OBSERVATIONS ON THE ANTI-GESTATION EFFECT OF AIMAX (METHALLIBURE) IN RECENTLY BRED GILTS

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INTRODUCTION

An anti-gestation effect has been reported by Barker (1) in recently bred gilts fed Aimax. It was suggested (1) that the first 20 to 21 days of the gestation period may be the specific period during which the estrous synchronizing dose (100 mg/gilt/day) of Aimax acts anti-gestationally. While this may be the first report on an anti-gestation effect in swine, Paget et al. (8) first reported the effect in 1961 in rats. They observed termination of pregnancy with oral doses of 100 mg/kg/day on any three consecutive days of pregnancy. Harper (4) presented results in rats that showed the compound has a marked effect on fertility. Oral doses of 100 mg/kg/day for three consecutive days did not inhibit implantation when the treatment was initiated on days 1, 2, 3, and 4 of pregnancy. Treatment on days 2 or 4 did completely prevent pregnancy. Harper (4) also commented that in rats treated on the days previous to days 2 to 4 of those eggs that implant very few develop into viable fetuses. Thus treatment on days 0–2, 1–3 or 2–4 was most likely to demonstrate the greatest effects of the compound on pregnancy in rats. Administration at earlier or later stages produced much less effect on the number of eggs implanting.

Groves (3) reported birth of a normal litter of piglets from a gilt accidentally assigned to a 20 day period of treatment at mid-pregnancy. Barker (2) has reported a similar observation at near term and in unpublished data on feeding trials within 10 days of the termination of pregnancy no effect was noted.

The observations noted in (1) suggest that a brief period exists during early gestation in gilts when the compound exerts its greatest effect and the accidental or intentional feeding at this time would interrupt pregnancy or seriously affect the embryos.

This paper reports observations on the anti-gestation effect following oral treatment with Aimax of recently bred gilts.

MATERIALS AND METHODS

Three experiments were conducted with gilts of the Yorkshire, Landrace, and Hampshire breeds and Hampshire-Yorkshire crossbreds. Their body weights ranged from 180 to 265 pounds (80–120 kg) and their ages were from seven to nine months. Estrus had been recorded at least once in each. They were bred naturally, usually once, sometimes twice or three times either to a Hampshire or Yorkshire boar. The first day of breeding was designated day 0 of gestation.

Aimax was supplied as a premix in 25.0 gm units. A unit was thoroughly mixed with a volume of the diet so that the final volume to be fed (once a day – evening feeding in two experiments and twice a day in another) contained 100 mg of the compound. The gilts were penned in pairs, if bred the same day, otherwise singly, to assure accurate intake of the treated feed.

Daily observations were made for the occurrence of estrus during and after the treatment. The gilts were assumed to be pregnant if estrus was not detected within 42 days of breeding. If estrus recurred, rebreeding was usually done for the purpose of further experimentation in the same experiment or a similar experiment. Necropsies were performed on all presumably pregnant gilts, noting litter size, litter weight, gross fetal appearance, number of corpora lutea and ovarian abnormalities.

Experiment 1

The purpose of this experiment was to determine the least number of daily successes.

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1Aimax. Trade name for Imperial Chemical Industries Compound 33828 (Methallibure). Supplied for investigational purposes in Canada by Ayerst Laboratories, Montreal, Canada.

2Four pounds total feed/day (2 lbs. morning and evening) containing 16% protein (min.), 3.0% fat (min.), 3.5% fibre (max.), 0.5% salt, 0.6% calcium, 0.5% phosphorous, 0.0008% zinc, 3000 i.u. Vitamin A/lb., Arsanilic acid 90 gms/ton.
sive doses that would interrupt pregnancy in gilts 14 days bred.

Twelve gilts including two controls were used. A number of gilts were treated with Aimax to synchronize their breeding. Ten gilts were thus obtained and grouped into pens of two for treatment periods of 2, 5, 10, 15 and 20 days respectively. By rebreeding as estrus recurred two periods of 3 and 4 days were also obtained. The two controls were penned together and fed the basic non-treated diet.

The first feeding of the compound was on day 15 of gestation.

Results

Estrus did not recur in the control gilts. They were killed at 95 and 96 days after breeding respectively and were found pregnant. All the fetuses (12 and 11 respectively) were normal. The mean fetal weight for each gilt was 751.0 and 840.0 grams. The ovaries of the control with 12 fetuses contained 17 corpora lutea, the ovaries of the other control contained 13.

Estrus did not recur in the gilts treated for two days. Necropsy findings at 74 days post breeding on one of these gilts were 17 corpora lutea, four fetuses (mean weight 254.8 gms, each appeared normal) and five uterine areas in which only fetal membranes were present. They contained a small amount of dark brown fluid and were dark brown color. The other gilt was killed 93 days post breeding and bilateral cystic ovaries were noted at necropsy.

In three of the four gilts treated for three days estrus recurred at intervals of 30, 34 and 32 days post breeding. The fourth gilt at necropsy was assumed to have conceived on the basis of the findings of remnants of fetal membranes. Fetal resorption was presumed. The ovaries contained 17 corpora lutea.

Estrus recurred in all the gilts treated for 4, 5, 10, 15 and 20 days respectively. These gilts were rebred and the experiment repeated with the same results. The interval from breeding to recurrence of estrus ranged from 26 to 40 days.

Experiment II

The findings in experiment I suggested that two and three consecutive treatments could seriously affect reproduction in gilts bred 14 days. Experiment II was an attempt to determine the effects of three successive treatments on animals bred for a shorter and a longer period than 14 days, however, gilts bred 14 days were included also.

Results

Twenty-seven gilts were used in this experiment. Two were used as controls (simultaneous use of controls of experiment I) and the balance after estrous synchronization with Aimax were paired according to breeding dates to provide groups as follows: Bred 0 days - 2; 3 days - 2; 6 days - 3; 9 days - 2; 12 days - 2; 14 days - 4; 15 days - 2; 18 days - 2; 21 days - 2; 24 days - 2 and bred 27 days - 2.

Gilts in which estrus had not recurred by 42 days post breeding were considered to be pregnant. They were slaughtered 90 to 96 days post breeding and a necropsy was performed on each. Gilts in which estrus recurred were rebred for another experiment.

Results

There was no recurrence of estrus in the gilts bred 0, 3, 6, 9, 21, 24 and 27 days respectively. However, one of the two gilts bred 12 days and in all of the gilts bred 14, 15 and 18 days estrus recurred. The recurrence range was 28 to 34 days post breeding.

All of the fetuses recovered at necropsy from treated gilts were normal. The gilt treated when bred 12 days that conceived contained four areas of partially resorbed fetal membranes but no fetuses (Figure 1).

Two of the treated gilts presumed pregnant were found at necropsy to be non-pregnant. Each had bilateral cystic ovaries and one also had hydrosalpinx. These gilts were in the 0 days and 27 days bred groups.

Experiment III

This experiment was planned to observe the effects of the drug when fed twice daily.
(200 mg/gilt/day) for two consecutive days during the first 28 days of pregnancy. Eight gilts which had been bred 3, 8, 18, 23 and 28 days respectively were used with the following number in each group: 3 days bred – 1; 8 days – 1; 13 days – 1; 18 days – 3; 23 days – 1 and 28 days – 1. The control gilts were those used in experiment II. Gilts in which estrus had not recurred by 42 days after breeding were considered to be pregnant and were killed for necropsy at 91 to 96 days of gestation.

One of the three gilts in the 18 days bred group was re-treated twice thus producing five observations for this stage of pregnancy.

**Results**

All of the gilts except those treated when 18 days bred were pregnant at necropsy. Estrus recurred in the two gilts treated once in the 18 day group, at 35 and 37 days respectively after breeding. The single gilt treated three times (re-treated twice) showed recurrent estrus at 34, 33 and 35 days respectively post breeding. This gilt conceived (in another experiment) after one breeding. The control fetuses were similar to the treated fetuses.

**Discussion and Conclusions**

Failure of estrus to recur within 20 to 21 days of breeding is presumptive evidence of conception in swine, however, post-breeding anestrus may also be related to cystic ovaries. Embryonic death occurs in all species of animals and until the resorption of the embryos and membranes has been completed or nearly so the recurrence of estrus is inhibited.

The results demonstrated that three feedings at daily intervals affected the continuation of pregnancy in presumably pregnant gilts (15 days post breeding) and four days or longer on the treatment would result in a recurrence of estrus in all gilts. The observation of estrus recurring at irregular periods of time post breeding led to the assumption that conception had occurred and embryonic death followed, induced by the treatment. Because necropsies were not performed to examine embryos, it can only be assumed that embryonic death existed.

Experiment I in part confirmed the observations and suggestion previously made by one of us (1), i.e. that the compound exerted an anti-gestational effect in the early stage of gestation. The selection of the number of days bred was a random choice partially based on unpublished data which suggested this period of gestation was one during which an anti-gestation effect might be demonstrated.

Experiment II was based on the findings of experiment I. If the compound exerted an anti-gestational effect with as few as three daily feedings in 14 days bred gilts, would the same effect occur in gilts bred for a much shorter or longer period? Barker (1) reported an adverse effect on reproduction with a dose of 125 mg per day for feeding periods of 21, 31 and 41 days respectively in pair-fed gilts bred 18, 16, 12, 8 and 19 days. From experiment II it is obvious that gilts bred 14, 15 and 18 days are affected by the compound. It is possible that as early as 12 days post breeding an anti-gestational effect may be induced by three daily feedings of 100 mg/gilt as in experiment I there was a longer than normal period between breeding and recurrence of estrus, suggesting these gilts were pregnant but embryonic death occurred, followed by resorption.

These experiments established and confirmed the fact that Amax exerts an anti-gestational effect if fed at a level as low as 100 mg per gilt/day for three days commencing about 12 days after breeding. A highly anti-gestational effect occurs during the period 14 to 18 days inclusive and perhaps this period may be 13 to 20 days. Thus in swine as in rats, there is a brief period during early gestation when the embryos are slightly to highly susceptible to the effects of the compound, the susceptibility evidenced presumably by embryonic death.

Assuming an embryonic effect was being exerted with a total dose of 300 mg of the compound during a 72 hour period it was decided to observe the effect of a total dose of 400 mg during a two day period. This would simulate the accidental feeding which might occur on a weekend in a herd in which the compound was being used for estrous synchronization. The results of experiment III showed that this total dosage would exert an anti-gestational effect definitely in gilts 18 days bred. Gilts bred up to and including 13 days and those bred 23 days or more are seemingly not affected in their ability to maintain pregnancy. Barker (1) has previously indicated that in trials commencing 24 days after breeding and extending to within 10 days of farrowing no anti-gestation or abortifacient effect was observed.

These experiments have shown that feed containing Amax at the level recommended

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3 The quantity approximates the maximum amount that a gilt would consume during a two day period.
for estrous synchronization of gilts should not be fed to gilts bred 12 – 18 days. Three consecutive daily feedings at this level and time post breeding are anti-gestational and four feedings are highly anti-gestational. Results similar to these were observed by Harper (4) in rats.

The findings of three gilts with cystic ovaries should not be construed to be a result of the use of Aimax although perhaps further observations may contradict this opinion. Cystic ovaries are of frequent occurrence in swine and are considered to be an important cause of infertility characterized by anestrus (7). Estrous synchronization trials with Aimax by several investigators have failed to associate the compound with this ovarian pathology.

The assumption of embryonic death as previously discussed was not founded on embryonic examinations and this requires further studies. The experiments were not designed to determine the mode of action of Aimax. Paget et al (8) and Harper (4) have suggested the compound interferes with implantation. It is believed that pituitary gonadotrophins are in some way inhibited. Harrington and Linkenheimer (5) postulated that since the level of compound necessary for inhibition of the estrous cycle in rats is somewhat greater than that necessary for anti-fertility effects it appears that the compound may also have an effect on the uterus after the early stages of implantation. It is possible that in swine through the compound's effect on gonadotrophins there is an interference with placental attachment which results in embryonic death.

Teratogenic effects have been reported (1,6) in piglets from gilts fed the compound for 20 days commencing 24 days or more after breeding and extending to the 69th day. In the three experiments of this paper no teratogenic effects were observed. Wilson (9) has stated that at the time of cleavage and at the time which would correspond to the blastular stages in mammalian embryos there is typically no teratogenic response to even the highest doses of agents that in later stages are very effective.

Observations were made on litter size, litter weight and number of corpora lutea however the results in general did not differ greatly from the controls and no significant conclusions were drawn from the data.

SUMMARY

Three experiments were conducted in recently bred gilts to investigate a previously observed anti-gestation effect of Methallibure (Aimax) when administered orally at a dose of 100 mg/gilt/day for a variable number of successive days or at a dose of 200 mg/gilt/day for two successive days.

The results at the 100 mg level showed an anti-gestation effect in gilts bred 14 days and treated 3, 4, 5, 10, 15 and 20 days successively but not in those treated 0 and 2 days. At the same dose and for the same period of time (3 days) no anti-gestation effect was observed in gilts 0, 3, 6, 9, 21, 24 and 27 days bred. An anti-gestational effect was shown in the groups 12, 14, 15 and 18 days bred. Gilts tested at the 200 mg level for two successive days at 3, 8, 23 and 28 days bred were not affected, however, those treated when 18 days bred were affected.

Affected gilts were characterized by a delayed recurrence of estrus, ranging from 28 to 40 days after breeding. It was assumed that embryonic deaths occurred in the gilts affected by the compound. In three gilts non-occurrence of estrus was related to bilateral cystic ovaries. No teratogenic effects were observed.

RÉSUMÉ

Les auteurs ont réalisé trois expériences chez des jeunes truies récemment saillies, dans le but d'étudier l'effet anti-gestation du Méthalibure (Aimax) précédemment observé à la suite de l'administration orale de 100 mg/truie/jour pour un nombre variable de jours consécutifs ou de 200 mg/truie/jour pendant deux jours consécutifs.

L'administration d'une dose de 100 mg a produit un effet anti-gestation chez les truies saillies depuis 14 jours et traitées pendant 3, 4, 5, 10, 15 et 20 jours consécutifs, mais non chez les truies traitées pendant 0 et 2 jours. L'administration de cette dose pendant la même période de temps (3 jours) n'a pas produit cet effet chez les truies saillies depuis 0, 3, 6, 9, 21, 24 et 27 jours. On a, par ailleurs, observé l'effet anti-gestation dans les groupes de truies saillies depuis 12, 14, 15 et 18 jours. Les truies ayant reçu 200 mg pendant deux jours consécutifs, 3, 8, 23 et 28 jours après la saillie, ne furent pas affectées, tandis que celles qui reçurent cette dose 18 jours après la saillie le furent.

Les résultats se caractérisaient par un retard du retour de l'estrus, allant de 28 à 40 jours après la saillie. Il semble que des mortalités embryonnaires se soient produites chez les truies affectées par le composé. Chez trois truies, l'anestrus était relié à des kystes ovariens bilatéraux. Les auteurs n'ont pas observé d'effet tératogène.
ACKNOWLEDGMENTS

This work was supported by a fellowship granted to the senior author by the Canadian International Development Agency, Government of Canada. Financial support was also provided by the Ontario Department of Agriculture and Food, Government of Ontario, Toronto, Canada.

REFERENCES


BOOK REVIEW

*Herm's Medical Entomology, 6th Edition.*

One of the standard texts in the field of medical entomology has for many years, been "Herm's Medical Entomology". This edition continues to provide student and research worker with broad and up-to-date coverage of the field. The reference material provided is very current for a textbook, including literature to the time of printing.

The format of the book is somewhat changed, to include chapters on the general description of arthropod structure and physiology, the relationship between the feeding process and transfer of pathogens, and control measures. Included also in this general section is an excellent discussion of the principles of epidemiology as they apply to arthropod-borne diseases. There appears to be somewhat less emphasis placed on taxonomy. It is worth mentioning that the chapter on control has swung from the former pattern where specific measures were outlined for specific pests, toward a treatment of broad general principles.

This is undoubtedly a step in the right direction, in order that those involved in insect pest control have reference to basic principles. This seems especially true in the light of modern knowledge concerning the hazards and long time residual properties of many of the compounds employed.

Following these introductory chapters, which incidentally include one of the best illustrated and complete treatments of arthropod feeding mechanisms, the book goes on to cover the various groups of medically important arthropods individually. This is followed, to conclude, by a chapter on venoms and allergens.

The illustrations, for the most part, are outstanding. One exception, perhaps, is Fig. 3-10, which is stated to be an "electron micrograph".

The veterinary material is supposed to have increased from earlier editions, and this is probably so. The book continues, however, to place its main emphasis on medically important species. This is not intended to be a criticism, for this is the object of the book, and it is attained in an efficient, lucid, and up-to-date manner that will be found useful by all interested in this important field. D. P. Gray.