THE INDUCTION OF CALVING USING BETAMETHASONE AND THE PHARMACOLOGICAL ACTIVITY OF SELECTED FORMULATIONS HAVING DIFFERENT RATES OF ABSORPTION

A thesis presented in partial fulfilment
of the requirements for the
Degree of Doctor of Philosophy
at Massey University

STUART CAMPBELL MacDIARMID

1982

Abstract of a thesis presented in partial fulfilment of the requirements for the Degree of Doctor of Philosophy.

THE INDUCTION OF CALVING USING BETAMETHASONE AND THE PHARMACOLOGICAL ACTIVITY OF SELECTED FORMULATIONS HAVING DIFFERENT RATES OF ABSORPTION

by Stuart Campbell MacDiarmid

A series of experiments was undertaken in cows to study the disposition and duration of activity of selected formulations of the synthetic corticosteroid betamethasone (BM). The aim was to select a combination of formulations which would be suitable for use in a two-injection treatment regimen designed to induce premature parturition in cattle.

In an initial experiment, 10 cows each received a subcutaneous injection of 20 ml of 2 mg/ml aqueous suspension of BM, 10 received 2 ml of a 20 mg/ml suspension and a further 10 cows served as saline-treated controls. The BM formulations differed only in their solids:vehicle ratio. Plasma BM, cortisol and glucose concentrations, and differential blood cell counts were studied for 3 days before, and for 19 days after, treatment.

The 2 mg/ml suspension produced a markedly higher peak plasma BM concentration than the 20 mg/ml suspension. However, plasma BM levels tended to be maintained for longer by the suspension having the higher solids:vehicle ratio.

The administration of BM resulted in depression of early-morning cortisol concentrations, elevation of plasma glucose levels, and elevation of circulating neutrophil numbers. The magnitude and duration of these changes was related to the solids:vehicle ratio of the injected suspensions, with the more concentrated formulation producing effects of greater duration.

A second experiment involved 9 cows which were divided into 3 groups, each of which was treated at a dose rate of

0.1 mg/Kg with sodium phosphate solution or a 2 mg/ml BM suspension or a 20 mg/ml BM suspension. Over a period of several weeks each cow received its allocated formulation by each of 3 routes; intravenous, intramusuclar and subcutaneous.

The bioavailability of the BM suspensions was low and the solids:vehicle ratio exerted a profound effect on the rate at which the steroid was absorbed. The disposition curves of the BM solution were similar regardless of the route of administration and the plasma half-life values of BM sodium phosphate, estimated from 3 experiments in each of 3 cows, were 5.64, 6.06 and 6.43 hours.

Ten cows were included in a third experiment. They were treated by subcutaneous injection with 2 ml of a 10 mg/ml BM suspension; a preparation intended for use in the induction of calving. Mean plasma concentrations of BM and glucose were elevated above pre-treatment values for 4 days and 8 days respectively. Mean plasma cortisol levels were profoundly depressed for 2 weeks and in some individuals showed no signs of returning to normal 4 weeks after treatment.

Two field trials, involving 619 and 553 cows respectively, were conducted to assess the suitability of BM formulations for the induction of premature calving in commercial dairy herds.

In the first trial, the mean stage of pregnancy at which cows were treated was approximately 250 days. Cows received an initial injection of either 2 ml of a 10 mg/ml suspension of BM, 2 ml of a 15 mg/ml BM suspension or 4 ml of a 5 mg/ml suspension of dexamethasone trimethylacetate (DTMA). All cows which had not calved within 10 days of this initial treatment received a 12.5 ml dose of a 2 mg/ml suspension of BM.

In comparison with those cows treated with DTMA, significantly fewer cows treated with the concentrated BM suspensions required a second corticostercid injection. In all other respects, such as calf mortality, incidence of retained foetal membranes and maternal illnesses, the results

of the treatments were not significantly different. The 10 mg/ml BM suspension was therefore deemed to be suitable for use in the induction of calving.

The second field trial confirmed the suitability of the 10 mg/ml suspension as an initial treatment to induce calving. Cows which had not calved within 7 days of the initial treatment were injected with 20 mg of BM, either as a 2 mg/ml suspension or as a 2 mg/ml solution of the sodium phosphate ester.

After the second steroid injection, those cows which had received the more rapidly absorbed BM solution calved sooner than those which had been treated with the 2 mg/ml suspension.

The results of these studies clearly showed that the duration of activity of BM suspensions could be prolonged by increasing their solids:vehicle ratio. It was also shown that a treatment regimen consisting of an initial injection of a 10 mg/ml BM suspension, followed 7 to 10 days later by an injection of a more rapidly absorbed BM formulation, was suitable for the induction of calving as currently practised in New Zealand.

ACKNOWLEDGEMENTS

I wish to gratefully acknowledge the advice, encouragement and assistance of my chief supervisor, Dr B.S. Cooper.

My thanks are also due to my supervisor, Dr K.R. Lapwood, whose advice on the subject of radioimmunoassays was particularly helpful.

I received invaluable advice regarding experimental design and statistical analysis from Professor R.E. Munford and the late Dr R.E. Harris.

Dr R.J. Fairclough of Ruakura Agricultural Research Centre kindly provided cortisol antiserum, and Dr K.J. Child of Glaxo Group Research Ltd., London, betamethasone antiserum.

I thank Miss Geraldine Borrie for carrying out the majority of the plasma glucose estimations, Mr J. Elgar for assisting with some of the radioimmunoassays and Mr G. Locke, Mr J. Thompson and Mr V. Smith for their help in the restraint and care of experimental animals.

I am grateful to the staff and clients of Cambridge Veterinary Services Inc. for their co-operation in the two field trials, and to Glaxovet Australia Pty. Ltd. for supplying the betamethasone sodium phosphate used in one of those trials.

Finally, I must express my sincere thanks to Glaxo New Zealand Limited for their generous financial support, and to Mr D.J. Jull, Technical Director of that company, for his advice and encouragement.

TABLE OF CONTENTS

LIST OF FIGURES

Figure | Page

LIST OF TABLES