The Effect of Anti-Prostaglandin Therapy in an Acute Respiratory Distress Syndrome Induced in Experimental Cattle by the Oral Administration of 3, Methylindole

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Introduction

Oral and intravenous administration of 3, methylindole (3MI) to yearling and adult cattle results in the development, usually within 12-24 hours, of an acute respiratory distress syndrome (1, 2), the major pathological features of which are pulmonary congestion and oedema, hyaline membranes, interstitial emphysema and alveolar epithelial hyperplasia (2, 3). The practical implications of this phenomenon are that it almost certainly represents one step in the pathogenesis of acute bovine plumonary emphysema (ABPE) or fog fever (1, 4). In certain countries, this is a common and costly disease problem for which neither adequate prevention procedures nor effective therapeutic regimes currently exist. The following experiment was designed to investigate the effect of the anti-prostaglandin compound flunixin meglumine (Finadyne, Fisons Animal Health, UK/Schering Corporation, USA) in what is now generally accepted as a valid experimental model for ABPE/fog fever, namely 3MI intoxication.

Materials and Methods

Experimental design

Twelve yearling Friesian steers were obtained from local sources. Throughout a one week "settling in" period no significant clinical abnormalities were detected. During this period and the subsequent trial the steers were housed together in a semi-open yard with hay and water available *ad libitum*.

The basic design of the trial was as follows:

Group	No.	Administration of 3MI*	Test treatment**
1	5	Yes	Yes
2	5	Yes	No
3***	2	No	No

* 3MI (Sigma Chemical Co. Ltd., Poole, Dorset, U.K.) administered via a stomach tube as a suspension in approximately 5 L cold water at 0.1 g/kg.
** Flunixin meglumine administered intravenously at the manufacturer's recommended rate (for cattle) of 2.2 mg/kg.
***Environmental controls.

3MI was administered on the morning of day 0 immediately after the routine clinical examination. Flunixin meglumine was administered on three consecutive days starting from the morning of day 1.

The decision when, and which steers were to be treated rested with one clinician (HAG) and this, together with the task of carrying out subsequent treatments, was the sole responsibility of that person. The decision to treat was based on clinical criteria established by examinations carried out by HAG several times daily during day 0 and 1, at times other than those of the routine twice daily examinations that were the responsibility of a second party (RD) who had no knowledge of which animals were undergoing or had undergone treatment. Criteria for treatment were either a doubling of the initial (day 0, pre-dosing) respiratory rate or else an increased respiratory rate with obvious dullness. Decisions as to allocation of steers to Groups 1 or 2 were

made on the basis of alternate allocation as and when necessary criteria were established.

Clinical observations

Cattle were examined once daily prior to day -1 (09.00 hrs) and twice daily thereafter until day 7 (09.00, 17.00 hrs). Information regarding respiratory rate and character and degree of dullness were recorded at the time of each routine examination.

Pathological procedures

Initially it was intended to slaughter two calves from each of Groups 1 and 2 on day 4 and the remainder on day 7; in the event a number of calves died outwith these times (Table 1) and procedures were adjusted accordingly.

Slaughtered steers were examined pathologically within minutes of being shot and ex-sanguinated. Those that died were examined within a few hours of death. Post-mortem examination was limited to the contents of the thoracic cavity. Lungs, trimmed of heart, diaphragm, fat, etc., were weighed and therafter, examined grossly and photographed. Tissues were removed from standard sites for histopathological study following fixing and staining by conventional methods.

Results

Clinical observations

Information regarding designation bodyweights, dose of 3MI administered, fates, survival times, lung weights and pathological features of individual animals are summarized in Table 1.

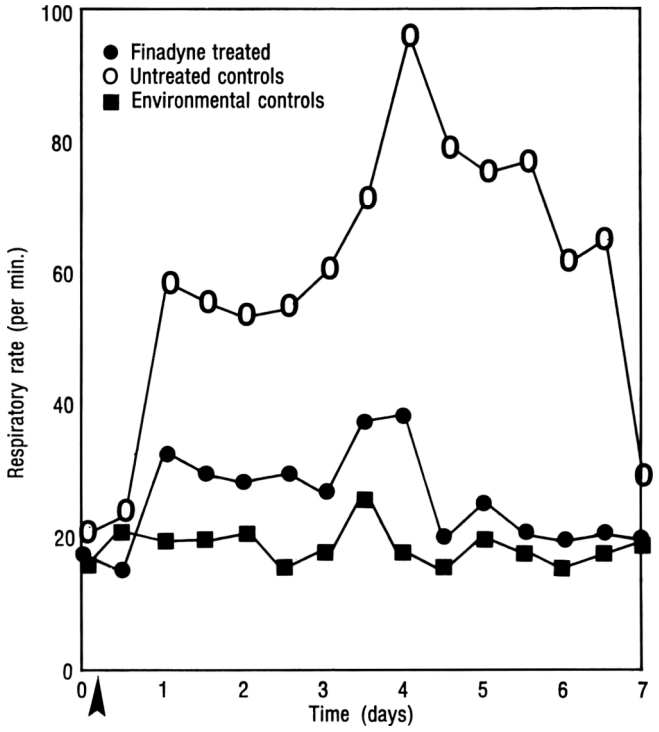
Two steers (1, 6) died overnight between day 0 and 1 but as no marked respiratory response had been detected on the evening of day 0 neither received the test treatment. (For the sake of simplifying the presentation of data these animals have been alloted to Groups 1 and 2 respectively but they are not considered further except as examples of severe 3MI-induced pulmonary disease.)

By the morning of day 1, five of the surviving eight calves had more than doubled their pre-dosing respiratory rates and since two others were found to have also done so during one of the *ad hoc* examinations carried out a little later by HAG, all of the remaining eight calves were then allocated to either group 1 (treatment) or Group 2 (controls). Flunixin meglumine was therefore administered to the test 4 animal on the mornings of days 1, 2 and 3.

Soon after the first treatment was administered there was a prompt return to normal or near-normal respiratory rates, a situation that was maintained until the termination of the study except for one animal (2) which, although not excessively depressed, suddenly developed an increased respiratory rate on the evening of day 3 and the morning of day 4. Marked differences were recorded in the mean respiratory rates of the treated, untreated and environmental control steers and by the end of day 4, the treated steers were clinically normal with respiratory rates less than half those of the controls. (Figure 1).

Differences were also evident in the demeanour of the two groups, treated animals remaining bright and alert throughout whereas controls were persistently, and in two instances profoundly, depressed.

Figure 1. Mean respiratory rates of (i) 3MI dosed — flunixin meglumine treated steers (●), (ii) 3MI dosed — untreated steers (O) and (iii) environmental controls (■).



Pathological findings

Lungs of the two steers (1, 6) that died within 24 hours of receiving 3MI were heavy, firm and oedematous with extensive dilatation of the interlobular septa. On section, the tissues were fawn-purple, uniform in appearance with much oedema fluid being released from the lung tissue. In one animal there was marked interstitial emphysema. Microscopically, there was extensive pulmonary oedema with marked congestion, slight haemorrhage into the alveolar air spaces and a little hyaline membrane formation.

One control steer (7) was found dead on day 3. The lungs of this animal were very heavy (Table 1) due to extensive oedema and severe interstitial emphysema was particularly obvious in the caudal lobes. Microscopically, the distribution and degree of severity of pulmonary oedema was similar to that seen in the steers that died earlier (1, 6); however, there was also extensive alveolar epithelial hyperplasia. Epithelial hyperplasia was also present in many bronchioles and hyaline membrane formation was

widespread. Globule leucocytes were abundant in bronchial epithelia and in the submucosal glands and mast cells were found in large numbers throughout the lung tissue.

One of the two test steers slaughtered on day 4 (2) was similar, pathologically, to the control animal (8) examined on that day. Their lungs were both heavy and pale with extensive interstitial emphysema. Alveolar epithelial hyperplasia was present in all lobes with a small number of bronchioles showing a marked degree of epithelial hyperplasia. In contrast, the second test steer (3) slaughtered on day 4 had only slightly heavier lungs than normal (Table 1) although they were pale and rubbery. Microscopically, there was slight thickening of the alveolar walls in all lobes, mostly due to the presence of collagen and a small number of infiltrating neutrophils and eosinophils. There were only occasional foci of alveolar epithelial hyperplasia with a minor degree of bronchiolar epithelial hyperplasia.

The lungs of the animals slaughtered and necropsied on day 7 fell into two distinct groups. The weights of the lungs of the two test steers (4, 5) were only about half that of the two controls (9, 10). In addition, the lungs of the two treated animals were normal macroscopically while the lungs of the two controls were pale, firm, rubbery and, on section, of a uniform, dry appearance. Microscopically, most of the lung tissue of the two test animals was normal whereas there was marked alveolar wall thickening in the lungs of the two controls due to extensive alveolar epithelial hyperplasia.

Discussion

No detailed evidence is available to support the widespread practice of administering corticosteroids to cattle suffering from ABPE/fog fever and, since at the time of year the problem usually arises most breeding females are pregnant, their use is often followed by abortion (4). For this reason the use of the anti-prostaglandin compound, flunixin meglumine, was investigated. However, since only limited information is currently available regarding the action of 3MI metabolites on cells of the bovine respiratory tract and none appears to be available on the role of prostaglandins in 3MI-induced pneumopathy, this investigation was of an empirical nature.

Two steers, which exhibited a very prompt and severe response, died within 24 hours of receiving 3MI; they were thereafter excluded from the study except as examples of very severe 3MI intoxication. In the remaining eight animals, clearcut clinical differences were seen, depending on whether or not they received flunixin meglumine. These differences were still apparent seven days later.

The main pathological difference between the test and control steers was that there was far more severe and widespead alveolar epithelial hyperplasia in the untreated cases, even on day 7. In fact, unlike the controls, the lungs of one test steer slaughtered on day 4 and both test steers slaughtered on day 7 were macroscopically normal with few significant lesions even on histopathological examination. In addition, there were obvious differences in lungweights, the mean weight of the treated animals (3.1 kg) being very markedly lighter than that (5.9 kg) of the controls, even when these differences (1.4, 2.2 respectively) were expressed as a percentage of bodyweight. Marked differences were also found between the lungweights and pathology of the test and control steers slaughtered on day 7 (table 1). In fact the lung-weights of the test animals, when expressed as a percentage of bodyweight were almost identical to those of the normal (environmental control) animals.

Thus, the intravenous administration of an anti-prostaglandin compound to cattle previously dosed with 3MI resulted in a clearcut and beneficial therapeutic response. The basis of that response latterly was apparently due to a limitation in the extent and severity of alveolar epithelial hyperplasia. The clinically-apparent benefits on days 1, 2 and 3 were probably due to a reduction in the extent and severity of pulmonary congestion and oedema since it has been shown that these are the significant changes during the first two days post-dosing (2, 3).

References

1. Carlson, J.R. and E.O. Dickinson: 1978 Tryptophan-induced pulmonary edema and empysema in ruminants. In, Effects of poisonous plants on livestock. Ed. Keeler, R.F., Van Kampen, K.R. and James, L.F. Academic Press. 2. Logan, A., I.E. Selman, A. Wiseman, E.M. Allan and H.M. Pirie: 1982 in cattle: the effects of repeated dosage with 3, methylindole. Res. Vet. Sci., 34: 97. 3. Pirie, H.M., R.G. Breeze, I.E. Selman and A. Wiseman: 1978 Indoleacetic acid, 3-methylindole and type 2 pneumonocyte hyperplasia in a proliferative alveolitis of cattle. Vet. Rec., 98:259. 4. Selman, I.E.: 1982 D.V.M. Thesis, University of Glasgow.

Summary

Ten yearling Friesian steers were given 0.1 g/kg 3MI by stomach tube. The respiratory distress syndrome that subsequently arose was alleviated by the administration of flunixin meglumine. After seven days there were still distinct clinical differences between test and control cattle. The initial therapeutic response was probably due to a reduction in the severity of pulmonary congestion and oedema; the latter benefits were probably due to the differences between test and control steers in the extent and severity of alveolar epithelial hyperplasia.

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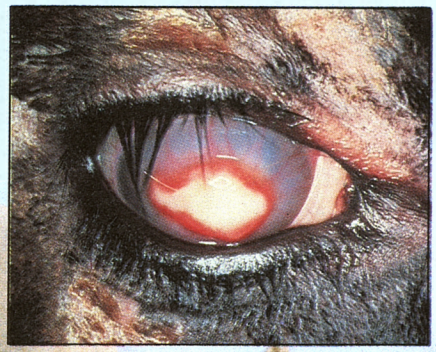

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