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Effects of Phenylbutazone and Indomethacin on the Post-operative Course following Experimental Orthopaedic Surgery in Dogs

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Mbugua, S. W., L. A. Skoglund and P. Løkken: Effects of phenylbutazone and indomethacin on the post-operative course following experimental orthopaedic surgery in dogs. Acta vet. scand. 1989, 30, 27–35. – Randomized placebo-controlled crossover studies were carried out in dogs to evaluate how two non-steroidal anti-inflammatory drugs (NSAID) might modulate an acute post-traumatic inflammatory reaction. Two "identical" surgical interventions were performed on the forelimbs of each animal with an interval of 28 days, to enable a paired comparison of the inflammatory signs and the wound/bone healing processes. At one operation 8 dogs received 300 mg phenylbutazone twice daily for 8 days starting on the day before surgery, and at the other operation matching placebo tablets were given. In a similar placebo-controlled trial another group of 8 dogs received 5 mg indomethacin twice daily. With phenylbutazone the post-operative swelling was not significantly reduced compared to placebo, but there was less pain and limping. With indomethacin the swelling was somewhat reduced, but there was no consistent difference to placebo in the pain and limping assessments. None of the drugs appeared to distinctly effect the wound or fracture healing, as evaluated by clinical inspection, comparison of radiographs and comparison of bone sections from the sites of surgery. It proved difficult to select an appropriate dosage of indomethacin due to its high potential to induce GI ulceration and bleeding in dogs.
In this experimental surgical model with an acute inflammation, neither phenylbutazone nor indomethacin showed impressive anti-inflammatory or analgesic properties. In the same model paracetamol has proved to significantly and more efficiently, reduce both swelling and pain without any noticeable adverse effects, and appears to be a better alternative than the two presently tested NSAID.

anti-inflammatory effects; swelling; pain; wound/bone healing.

Introduction

With phenylbutazone and indomethacin as forerunners, a host of new non-steroidal anti-inflammatory drugs (NSAID) has been introduced during the past 20 years. They belong to many chemical classes, but have similar or identical modes of action related to their ability to interfere with the formation of mediators of inflammation, such as the prostaglandins. The prototype is acetylsalicylic acid, hence they are often referred to as "aspirin-like" drugs. With some variation they share anti-inflammatory, analgesic and antipyretic properties, as well as side effects such as gastrointestinal irritation and bleeding.

NSAID are widely used in veterinary practice, although not as frequently as in human medicine. They are, as stated by *Higgins* (1985), prescribed for conditions as clinically diverse as equine exertional myopathy ("azoturia"), spasmodic colic, arthroses and arthritic conditions, tendonitis, and as post-operative prophylaxis to control untoward inflammatory sequelae.

The anti-inflammatory drugs used in human surgery and traumatology seem mostly to have been selected according to their performance in patients with rheumatoid arthritis (*Løkken & Skjelbred* 1981), and essentially the same drugs have been adopted for use in veterinary surgery. Rheumatoid inflammation, however, differs markedly from an acute post-traumatic inflammation, and anti-inflammatory drug effects are not necessarily the same in these different conditions.

There is a lack of reliable models for clinical assessment of anti-inflammatory effects, which is unfortunate since recent research has showed clearly the wide gap between our concepts garnered mainly from in vitro studies and the almost complete lack of data indicating that the results obtained in vitro are meaningful in vivo (*Vinegar & Truax* 1982).

A well controlled model for evaluation of drug effects in human surgery, is based on bilateral oral surgery. Studies in this model revealed that drugs which efficiently reduce rheumatoid swelling, e. g. acetylsalicylic acid, oxyphenbutazone and ibuprofen, had a little or no effect on the post-operative swelling, while paracetamol which often is said to be without anti-inflammatory activity, reduced the swelling by about 30 % (*Løkken et al.* 1975, *Album et al.* 1977, *Løkken & Skjelbred* 1980, *Skjelbred* 1984). Glucocorticoids reduced the swelling by about 50 % and gave in addition a striking pain relief (*Skjelbred & Løkken* 1982a, b). Conclusions from oral surgery, however, may not necessarily apply to surgery and traumata in other parts of the body, e. g. the extremities, in connection with which NSAID are frequently prescribed.

An experimental model with bilateral orthopaedic surgery on the forelimbs of dogs has recently been established to allow placebo-controlled studies on how steroidal and non-steroidal anti-inflammatory drugs might modulate the signs of an acute post-traumatic inflammatory reaction and the healing process (*Mbugua et al.* 1988). For the present trials phenylbutazone and indomethacin were selected to be tested in this model. Phenylbutazone is probably still the most widely used NSAID in veterinary practice *Lees & Higgins* 1985). Indomethacin is another NSAID which has been commonly used in humans, but only infrequently in veterinary medicine. A main reason for including indomethacin was that it has been reported to delay or inhibit fracture healing in experimental models using rats (*Sudmann et al.* 1979, *Elves et al.* 1982).

Materials and methods

Experimental design

The trials were carried out as randomized, placebo-controlled crossover studies in which two "identical" surgical soft tissue/bone interventions were performed on the forelimbs of each animal with an interval of 28 days to allow paired comparison of the post-operative courses.

Animals

Mongrel dogs of either sex, weighing from 12 to 21 kg, were used. They were all dewormed, but had no other verifiable diseases. The ethical aspects of the study were approved and supervised by the relevant authority at the Faculty of Veterinary Medicine, University of Nairobi.

Drugs

Phenylbutazone: For one operation 8 dogs received orally 300 mg phenylbutazone (Mac's Pharmaceuticals, Nairobi, Kenya) twice daily. Medication started the day before surgery and lasted for 8 days. Placebo medication was given at the other operation. The treatments were allocated according to a randomization list, so that half of the dogs received the active drug at the 1st operation. To keep the trials blind to the surgeon, the drugs were administered by an assistant who had no other responsibilities in the trial.

Indomethacin: Our plan was to administer to another group of 8 dogs, 25 mg indomethacin (Indocid®, Merck-Sharp & Dohme, N. Y., USA) twice daily for 8 days, in a similar placebo-controlled manner. This medication, however, had to be discontinued on the 1st post-operative day because of signs of toxicity. A third group of 8 dogs was then included which received 5 mg indomethacin (Confortid®, Dumex, Copenhagen, Denmark) twice daily administered in a similar way as phenylbutazone.

Surgical procedure

The operations were carried out under general thiopentone/halothane anaesthesia after premedication with acetylpromazine and atropine, as described by *Mbugua et al.* (1988). The surgical procedure involved transsection of the 3rd metacarpus with an oscillating saw and thereafter stabilization with a 6 hole mini Dynamic Compression Plate.

Assessments

A device designed for foot/limb volumetry (*Mbugua et al.* 1988) was used to measure the swelling of the limb. The limb was immersed into a cylinder filled with water, until a mark on the shaved skin of the limb reached the top of the cylinder. This was done pre- and post-operatively and the difference in volume of displaced water recorded. The average of 3 successive measurements was used to represent the volume of the dogs' limb.

Pain was estimated by the surgeon who exerted digital pressure on the site of surgery and marked on a visual analogue scale (VAS) that ran from "no pain" (0 mm) to "pain cannot be worse" (100 mm). Limping was marked on a 100 mm VAS from "no limping" to "limping cannot be worse". These assessments were made between 8 and 9 a. m. every day for a week after each operation and then on days 10, 14 and 21 after surgery. At the same time any abnormalities in wound healing as well as any other noticeable clinical signs were recorded.

Bone healing was monitored according to *Mbugua et al.* (1988) by comparison of radiographs taken 2, 4, 6 and 8 weeks after the two operations for bone union, callus formation, signs of infection and foreign body acceptance. The bone healing was also assessed by comparing bone sections from the sites of surgery obtained when the dogs were euthanized 8 weeks after the 2nd operation. The sections were cut in a cryo-microtome before staining and comparative assessment.

Statistical analyses

Statistical analyses of the assessments of swelling, pain and limping were performed with a two-sided Wilcoxon signed rank test with corrections for ties (*Lehman & d'Abrera* 1975). A significance level of 5 % was used.

Results

Phenylbutazone

Swelling

Phenylbutazone did not reduce the post-operative swelling significantly compared to placebo (Table 1).

Table 1. Swelling measured by limb volumetry and pain and limping assessed by visual analogue scales in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 8 dogs given 300 mg phenylbutazone orally twice daily for 8 days starting the day before surgery.

Day after surgery	Mean swelling (ml)				Mean pain (mm)				Mean limping (mm)			
	Phenyl-butazone	Placebo	Differ-ence	P-value	Phenyl-butazone	Placebo	Differ-ence	P-value	Phenyl-butazone	Placebo	Differ-ence	P-value
1	24	26	–2	0.46	18	34	–16	0.20	12	49	–37	0.03
2	25	26	–1	0.42	8	20	–12	0.09	10	30	–20	0.05
3	23	25	–2	0.43	6	16	–10	0.04	4	9	– 5	0.07
4	30	28	2	0.43	11	13	– 2	0.31	5	16	–11	0.08
5	34	32	2	0.44	10	12	– 2	0.36	5	24	–19	0.03
6	34	32	2	0.45	9	11	– 2	0.47	12	20	– 8	0.44
7	30	30	0	0.48	9	12	– 3	0.34	6	19	–13	0.15
10	27	23	4	0.44	6	8	– 2	0.28	3	16	–13	0 31
14	28	23	5	0.36	6	4	2	0.24	3	7	– 4	0.42
21	20	15	5	0.24	4	2	2	0.26	3	6	– 3	0.37

Pain and limping

Less pain was assessed during the first days after the operation when phenylbutazone was administered (Table 1). The difference was significant on Day 3. There was also less limping after the operation when phenylbutazone was given (Table 1). The differences were significant on Days 1, 2 and 5.

Toxicity/adverse effects

No clinical signs of gastrointestinal toxicity or other potential adverse drug reactions were observed.

Wound and bone healing

Clinically there appeared to be a tendency towards slightly better wound healing after the operation when placebo was given. Comparison of the two sets of radiographs taken 4 and 6 weeks after surgery also revealed tendencies in favour of placebo, both with regard to bone union, callus formation and the tissue acceptance of the plates and screws. After 8 weeks, however, there were no noticeable differences. Comparison of the bone sections after the two operations revealed no clear-cut difference in the healing process.

Indomethacin (25 mg twice daily)

The medication was discontinued on day 1 post-operatively, since signs of toxicity were observed in all dogs, e. g. lethargy, vomiting and bloody stool. They had then received a total dose of 125 mg indomethacin. One dog died on Day 5 post-operatively. Autopsy revealed intestinal ulcers in all dogs that had been given this dosage of indomethacin.

Indomethacin (5 mg twice daily)

Swelling

There was a tendency towards less swelling after the operation when indomethacin was administered. The differences were significant on Days 7, 10 and 14 (Table 2).

Table 2. Swelling measured by limb volumetry and pain and limping assessed by visual analogue scales in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 8 dogs given 5 mg indomethacin orally twice daily for 8 days starting the day before surgery.

Day after surgery	Mean swelling (ml)				Mean pain (mm)				Mean limping (mm)			
	Indo-methacin	Placebo	Differ-ence	P-value	Indo-methacin	Placebo	Differ-ence	P-value	Indo-methacin	Placebo	Differ-ence	P-value
1	31	39	– 8	0.07	35	23	–12	0.22	40	48	– 8	0.39
2	30	33	– 3	0.26	27	28	– 1	0.42	36	39	– 3	0.50
3	26	31	– 5	0.18	19	16	3	0.42	29	34	– 5	0.36
4	24	26	– 2	0.42	16	16	0	0.50	26	16	10	0.24
5	21	23	– 2	0.47	7	15	– 8	0.24	12	7	5	0.24
6	17	24	– 7	0.10	9	14	– 5	0.44	8	4	4	0.10
7	14	27	–13	0.02	8	26	–14	0.25	3	1	2	0.14
10	21	29	– 8	0.04	17	8	9	0.14	3	6	– 3	0.34
14	17	25	– 8	0.02	9	15	– 6	0.47	2	4	– 2	0.50
21	17	21	– 4	0.19	3	5	– 2	0.50	1	4	– 3	0.32

Pain and limping

There appeared to be no consistent difference between the pain assessments after the two operations (Table 2). There was no significant difference in the limping after the two operations (Table 2).

Toxicity/adverse effects

One of the dogs developed bloody stool on Day 5 post-operatively. Otherwise there were no evident clinical signs of toxicity. All dogs, however, showed healing intestinal ulcers at autopsy.

Wound and bone healing

No noticeable differences were observed in the wound and bone healing, either by the clinical examination or when the two sets of radiographs and bone sections after the two operations were compared.

Discussion

Many traumatic painful swellings have been treated with phenylbutazone. Results reported from clinical trials range from excellent to no effect, most of them based on subjective impression. The present controlled experiment in dogs did not reveal any phenylbutazone-induced reduction of post-operative swelling, although the drug gave significant pain relief. Our findings agree with some studies in humans based on objective measurements of swelling, according to which phenylbutazone and its bioactive metabolite oxyphenbutazone have little or no capacity of reducing an acute post-traumatic swelling (*Olesen & Zachariae* 1965, *Goldie et al.* 1974, *Album et al.* 1977).

With indomethacin there was a tendency towards less swelling, which became significant after one week. As for many other NSAID, the reports regarding the effects of indomethacin on acute inflammatory reactions are conflicting. Some investigators

have reported the drug to significantly reduce post-surgical oedema in rats (*Amin et al.* 1983) and humans (*Penners* 1971), while others have found no decrease in the post-traumatic swelling (e. g. *Huskisson et al.* 1973, *Petersen* 1975).

With regard to the effects of the two drugs on fracture and wound healing, it has been suggested on the basis of clinical observations in humans (*Pfeifer* 1967), as well as from experiments in animals (*Lindner* 1967), that oxyphenbutazone does not disturb the healing of bone injuries. Actually, oxyphenbutazone has been reported to accelerate repair of damaged muscular fibres (*Morger* 1967), and in contrast to indomethacin the drug has been found to increase the tensile strength of experimental wounds in animals (*Zederfeldt & Gruber* 1967). So far, there seems to be only one report which suggests that human fracture repair is inhibited by indomethacin (*Sudmann & Hagen* 1976), but there is also evidence from experimental models in rats that indomethacin may delay or inhibit fracture healing (*Sudmann et al.* 1979, *Elves et al.* 1982).

With the present methods of assessment, we were neither able to detect any beneficial effect of phenylbutazone on wound and bone healing, nor any deleterious effect of indomethacin on these processes. Our findings with regard to indomethacin agree with those of *Allgöwer et al.* (1963), who concluded that short-term treatment with indomethacin has no effect upon the healing of fractures. It might be that our period of drug administration was too short to reveal effects on bone healing, since it appears that the effect of indomethacin is short-lived and cessation of treatment soon after a fracture will allow normal healing to occur (*Elves et al.* 1982).

Difficulties were encountered in selecting an appropriate dosage of indomethacin. This drug gives a striking example of how differences in the pharmacokinetics of a drug may explain differences in drug response both within as well as between species. While the present mongrel dogs developed gastrointestinal lesions with a total dose of 4–7 mg indomethacin/kg bwt, beagles have been reported to tolerate a single oral dose of 20 mg/kg bwt without visible gastrointestinal lesions, and even a total dose of 100–200 mg/kg bwt over a 5 to 10 day period was tolerated without excessive signs of toxicity (*Tabata et al.* 1984). Other workers have also found indomethacin to be more toxic in mongrel dogs than in beagles (*Ruckebusch & Toutain* 1983). Beagles are known to metabolize drugs more rapidly than most other dogs (*Frey at al.* 1979), and this may explain why indomethacin is less ulcerogenic in beagles.

The much higher ulcerogenic potential of indomethacin in carnivores compared to many other species, is likely to depend on their predominantly biliary excretion and enterohepatic recirculation of the drug and thus prolonged exposure of these organs, while for example in humans the drug is eliminated mainly by the kidney. *Duggan et al.* (1975) found that the total accumulative amount of indomethacin excreted through the *Ductus choledochus* of the dog was 362 % of the originally administered dose, while the corresponding value in man was only 10 %. In contrast to indomethacin, phenylbutazone has a half-life of only 6 h in dogs compared to 72 h in humans (*Dayton et al.* 1973). These pharmacokinetic differences may explain why, calculated as mg/kg bwt/day, the ulcerogenic dose of indomethacin for dogs is only 1/8 to 1/2 of the therapeutic dose usually given to humans, while for phenylbutazone the ulcerogenic dose in dogs is 10 to 20 times the usual therapeutic dose in humans (*Telemann* 1983).

Accordingly, when administering NSAID in veterinary practice, it is important to keep in mind the large variations in the pharmacokinetics. The utilization of doses recommended for one species, may result in unacceptable toxicity in some species or lack of effect in other species.

For dogs, indomethacin does not appear to be recommendable, while phenylbutazone presents a relatively wide margin of safety. The short half-life of phenylbutazone in dogs is, however, a disadvantage if it is intended to maintain relatively constant plasma concentrations, since the drug then has to be dosed 4 times daily (*Kaergaard et al* 1969).

The unwanted results of an excessive inflammatory reaction has long been recognized in surgery and traumatology (*Peacock & van Winkle* 1976, *Schiller & De Silva* 1979). It has been uncertain whether the results obtained with anti-inflammatory drugs in bilateral oral surgery would also apply to acute traumatic swellings in other parts of the body, e. g. of the extremities. The results obtained so far in the experimental model with bilateral orthopaedic surgery on the forelimbs of dogs, agree well with the results from human oral surgery. Phenylbutazone did not reduce the swelling significantly, and the reduction obtained with indomethacin was not impressive. In a similar placebo-controlled crossover study in dogs, a single preoperative injection of a glucocorticoid (betamethasone) reduced the swelling significantly. On the 3rd day the reduction was 43 % (*Mbugua et al.* 1988). Significant reductions in the post-operative swelling were also recorded when paracetamol (0.5 g × 3 daily) and acetylsalicylic acid (0.5 g × 3 daily) were tested against placebo in the model. On the 3rd post-operative day a reduction of 33 % was observed with paracetamol and 24 % with acetylsalicylic acid (*Mburu et al.* 1988). Paracetamol has traditionally been said to be devoid of anti-inflammatory activity. At a dosage of 0.5 g three times daily, paracetamol was observed not only to result in marked reduction of the swelling, but also gave a very good analgesic effect. No adverse effects were observed.

Accordingly, neither phenylbutazone nor indomethacin seem to compete favorably with paracetamol in this model with an acute post-traumatic inflammatory reaction in the forelimbs of dogs.

This conclusion agrees with the results obtained in human oral surgery, according to which NSAID such as ibuprofen, oxyphenbutazone and acetylsalicylic acid (*Løkken et al* 1975, *Album et al.* 1977, *Skjelbred* 1984) are less efficient than paracetamol in curbing an acute post-traumatic inflammatory reaction (*Løkken & Skjelbred* 1980, *Skjelbred et al.* 1984).

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Sammendrag

Effekt av fenylbutazon og indomethacin på det post-operative forløp etter eksperimentell ortopedisk kirurgi på hunder

Randomiserte placebo-kontrollerte overkryssningsstudier ble utført på hunder. To non-steroide anti-inflammatoriske legemidlers (NSAID) evne til å påvirke det akutte inflammatoriske post-operative forløp ble undersøkt. To "identiske" kirurgiske inngrep ble utført på forlabbene på hvert dyr med 28 dagers mellomrom slik at en parvis sammenligning av kliniske post-operative inflammasjonssymptomer og tilheling kunne utføres. I en studie ble 300 mg fenylbutazon gitt 2 ganger daglig i 8 dager og sammenlignet med placebo. I en annen studie ble 5 mg indomethacin gitt 2 ganger daglig i 8 dager og sammenlignet med placebo. Fenylbutazon reduserte ikke den post-operative hevelse, men reduserte smerte og haltning. Indomethacin viste en tendens til å redusere den post-operative hevelse, men reduserte ikke smerte eller haltning. Ingen av de undersøkte NSAID syntes å påvirke den kliniske sår- eller frakturhelingen. Det var vanskelig å velge en optimal klinisk dosering av indomethacin pga stor evne til å fremkalle gastrointestinale ulcerasjoner og blødninger på hundene. I denne eksperimentelle kirurgiske modellen med akutt inflammasjon viste hverken fenylbutazon eller indomethacin noen betydelig anti-inflammatoriske eller analgetiske egenskaper. Paracetamol har tidligere i den samme modellen vist seg å redusere post-operativ hevelse og smerte uten noen tilsynelatende bivirkninger. Paracetamol synes å være et bedre alternativ enn fenylbutazon og indomethacin til å redusere akutt post-operativ hevelse og smerte.

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