) comment that increased respiratory compromise is created by the oxidizing and nitrating action of high concentrations of NO. Nitrous oxide becomes cytotoxic and a pro-inflammatory agent by reacting with O₂⁻ to form peroxynitrate (ONOO⁻). Peroxynitrate causes oxidation and nitration, producing further tissue damage and lung inflammation (Enkhbaatar and Traber 2004).

To reduce nitric oxide production, Enkhbaatar and colleagues (2003) examined the use of an iNOS inhibitor, BBS-2, on sheep. BBS-2 showed beneficial effects on pulmonary gas exchange and shunt fraction, lung lymph flow, lung water content, airways obstruction, airways blood flow and airways pressures.

**Cyclooxygenase (COX) pathway**
Elevated prostacyclin and thromboxane A₂ are significantly elevated post burn and smoke inhalation (Kimura, Traber et al 1988). Both are produced by the action of the enzyme
COX. A number of studies consequently look at nonsteroidal anti-inflammatory (NSAID) medications. Ibuprofen was shown by Stewart and colleagues (1990) to reduce early-onset lung water after smoke inhalation injury alone, or in combination with a thermal injury in adult rabbits. Sakurai and colleagues (1998) demonstrated that ibuprofen improved intestinal organ blood flow during the acute hypovolemic period. Finally, Kimura and colleagues (1988) found that ibuprofen attenuated the elevation of lung lymph flow, microvascular permeability and pulmonary edema in an ovine model.

The advantage of the nonselective COX inhibitor, ketorolac, is its availability as a parenteral preparation. Enkhbaatar and colleagues (2003) showed in sheep that it slowed the decline in the PaO2/FiO2 ratio, the increase in lung lymph flow and significantly lowered bronchial obstruction and airway pressures. They found that ketorolac had multiple favorable pharmacodynamic attributes including significantly less cardiac myocardial contractility depression, hemoconcentration, and bleeding tendencies.

Conversely, Abdi and colleagues (1995) iterated concern regarding the use of ibuprofen. They found that myocardial depression seen post inhalation injury is worse in animals treated with ibuprofen. This was not seen with ketorolac by Enkhbaatar and colleagues (2003).

Other than a strong association, the role of eicosanoids in inhalation injury is less well understood. Prostacyclins prevent increase in microvascular permeability. Kimura and colleagues (1988) propose that the COX inhibition stabilizes lysosomal membranes, inhibits leukocyte migration and prevents the release of oxygen free radicals. Additionally, COX inhibitors are reported to lower plasma NO levels by down regulating iNOS (Enkhbaatar et al 2003).

Lipoxygenase pathway
Several studies have implicated leukotrienes in the etiology of edema after smoke exposure. Witten and colleagues (1990) demonstrated and increase in leukotriene B4 in bronchoalveolar lavage (BAL) after inhalation injury in rabbits. They further demonstrated that piriprost, a leukotriene synthesis inhibitor, given 1 hour prior to smoke exposure resulted in attenuation of the swelling in type 1 alveolar cell epithelium, BAL leukotriene B4, prostaglandin E2 and thromboxane B2 levels at 1 hour post smoke exposure. Hales and Musto (1995) compared a combined COX and lipoxygenase inhibitor (BW-755C) to the NSAID, indomethacin. They found that BW-755C prevented edema, whereas indomethacin did not.

Finally, Janssens and colleagues (1994) compared three eicosanoids by inhibiting them in isolation. They gave sheep either BW-755C, U-63557A (a specific thromboxane synthetase inhibitor), or indomethacin. They found that neither indomethacin nor U-63557A prevented the increase in lymph flow or reduced the lung wet-to-dry weight ratio. However, these did blunt and delay the rise in airway pressure and the rises in pulmonary arterial pressure and pulmonary vascular resistance. They concluded that leukotriene B4 may be the main oedematogenic eicosanoid. This was echoed by Abdi and colleagues (1995) who looked at the effects of ibuprofen on bronchial blood flow in the ovine model. They concluded that vasodilatory prostaglandins do not play a major role in the bronchial vascular response to smoke inhalation injury. This last comment conflicts with the above mentioned COX annotations.

B2 agonists/bronchodilators
These are successful in the management of airways pathology for conditions such as asthma, causing bronchodilation and subsequent increase in airway caliber (Palmieri et al 2006). A controlled experiment by Palmieri and colleagues (2006) looked at continually nebulized albuterol in sheep. Results were promising; with comparison to the control group, those given the albuterol had lower pause and peak inspiratory pressures, decreased pulmonary trans-vascular fluid flux, a significantly higher PaO2/FiO2 ratio and decreased shunt fraction.

Oxidative stress
There is increased oxygen-free radical activity after smoke inhalation (Maybauer et al 2005). This arises from both direct
inhibition of xanthine oxidase. A study on sheep by Ahn
Drug Design, Development and Therapy 2008:2

13

agent is allopurinol. This is proposed to decrease O$_2$
edema or pulmonary gas exchange. Another unsuccessful
delivery to smoke exposed sheep failed to improve lung
Maybauer and colleagues (2005). They found that nebulized
converts the superoxide radical to peroxide, was looked at by
the use of manganese superoxide dismutase, an enzyme that
Shimoda et al 2006; Morita, Traber et al 2006). In contrast,
air aerosolized vitamin E and demonstrated decreased pulmo-
increased microvascular permeability, and edema formation (Stothert et al 1990).

Endogenous production of oxidizing agents is mostly
released from marginating polymorphonuclear leukocytes
(Brown et al 1988). In an ovine experiment, Murakami
and Traber (2003) used nitrogen mustard to suppress bone
marrow. They found, in the leukocyte-depleted sheep, that
smoke-inhalation pulmonary edema and vascular perme-
were prevented. There was also significantly less
lipid peroxidation and cellular oxidation (Murakami and
Traber 2003).

There are a number of methods proposed to curb damage
associated with oxygen-free radicals. A number of papers
look at the use of anti-oxidant agents. Brown et al looked at
the use of dimethylsulfoxide, an O$_2$-free radical scavenger
(Brown et al 1988). Their trial had four arms; control sham
group, sheep treated by dimethylsulfoxide or heparin, and
sheep given both. They found that dimethylsulfoxide signi-
ficantly diminished the pulmonary lymphatic response,
concluding this was a result of attenuated rise in microvas-
cular permeability.

Several other studies showed promising results with the
administration of various anti-oxidant agents. La
Londe and colleagues (1994) found that aerosol delivery of
deferoxamine-pentastarch complex prevented progression to
pulmonary edema. Three studies by Wang and colleagues
(1996, 1997, 1999) found that lazaroid analogue U75412E,
a free radical scavenger, ameliorated interstitial edema. Vita-
min E (alpha-tocopheral) is another example of an oxygen
superoxide scavenger. Depleted vitamin E levels have found
to occur after combined burn and inhalation injury (Morita,
Shimoda et al 2006). Morita and colleagues administered
aerosolized vitamin E and demonstrated decreased pulmo-
mary oedema and significant improvement in pulmonary gas
exchange in sheep with burn and smoke inhalation (Morita,
Shimoda et al 2006; Morita, Traber et al 2006). In contrast,
the use of manganese superoxide dismutase, an enzyme that
converts the superoxide radical to peroxide, was looked at by
Maybauer and colleagues (2005). They found that nebulized
delivery to smoke exposed sheep failed to improve lung
edema or pulmonary gas exchange. Another unsuccessful
agent is allopurinol. This is proposed to decrease O$_2^-$ by its
inhibition of xanthine oxidase. A study on sheep by Ahn
and colleagues (1990) looked at the effects of allopurinol on
sheep. They found no significant difference in those managed
with or without allopurinol.

There are several papers looking at approaches to attenu-
ate neutrophil response. The selectin family of anti-adhesion
molecules mediate neutrophil migration by allowing endothe-

tial cell contact (Katagiri et al 2002). In sheep, Katagiri
and colleagues (2002) found that pre-treatment with the antibody
for L-selectin called leukocyte adhesion molecule (LAM) 1
hour after smoke exposure decreased the lung lymph flow and
pulmonary permeability. Similarly, several authors reported
that the oligosaccharide Sulfo lewis C, a putative ligand of
E-selectins, attenuated lung injury after smoke exposure
on sheep (Tasaki et al 1998; Mandel and Hales 2007). In a
comparable experiment, Chandra and colleagues (2003) gave
an anti-P-selectin antibody. This did not protect against lung
injury in sheep exposed to smoke (Chandra et al 2003).

**Inflammation and Airways Cast Formation**

Pathological lung specimens, after inhalation of smoke,
demonstrate the presence of obstructive casts in the airways.
In sheep, Cox and Burke (2003) found that casts formed at
all three studied airways levels (bronchial, bronchiolar and
terminal bronchiolar). Obstructive changes were maximal at
24 hours in large airways, and rose continually to the cut of
time of 72 hours at the bronchiolar level. Casts are composed
of epithelial cells, neutrophils, mucus and fibrin. Mucosal
hyperemia, increased microvascular permeability, acute
inflammatory cell influx, exfoliation of epithelial lining, and
mucous secretion are the causative factors (Cox et al 2003).
Airway obstruction leads to further ventilation/perfusion mis-
mismatch, and complications such as atelectasis and pneumonia.
Barotrauma may ensue from overstretching of alveoli supplied
by the remaining patent airways (PatientPlus 2007).

One method to reduce cast formation is the attenuation of
the inflammatory response. The use of anti-inflammatories
and anti-adhesion molecules may be indicated for this rea-
son. In their experiment with dimethylsulfoxide, Brown and
colleagues (1988) found the administration of this O$_2$-free
radical scavenger also reduced airways cast formation (pres-
umably as a succeeding effect).

An alternate approach to over-coming airways obstruc-
tion is the use of heparin. The main action of heparin is
potentiating anti-thrombin III mediated inactivation of
thrombin. Heparin may also act as a free radical scavenger
(Tasaki et al 2002). There have been multiple experiments
looking at both parenteral and nebulized heparin. Cox
and colleagues (1993) found that in sheep given a heparin

Pharmaco-management of inhalation injuries for burn survivors
infusion, there was significant improvement in oxygenation, with less barotrauma and pulmonary edema. At necropsy, those treated with heparin had significantly fewer tracheobronchial casts.

Murakami and colleagues (2002) found that high dose heparin attenuated lung dysfunction after combined smoke and septic lung injury. They found in histological specimens, decreased lung cellular infiltrates, lung edema, congesting, and cast formation. Their study differed from Cox and colleagues (1993), in that the sheep were also exposed to *Pseudomonas aeruginosa* and heparin was administered by nebulization. Conversely, Murakami and colleagues (2002, 2003) in an analogous experiment to one previously reported from the same setting, found that high dose heparin did not prevent lung dysfunction after combined smoke and septic lung injury. In this experiment the heparin was given via intravenous infusion. Nebulized heparin was effective in the applicable arm in the controlled experiment by Brown and colleagues (1988).

More importantly, in a comparative case series with historical controls by Desai and colleagues (1998), the effect of giving a regime of aerosolized heparin alternating with a solution of 20% acetylcystine was performed on a pediatric human population. Acetylcystine is a mucolytic agent, and hence should diminish airway cast formation. The study included 90 patients with a mean age of 8 years, suffering from inhalation injury, diagnosed by bronchoscopy. They found a significantly decreased mortality, incidence of atelectasis, and re-intubation rate in the treatment group.

Another approach to overcoming airways cast obstruction is the administration of antithrombin. It should have comparable effects to heparin. This was confirmed by Murakami and colleagues (2002) in sheep exposed to smoke and septic injury an infusion of human recombinant antithrombin.

Lastly, as casts are also composed of fibrin, Enkhbaatar and colleagues (2004) experimented with aerosolised tissue plasminogen activator (TPA) in sheep. TPA lyases fibrin clots. They found that TPA, attenuated airways obstruction as expected.

**Aerosolized surfactant**

Within the lung alveoli, there is a delicate balance between negative intrathoracic pressure, alveolar wall surface tension and tissue elasticity. The presence of surfactant lining the alveolar walls results in lower alveolar surface tension and stabilizes the fluid balance in the lung. The removal of which allows increased microvascular permeability and subsequent lung edema formation. This has been demonstrated in multiple animal experiments (Brendenberg et al 1983; Nieman and Brendenberg 1985; Nieman et al 1990; Wang et al 1993). Pulmonary surfactant also assists with removal of inorganic dust particles, opsonization of bacteria and activation of alveolar macrophages (Pallua et al 1998).

The loss of surfactant is thought to arise from: direct deactivation or inhibition of the alveolar surfactant by oxidants, proteases, fibrin and protein rich exudate; incorporation of hyaline membranes in fibrin polymers; lifting of the surfactant away from the alveolar wall by edema; and disturbed synthesis resultant of damage to the type II pneumocytes (Wang et al 1993).

The benefit of surfactant therapy has been demonstrated in the context of ARDS and infant respiratory distress syndrome (Wang et al 1993). However, there is a dearth of literature regarding it application in the setting of burns. Pallua and colleagues (1997, 1998) provides two case series of 4 and 2 patients respectively, with severe burns and poor prognosis that benefited from surfactant therapy. After the limits of mechanical ventilation had been reached, they introduced intrabronchial surfactant via bronchoscopy. They subsequently found that there was temporary improved gas exchange, an increase in arterial oxygenation (PaO2), a reduction in required inspiratory O2 concentration (FiO2), and improved lung compliance (Wang et al 1993; Pallua et al 1997).

**Steroids**

Controlled experiments thus far looking at the usefulness of steroids in burn and inhalation injuries have been disappointing. No direct data support their use in smoke inhalation and this was confirmed by a recent disaster case series report (Herndon et al 1988; Cha et al 2007). In fact, due to their immuno-suppressive effects, steroids are likely to lead to the increased risk of infection and delayed wound healing. Nieman and colleagues (1991) found in sheep, that methylprednisolone did not protect the lung from the acute physiological consequences of inhalation injury.

**Prophylactic antibiotics**

Pulmonary infection is a sequela of inhalation injury, and hence antibiotic prophylaxis is not considered here in depth. Patients with pulmonary damage from inhalation injury are at increased risk for secondary bacterial infection, commonly *Staphylococcus aureus* and *P. aeruginosa*. Though appealing in concept, usage of antibiotics is recommended on clinical grounds of definitive microbiologic evidence.
of infection only (Herndon et al 1987). Administration of prophylactic antibiotics increases the risk of resistant organism emergence.

Clinical implications and future studies

The research on inhalation injuries thus far has given important insight into the etiology and potential pharmacointerventions. The amalgamated algorithm outlining the key patho-physiological steps also highlights the various points at which interventions have been proposed (Figure 1).

Of note, there are several parallel pathways that eventually result in organ hypoxemia, suggesting that multiple medications may be warranted in for meaningful intervention. This was illustrated in the study by Brown and colleagues (1988) who looked at the use of heparin and dimethylsulfoxide. Both of the groups treated with either of these performed favorably but those given both outperformed those given either preparation alone.

The physical management of pulmonary edema, airway obstruction by cast formation and sputum, ventilation/perfusion mismatch and atelectasis was not within the scope of this review. Ventilation strategies as well as physical (or respiratory) therapy are obvious adjuncts to pharmacotherapy and must be considered as part of a multi-disciplinary approach to improving inhalation injury outcomes. The recent review paper by Cancio and colleagues (2007) provides an excellent summary of ventilation and artificial lung strategies for management of inhalation injury. Finally, cell replacement therapies delivered into the lungs remain a largely unexplored but promising area with respect to ‘surgical’ management of tissue damage in the lungs after inhalation injury (Duncan et al 2005).

Conclusion

There are several striking limitations of the literature. Firstly, the discussion illustrates the complicated immunobiochemical pathways that have conflicting roles and importance throughout the journal papers, complicating integrated understanding. The experiments and hypotheses generally only consider one process in isolation. Secondly, there is a complete absence of high quality data collected from humans. At best, human case series data supports short term positive effect from aerosolized surfactant and, negative outcomes from prophylactic antibiotics and corticosteroid use.

It is fair to comment, within the ‘ABC’ paradigm of burns care, with satisfactory airways and circulatory management strategies, the ability to control the inflammatory response of the lungs with medication lags in comparison. The advances in the management of inhalation injuries may well herald the next significant step forward in severe burn management. However, thus far, the clinical use of pharmaco-therapies for inhalation injuries is limited by the lack of commercial availability, dearth of human trials and confounding experimental results.

Disclosure

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Bartley et al.


