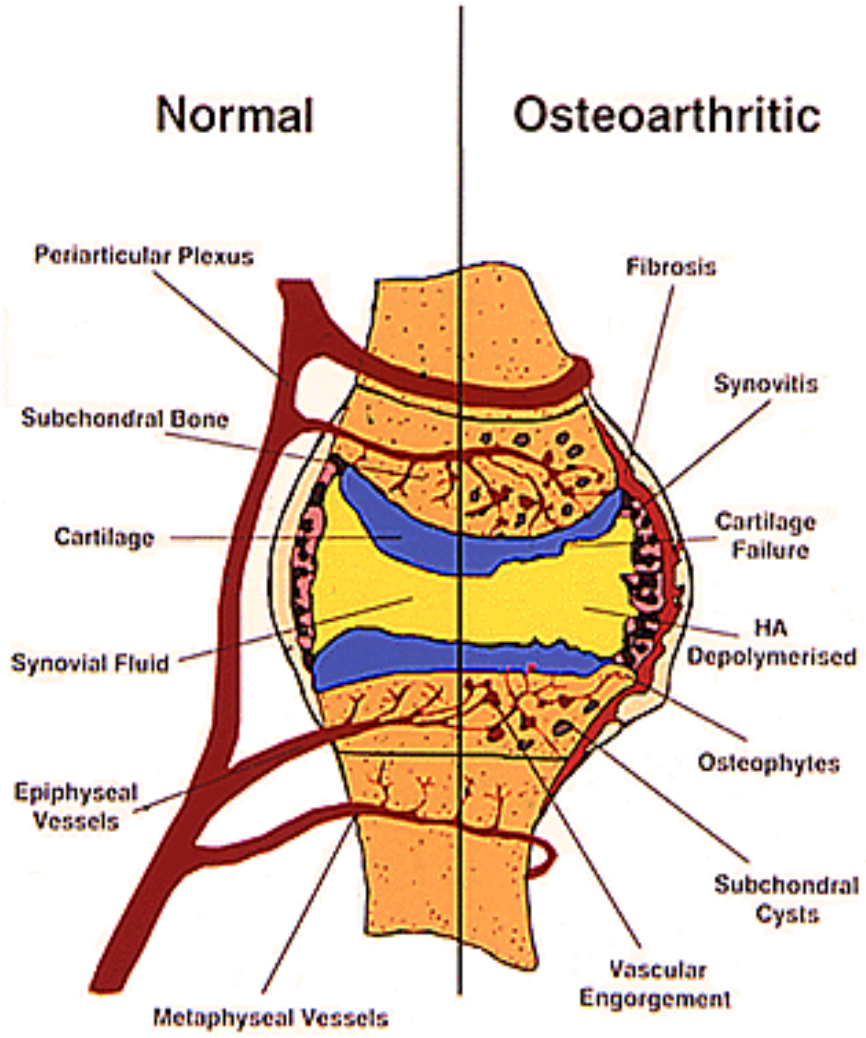
Specialised Veterinarian Main Project December 2005.

Investigation of clinical effect after treatment by Cartrophen Vet. or Rimadyl Vet. on dogs with Osteoarthrosis(OA), Osteochondritis(OD) or Hip Joint Dysplasi(HD).



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Resume:

The background for this investigation was the wishes for more treatment possibilities concerning dogs with Osteoarthrosis (OA), Osteochondritis (OD/OCD) Hipdysplasia (HD). Cartrophen Vet. injection (Pentosan natriumpolysulfat) and Rimadyl Vet. tablets 100 mg (Carprofen) was investigated in an open clinical trial at 3 veterinary clinics and Hospitals in Northern Jutland, Denmark. Included in the trial was 37 dogs with the above mentioned diagnosis, and both veterinarians and owners judgement in lameness and pain were recorded in an 8 week trial period under treatment. Investigation took place from 2003 to 2005; only 4 veterinarians in 3 clinics were involved, using the same detailed protocol. Clinical diagnosis was verified with X rays. The choice of treatment was free for the owners, and there by not blinded for either owner or veterinarian. Cartrophen Vet was injected sc. 4 times on weekly intervals, doses 1 ml/33 kg of dog. Rimadyl Vet. 100 mg chewing tablets were given for the total of 4 weeks (28 days) at doses 4 mg/kg/day. Lameness and pain were judged in week's nr. 0, 1 , 2, 3 and 7. The veterinarian manipulated the joints involved in the diagnosis and observed the dogs in the clinic/hospital, in order to evaluate a "score" determined from 0-4 for lameness and 1 -5 for pain. The owner supplied the same score after evaluating the dog in the home and during exercise/training .A detailed protocol was made for every dog, and submitted with all the relevant X rays to Brunder Animal Hospital, where a database with all information according to general health, anamnesis, treatment chosen, X rays and scores from veterinarians/owners was created. The score values were chosen from a previous made, double blinded investigation in Germany, using pictures from a "Lickert-Scale".
The resulting scores from the two groups investigated were evaluated with non paired t – test and a Mann Whitney Rank Sum Test. The distribution of age, weight, diagnosis in the two groups was compared to access equal starting point of both groups. The lameness and pain scores starting from week 0 were compared with week 7, and also compared from week to week.
In total there were 26 dogs in the Cartrophen Vet. group, of which 11 dogs(42 %) were totally free of lameness/pain. In total there were 11 dogs in the Rimadyl Vet. group, of which 1 dog (9 %) was totally free of lameness/pain. By Friedman Repeated Measures Analysis of Variance on Ranks, both groups had significant improvement in both lameness and pain($P<0,05$) , already from week 1. The improvement was significant for all weeks (1 – 7) compared to week 0 (Dunns Method).
6 dogs (23 %) had mild side effects like quiet/tired or lack of appetite a few days after the injection with Cartrophen Vet. There were no side effects among the 11 dogs in the Rimadyl group.
The conclusion of this investigation was that the treatment with disease modifying anti osteoarthrosis drug (DMAOD) Cartrophen Vet represents a new possibility for efficient treatment in chronic degenerative joint disease like OA, OD/OCD, and HD. Lameness and pain reduction was always more efficient with early diagnostics and treatment, in both the Cartrophen and Rimadyl groups investigated.

Introduction:

Purpose of investigation:
A)To evaluate the clinical effect on 1) Lameness and 2) Pain after treatment with Cartrophen Vet. or Rimadyl Vet. in dogs. The chosen disease groups are: 1) Osteoarthrosis (OA) 2) Osteochondritis or Osteochondritis dissecans (OD/OCD) 3) Hipdysplasia (HD).
B) Comparison of a disease modifying anti osteoarthrosis drug (DMAOD), Cartrophen Vet. Injection and a well known NSAID drug, Rimadyl (Carprofen) Vet. Tablets.Evaluating the side effects in the investigation and speculation at possible side effects in long term treatments over months or even years.
After seeing a number of new "chondroprotective" drugs, e.g. Cartrophen Vet., a clinical well documented investigation in DK on the above mentioned disease diagnosis seems relevant. There has not been many veterinarian investigations of Cartrophen(1,2,3,4,5,6,7).Side effects within EU has only been registries on regular basis in UK (8).
Reasons for developing OA are numorous: 1) Osteochondritis (OD) or (OCD) 2) Dysplasia in elbow or hip joints3) Mechanical/traumatic damage in joint/cartilage 4) Rheumatisk or Septic joint inflammation 5) Circulation disturbances 6) Chronic or neurogene pain 7) Obesity and diabetes mellitus 8) Age and genetically or hormonal predisposition (6, 9, 10, 11, 12). These diseases are well known in general

practice e.g.: Cruciatum rupture. Lumbosacral instabilitet L6-7/S1.Trauma after traffic accidents or training incidents, with involvement of joints, ligaments or bones.
The many reasons for OA, and the progressive degenerative nature means that management & treatment of OA is often complex and should/could involve a number supportive diets (12, 13, 14). Comparison with a already well known and clinical tested NSAID drug, Rimadyl Vet. (Carprofen), with positive effect on OA and HD was chosen .This drug has been clinical tested in Denmark, Norway and Sweden within the last 5 years and has also been tested in OA models (15,16,17,18,19,20). OA is seen relatively often in dogs and cats. It is estimated that up till 20 % of a population can be suffering from mild to serious OA , especially cats are often overlooked(11,13). The reasons for this might be the slow and progressive nature of OA, and that pain estimation with dogs and particular cats are very subjective in clinical practice(13,15,16,20).

Main symptoms in OA conditions are PAIN and the thereby following Lameness. Figure 1 summarises the main pain contributions by OA conditions in one or more joints, but also more detailed contributions are made from specific joint receptors. These receptors are divided into four classes, responsible for securing stabile conditions under static or dynamic strains/loads of the joint (9, 11). Three areas, all responsible for neurogenic contribution to OA development, are mentioned here.
A) Pain receptors feeling sensibility, with A and C nerve fibres. C fibres are free nerve endings without myelin sheds. Chemical stimuli will make an impulse for C fibre (e.g. Prostaglandins, Substance P, Bradykinin or Cytokines). Increased sensibility will be seen in OA which can create hyper tonus or spasms in the muscles that stabilise the joints. Increased sensitivity in the dorsal spinal horn, followed by excretion of neuron peptides in chronic pain conditions increases sensitivity. Wind-up pains are an expression of prolonged depolarisation in the dorsal spinal horn = CNS increased sensitivity (13, 17).

B) Mechanoreceptors for balance/positioning of the joint .A fibres are with myelin sheds. Instabilitet of a joint promotes pain perception from the receptors. Normal strain/load is experienced as pain (9).

C) Pain from subchondrale bone tissue, developed by circulation disturbances. Pin will be increased by neuropeptider and the signal drugs from pain receptors. Increased intra osseous pressure, hypoxia, increased lactic acid levels are important reasons for pain together with vasodilatation (1, 6, 9, 10, 11).

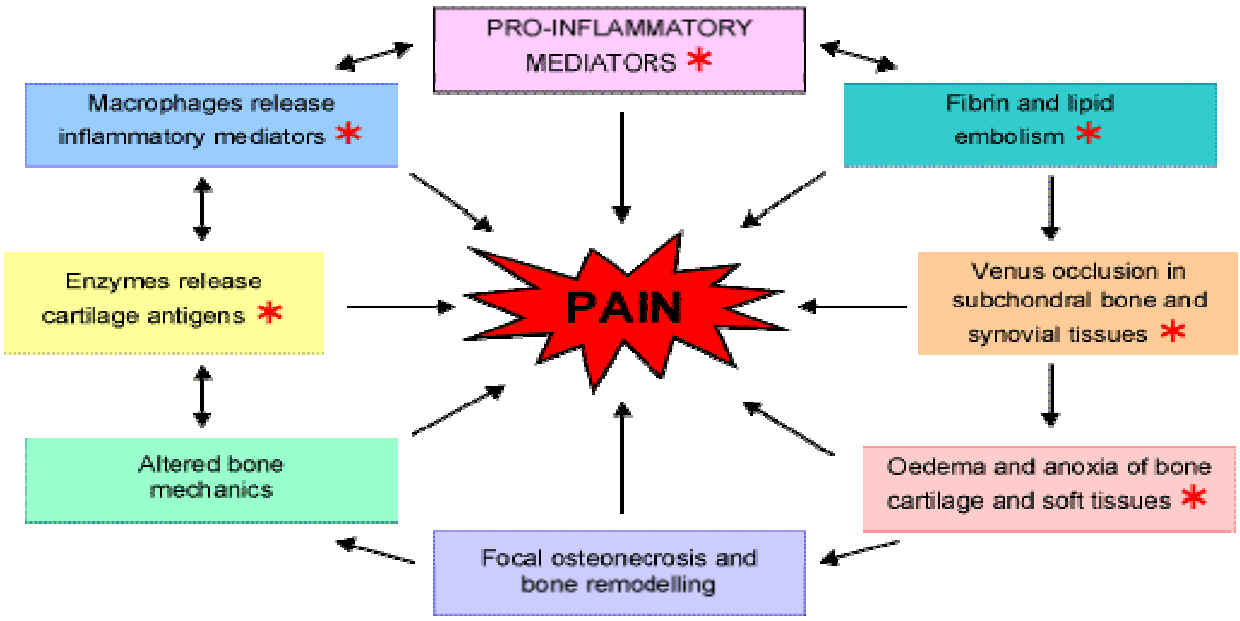

Figure1. Main symptom in OA= Pain
Cartrophens effects are marked in red (1).

Because many of the early changes in all disease groups occur in the joint cartilage, a detailed description together with joint construction will be presented, to obtain a probable pathogenesis in OA.
Joint cartilage: A nonvascular, anural and nonlymfatic tissue. It consists of 5 % Chondrocytters and 95 % Cartilage matrix**. Matrix** consists of 3 ground substances: A) Collagen B) Proteoglycan C) Water.
A) Collagen is stacks of monomer protein (polypeptide chains).
B) Proteoglycan monomer is built on a core of protein, with attachment of glycosamin glycan chains (Disaccharides bound together by S or C groups). Such proteoglycan are e.g.: Chondrotinsulfate, Keraten sulfate and Dermatan sulfate.
C)Negative charge on Proteoglycan gives a huge molecule together with collagen fibres, and this implies great contents of water molecules(up till 50 times dry weight). This is the reason for joint cartilage ability to be elastic (turgidity) and to absorb the many forces a joint have to withstand(11)**.**

The joint cartilages are divided into four zones:
Zone 1 acts like a "coating" of the cartilage. Early degenerative changes here are called"fibrillation".
Zone 2 + 3 contains high amounts of proteoglycan to be extra Schok absorbent. Slow pressure gives"soft" cartilage, while fast pressure gives" firm" cartilage.
Zone 4 is the "osteochondrale junction", a calcified layer of the deepest joint cartilage. It is important for transaction from pressure in the joint cartilage to the subchondrale bone tissue, which in itself can be deformed up till 10 times more than ordinary bone tissue (11).

Joint capsule and Synovium: (Neurogene build up are divided into 4 and already mentioned)
Divided into 3 layers: A) Synovial membrane B) Subsynovial membrane C) Fibres joint capsule.
A) Type A synoviecytter are macrophage like cells. Type B synoviecyttes produces hyaluron acid and enzymes for braking down process.
B) Fibroblasts are seen in the Subsynovial membrane. It is vascularised and contains free nerve endings. Gives ability for the other layers A and C to move.
C) The fibres joint capsule are sitting directly attached into the bone tissue by a fibro cartilage insertion. There are also ligaments and numerous nerve fibres and a certain degree of vascularisation (9, 11).
In normal conditions synovial membrane prevents inflammation cells and proteins in the joint cavity. Changes in synovium allowing e.g. invasion of lymphocytes, starts early breakdown of cartilage(11).

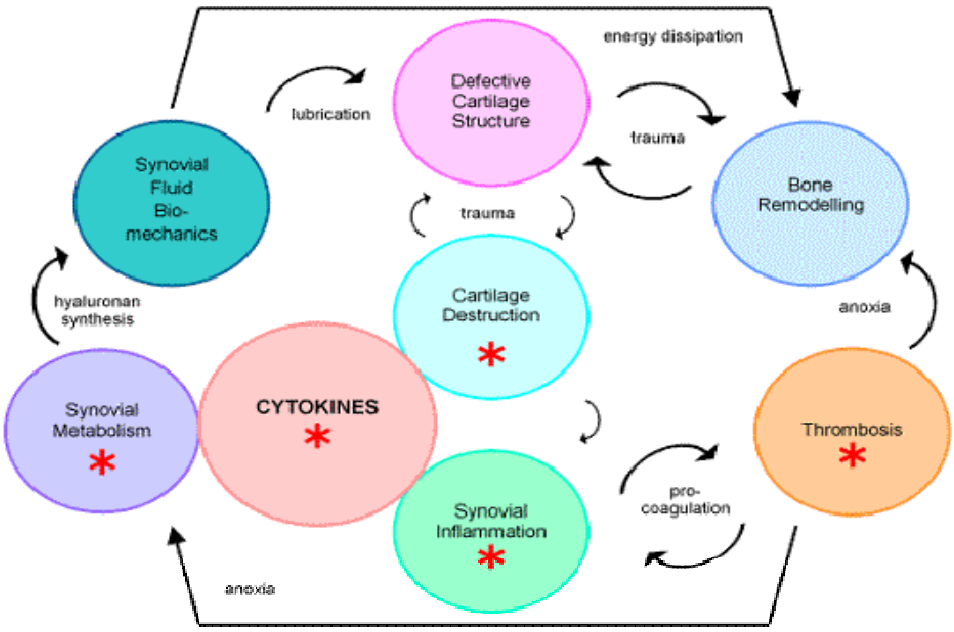

Figure Nr.2. Possible pathogenesis in osteoarthrosis.(1)
Cartrophen Vet. Interactions are marked in red.

Pathogenesis suggestion developing OA: Overview on Figure 2 (free after Cullis-Hill).

1) Inflammation of synovium, cartilage damage (”fibrillation”) and damage on joint capsule. Early circulation disturbance.
2) Catabolic > Anabolic process. Chondrocytters production of proteoglycan, collagen and hereby”cartilage matrix” is reduced. Hyaluron acid amount decreases and its viscosity is reduced.
3) Antigenic effect of cartilage breakdown products gives an activation + migration by leucocytes, monocytter and lymphocytes.
4) Fibrin creation (complement cascade) enhances circulation disturbances from the inflammation and develops mikrotromber in the subchondrale bone tissue.
5) Proteolytical enzymes (metalloproteinase), prostaglandins (PGE2) and cytokines (interleukin 1 + 6, TNF Alfa) and free radicals brings together a so called”inflammation soup” enhancing pain.
6) Long-term changes create osteofytter, damage in the transforming zone for subchondrale bone tissue and creation of fissures in the bone tissue (1, 4, 6, 10, 11).

Treatment possibilities in OA:
NSAID: The effect are well known and Rimadyl Vet. (Carprofen) are one of more new potent products with a more selective reduction in Cyclooxygenase (COX2/COX1) enzymes, in relation > 100/1. Especially prostaglandin PGE2 production is reduced and the also suppression of the Wind–up effect in the dorsal horn of the spine is seen. These are major reasons for less pain in OA conditions in joints (9, 12, 13, 17, 18, 19, 20). Because of the long term treatment side effects are discussed (21, 22, 23, 24).

DMAOD: The idea behind these products are a cartilage protective and anti inflammation effect.
Cartrophen Vet: The drug consists of Natrium Pentosan Polysulfate (NaPPS) and it is produced in solution at 100 mg / ml. The expected effect, after 4 x injection, stretches from 6 – 12 months. The drug is extracted from”Beachwood hemicelluloses” and it has been used in human treatment through 40 years as treatment in heart/brain infarcts and OA knee and finger joints. The effects have been documented in vitro (6, 7) and in vivo (1, 4, 5, 6).

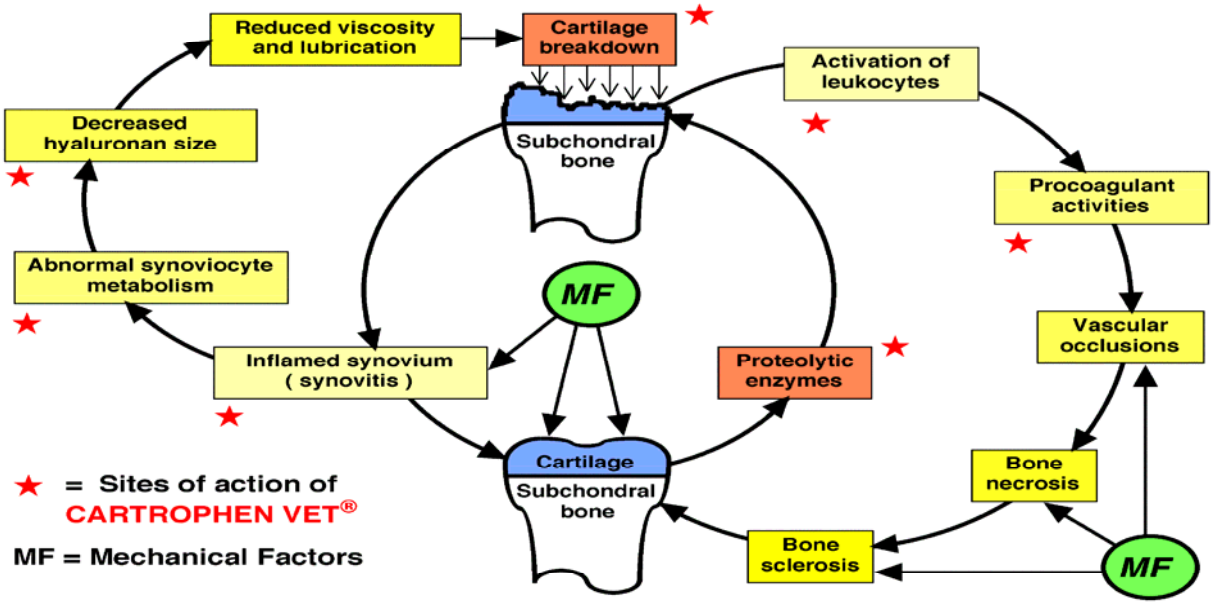

Figure3. Cartrophen Vet. and OA (1).

Cartrophens effect on OA conditions (acute/chronic inflammation in joints): Figure 3. (free after Cullis-Hill)

1) Reduction of inflammation, by suppressing prostaglandins (PG), metalloproteinaser (MP), and aggrecanaser.
2) Suppression of neutrofile granulocytter and macrofager activity, including suppression of lysosomale enzymes and hyaluronidase and collagenase.
3) Stimulation of chondrocytter for normal production and proteoglycan.
4) Stimulation of Synovium for normal production of hyaluron acid.
5) Improvement of circulation with the resolution of mikrotromber and hereby reduced stasis in the subchondrale bone tissue in particular (1, 4, 5, 6, 7).

Materials and Method:
The investigation of dogs with Lameness / Pain was conducted on 3 hospitals and clinics in Northern Jutland Denmark from March 2004 to October 2005, mainly at Brunder Animal Hospital. Other contributors were Løkken Animal Clinic and Hobrovejens Animal Hospital, represented by specialized veterinarians Niels Østergaard and Thomas Larsen.
A detailed investigation protocol with inclusions criteria and exclusion criteria for patients were available. Lameness and Pain score schematics were evaluated together with the involved veterinarians before starting the investigation and the formulated scores compared with previous used Lickert Scales figures. The scores schematics have not validated in any other investigations. The whole protocol is seen in appendix nr. 3, page 17 – 19.
Dogs with varied degrees of lameness and pain were all investigated clinically as well as X rayed to complete diagnosis. All the gathered data from the protocols was placed in a central database and the X rays were transferred after digital photos. They were placed in the same case number as other clinical information and scores in the database.
The required X ray changes for OA and OD/OCD were e.g.: 1) Osteofytter formation 2) Joint cavity changes (reductions/unclear lines) 3) Increased density in Periost and unclear (“mouse eaten”) edges. 4) Osteochondritis Dissecans 5) Sclerosis in Subchondrale bone tissue 6) Soft tissue enlargement or calcification around the joints 7) Osteochondritis changes by Fossa Glenoidale in the shoulder joints 8) Elbow Dysplasia with Ununited Processus Anconeus or Fragmentized Processus Coronoideus. Dogs with acute lameness/pain and no visible X ray changes were excluded. Dogs with HD diagnosis had to be equal/worse than C-left or C-right. In some cases secondary OA changes to HD was also seen. Dogs with Lumbar Sacral instability and lumbar pains were included with specific X ray changes around L7/S1 joints and ventral exostosis. X rays were taken in lateral and dorso-ventral position in all extremities and columnar joints. In the HD dogs both knee joints and a lateral lumbar projection was included. Main part og dogs were without prior treatment, but for others a ”wash out” period at 14 days for NSAID and 28 days for steroid treatment was demanded. For food additives like Oil of life, Artroflex, Ginger tablets and so on a ”wash out” period for 8 days was demanded.
Lameness and Pain were scored in weeks 0,1,2,3, and 7. Lameness score from 0 – 4. Pain score from 1 – 5. The lower values the better condition. Lame free = 0, Total lameness (not using) = 4. Pain free = 1. Judgements of score values were divided into three areas: A) Visual inspection. B) Joint manipulation C) Owners daily visual inspection og the dog resting, getting up/laying down, and ordinary exercise or training. Score values are chosen to compare with earlier investigation of Cartrophen Vet.(1, 3, 4). With any doubts to veterinarians score the dogs were observed outdoors, to evaluate if manipulation or running in a leach with the owner gave increased or renewed lameness/pain.
The Rimadyl Vet. group was used as a ”control group”, because a positive effect on OA and HD already was established through clinical investigations (16,17,18,19,20), and also avoiding ethical problems with dogs having pain in 8 weeks on placebo drugs. Owners had a free choice between Cartrophen Vet 1 ml/33 kg 4 x with one weeks interval, or Rimadyl (Carprofen) chewing tablets 100 mg, 4 mg/kg daily for 28 days. Decisions were taken after X rays had confirmed diagnosis. Owners were questioned about side effects week 1, 2, 3, and 7.Treatment with injection was started with either

Cartrophen Vet. (100mg/ml)1 ml/33 kg or Rimadyl Vet.(50 mg/ml), 1 ml/12,5 kg on the first day of X raying.
All owners had to observe the four clinical control visits, and the 11 Rimadyl Vet. dog owners checked on use of tablets. In the database was noted"compliance" of all owners in the investigation.

Results:
In total 37 dogs were included in the investigation.
Brunder Animal Hospital 26 dogs, Løkken Animal Clinic 5 dogs and Hobrovejens Animal Hospital 6 dogs. A German Shepard puppy (Nr. 38, HD & OA elbows) 6 months was terminated because of aggression. It was registered with basis data, but without scores on lameness/pain in week 3 and 7.
Database out print for statistical analysis of results is shown in page 15 and 16(Appendix 1 & 2).
In total there were 26 dogs in the Cartrophen Vet. Group (C in column diagrams) and 11 dogs in the Rimadyl Vet. Group (R in column diagrams).

1) Age average is 6, 3 years in C- group and 8, 3 years in R- group. Non paired t- test showed no significant difference in the two groups (P=0, 1210) (Figure 4).

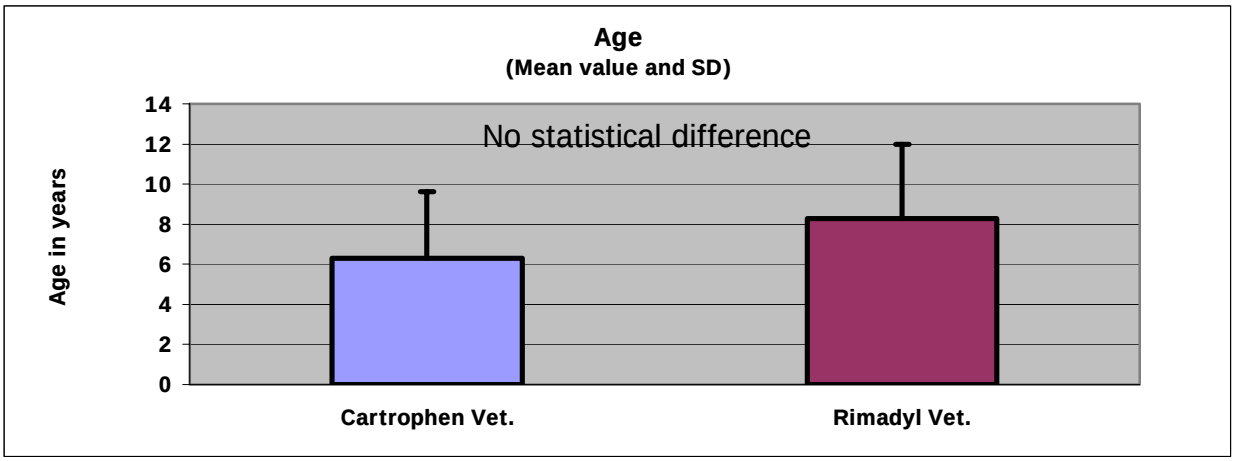

Figure 4. Age variation.

2) Weight average is 29,2 kg in C – group and 30,3 kg in R – group. Non paired t - test gave no statistical significant difference in the two groups (P=0,7716)(Figure 5).

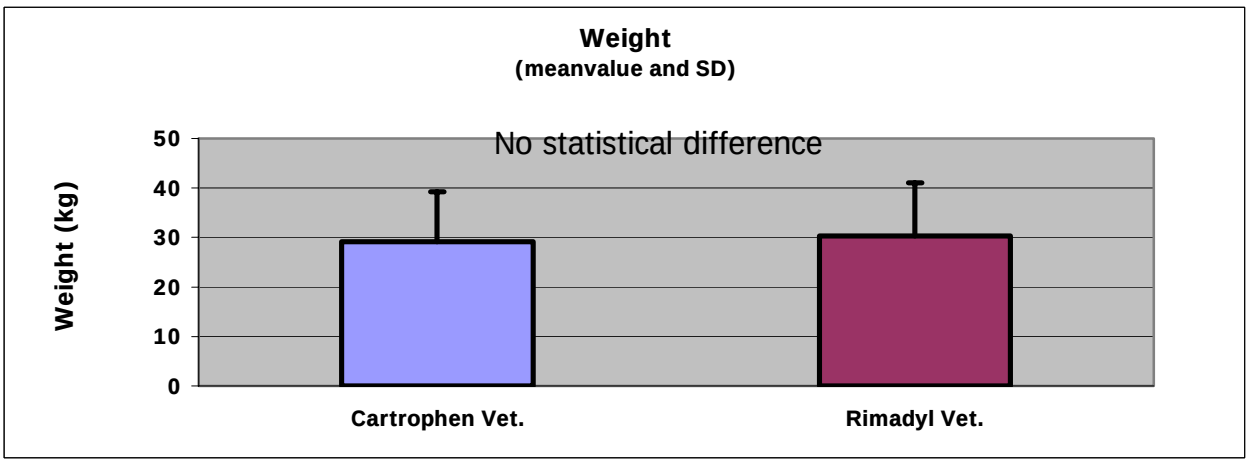

Figure 5. Weight variation.

3) Table 1 and 2 shows distribution and diagnosis between small/large dogs (% shares) in the 2 groups.

Table 1. Diagnoses and weight distribution of the Cartrophen group.

Cartrophen Vet. / Race	Numbers	Hip Dysplasia.		Osteoarthrosis/Osteochondritis.	**Total**
Small dogs (<25 kg)	7 (27 %)	1 (3,85 %)		6 (23,08 %)	**26,92 %**
Large dogs (>25 kg)	19 (73 %)	9 (34,61 %)		10 (38,46 %)	**73,08 %**
Numbers	26	10		16	**26**
Percent	**100 %**	**38,46 %**		**61, 54 %**	**100 %**

Table 2. Diagnoses and weight distribution of the Rimadyl group.

Rimadyl Vet. / Race	Numbers	Hip Dysplasia.		Osteoarthrosis/Osteochondritis.	**Total**
Small dogs (<25 kg)	3 (27,27 %)	2 (18,18 %)		1 (9,09 %)	**27,27 %**
Large dogs (> 25 kg)	8 (72,72 %)	1 (9,09 %)		7 (63,63 %)	**72,73 %**
Numbers	11	3		8	**11**
Percent	**100 %**	**27,27 %**		**72,73 %**	**100 %**

4) By comparison of the starting point for the two groups C (Cartrophen Vet.) and R(Rimadyl Vet.) at time 0 (week 0) for veterinarian lameness score (DH) and veterinarian pain score (DS), the Mann–Whitney Rank Sum Test of the group of numbers (scores) were not normally distributed, and there was non statistical difference (P=0,1061).By comparison for owners lameness score (EH) there was a small significant difference(P= 0,0389), meaning that the C group scored slightly lower from the start than the R group. The Median were lower for the C groups .For the owner pain score (ES) there was no significant difference on the two groups (P=0,2438), and both number groups of scores were not normal distributed. The results in section 1 - 4 showed that the two groups were compatible, and not statistical significant different in the starting point at week 0.

How the two investigated drugs affected lameness score and pain score in the investigation period for 8 weeks, were investigated by **Friedman Repeated Measures Analysis of Variance on Ranks**. The results consisted of scores on the same animal, and a Median was established for the single weeks 0,1,2,3, and 7.

5) For DH (Veterinarian Lameness score) in C (Cartrophen group) there was a significant fall from week 0(u0) to week 7(u7). (X2=65,8. P=<0,0001). By comparing the individual weeks**, T – test, ANOVA**, where groups of numbers or scores from the individual weeks were tested against each other, there was a significant fall in all weeks (P<0,05) measured against week 0**(Dunns Method)**. There was a significant effect (marked"*") already from week 1 with treatment. For DH (Veterinarian Lameness score), in R (Rimadyl group) there was also a significant fall from week 0 to week 7. (X2 =32,1, P<0,0001). By comparison of the single weeks against week 0, a significant fall (P<0,05), was also seen from week 1 with treatment (Figure 6).
In the graphs for Cartrophen the slightly lower starting point of lameness is noted, and the continues fall (improvement of lameness) is seen in all weeks, including 4 weeks after last treatment. In the graphs for Rimadyl a slightly higher starting point is noted, and the continues fall (improvement of lameness) is seen in the first 4 weeks. However the continues improvement stops after the 4 weeks of treatment, but still remains lower than the starting point, even after another 4 weeks of pause. This pattern is also seen for DS (Veterinarian Pain score), and develops in the exact same way for Cartrophen, continues improvement all weeks, and for Rimadyl, continues improvement the first 4 weeks, and then stagnation.

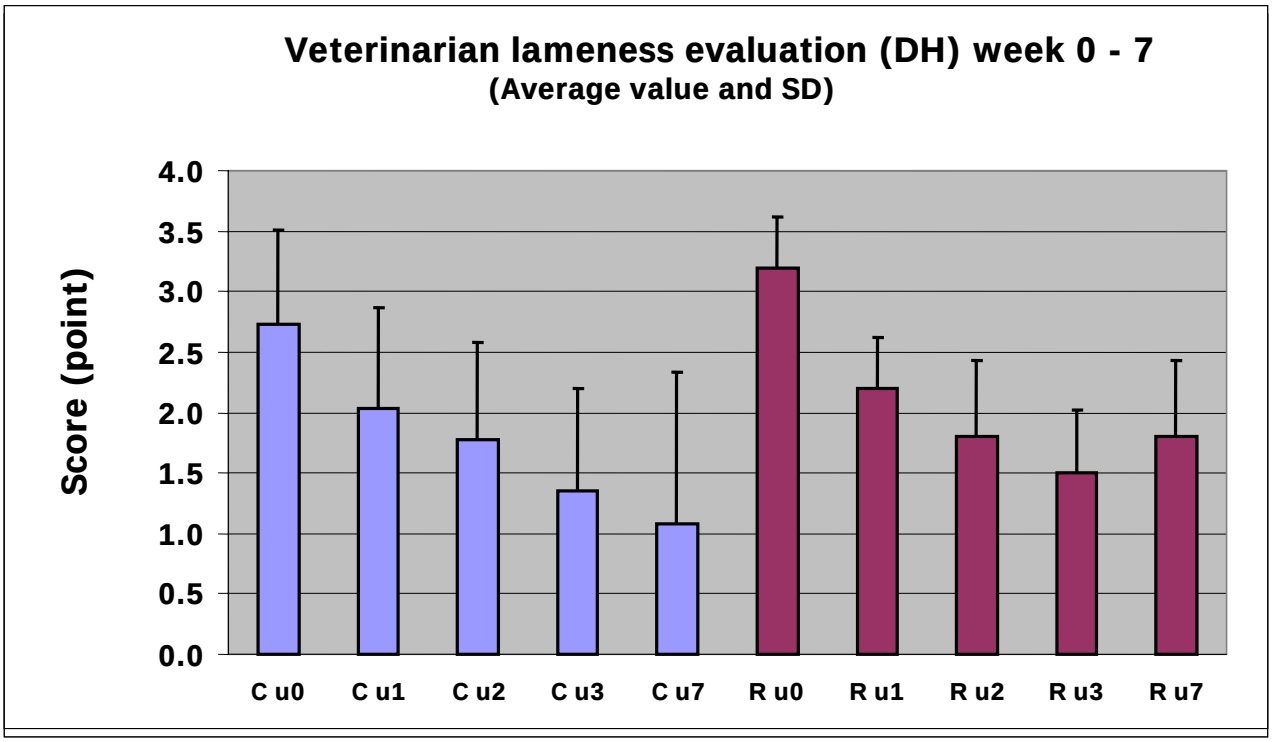

Figure6. Lameness Veterinarian. Cartrophen (C) and Rimadyl (R). Week (U) 0 – 7.

6) For DS(Veterinarian Pain score), C (Cartrophen group), there was a significant fall from week 0 to 7. (X2 =70, P=<0,0001). By comparison of the individual weeks, there was a significant fall in all weeks (P<0,05), and already significant fall from week 1. For DS (Veterinarian Pain score), R (Rimadyl group) there was a significant fall from week 0 to 7. (X2=29,5 P<0,0001), and weeks measured against week 0 showed significant fall (P<0,05), already from week 1(Figure 7).See comment in section 5).

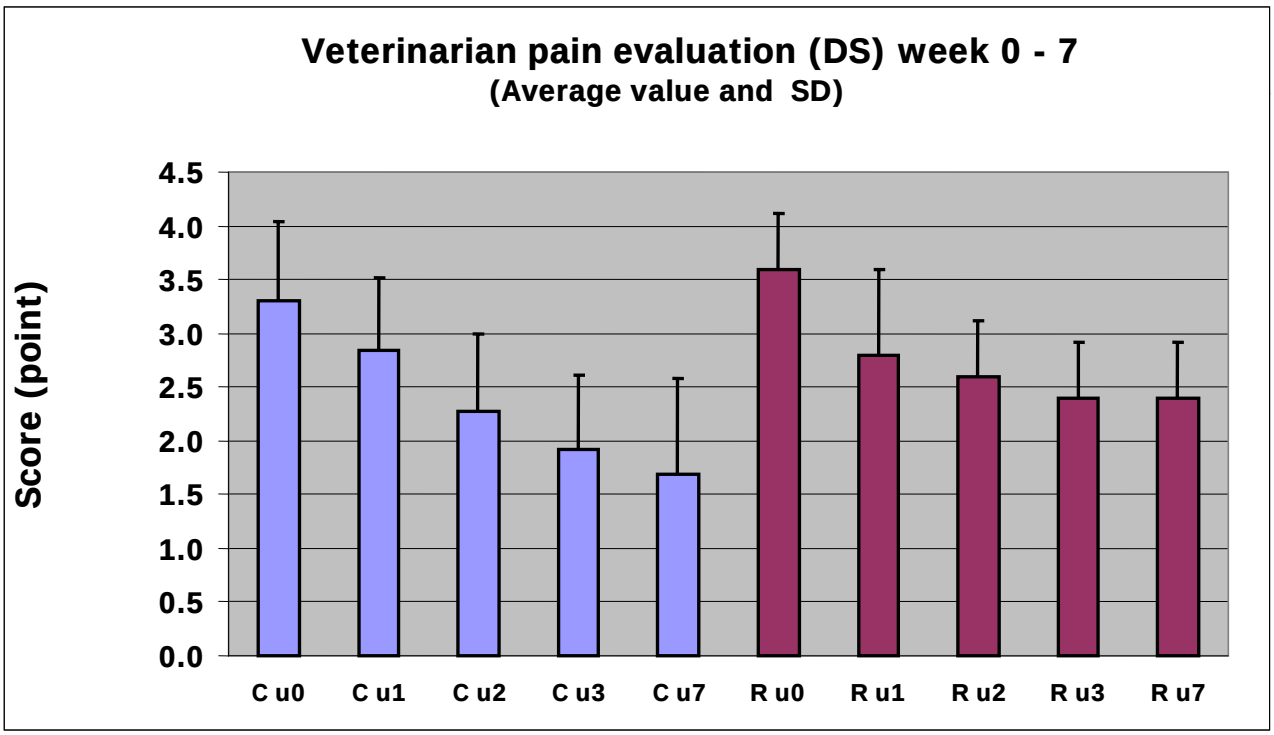

Figure 7. Pain Veterinarian. Cartrophen (C) and Rimadyl (R) . Week (U) 0 – 7.

7) To make a comparison between the two groups in treatment effect at DH and DS over time, from week 0 to week 7, a Mann - Whitney Rank Sum Test at Cartrophen against Rimadyl was made. There was no statistical difference at ”baseline changes”, meaning the accumulated lameness/pain score from week to week, measured against each other(Tabel 3) /(Tabel 4). R = Rimadyl. C = Cartrophen.

Table 3: DH evaluation of **changes** under treatment: R against C. Mann Whitney RANK Sum Test

Time	Score changes R (n = 10) Median (25 og 75 %)	Score changes C (n = 26) Median (25 og 75 %)	**P-værdi**
Delta week 1 (week 0 – week 1)	1 (0-1)	1 (1-1)	**0.21**
Delta week 2 (week 0 – week 2)	1 (0-1)	1 (1-2)	**0.12**
Delta week 3 (week 0 – week 3)	2 (1-2)	1 (1-2)	**0.18**
Delta week 7 (week 0 – week 7)	1 (1-2)	2 (1-2)	**0.54**

Table 4: DS evaluation of **changes** under treatment: R against C. Mann Whitney RANK Sum Test

Tidspunkt	Score changes R (n = 10) Median (25 og 75 %)	Score changes C (n = 26) Median (25 og 75 %)	**P-værdi**
Delta week 1 (week 0 – week 1)	0 (0-1)	0 (1-1)	**0.24**
Delta week 2 (week 0 – week 2)	1 (1-1)	1 (0-2)	**1.00**
Delta week 3 (week 0 – week 3)	1 (1-1)	2 (1-2)	**0.45**
Delta week 7 (week 0 – week 7)	2 (1-2)	2 (1-2)	**0.15**

8**) None or reversible results in C group**: Two dogs (Number 25 + 26) with highly developed OA in knee joints, from Løkken Animal Clinic. Two dogs (Number 29 + 31) with Lumbosacral instability and OA L7/S1 from Hobrovejens Animal Hospital. They showed only temporary improvement in week 3, but fell back to starting point in week 7. Total of 15 % (Appendix 2).
None or reversible results in R group: One dog/puppy (Number 38) 6 month old with HD + OA/OCD in both elbows. The dog was euthanised after two weeks of treatment .Total of 9 %(Appendix 2).

9**) Side effects** in **C group**: In total 6 dogs with mild side effects out of 26 dogs, corresponding to 23 %. There were 3 cases of reduced appetite and 3 cases of lethargic dogs (temporary tiredness/weakness) right after injection time. Symptoms were brief, lasted only 1 -2 days, and often starting weeks 1 - 3.
Side effects in R group: There was no registration of the typical GI side effects for NSAID. No biochemistry was made to evaluate the patients liver or kidney enzymes.

10) **Other results:**
The number of large dogs (>25 kg) are three times larger than that of smaller dogs (<25kg) in both examination groups (Tabel 1 + 2). Also more male dogs (22 dogs) than female (15 dogs) app. 1,5/1 (Appendix 1).
By the end of examination period 11 dogs in the Cartrophen group was lame free and pain free (42 %), and 1 dog in the Rimadyl group (9 %) was lame free and pain free(Appendix 2, enhanced with colour).

Discussion:
The intention for this investigation was to have two equally large groups of dogs app. 25 in each group. This amount of dogs was obtained for the Cartrophen Vet. dogs, but not for the Rimadyl Vet. dogs, because of lack of time and funding. The aims for a ”paired” investigation, with equal numbers of diagnosis, was not obtained . The results in figure 4 + 5 concerning age/weight variation and Tabel 1 and 2 about distribution between diagnose groups, HD and OA/OD/OCD shows no statistical difference, and a percent wise equal distribution.

Beside this a statistical investigation og the starting point for lameness and pain score has been made, for both veterinarians and owners, that showed only one single significant deviation, namely a slightly lower estimation og lameness score from the owners in the Cartrophen Vet. group.
The diagnostic evaluation in the dogs also seemed more difficult in practice , because dogs with osteochondritis(OD) or osteochondritis dissecans(OCD) already had starting signs of OA changes in the X rays. This is the reason for combining all the diagnostic results of OA/OD/OCD in table 1 and 2, but all details in diagnostics are accounted for in the database (Appendix 1, Diagnose).
Total of 3 dogs with Lumbosacral instabilitet and OA changes around L7/S1 and 1 dog with Spondylose L1-2 and L 4-5 was included in this combined group. Only two dogs (Number 33 and 36), one from each group, responded positively on the treatment with Rimadyl Vet. Because these dogs often can be difficult to treat in practice, because of the severe lameness/pain, I see positive treatment possibilities with permanent NSAID therapy. For the Cartrophen Vet. treatment on the two other dogs with the same diagnosis (Nr.29 +31) , there were only temporary relieve and no better prognosis .

In the HD group there were several dogs (Nr.8, 13, 15, 40, 28) without OA changes, and especially these dogs became totally free of lameness/pain in both treatments. There was a clear tendency for better results in early diagnostics and early treatment results. In particular in the Cartrophen Vet. group, where the period of investigation was about 18 month, which e.g. included 2 barely grown dogs (Nr. 6 + 10). In the OA/OD/OCD group there were also several dogs totally free of lameness/pain (Nr.3, 4, 5, 11, 14, 18, 27) even though several dogs had enhanced chronically OA changes.

It would seem ideal with single or double blinded investigations to reduce ”bias” as much as possible. For this investigation that was not possible to administrate, but the owner had a open/free choice after a ”neutral” presentation of treatment possibilities from their own veterinarian. However there was a clear tendency to get introduction to the ”new” treatment with Cartrophen Vet., because several owners disliked the idea of constantly feeding their dogs with tablets every day. Also a knowledge of NSAID products side effects from especially humans but also veterinary areas was known by the owners.
In general both veterinarians and owners were critical towards what improvements should be accomplished during/after the treatments. An improvement of the dog’s level in both lameness and pain had to be seen both in the clinic & after manipulation, plus to be observed in the home area, in exercise or training/hunting. That meant that scores were not changed until certain of changes clinically + home.

The biggest problems however , in these kinds of clinical investigations of lameness and pain in dogs, was clearly the very subjective measuring method with comparison of non validated scores and involvement of three veterinarians(15).More precise techniques like ”force plate gate analysis” on lameness or VAS score systems, like known from human sector, could evaluate the positive results further. A direct evaluation of the Synovial fluid in the affected joints was also obvious choice in week 0, 3 and 7, but both time consuming and a relative risk for the involved animals under extra anaesthesia. An interesting, but rather invasive and expensive technique like arthroscopy, for evaluations of the cartilage healing effect from week 0 to week 7 would clarify many of the relevant questions in particular according to Cartrophen Vet. and its chondroprotective abilities.
By other numerically larger investigations on e.g. Rimadyl Vet. reducing lameness, the comparison/control groups were also missing, as well as double blinded investigations , and the expensive techniques mentioned above(17,18).

Even though every dog was scored 5 times in 8 weeks in this investigation, both a continuously treatment of dogs with Rimadyl Vet. in e.g. 3 – 6 month. , compared with Cartrophen Vet. treated dogs, as well as a follow up on both groups of dogs after 6 month would be preferred . However it has been estimated that 85 % of dogs, that will respond positively on treatment with NSAID drugs, are doing so within a 28 day period(17).Also this investigation showed a positive result for both lameness/pain in 85 % of the dogs with a ”significant” reduction within 8 weeks, including both Cartrophen Vet. and Rimadyl Vet. groups (Appendix 2, only 5 dogs with score reduction 0, 1 or lacking/euthanised out of 38).

The difference between veterinarian and owners results in lameness and pain was almost non existents, and only the veterinarians results are shown in the database prints(Appendix 2) plus in graphics (Figure 6+7). Sometimes manipulation in the clinic could provoke pain that was not seen home or in exercise.

The background for clinical studies of Cartrophen Vet are not as thorough as for NSAID drugs, but 3 veterinarian clinical investigation of 40, 19 and 104 dogs will be mentioned(1,2,4,5). Besides that there are 4 human clinical investigations with 114, 23, 50 and 86 patients, all with OA (6). These investigations are all double blinded and there for a high truth value. There are consistent positive results with reduced lameness and pin in dogs, and improved joint function, less stiffness in joints and better walking results in human patients, evaluated from VAS validated pain scores/scales(6). Cartrophen Vet. have been investigated in several laboratorial investigations, where different "in vitro" models proves anti inflammatory abilities, and affection of molecular weight for hyaluron acid in OA affected joints, where the viscosity is too low (6,7). Also investigations of chondroprotective ability, in models with experimental Cruciatum rupture in rats and sheep have been have shown, that Cartrophen Vet. treated animals had markedly reduced damages on the joint cartilage, judged in special colouring after test animals was euthanised and autopsied (6.7).

Rimadyl Vet.(Carprofen) have been investigated in relative large populations of dogs, but often without control groups, and without comparison towards other NSAIDs or opiates (15,16,17,18,19,20). The longest investigation period goes from 1 to 6 month, but a few as long as 12 month (17).

In OA/HD its important to evaluate side effects from long term or "lifelong" treatment.
For Cartrophen Vet, side effects have been reported in UK, from 1991 to 1999(8). A low amount was seen, despite 4 treatments pr. patient pr. year. The frequency were about 0,5 %, and was described as vomiting (within 1 -2 hours) or light lack of appetite or lethargy a few days after injections. Bleeding time was shortly raised in 2 – 8 hours after injection, but even in doses at 10 times recommended doses (30 mg / kg), there was no spontaneous bleedings, and all values were normal after 24(8).
Same types of relative mild side effects were reported in this investigation with lowered appetite and lethargy in 2 – 3 days. Neither owners nor veterinarians found these side effects to be a serious problem.

In NSAID in general, but especially for Rimadyl Vet (Carprofen) the typical side effect frequency were about 3 – 5 % (15, 16, 17, 18). For long-term treatments in Norway and Sweden in 90 days with Carprofen 4 mg / kg / day were registered 10 % side effects, mainly with typical GI disturbances like vomiting and diarrhoea but also more serious bleeding disorders and toxic liver syndrome. 4 dogs out of 515 were euthanised because of repeated GI bleedings (17, 18).
Hepatotoxicose have been reported as a specific result from use of Rimadyl Vet. or Carprofen. 21 cases were described, among these 13 Labrador dogs(23). The clinical signs arose 5 – 30 days after starting the treatment and all cases was verified with raised values of liver enzymes (ALAT, ASAT, ALKP, TBIL, ALB) and with liver biopsy on18 of the 21dogs. Also signs of Renal Toxicosis with acute interstitial nephritis, papillary necrosis and acute or chronic renal damage were detected (23).

The understanding of the dynamics involving COX enzymes and the investigation of prostaglandins (PG) today are incomplete. The consideration by COX 1 as physiological PG creator and COX 2 as inflammation PG creator, does not explain the problems in chronic inflammation, like e.g. OA , Rheumatoid Arthritis or Sclerosis in humans. There are also thoughts about another variant of COX 1 enzyme, called COX 3(13, 22).
Typical investigations have been focusing on PGE prostaglandins, in particular PGE 2, but only for short periods of time, hours or days.
Arachidonic acid is converted by COX1/COX 2 to PHG, and from this other PG types are made.
A new group of PG, called "Cyclopentone Prostaglandins", especially PGD 2 and PGJ 2, seems to be having coinciding peak values with COX 2 enzymes in the end stages of acute inflammation. This is also the starting point of wound healing and reconstruction processes (22).

The problems around lack of healing in chronic stomach ulcers or cornea ulcers can be explained, because of the specific COX 2 inhibitors ability to reduce formation of Cyclopentone prostaglandins. It is there for possible that some inflammation forms can become chronicle when using specific COX 2 inhibitors e.g. Rimadyl Vet. for extended amounts of time(13,21,22).
COX 2 enzymes seems to be attached to an immune mediating roll in Colitis. In models using treatment with COX 2 inhibitors, mice and Guniapigs, perforation ulcers were found in the Colon (22).
From other animal models with fracture healing and at the same time using different NSAID products, an inhibition of Osteoblasts and Osteoclasts was reported.This inhibition lead to problems in the healing process of fractures, ligaments, tendons, and skin wounds in rats (21). Also a reduction of bloodflow around 35 % to 43% in resting rats, was found after treatment with Carprofen and Romefen (21).
The uses of pain relieving drugs are commonly used in dogs/cats with OA/OD/OCD or HD, and often relatively late in age. The typical OA patient are 7 – 9 years in average,, which makes them more vulnerable for reduced liver and kidney function. Average age in my investigation were 6,3 years in the Cartrophen Vet group and 8,3 years in the Rimadyl Vet. group.
Symptoms and cartilage damage are often larger in older dogs, and all negative cartilage effects should be avoided. Rimadyl Vet and Metacam Vet. are regarded as neutral in the concerns for reduced synthesis of joint cartilage (12). Long-term studies are still not performed.
In my investigation, no side effects were seen in the Rimadyl Vet. group in the 28 day period. Among the 26 dogs in the Cartrophen Vet. group were 2 dogs, which previously had been showing typical GI side effects on NSAID treatment with Rimadyl Vet. and Metacam Vet. These dogs responded favourable to Cartrophen Vet. treatment and showed no side effect after injections.
Last, but not leas tit is important with weight reduction, good feeding (”mobility diets” or geriatric diets), physiotherapy and well documented diet supplies when OA, OD, OCD or HD condition have been diagnosed. Remembering the background and chronic progressive degeneration in OA, no matter of the primary condition (OD/OCD, HD etc.) it is important to take all possible tools into consideration (12, 13, 14).

Recommendations for treating chronic pain in OA, OD/OCD and HD conditions in dogs:
1) Cartrophen Vet is a useful and efficient alternative to NSAID treatment, and can reduce the loss of joint cartilage together with sufficient pain and lameness reduction (1, 4, 6, 7).
2) The use of specific COX 2 inhibitors with a minimal effect in joint cartilage development can be chosen, e.g. Carprofen (Rimadyl vet.) or Metacam (12, 19). The dose of these NSAID can sometimes be reduced to 50% with prolonged treatment, e.g. 2 mg pr. kg pr. day for Rimadyl Vet. (13, 17, 18, 19).
3) In combining opiates and NSAID a really good pain reduction can be achieved in conditions with OA or in relieving pain after surgery. This is particular crucial in bone fracture, tendon and skin healing. The dose can be reduced 50 % for both drugs, reducing the side effects considerable (5, 13, 17, 24).
4) Combination of multiple treatment regimes, e.g. NSAID in acute stages of pain, and after 2 to 4 weeks treatment, 4 weekly treatments with Cartrophen Vet. Because of bleeding time influence, the drugs should not be used together, but separated (12, 13, 22).
5) It is obvious to use Cartrophen Vet as after treatment in joint surgery (OD/OCD), where damage to joint cartilage often leads to OA within months (5, 6, 22, 24). Same treatment can be recommended in ligament damages like Cruciatum rupture or other traumatic injuries , leading to hyper mobile joints, or immobilised joints which also creates OA conditions within weeks (5,6,21,22,24).
6) Supportive treatment for OA patients e.g. Glucosamin, MSM, New Zealand Green Lipped Mussel, Omega 3/6 fatty acids in the relation 1/5 – 1/10 have all been shown to give effects in reduction of pain, lowering of PGE levels, reducing the catabolic process and enhancing cartilage formation(6,12,14).
7) An alternative drug to Cartrophen Vet is called Adequan. It is made from glycosamin glycan polysulfate ester (GAGPS) and has to be injected 2 x weekly in 4 weeks. Good results have been found in HD dogs in an US investigation, and it is considered to be chondroprotective (12, 14).
8) NSAID treatment should be limited to shorter periods, typical 5 - 10 days, after surgical treatment, in order not to compromise skin and wound healing, bone and ligament healing (21, 22, 24).

Conclusion:

Cartrophen Vet. : Reduces lameness and pain significant in dogs with OA/OD/OCD and or HD cases. There was a lack of response in 2 cases of Lumbosacral instabilitet including OA changes in the L7and S1 region.
Especially in early diagnosis and treatment, lighter X ray changes and less severe lameness, it was possible to achieve total freedom of lameness and pain in dogs. In total 11 dogs out of 26 became totally free from lameness and pain after treatment, which is 42 %. The distributions were 5 dogs with HD and 6 dogs with OA/OD (knee, tarsus, elbow, shoulder and hip joint).
Side effects on 6 dogs (23 %) were mild and temporary, with lethargy and reduced appetite one or two days after injection.
Rimadyl Vet. : Reduces lameness and pain significant in dogs with OA/OD/OCD and or HD. No side effects were reported in the 28 days of treatment of the 11 dogs included.

By comparison between the two drugs, the effect of Cartrophen Vet. on lameness and pain were at the same level or higher than the clinically well investigated drug Rimadyl Vet**.**

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Appendix: Enclosure 1 – 3

Enclosure 1: Database out print 1, page 15.
Enclosure 2: Database out print 2, page 16.
Enclosure 3: Investigation protocol page 17 – 19.

Appendix page 15 .Enclosure 1. Database outprint.

Klinik	ID Dog	Dog Race	Age	Weight	Sex/Gender	Diagnose			Treatment	Osteofyt	Changed Jointspace
						HD	OA	OD			
Brunder Dyrehospital	1	Kleiner Munsterlænder	10	33	Male		/		Cartrophen	+	-
Brunder Dyrehospital	2	Labrador	11	40	Male	/			Cartrophen	+	+
Brunder Dyrehospital	3	German Roughhair	7	26	Female		/		Cartrophen	+	+
Brunder Dyrehospital	4	Mixed Breed	10	28	Female		/		Cartrophen	+	+
Brunder Dyrehospital	5	Mastiff Mixed Breed	4	52	Sterilised		/	/	Cartrophen	+	+
Brunder Dyrehospital	6	Boxer	1	26	Male		/	/	Cartrophen	+	+
Brunder Dyrehospital	7	Mixed Breed	9	37	Kastrated		/	/	Cartrophen	-	+
Brunder Dyrehospital	8	German Shepard	2	40	Kastrated	/			Cartrophen	-	+
Brunder Dyrehospital	9	Labrador Mixed Breed	7	23	Female		/		Cartrophen	+	+
Brunder Dyrehospital	10	Golden Retriver	1	30	Male	/			Cartrophen	-	-
Brunder Dyrehospital	11	Kleiner Munsterlænder	11	22	Sterilised		/		Cartrophen	-	+
Brunder Dyrehospital	12	German Shepard	4	32	Female	/	/		Cartrophen	+	+
Brunder Dyrehospital	13	Labrador	7	40	Female	/			Cartrophen	-	-
Brunder Dyrehospital	14	Puddel	8	6	Female		/		Cartrophen	-	+
Brunder Dyrehospital	15	Labrador	10	31	Female	/			Cartrophen	+	-
Brunder Dyrehospital	16	Beagle	6	20	Male		/	/	Cartrophen	-	+
Brunder Dyrehospital	17	Cocker Spaniel	6	15	Kastrated	/	/		Cartrophen	+	+
Brunder Dyrehospital	18	Longhair Dachshound	10	9	Male		/	/	Cartrophen	+	+
Brunder Dyrehospital	19	Mastiff/Boxer Mixed	2	33	Male	/			Cartrophen	+	-
Brunder Dyrehospital	22	Cocker Spaniel	11	15	Female	/			Rimadyl tab.	+	+
Brunder Dyrehospital	23	Cairn Terrier	13	10	Male	/	/		Rimadyl tab.	+	+
Brunder Dyrehospital	24	German Shorthair	11	46	Female		/		Rimadyl tab.	+	+
Brunder Dyrehospital	35	Labrador Mixed Breed	3	27	Female		/		Rimadyl tab.	+	+
Brunder Dyrehospital	36	Collie	10	37	Male		/		Rimadyl tab.	-	+
Brunder Dyrehospital	38	German Shepard	1	22	Female	/	/	/	Rimadyl tab.	+	+
Brunder Dyrehospital	40	Golden Retriver	6	37	Male	/			Rimadyl tab.	+	-
Hobrovejens	29	Golden Retriver	9	36	Female		/		Cartrophen	-	+
Hobrovejens	30	Dalmatien	7	33	Male		/		Rimadyl tab.	+	+
Hobrovejens	31	Finnish Lap Dog	9	22	Male		/		Cartrophen	-	+
Hobrovejens	32	Labrador Retriver	10	38	Female		/		Rimadyl tab.	+	+
Hobrovejens	33	Golden Retriver	11	35	Male		/		Rimadyl tab.	+	+
Hobrovejens	37	Chow Chow	3	30	Male		/		Cartrophen	+	+
Løkken dyreklinik	25	German Roughair	7	33	Male		/		Cartrophen	+	+
Løkken dyreklinik	26	Berner -Sennen	5	38	Male		/		Cartrophen	+	+
Løkken dyreklinik	27	Golden Retriver	4	32	Male	/	/		Cartrophen	+	+
Løkken dyreklinik	28	Labrador Mixed Breed	1	25	Male	/			Cartrophen	-	-
Løkken dyreklinik	39	Labrador Mixed Breed	8	33	Male		/	/	Rimadyl tab.	+	+

Appendix page 16. Enclosure 2. Database outprint.

Klinik	ID Dog	Treatment	Vet. lamness score week 0	Vet. lamness score week 7	Vet. pain score week 0	Vet. pain score week 7	Drop in Score Total(Week 0 - 7)	Lame Free	Pain Free
Brunder Dyrehospital	1	Cartrophen	3	1	4	1	5		+
Brunder Dyrehospital	2	Cartrophen	4	2	5	3	4		
Brunder Dyrehospital	3	Cartrophen	4	0	4	1	7	+	+
Brunder Dyrehospital	4	Cartrophen	3	0	3	1	5	+	+
Brunder Dyrehospital	5	Cartrophen	2	0	3	1	4	+	+
Brunder Dyrehospital	6	Cartrophen	2	1	3	2	2		
Brunder Dyrehospital	7	Cartrophen	2	1	4	2	3		
Brunder Dyrehospital	8	Cartrophen	2	0	3	1	4	+	+
Brunder Dyrehospital	9	Cartrophen	2	1	3	2	2		
Brunder Dyrehospital	10	Cartrophen	3	1	3	2	3		
Brunder Dyrehospital	11	Cartrophen	3	0	3	1	5	+	+
Brunder Dyrehospital	12	Cartrophen	2	1	2	1	2		+
Brunder Dyrehospital	13	Cartrophen	2	0	4	1	5	+	+
Brunder Dyrehospital	14	Cartrophen	3	0	3	1	5	+	+
Brunder Dyrehospital	15	Cartrophen	3	0	3	1	5	+	+
Brunder Dyrehospital	16	Cartrophen	2	1	4	1	4		+
Brunder Dyrehospital	17	Cartrophen	3	1	4	2	4		
Brunder Dyrehospital	18	Cartrophen	3	0	3	1	5	+	+
Brunder Dyrehospital	19	Cartrophen	3	2	3	2	2		
Brunder Dyrehospital	22	Rimadyl tab.	3	2	4	2	3		
Brunder Dyrehospital	23	Rimadyl tab.	3	2	4	3	2		
Brunder Dyrehospital	24	Rimadyl tab.	4	2	4	3	3		
Brunder Dyrehospital	35	Rimadyl tab.	3	1	3	2	3		
Brunder Dyrehospital	36	Rimadyl tab.	3	2	4	2	3		
Brunder Dyrehospital	38	Rimadyl tab.	3		3				
Brunder Dyrehospital	40	Rimadyl tab.	3	0	3	1	5	+	+
Hobrovejens Dyrehospital	29	Cartrophen	4	4	4	3	1		
Hobrovejens Dyrehospital	30	Rimadyl tab.	4	3	4	3	2		
Hobrovejens Dyrehospital	31	Cartrophen	4	4	4	4	0		
Hobrovejens Dyrehospital	32	Rimadyl tab.	3	2	4	3	2		
Hobrovejens Dyrehospital	33	Rimadyl tab.	3	1	3	2	3		
Hobrovejens Dyrehospital	37	Cartrophen	3	2	4	2	3		
Løkken dyreklinik	25	Cartrophen	3	3	3	3	0		
Løkken dyreklinik	26	Cartrophen	3	3	3	3	0		
Løkken dyreklinik	27	Cartrophen	2	0	2	1	3	+	+
Løkken dyreklinik	28	Cartrophen	1	0	2	1	2	+	+
Løkken dyreklinik	39	Rimadyl tab.	3	2	3	2	2		

Specialised Vet. Main project 2005.

Investigation of clinical effect after treatment with Cartrophen Vet. inj. or Rimadyl Vet. tablets on dogs with OA, OD or HD.

Owner	**First Name**		**Titel**	Mr./Mrs./Miss.	
	Last Name				
	Telephone		**Journal number**		
Dog	**Name**		**Age (Years)**		
	Race		**Weight (Kg)**		
	Chip or tattoo.		**Sex(Male/Female)**		
Clinic	**Clinic**				
	Veterinarian				
	E mail		**Telephone**		
	Treatment	❑ **Cartrophen Inj.** (1 ml / 33kg each week for 4 weeks) Starting Date: ❑ **Rimadyl tab. 100 mg(Carprofen 100mg)** (Dosage 4 mg / kg daily for 28 days)			
	Diagnose				
	X-RAY findings				

Veterinarian Evaluation	**Week 0**	**Week 1**	**Week 2**	**Week 3**	**Week 7**
Lameness (Index 0-4)					
Pain by manipulation (Index 1-5)					

Owners Evaluation	**Week 0**	**Week 1**	**Week 2**	**Week 3**	**Week 7**
Lameness (Index 0-4)					
Pain by observation (Index 1-5)					

Anamnesis :(Dogs history prior to examination)

- Experienced lameness before? Yes/No.
- If yes, how long? _____ Weeks/Month/Years.
- Which treatment: NSAID/Steroid/Cartrophen/Others/None.
- Interval before treatment started: _____ Weeks/Month/Years.
- Use of dog in general: Family/Hunting/Training/Lapdog.

Clinical investigation:

- General comments to health check.
- Lameness in one or more legs? Yes/No. Swelling around joints involved? Yes/No. (only distal limbs)
- Ataxia, wobbliness, reduced activity? Yes/No
- Muscle atrophy visible? Yes/No
- Present Lameness acute/chronic? Yes/No
- Dogs pain & lameness must be evaluated after the scores on the next page (19).

Anaesthesia:

- Zoletil mixture? Yes/No
- Domitor/Antisedan/Torbugesic mixture? Yes/No
- Other anaesthesia? Yes/No

X-RAY investigation & Diagnosis: Which limbs or joints are affected?

- Foreleg (shoulder/elbow/carpal joint).
- Hind leg (knee/metatarsus/tarsus joint).
- Hip joint (left/right).
- Neck joints.
- Lumbar joints.
- Placement of Osteofyttes and/or Calcifications.
- Joint space alterations? Yes/No. Other alterations? Yes/No. If yes, describe these.

Treatment:

- Starting date and choice of treatment. Protocol page 1 must be used for both.
- By Carprofen/Rimadyl Injection on day one (week 0), and after that tablets daily for 4 weeks 4 mg/kg.
- By Cartrophen Vet. Injection on day one (week 0) and then the following 3 weeks (week 1, 2, 3).

Side effects: Yes/No. If Yes, Please describe details and time of appearance.

- Must be noted from week to week.
- If tablet treatment will be stopped more than one day, notes must be taken.

Owner's ability and willingness to maintain protocol observation and treatment:

- Dose 4 mg/kg? (Rimadyl) Yes/No, (Tablets counted on the last day). Agreed controls? Week 1,2,3,7 (Cartrophen/Rimadyl) Yes/No. If No, please give reason?:
- The owners are making observations on the dog? Yes/No
- Do the veterinarian and owner agree on the results? Week 4 Yes/No, Week 8 Yes/No.

Lameness Score (Index 0 – 4):

Veterinarian (Clinic/Manipulation). Owner by observation at home/exercise.

- 0: No visible lameness at all. Can be manipulated and/or exercised heavily/long time without any lameness.
- 1: No lameness resting or after manipulation. Light lameness after exercised heavily/long.
- 2: Light lameness resting and increased lameness after manipulation. Increased lameness after ordinary exercise in a leach.
- 3: Visible support lameness and unwilling to exercise. Manipulation makes the dog lamer and the dog is unwilling to manipulate. The dog can not exercise for ordinary time in a leach.
- 4: Lameness 100 % .Will not uses the leg(s). Can not be exercised normally. Will resist and vocalise on attempt to manipulate. The Dog will barely move or lay down.
- **The veterinarian's lameness score can be supported by exercise test outside the clinic with the dog in leach. Also direct evaluation of any support lameness or 100 % lameness inside the clinic before and after manipulation.**

Pain Score (Index 1 – 5):

Veterinarian (Clinic/Manipulation). Owner by observation at home/exercise.

- 1: No pain at all, and no pain after manipulation. The dog can exercise heavily or long without pain.
- 2: No pain resting/walking or by laying down & getting up. No pain by manipulation. The dog can be exercised normally in a leach. Few signs of pain or passing lameness after heavily or long exercise.
- 3: No pain resting. Light pain by manipulation. Light permanent pain after heavily or long exercise.
- 4: Light pain by resting or lying down or getting up. Increased pain by manipulation. In general unwillingness to exercise. Increased pain by heavily or long exercise.
- 5: Clearly pain resting and by any attempt to use the leg or legs. The dog will resist manipulation, articulate pain and maybe attempt to bite. Must be helped on urination and defecation.

Inclusions criteria:

- The dog is well in clinical investigation and did not receive any medical treatment 2 to 4 weeks prior to the start of the trial period.
- As far as possible the OA or HD patients that are treated are new cases and that X ray images gives clear indications on OA changes or HD status from C to E in one or both sides.
- The radiographic evaluation must show Joint space changes, Osteofyttes, OCD or other bone changes typical for OA cases. If any doubts please send in the X rays for evaluation.
- All information on basic data and sick history must be filled out according to the first two pages of protocol, and the lameness and pain scores must be recorded for week 0, 1, 2, 3, and 7 after the start of every single dog. A database will be created for all dogs.

Exclusions criteria:

- Use of dietary support products: Glucosamine&MSM products etc., Fish&Plant Oil products, Ginger Tablets or any other product as long as the 8 week trial period occurs.
- Lack of any controls dates or treatment dates within 1 / 2 days. (Owners are motivated by receiving payment from week 0 and by receiving tablets for one week at a time)
- Receiving any other treatment of painkillers(NSAID, Prednisone or Human Products)
- If acute sickness occurs, this will not allow for precise protocol follow up at all weeks 0 to 7.
- If side affects occur, that are serious or repeated, so that the dogs health condition deteriorates. Especially GI side effects, or bleeding disorders, Liver and Kidney problems.