PAPERS

A review of the use of corticosteroids in the management of pulmonary injuries and insults

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Despite the multitude of types of insult and injury that can occur to the lungs, their response both macro- and microscopically is uniform, although the time-course for the sequence of events varies with the severity and duration of the primary stimulus.

In 1968, it was noted that during membrane haemodialysis, transient neutropenia occurred and the neutrophils were found sequestered within the pulmonary microcirculation (Kaplow & Goffinet, 1968). Further investigation indicated that complement activation, and in particular the generation of C5a, causes leucocyte aggregation in the lung (Jacob *et al.*, 1980). Platelets and neutrophils then produce a secondary injury as the result of release of vaso-active substances and toxic oxygen radicals (Hechtman *et al.*, 1978; Demling *et al.*, 1980). The neutrophils then produce proteases which destroy structural lung proteins such as collagen, elastin and fibronectin which order the interstitial cell framework of the lung (Janoff *et al.*, 1979; McDonald *et al.*, 1979). The normal pulmonary defence enzymes such as alpha-antitrypsin have been shown to be inactivated in the presence of super-oxide radicals and oxygen, while circulating Hageman factor, fibrinogen and complement promote further local inflammatory changes.

Although Type I alveolar cells are the least numerous of the lung cell types, they cover 95% of the interalveolar septae and as a consequence of their large surface area are extremely susceptible to air- or blood-borne insults. To compound this susceptibility, Type I cells are incapable of division (Scadding & Cumming, 1981). The larger Type II pneumocytes, which normally secrete surfactant, are, however, less susceptible to injury and proliferate as a consequence of Type I cell necrosis. They temporarily repopulate the damaged alveolar walls and later transform to functional gas-exchanging Type I cells. However, before this transformation occurs, the alveolar septae are thickened and the development of fibrosis is manifest, with disruption of normal cell

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relationships and channels of communication between epidermal and endothelial cells and supporting interstitial cells (Rinaldo & Rogers, 1982).

These processes have been established as developing after various lung insults, and their elucidation has suggested that for the first time specific therapy may be able to prevent the cascade of events with its formidable clinical sequelae. For almost 30 years corticosteroids have been thought to offer a key to this problem. They have been shown to inhibit complement-induced leucocyte aggregation (Hammerschmidt et al., 1979), and to block the increase in microvascular permeability following a variety of insults in experimental animals and humans (Brigham et al., 1981; Sibbald et al., 1981), probably as the result of inhibiting super-oxide radical release (Bihan & Tinker, 1982). Stabilization of cell and lysosomal membranes also occurs and some reports show improved pulmonary circulatory flow related to a fall in pulmonary venous resistance (Lucas & Ledgerwood, 1981; Svennevig et al., 1980; Dietzman & Lillehei, 1968). There follows an examination of some common clinical situations for which the use of steroids remains in contention.

In 1964, Hamelberg induced aspiration pneumonitis in dogs using sterile gastric juice introduced into the lungs via an endotracheal tube. Hydrocortisone was given to one group of animals, and with respect to a control group, chest radiographs showed a more rapid improvement (Hamelberg & Bosomworth, 1964). The number of animals in this study was small and the end-points somewhat hazy, but further investigators were prompted to repeat similar experiments under more controlled conditions. Downs and his co-workers administered 0·1 N hydrochloric acid (pH 1·0) to spontaneously breathing dogs and found the response unaltered by methyprednisolone in pharmacological dosage (Downs et al., 1974). The mortality in the study was 80% and criticism was made that perhaps too severe an insult had been administered; therefore the experiment was repeated, this time instituting controlled positive pressure ventilation; the mortality in both control and steroid-treated groups dropped to 60% but there was again no difference in the clinical course of either group (Chapman et al., 1974a). Generally, these results have been confirmed in a variety of animals (Chapman et al., 1974b; Dudley & Marshall, 1974) and in the few studies involving humans. In particular, Wolfe's carefully controlled study showed no difference in mortality between patients treated with or without steroids, but noted an increase in bacterial lung infections in the steroid-treated group (Wolfe et al., 1977).

Because of the clinical and pathological similarities between aspiration syndrome and near-drowing, Sladen gave seven such patients methylprednisolone (5 mg/kg per 24 hrs i.v.) (none died) and compared them with three patients who were not given steroid, one of whom died (Sladen & Zauder, 1971). Modell has reported his experience for the utilization of steroid therapy with an animal model (Calderwood et al., 1975), and showed no improvement in survival or arterial oxygen saturation in 80 dogs subjected to freshwater near-drowning. His study in 1976 of 91 consecutive near-drowning victims (Modell et al., 1976) was retrospective and uncontrolled but of 38 patients who were not given steroids two died (5%) while of 52 patients given steroids, eight died (15%). Steroids used included 'methylprednisolone, dexamethasone, prednisolone and hydrocortisone in doses ranging from therapeutic to pharmacologic'. While acknowledging that this study was not designed to test the efficacy of steroid therapy the conclusions of the workers were that neither steroids, nor prophylactic antibiotics, were of any clinical value in this situation.

The other common case of exogenous lung injury is smoke inhalation. There is relatively little experimental work to suggest the advantageous use of steroids in this situation. Dressler subjected rats to white pine smoke and his results appeared to show a beneficial effect, as measured by a reduction in interstitial oedema, in methyl-prednisolone treated animals but his results are somewhat difficult to interpret when one considers that the control mortality varied between 34% and 68% (Dressler *et al.*, 1976).

Beeley indicated that in rabbits exposed to Acreolein at 376 parts per million for 15 minutes, a placebo group showed a significantly increased mortality when compared to steroid-treated animals either given as a single dose or 12 hourly (Beeley *et al.*, 1982); however, the number of animals involved in this study was small, the histological damage was similar in all three groups, and all the animals were sacrificed at three days so that full assessment of mortality was invalid. A study performed by Welch (1977) used goats exposed to nitrogen tetroxide and showed no beneficial effect from the use of steroids on acute pulmonary dysfunction and indeed suggested that small airway obstruction in the early phases of injury was worse in the steroid-treated group.

The best human study has been performed by Moylan, who studied 26 patients all with objective bronchoscopic evidence of inhalational injury in a double blind study using methylprednisolone in a pharmacological dose (30 mg/kg IV stat, then 30 mg/kg qid for 48 hrs) as an initial intravenous bolus and then 6 hourly for 2 days. The mortality for the steroid-treated groups was 53% and in the control group 30%. The steroid group had nearly three times the incidence of infective complications either as pneumonias or bacteraemias (Moylan & Chan, 1978).

A number of studies have shown an inhibitory effect for various steroids on intracellular killing, phagocytic bacteriocidal activity by neutrophils and also a reduction in the bacteriocidal activity of monocytes (Fuenfer *et al.*, 1975; Rinehart *et al.*, 1974). In a study giving normal and burned rats pseudomonas organisms by aerosol, steroid treatment resulted in a depressed ability of the lungs to clear bacteria related to a reduction in the migration of macrophages within the lung (Skormit & Dressler, 1974). Indeed, alveolar macrophages were eliminated from the lung within 12 hours of steroid administration and since the re-supply time for these cells is between 36 and 48 hours it would be anticipated that further steroid administration would keep their levels low. The mechanism for the post-steroid suppression of intracellular killing of neutrophils is thought to be related to inhibition of NADH oxidase which is essential for the production of hydrogen peroxide, the primary agent responsible for bacterial killing (Fuenfer *et al.*, 1975; Yielding & Tomkins, 1959). A combination of these factors may thus explain the increase in late pulmonary infective complications in steroid-treated groups (see above).

In the late 1960s anecdotal reports suggested that steroids might benefit the clinical course of patients who had sustained pulmonary contusion as a consequence of blunt chest injury (De Muth & Smith, 1965; Fulton *et al.*, 1970). Subsequent animal studies showed a diversity of opinion with regard to the efficacy of steroids in this situation; some studies showed that the effect depended upon the nature of the steroid given while others indicated that the relationship depended upon the dosage (Shephard *et al.*, 1969; Trinkle *et al.*, 1975; Frantz *et al.*, 1974). Frantz in 1974, using an experimental model, was able to cause a reproducible focal concussive lesion and in animals treated with methylprednisolone showed a dramatic reduction in the volume of contused lung in

comparison with control groups, although within the affected areas there were no pathological differences. The effects were attributed to a reduction in pulmonary vascular resistance (Frantz *et al.*, 1974). Trinkle *et al.* (1975) reported on patients who had sustained direct chest injury and his results appeared to indicate a marked benefit from the use of steroid as evidenced by the reduction in the length of intensive care and hospital stay, and also infective complications and mortality. However, although his two groups of patients were comparable with respect to their injury, the treatments given were completely different, not only with respect to the administration of steroids but also with relation to ventilation, fluid requirements, diuretics and intercostal nerve blocks. Svennevig's study in 1980 compared 20 patients with pulmonary contusion, all of whom received standard treatment with randomization into steroid and non-steroid groups. No patient died in either group but there appeared to be a shorter period of hospitalization, requirement for ventilation and less infective complications in the steroid-treated group (Svennevig *et al.*, 1980). Evidence from large numbers of patients with this condition has yet to be reported, although Lucas in 1984 could find no pulmonary benefit from the use of steroids in patients who had sustained blunt injuries to chest and other body regions (Lucas & Ledgerwood, 1984).

In early retrospective reports during the 1960s and early 1970s the use of steroids in fat embolism syndrome indicated that there may be some pulmonary benefit obtained (Ashbaugh & Petty, 1966; Fischer *et al.*, 1971).

In the 1970s a number of animal studies were performed administering oleic acid to simulate the effects of fat embolism and a number of workers suggested that there was better ventilation/perfusion matching together with improved cardiac output and improved oxygenation when such animals were given steroids (Hofman & Ehrhart, 1981; Bradley *et al.*, 1972; Kreis *et al.*, 1973). Some workers have reported a reduction in pulmonary oedema in such dogs treated with methylprednisolone and it has been postulated that the benefits have been related to a reduction in pulmonary venous resistance and possibly also due to the improved proliferation and maturation of Type II pneumocytes (Jones & King, 1975; Cheney *et al.*, 1979). Stoltenberg in 1979 randomized 64 patients with lower limb fractures into placebo, steroid and hypertonic glucose treatment groups. In patients treated with methylprednisolone (1 g methylprednisolone I.V. given on admission and repeated at 8 and 16 hrs) there was an improvement in arterial oxygenation and no patient in this treatment group developed fat embolism syndrome, while three patients in the placebo group and two patients in the hypertonic glucose group developed the syndrome. However, numbers were such that the difference in mortality was not statistically significant (Stoltenberg & Gustilo, 1979). Schonfield *et al.* (1983), in a prospective randomized double blind study of high-risk patients, showed a significant difference in the incidence of fat embolism syndrome in steroid-treated patients (dose 7·5 mg/kg every 6 hrs for 12 doses). They were unable to find any complications related to steroid treatment and suggest that prophylactic corticosteroid treatment is indicated in patients at high risk of the syndrome.

Current ideas on the pathogenesis of the fat embolism syndrome postulate the liberation of neutral fat globules from bone marrow following injury, followed by filtration in the pulmonary microcirculation. This embolization is usually asymptomatic but is followed by the direct action of lung lipoprotein lipases which hydrolize neutral triglycerides to glycerol and highly toxic free fatty acids. This process takes 24–27 hours

and explains the latent period before full development of the so-called fat embolism syndrome (Herndon *et al.*, 1971). Thus, the administration of steroids to such patients is to pre-treat the condition, as in the majority of cases this administration is before the full action of the lipases occurs. Further work is urgently required to identify those patients at high risk of the syndrome to allow such prophylaxis, as at present the blind administration of such potent agents cannot be wholeheartedly recommended.

Despite the many theoretical attractions for the use of steroids in many forms of chest injury and insult, there are as yet few definite situations where their use can be unreservedly recommended. Certainly, at present the weight of evidence suggests that for smoke inhalation, aspiration and near-drowning, steroids cause more harm than good. With regard to blunt chest injury and fat embolism syndrome, more promise is shown, but considerably more prospective work will be required before the routine early use of steroids can be advocated.

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