Effective treatment of bovine ephemeral fever

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The paper by Fenwick and Daniel[1] on the effect of ketoprofen on experimentally induced ephemeral fever may mislead readers on the clinical course of this disease and seems to suggest that no drug treatment has been effectively assessed. The detailed published assessments on phenylbutazone and flunixin meglumine and supporting biochemistry[2-4] have not been cited in their bibliography. The essential information in these papers is summarised in this letter.

Their methodology used twice daily observation which did not allow for short term effects of the drug to be taken into account. My experience of the value of continuous observation relates to two groups of four adult steers which were observed for clinical signs and sampled for haematological and biochemical analysis on an hourly basis for the period of their experimentally induced ephemeral fever (TD St George unpublished).[5] This close observation disclosed that the initial temperature rise was steep, that the fever was phasic and that the clinical signs related to fever.

The assessment of the clinical observations and biochemical and haematological analysis showed that the interval could be increased to 2-hourly with a small loss of accuracy for drug evaluation purposes.[2,4] Zero time was taken as the observational time that preceded a 1°C rise in rectal temperature. This reduced the variation for pooling data related to the onset of fever from animal to animal to less than 2 h. The interval between inoculation, with the same strain of bovine ephemeral virus as was used by Fenwick and Daniel,[1] and the onset of fever varied from 65 to 122 h. The fever in untreated cattle occurred in two phases separated by a normal rectal temperature for 2 to 12 h or else the second and third rises began before the temperature fell fully to normal. Three of the patterns have been illustrated by St George et al[2] and Uren et al[4] These variations limit the value of pooling rectal temperatures on a 12 hourly basis for drug efficacy assessment and obscures the phasic nature of the fever.

In the first febrile phase of experimental ephemeral fever, clinical signs were much milder than in later phases. Muscle trembling commonly occurred during the rapid rises of body temperature in both yearling and adult cattle. This trembling was apparently missed in all except three of the animals observed by Fenwick and Daniel.[1] The reluctance to put weight on one limb (which is expressed as lameness in natural disease) can occur in the first febrile phase but is commoner, more persistent and more severe in the subsequent phase or phases.

Treatment, or prevention, of clinical ephemeral fever with phenylbutazone and flunixin meglumine has been assessed in a total of 14 and 16 experimental cattle respectively. The results were described in detail by St George et al[2] and Uren et al.[4] Phenylbutazone (8 mg kg^{-1} intramuscularly) given before the first rise in temperature and 8-hourly thereafter for the expected duration of the disease could prevent fever and other signs of ephemeral fever completely, something unique for viral diseases. When the drug was given after fever commenced, the fever subsided within 4 h and other clinical signs were suppressed and remained normal while treatment was continued 8-hourly.

Flunixin meglumine was administered daily to a total of 16 cattle (doses 2.2, 4.4 or 6.6 mg kg^{-1}). Rectal temperatures returned to normal within 2 to 4 h but rose again 5 to 26 h later. The effect on other clinical signs was variable and there was the higher dose caused signs of toxicosis.

The fibrinogen concentrations in cattle treated with phenylbutazone[2,4] were markedly reduced in contrast to those treated with ketoprofen by Fenwick and Daniel.[1] However, ketoprofen was administered later in the course of the disease, after the inflammatory damage was in place. Fenwick and Daniel[1] also commented on the lack of effect on respiratory abnormalities. An increased respiratory rate occurs in each of the febrile phases. However, characteristically, dry then moist râles were first noted early in the second febrile phase with cough. Early treatment with phenylbutazone prevented respiratory signs but ketoprofen may have been given too late to have an effect.

Fenwick and Daniel[1] postulate that, as they used yearlings, plasma calcium may not have shown the effect as reported by Uren.[5] There is no doubt that plasma calcium concentrations are depressed in natural and experimental ephemeral fever in yearlings as well as adults.[3,6-8]

The observation by Fenwick and Daniel[1] that two Jersey heifers did not develop clinical signs of ephemeral fever cannot be taken as evidence of breed resistance. No serological or virological studies were undertaken.

Their experimental design did not test the full potential of ketoprofen as short interval observation is necessary to record clinical signs and to observe the more immediate effects of any drug under assessment. The remarkable efficacy of phenylbutazone in prevention or reversal of the clinical signs of ephemeral fever means that any drug should be assessed in parallel with the one that completely suppresses clinical signs. The remarkable change in animals treated effectively with anti-inflammatory drugs means that they are outwardly normal. Calcium borogluconate is a useful but short term supplementary treatment in specific cases where calcium related signs are life threatening[6] as for milk fever.[7] However, in spite of these responses to treatment the underlying viraemia and most of the biochemical dyscrasias which occur in ephemeral fever remain.[3,7] Creatine kinase levels rise rapidly in individual animals which start moving after treatment with phenylbutazone indicating muscle damage. Rest remains important with or without treatment.

A small proportion of cattle with ephemeral fever remain paralysed for days or weeks after fever has resolved and blood biochemical values related to inflammation have returned to normal. The pathogenesis of this form of paralysis, which is not related to the plasma calcium concentration, is still unresolved.

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REPLY

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We would like to point out that the intention of the trial by Fenwick and Daniel[1] was not to provide a detailed study of the clinical course of ephemeral fever nor of the pathophysiological changes occurring in the disease. These aspects have been adequately described in the past by the authors cited by Dr St George.

The intention of our study was to test the effects of ketoprofen on the clinical course of the disease once obvious signs, such as anorexia, lameness and/or stiffness and/or recumbency, had occurred. These are the signs that would normally be first noticed under field conditions and which would alert owners to the need for therapeutic action. Even rectal temperatures and respiratory rates would be less reliable indicators in the field because ephemeral fever usually occurs in the hot summer months when high ambient temperatures can confuse both of these signs.

As pointed out by St George, Uren et al[2] evaluated the effects of phenylbutazone and flunixin meglumine on the course of ephemeral fever, which was closely monitored from the onset of pyrexia. In their report the drugs were either administered 2 h (or 2 to 4 h for flunixin) after a 1° rise in temperature or 44 h and 18 h post-inoculation of the virus for phenylbutazone and flunixin respectively. As St George states, the start of therapy in the report of Uren et al[2] was thus earlier than that of keto-profen in the report of Fenwick and Daniel.[1] However, it is likely that the initiation of treatment in the latter study would be more similar to field situations where it is unlikely that cases would be treated before the onset of locomotor problems or within 2 to 4 h after the onset of fever. In most cases treatment would occur several hours after the onset of clinical signs and this is a logical time to evaluate a treatment unless it is being evaluated as a preventive measure.

In our report, ketoprofen was shown by statistical evaluation to effectively ameliorate the signs of stiffness and lameness within 12 h compared to cattle which received a placebo. Similarly, the mean duration of anorexia was reduced by 9 h in the ketoprofen-treated group, which strongly supports the theory of a more rapid clinical recovery in the treated groups. This was achieved after the first of a 3 day course of injections of ketoprofen, compared to the regimen of injecting phenylbutazone at 8 h intervals for 3 to 5 days in the study by Uren et al.[2] The ketoprofen regimen would be much more convenient for field cases than the 8-hourly injections required for phenylbutazone.

We concede that the fact that two Jersey heifers did not develop the disease can not be taken as evidence of breed resistance. However, the suggestion was also based on the difference in respiratory abnormalities between clinically affected Jersey and Holstein cattle. The mean duration of respiratory signs was 1.1 days in Jerseys and 3.25 days in Holstein cattle and the difference was statistically significant.

Ketoprofen may be useful in suppressing the early fever phases of ephemeral fever if administered earlier in the course of the disease and this could be evaluated in another study. However, ketoprofen is likely to be administered when the most severe signs occur and under experimental conditions approximating a field situation, it has been shown to be a useful drug . Also, in a limited number of field cases with locomotor disturbances observed by one of us (DCF), the drug was equally effective in reversing the signs .

The question of plasma total calcium concentrations (Ca_T) in the clinical course of ephemeral fever requires further evaluation. Uren et al[2] showed that mean Ca_T diminish from around 2.3 mmol/L to 2.0 mmol/L and stated that four cattle showed 'clinical hypocalcaemia (Ca_T <2.0 mmol/L)'. Normally clinical signs of hypocalcaemia do not show until Ca_T fall to below 1.75 mmol/L. It could also be difficult to differentiate recumbency that is caused by the polyserositis of ephemeral fever, from recumbency that is caused by hypocalcaemia. Most cows with hypocalcaemic recumbency will have Ca_T of less than 1.5 mmol/L9 and with the experimental induction of hypocalcaemia recumbency occurs with concentrations of less than 1.0 mmol/L.[5]

Many cattle with ephemeral fever will show a transient drop in Ca_T, but this is probably only of significance when the concentration diminishes below 1.75 mmol/L. Certainly transient falls in Ca_T occur in lactating dairy cattle without any overt clinical signs being observed.[6] A possible explanation for the transient hypocalcaemia observed in ephemeral fever is the period of anorexia that may interfere with the absorption of calcium from the intestines. This effect is likely to be more severe in situations where cattle have been on a good diet, are in good body condition and where their intakes of calcium have been larger than their requirements. In such animals the gut absorptive and bone resorptive mechanisms that normally maintain Ca_T would not be as enhanced as they would be in cattle on relatively lower intakes of calcium. Pregnant beef cattle on a high plane of nutrition have difficulty maintaining normal Ca_T when placed on a lower plane of nutrition (Daniel and Young, unpublished). Similarly, late pregnant ewes subjected to a short period of starvation are likely to develop clinical hypocalcaemia.[9]

Such a proposition could explain the variable degrees of hypocalcaemia found in ephemeral fever and also the clinical observation that ephemeral fever affects cattle in good condition more severely than those in poor condition.

Factors that do not support the proposition that milk fever is prefaced by an inflammatory process, made by St George et al[8] include the following:

Hypocalcaemia induced in cattle and sheep by the intravenous infusion of Na_2EDTA is clinically identical to natural milk fever[4] and includes signs of hypophosphataemia, neutrophilia, a diminished eosinophil count and elevated plasma creatinine phosphokinase concentrations.[7]

Hypocalcaemia of varying degrees occurs in dairy cows at times other than at parturition and is not associated with the 'inflammatory stimulus' at parturition.[6]

Hypocalcaemia can occur in late pregnant ewes subjected to a brief period of starvation.[9]

Dr St George states that rest should be provided for cattle with ephemeral fever whether they receive other treatment or