

# Double-blind, placebo-controlled study of the efficacy of nandrolone laurate in the treatment of dobermanns with subclinical hepatitis

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**Twenty-one three-year-old dobermanns with subclinical hepatitis were treated with nandrolone laurate or a placebo in a double-blind trial. The dogs were scored clinically before and after four months of treatment and they were evaluated by clinical biochemistry and liver biopsies. After the treatment no significant differences were observed between the two groups in any of the clinical biochemistry values; eight of the 21 dogs had no histological evidence of hepatitis and five other dogs had improved, but there was no significant difference between the responses of the two groups.**

CHRONIC hepatitis is a common disease in dobermanns (Johnson and others 1982, Crawford and others 1985, van den Ingh and others 1988, Thornburg 1998); it is a chronic and rapidly progressive disease characterised by fibrosis, liver cell necrosis and progressive lymphocyte and plasma cell infiltration (van den Ingh and others 1988). Affected dogs usually show clinical signs between four and six years of age. Its aetiology is unknown but it is suspected that the disease is hereditary (Johnson and others 1982, Crawford and others 1985, van den Ingh and others 1988, Speeti and others 1996, Thornburg 1998). Many of the dogs studied had high concentrations of copper in their livers, and it has been concluded that the high concentration is due to cholestasis (Johnson and others 1982, Crawford and others 1985, van den Ingh and others 1988). Thornburg (1998) described a group of 35 dobermanns with chronic hepatitis in a pre-cirrhotic stage, and concluded that the high copper concentration was incidental and not the cause of the disease, because the histopathology of the liver was comparable in all the dogs and because five of them did not have high liver copper concentrations. In contrast, Speeti and others (1999) described a group of 40 dogs with subclinical hepatitis and chronic hepatitis with high liver copper concentrations associated with an inflammatory reaction. As only a few of the dogs showed histopathological signs of cholestasis, it was suggested that the inflammation was related to the accumulation of copper. Similar findings have been described by Mandigers and others (2004). However, the centrilobular distribution of the inflammation and the loss of hepatocytes also suggests possible immune-mediated damage (Thornburg 1998). More recently, Speeti and others (2003) described the expression of major histocompatibility complex (MHC) class II antigens in hepatocytes in dobermanns with hepatitis, a finding that is also suggestive of an immune-mediated aetiology.

Speeti and others (1996) described a group of clinically healthy dobermanns in which subclinical hepatitis was diagnosed when they were only two to four years of age. The dogs had high activities of liver enzymes in serum and the final diagnosis was made by histological examination of a liver biopsy. In dobermanns both the clinical form (Johnson and others 1982, Crawford and others 1985, van den Ingh and others 1988, Thornburg 1998) and the subclinical form occur predominantly in females (Speeti and others 1996, Mandigers and others 2004). In human beings, immune-mediated disease is also more common in females (Beeson 1994, Bijlsma 1998), in particular autoimmune hepatitis

(Vogel and others 2002, McFarlane and Heneghan 2004). The management of dobermanns with hepatitis with drugs such as prednisolone, azathioprine, colchicine, ursodeoxycholic acid and D-penicillamine has been unrewarding (Johnson and others 1982, Crawford and others 1985, van den Ingh and others 1988, Rothuizen and van den Ingh 1998).

Anabolic steroids such as androgens are used for many purposes (Pugh 1982), of which the most well known are to induce erythropoiesis and to treat metastasised mammary carcinomas in females (Hickson and others 1989). However, they have also been used to treat immune-mediated disorders. In human beings, Ahn and others (1985) found that nandrolone decanoate, a synthetic androgen, increased the haematocrit in 12 of 15 patients with immune-mediated haemolytic anaemia. The cell membrane-bound fraction of C3 on erythrocytes decreased significantly, suggesting that it had a role in decreasing autoimmunity. In another study, nandrolone decanoate appeared to be effective in human patients with immune-mediated thrombocytopenia (Mylvaganam and others 1989) and comparable results have been described by Schreiber and others (1987) and Pignon and others (1993). However, the exact mechanism of action of nandrolone decanoate in immune-mediated disorders is unknown.

It is not clear whether androgens are effective in treating immune-mediated disease in dogs. Bloom and others (1989) used one successfully to treat immune-mediated thrombocytopenia in a dog, and Holloway and others (1990) used two androgens successfully to treat a dog with immune-mediated anaemia and thrombocytopenia. However, to the authors' knowledge, there are no published controlled studies with a larger number of dogs. The objective of this study was to investigate whether nandrolone laurate might ameliorate or cure subclinical hepatitis in dobermanns.

## MATERIALS AND METHODS

### Dogs

One hundred and six dogs were selected at random from a group of 946 purebred dobermanns born in the Netherlands between August 1995 and July 1996. They were approximately three years of age, client-owned and, according to their owners, clinically healthy. They were included in the study only after informed written consent had been obtained from their owners. Permission for the study was obtained from the

*Veterinary Record* (2005)  
157, 313-317

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departmental ethical committee of Utrecht University and the Agency for Registration of Veterinary Medicinal Products (Ministry of Agriculture, Nature and Food Quality).

The clinical history of each dog was recorded and it underwent a physical examination. A blood sample was collected from the jugular vein to measure liver enzyme activities and the concentrations of bile acids and fibrinogen; fibrinogen was measured to assess coagulation. Two or three fine-needle aspirates were collected from the liver of each dog, from the right side at approximately mid-thoracic height of the 9th or 10th intercostal space. The samples were smeared on to a clean slide, air-dried and then stained with rubeanic acid to identify copper granules (Teske and others 1992). The smears were examined cytologically within four weeks of collection. The reference value used for fasting bile acids was less than 9  $\mu\text{mol/l}$ , for alkaline phosphatase (AP) it was 25 to 117 U/l, and for alanine aminotransferase (ALT) it was 23 to 90 U/l.

All the measurements were made in the same laboratory. If one or more of the three liver parameters was high and/or copper granules were found in the smears, the dogs were further examined by histological examination of large-bore needle biopsies. Four liver biopsies were obtained under local anaesthesia with a Menghini needle (16 G) as described by Lettow (1974). The liver tissue was fixed in 10 per cent neutral buffered formalin, dehydrated and embedded in paraffin, and 4  $\mu\text{m}$  sections were stained with haematoxylin and eosin, van Gieson's stain, Gordon and Sweet's reticulin stain and with rubeanic acid. All the histological evaluations were made by the same pathologist who did not know the animal's status.

If the histological diagnosis was hepatitis and the dog was clinically healthy, the owner was asked to participate in the study.

The liver biopsy was then scored as: 1 Slight hepatitis – a minimal inflammatory infiltrate in the hepatic parenchyma; 2 Minor hepatitis – a moderate to marked inflammatory infiltrate in the hepatic parenchyma/slight inflammatory infiltrate in the hepatic parenchyma and a solitary necrotic hepatocyte; 3 Moderate hepatitis – a slight to moderate inflammatory infiltrate in the parenchyma with some necrotic hepatocytes; or 4 Marked hepatitis – a moderate to marked inflammatory infiltrate in the parenchyma with several necrotic hepatocytes.

A dog was excluded from the study if it had received any steroid treatment during the previous 60 days, if it showed clinical signs of another disease that might influence the normal response to treatment of liver disease, or if it was pregnant. Topical or systemic treatment with other androgens, progestogens and/or corticosteroids or the feeding of specially prepared diets was not permitted during the study.

The dogs were allocated to one of the two treatment groups by using a randomisation table. The study was set up as a prospective double-blind study; the veterinarians were unaware of whether they were administering the placebo or treatment, and the liver biopsies were examined without a knowledge of the treatment.

After being included in the study the dogs were treated for four months with one injection each month and re-examined one month after the last injection. After 12 hours' fasting, a blood sample for the measurement of total bile acids, AP and ALT and a large-bore Menghini liver biopsy were taken and stained and evaluated as before. The liver biopsies were scored as described above, with a normal liver being scored 0, and the effect of the treatment was assessed in terms of the difference between the scores after and before treatment. A dog was classified as having improved if its score was -1 to -4, and having worsened if its score was 1 to 4. The study was unblinded only after the final scores had been calculated. Only the dogs that had a complete course of treatment and examinations were evaluated statistically. If the clinical condition of a dog deteriorated during the

**TABLE 1: Mean (sd) serum activities of alkaline phosphatase (AP) and alanine aminotransferase (ALT) and the concentrations of bile acids and fibrinogen before and after treatment in the 10 dogs that received nandrolone laurate and the 11 dogs that received the placebo. There were no significant differences**

Measurement	Placebo		Nandrolone	
	Before treatment	After treatment	Before treatment	After treatment
AP (U/l)	58.3 (21.6)	65.6 (35.5)	53.7 (25.3)	45.4 (10.5)
ALT (U/l)	76.9 (58.1)	56.8 (52.9)	41.8 (26.5)	38.4 (13.9)
Bile acids ( $\mu\text{mol/l}$ )	3.9 (2.2)	4.0 (2.5)	2.0 (1.2)	5.4 (4.6)
Fibrinogen (g/l)	1.4 (0.3)	1.7 (0.4)	1.4 (0.5)	1.3 (0.3)

study, its treatment was stopped and it was considered as a treatment failure.

### Treatment and dose

The placebo was prepared in identical vials with identical labelling but contained only arachis oil with 10 per cent benzyl alcohol. The test product was nandrolone laurate (25 mg/ml) in arachis oil containing 10 per cent benzyl alcohol (Laurabolin; Intervet International). The dose rate was 5 mg nandrolone laurate/kg bodyweight (equivalent to 0.2 ml solution/kg bodyweight). The treatment was administered by subcutaneous injection by either the investigator or the referring veterinarian. The vials were protected from light and stored at 15 to 25°C.

### Statistical analysis

The individual dog was considered as the statistical unit and the level of significance ( $\alpha$ ) was set at 0.05. The statistical analyses were made by using the software package Statistix 8.0 for Windows (Analytical Software). Descriptive statistics were used for the general data (sex, colour and weight), and a median test was used to compare the weights and ages of the two groups. The possible effect of the treatment on the blood chemistry values was evaluated by using a paired *t* test. The histology scores and the response to treatment were evaluated by using a chi-squared test.

## RESULTS

In total 24 purebred dobermanns (median weight 30 kg, range 25 to 46 kg; median age 3.4 years, range 2.7 to 7.0 years, born to three sires and 21 bitches) from different locations in the Netherlands were included in the study. A pedigree analysis showed that there was no over-representation of certain families. Twenty-one of the dogs completed the study. The results from two females, both treated with the placebo, could not be evaluated because of the non-compliance of their owners, and one female, treated with nandrolone, was euthanased for reasons unrelated to the hepatitis shortly after entering the study. These three dogs were excluded from the analysis.

### Treatment groups

Ten of the dogs received the nandrolone treatment, and 11 received the placebo treatment. The median age of the placebo-treated dogs was 3.5 years (range 3.0 to 7.0 years) and that of the nandrolone-treated dogs was 3.3 years (range 2.7 to 4.4 years); there was no significant difference between the two groups. The median weight of the placebo-treated dogs was 30 kg (range 25 to 36 kg) and that of the nandrolone-treated dogs was 30.5 kg (range 27.5 to 46.0 kg); there was no significant difference between the two groups.

### Blood analysis

There were no significant differences between the mean values of the measurements of fasting bile acids, AP, ALT and

**TABLE 2: Numbers of dogs with different degrees of hepatitis before and after treatment with either nandrolone laurate or the placebo**

Histopathological classification	Placebo		Nandrolone	
	Before treatment	After treatment	Before treatment	After treatment
No abnormalities	0	4	0	4
Slight hepatitis	5	3	6	4
Minor hepatitis	5	3	2	2
Moderate hepatitis	1	1	2	0
Marked hepatitis	0	0	0	0

fibrinogen made before and after the period of treatment in either of the two groups (Table 1).

### Cytology

At the start of the study the fine-needle aspiration smears showed copper-positive granules in the hepatocytes of 19 of the 21 dogs; the mean (sd) proportion of the liver cells that contained copper granules was 6.5 (5.6) per cent, and there was no significant difference between the two groups.

### Histopathology

In the evaluation of all 106 dogs selected at random, the histopathological abnormalities observed were subtle; the majority of the dogs had centrilobular copper-laden hepatocytes and a few apoptotic hepatocytes associated with activated pigmented Kupffer cells, lymphocytes, plasma cells and scattered neutrophils. In none of the dogs was there histopathological evidence of cholestasis.

Before the study, all 24 dogs selected for the study had histological evidence of hepatitis: 11 had slight hepatitis with a score of 1, seven had minor hepatitis with a score of 2, and three had moderate hepatitis with a score of 3. None of the dogs had signs of cholestasis. The dogs were assigned randomly to one of the two treatment groups without prior knowledge of their histopathological classification (Table 2), and before they were treated there was no significant difference between the histological grading of the two groups. After completing the treatment, eight dogs had no histological evidence of hepatitis (score 0), seven had slight hepatitis (score 1), five had minor hepatitis (score 2) and one had moderate hepatitis (score 3) (Table 2). None of the dogs had signs of cholestasis after the treatment.

Five of the dogs had improved and had an overall score of -2; two of them had been treated with the placebo and three had been treated with nandrolone (Table 3). Seven of the dogs had improved and had a score of -1; three of them had been treated with the placebo and four had been treated

**TABLE 3: Histopathological scores of 21 dogs with subclinical hepatitis before and after treatment with either nandrolone laurate or the placebo. Dogs with a negative difference improved, those with no difference showed no response and those with a positive difference deteriorated**

Before treatment	Placebo After treatment	Difference	Before treatment	Nandrolone After treatment	Difference
2	0	-2	2	0	-2
2	0	-2	3	1	-2
1	0	-1	3	1	-2
2	1	-1	1	0	-1
1	0	-1	1	0	-1
1	1	0	2	1	-1
2	2	0	1	0	-1
2	2	0	1	1	0
3	3	0	1	2	1
1	1	0	1	2	1
1	2	1			

with nandrolone. Six of the dogs did not respond to treatment (overall score 0), of which five had been treated with the placebo and one had been treated with nandrolone. Three of the dogs had deteriorated (overall score 1), of which one had been treated with the placebo and two had been treated with nandrolone. There was no significant difference between the responses of the two groups to the treatments.

Of the 11 dogs treated with the placebo, 10 showed no side effects, but one became slightly more aggressive. Of the 10 dogs treated with nandrolone, six showed no side effects, one gained 2 kg in weight, one had some swelling at the injection site after the first injection, one became slightly more aggressive and one became slightly more timid.

### DISCUSSION

Subclinical hepatitis in dobermanns is diagnosed histologically and has an unknown aetiology. The expression of the MHC class II antigens (Speeti and others 2003) and certain histological features (Thornburg 1998) suggest that it may be in part immune-mediated, and the fact that the disease predominantly affects females supports this hypothesis (Vogel and others 2002). It was postulated that nandrolone might be useful in treating subclinical hepatitis because of the effectiveness of anabolic steroids in the treatment of other immune-mediated disorders (Hughes and others 1995). Corticosteroids are useful for the treatment of autoimmune disease because they inhibit the production of, among others, interleukin-1 (IL-1), tumour necrosis factor-alpha (TNF $\alpha$ ) and other cytokines. Both IL-1 and TNF $\alpha$  are important modulators of the interactions between the neurological and endocrine systems (Roitt and others 1998). In inhibiting the production of IL-1 and TNF $\alpha$ , corticosteroids inhibit T cell activation, especially T helper 1 and T helper 2 cells of the CD4 subpopulation (Roitt and others 1998). T helper 1 cells of the CD4 subpopulation, and the formation of autoantibodies, play an important role in autoimmunity (Cruikshank and others 1998, Roitt and others 1998).

Corticosteroids have also been shown to induce the production of transforming growth factor-beta (TGF $\beta$ ), which may in turn inhibit the immune response (Roitt and others 1998). Nandrolone decanoate is thought to reduce antibody formation (Hughes and others 1995). However, it induces the production of the cytokines IL-1 and TNF $\alpha$ , which is in contrast to the effects of corticosteroids. IL-1 is, however, through its effects on corticotrophin-releasing hormone, able to stimulate adrenal corticosteroid production which, in turn, can inhibit IL-1 and TNF $\alpha$  (Roitt and others 1998). Nandrolone decanoate also inhibits the production of interferon-gamma (IFN $\gamma$ ), which is important for the communication between cells and the immune system. It is for these reasons that nandrolone decanoate is believed to have significant effects on the immune system (Hughes and others 1995). Nandrolone laurate differs from nandrolone decanoate only in that the corticosteroid is attached to a different fatty acid (Pugh 1982).

When treating a liver disease, anabolic steroids should be used with caution, particularly the oral 17- $\alpha$ -alkyl anabolic steroids, which may possibly induce several types of liver disease in human beings, including adenomas, cholestasis, peliosis hepatitis and hepatocellular carcinoma (Hickson and others 1989, Kopera 1993, Dourakis and Tolis 1998). However, there is considerably less risk when the injectable 17- $\beta$  esters such as nandrolone laurate and nandrolone decanoate are used (Kopera 1993), and the adverse effects described in human beings have not, to the authors' knowledge, been described in dogs. To induce a cholestatic hepatitis a 100-fold dose of a 17- $\beta$  ester would be required (Pugh 1982).

To minimise the possible risks, the dogs were given only four injections with a month between each injection. During

the period of treatment there was no significant difference between the side effects observed in the dogs receiving the active drug and the placebo, and the treatments had no effect on the serum activities of liver enzymes or the concentration of bile acids.

After four months of treatment, eight of the 21 dogs had no histological evidence of hepatitis and five others had improved. However, the dogs that responded were equally distributed between the two treatment groups. It seems safe to conclude that nandrolone did not adversely affect the dogs' liver status or induce cholestasis. However, it was not effective in treating the subclinical hepatitis. Several reasons for its lack of efficacy can be suggested. Only a small number of dogs was included in the study, and the results suggest that in some cases subclinical hepatitis may resolve spontaneously. It is also possible that the dose and dose rate, both advised by the manufacturer, were too low. In contrast, in people, nandrolone decanoate is administered orally at daily intervals (Ahn and others 1985). The dose and dose rate used were based on the drug's current registration status. It is also possible that this type of anabolic steroid is not effective in this type of disease in dogs. Although hepatitis in dobermanns is believed to be immune-mediated, its exact pathogenesis was unknown during the time the study was performed.

The observation that in eight of the 21 dogs the subclinical hepatitis resolved, and five other dogs improved, contrasts with the results of Speeti and others (1996), who found that most of the dogs they studied with subclinical hepatitis developed clinical hepatitis. However, Speeti and others (1996) used dogs in which the plasma activities of liver enzymes were at least three times higher than the upper reference value, whereas the dogs in the present study had only slightly high liver enzyme activities, suggesting that the dogs studied by Speeti and others (1996) might have had more advanced liver disease. Moreover, in this study the dogs were all three years old, where the dogs in the study by Speeti and others (1996) were up to seven years of age.

The results of this small, double-blind, controlled study indicate that nandrolone laurate was ineffective for the treatment of subclinical hepatitis in dobermanns.

## ACKNOWLEDGEMENTS

The authors thank Mr M. van Leeuwen for his help in preparing the fine-needle aspiration smears and Mr H. van Engelen for his help in taking the blood samples and the liver biopsies. For reviewing the English they thank Dr Clare Rusbridge.

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*Veterinary Record* 2005 157: 313-317

doi: 10.1136/vr.157.11.313

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