AN EVALUATION OF ANTI-INFLAMMATORY DRUG EFFECTS FOLLOWING SURGERY IN DOGS, WITH EMPHASIS ON PARACETAMOL AND ACETYLSALICYLIC ACID

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D E C L A R A T I O N

This thesis is my original work and has not been presented for a degree in any other University.

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D. N. MBURU

This thesis has been submitted for examination with our approval as University supervisors.

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ABSTRACT

AN EVALUATION OF ANTI-INFLAMMATORY DRUG EFFECTS FOLLOWING SURGERY IN DOGS, WITH EMPHASIS ON PARACETAMOL AND ACETYLSALICYLIC ACID.

Drugs which inhibit the synthesis of eicosanoids are widely prescribed in veterinary practice, e.g. for arthroses and arthritic conditions, tendonitis, and as post-operative prophylaxis to control inflammatory sequelae. Examples of such drugs are acetylsalicylic acid (ASA), phenylbutazone, flunixin, meclofenamic acid and naproxen. The use of these drugs in the veterinary clinic seems to be more based on traditions and drug marketing than on objective clinical trials, and often also on experiences from the human clinic. It has not been objectively shown that the newer and more expensive drugs offer major benefits over the older compounds.

ASA is the prototype of non-steroidal anti-inflammatory drugs. It was introduced into therapy in 1899, and has since been widely used. Paracetamol has been used since 1893, but did not gain real popularity until 1949, when paracetamol was recognized as the major metabolite of acetanilide and phenacetin.

ASA has often been recommended for alleviation of pain in inflammatory conditions, while paracetamol has

traditionally been claimed to be devoid of anti-inflammatory activity. The truth of this dogma has been challenged by findings in recent controlled studies with bilateral oral surgery in humans. These clinical results agree with some findings in rodents. The prevailing view is still, however, that paracetamol in contrast to ASA possesses little or no anti-inflammatory activity.

In the model with bilateral oral surgery, ASA in high doses reduced the post-operative swelling, while ordinary analgesic doses actually tended to increase the swelling. Recent research on prostaglandins and related products of arachidonic acid metabolism, has also given some evidence which indicates that ASA might exert a paradoxical effect depending on the dose.

There is a lack of reliable methods for clinical assessments of anti-inflammatory drug effects. 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, Ph.D. thesis, University of Nairobi, 1987).

The main aim of the present studies was to

investigate whether the effects of paracetamol and ASA on an acute post-traumatic inflammatory reaction in the extremeties of dogs are similar to those observed in bilateral oral surgery. If so, this might be of some importance for the choice between the two drugs in the veterinary clinic. The findings might, however, also be of interest as a contribution to the evaluation of benefits and disadvantages of the two drugs in human traumatology.

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. In three groups of dogs, daily doses of 1.5 g paracetamol, 1.5 g ASA and 0.5 g ASA were tested against placebo. Medication started in the morning of the day of surgery and continued for a total of 4 days. Swelling was measured by limb volumetry, while pain, limping and the surgeon's preference for post-operative courses were subjectively assessed by means of visual analogue scales. Pre- and post-operatively, laboratory analyses were carried out with commercial diagnostic kits to evaluate the liver and kidney functions. Routine clinical examinations, measurement of rectal temperature and paired assessments of the

wound/bone healing process were also done to disclose beneficial or adverse drug effects.

Paracetamol (1.5 g daily) compared to placebo in 7 dogs, reduced the post-operative swelling signficantly. On the 3rd day the mean swelling in paracetamol-treated dogs was 67% of that with placebo ($p=0.02$). During the first 4 post-operative days when paracetamol was given, the pain assessments were also significantly lower. On the 3rd day the pain estimate in paracetamol-treated dogs averaged 53% of that with placebo ($p=0.01$). It was difficult to obtain reliable and reproducible limping assessments, and the paired comparison revealed no consistent difference between paracetamol and placebo. Most of the preference scores were in favour of paracetamol. Neither the clinical examination nor the paired radiological evaluation of the fracture healing, revealed any significant differences between the two post-operative courses. The serum ALAT levels remained within the normal range in all dogs, except for one which had a moderate increase after the operation when paracetamol was given. The elevated level in this dog might indicate a certain liver affection. There were no gross clinical signs of any paracetamol-related toxicity.

In two groups of 8 dogs, ASA in a "high" (1.5 g daily) and a "low" (0.5 g daily) dose was tested against placebo.

With 1.5 g ASA daily, the post-operative swelling was significantly reduced. On the 3rd post-operative day the swelling averaged 76% of that with placebo ($p=0.03$). The pain estimates were lower when ASA was given, but the difference was only significant on the 2nd post-operative day ($p=0.01$). On the 3rd day the mean pain estimate in ASA-treated dogs was 68% of that with placebo ($p=0.07$). The limping estimates showed no clear-cut differences, while most of the preference assessments were in favour of ASA. No signs of drug-related adverse effects were detected.

With 0.5 g ASA daily, there were tendencies towards less swelling, but on no occasion did the difference reach a level of significance. On the 3rd post-operative day, the swelling in ASA-treated dogs averaged 85% of that with placebo ($p=0.18$). The pain estimates were also somewhat lower, but none of the differences were significant. On the 3rd post-operative day the pain estimate when ASA was given averaged 72% of that with placebo ($p=0.21$). As in the previous trials, the limping scores showed no consistent differences. The surgeon's preference scores tended to favour the post-operative course when ASA was administered. As in the previous study, neither the clinical examination nor the radiological evaluation or the laboratory tests revealed any drug-induced adverse effects.

At a daily dose of 1.5 g, both paracetamol and ASA proved to significantly reduce the post-operative swelling as well as pain, and both drugs appeared to be well tolerated. The 33% reduction in swelling recorded on the 3rd post-operative day when paracetamol was given, agrees well with corresponding results in oral surgery, and gives evidence to confirm that paracetamol may exert significant anti-inflammatory activity.

A daily dosage of about 0.4 to 0.6 g ASA has been recommended for pain relief in dogs. In the present trial with 0.5 g ASA daily, neither pain nor swelling were significantly reduced. At this selected "low" dosage of ASA, it was not possible to demonstrate a pro-inflammatory effect. It might be that the dose selected was too high to reveal a paradoxical effect of ASA at low doses.

So far, no controlled clinical trials have been published on the therapeutic use of paracetamol in veterinary medicine. According to the present results, paracetamol appears to be a valuable drug in veterinary as well as human traumatology, and at least as efficient as ASA in reducing pain and swelling associated with an acute post-traumatic reaction.

CHAPTER ONE

INTRODUCTION

The ideal agent for use in post-operative or post-traumatic care, should relieve pain, reduce swelling, alleviate impaired function, promote healing and have no adverse effects. Several drugs have been advocated for this purpose, but none has so far proved ideal. Analgesics may efficiently relieve pain, but in addition it may also be important that the therapy counteracts the detrimental effects of an excessive inflammatory reaction.

There are two main groups of analgesics, the opioid analgesics and the non-narcotic or non-steroidal anti-inflammatory drugs (NSAID). The prototype of NSAID is acetylsalicylic acid (ASA); hence these compounds are often referred to as ASA- or aspirin-like drugs. On a world basis, the two most commonly used analgesics are ASA and paracetamol. It has been, and still is, a common opinion that although paracetamol is equivalent to ASA as an effective analgesic and antipyretic agent, paracetamol differs by its lack of anti-inflammatory properties (Shearn, 1984; Rang and Dale, 1987). This old and often repeated statement has been challenged by more recent research. Controlled studies with bilateral oral surgery in humans have demonstrated

that paracetamol may reduce swelling and other inflammatory events at least as efficiently as ASA (Lökken and Skjelbred, 1980; Skjelbred et al., 1984). Similar observations have also been made in models of acute inflammation in rodents (Vinegar et al., 1976; Levine et al., 1981). Another recently published observation, which differs from the traditional view, is that while ASA in high doses exerts anti-inflammatory effects, the drug may in lower doses cause the opposite effect and actually increase swelling and other signs of an acute inflammatory reaction (Skjelbred, 1984).

Not least, because of the very frequent and widespread use of ASA and paracetamol, it was found relevant to attempt to make a contribution to the clarification of their effects in acute post-traumatic inflammatory reactions. As stated by the Nobel Prize winner, Sir John Vane, there are still great difficulties in finding any references to the anti-inflammatory effects of paracetamol (Vane, 1986. Personal letter to Dr. Skjelbred).

There is a lack of reliable methods for clinical assessments of anti-inflammatory drug effects. 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, 1987). She found the model useful in evaluating the effects of a glucocorticoid (betamethasone) and two NSAID (phenylbutazone and indomethacin).

The main aim of the present studies was to use this orthopaedic surgical model, with some modifications, to investigate in placebo-controlled crossover studies how paracetamol and ASA (in "low" and "high" dosage) may modulate the course and healing process after a standardized soft tissue/bone injury. A further motive for carrying out the investigations was that although the two drugs, and especially ASA are recommended for use in veterinary medicine (Davis, 1980; Bywater, 1982; Booth, 1982), controlled clinical studies to support this recommendation are virtually absent.

CHAPTER TWO

LITERATURE REVIEW

2.1 HISTORY

2.1.1 Acetylsalicylic acid

ASA-like compounds have been used since the dawn of mankind for relief of pain and treatment of inflammation. The use of salicylates as antipyretic agents appears to date from the report of Reverend Edmund Stone in 1763, when he claimed "an account of success of the bark of the willow in the cure of agues (fever)" (Flower et al.. 1985).

Salicin, the active ingredient in willow bark was discovered by Leroux in 1829. In 1838, Piria made salicylic acid from salicin, and six years later Cahours prepared salicylic acid from oil of gaultheria (oil of wintergreen). The synthesis of the acid from phenol was accomplished in 1860 by Kolbe and Lautemann. Sodium salicylate was first used as an antipyretic and anti-rheumatic agent by Buss in 1875. The discovery of its uricosuric effect and its utility in the treatment of gout soon followed. Phenyl salicylate was introduced into medicine in 1866 by Nencki (Flower et al., 1985).

ASA was first prepared in 1853 by Gerhardt, but was not clinically used for half a century. The drug was rediscovered during the search for an alternative to salicyclic acid for prolonged treatment of fever. The enormous success of salicylic acid prompted Hoffman, a chemist employed by Bayer, to synthesize ASA, based on the earlier work by Gerhardt. After demonstration of its anti-inflammatory effects, this compound was introduced into medicine in 1899 by Dreser under the name aspirin (cited by Capetola et al., 1983). The name was coined by taking the "a" from acetyl and adding it to "spirin" an old name for salicylic or "spiric" acid, which was once prepared from its natural source of spirae plants (Soine and Willette, 1966). Because of its great efficacy and lower cost, ASA replaced the natural products then in use and has remained one of the most widely employed remedies for years (Shearn, 1984). An excellent historical review is presented by Randall (1963).

2.1.2 Paracetamol

Paracetamol belongs to the para-aminophenol group of compounds with acetanilide as the parent member. Acetanilide was introduced into medicine in 1866, under the name antifebrin by Cahn and Hepp who

accidentally discovered its antipyretic action (Flower et al.. 1985). However, acetanilide proved to be excessively toxic, and the early reports of poisoning from acetanilide prompted the search for less toxic compounds. Para-aminophenol was tried in the belief that the body oxidized acetanilide to this compound. Toxicity was not reduced, however, and a number of chemical derivatives of para-aminophenol were then tested and phenacetin (acetophenetidin) was found to be more satisfactory. Phenacetin was introduced in medicine in 1887 and was extensively used as an analgesic until it was implicated in analgesic abuse nephropathy in man.

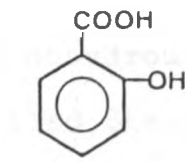
Paracetamol was first introduced in medicine by von Mering in 1893 (Smith, 1958). In 1949 it really gained popularity when it was recognized as the major active metabolite of acetanilide and phenacetin. The drug further proved less toxic than acetanilide and phenacetin at normal therapeutic dosage.

2.2 PHYSICAL AND CHEMICAL PROPERTIES

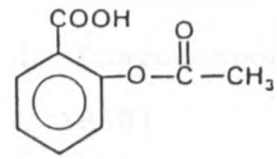
2.2.1 Acetylsalicylic acid

ASA which is also known as aspirin, is a member of the salicylate group of compounds e.g. salicylic acid and sodium salicylate (Fig. 1, p. 7). It contains not less

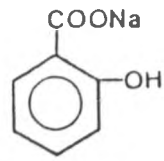
than 99.5% and not more than 100.5% of $C_9H_8O_4$ (180.2 mol. wt) calculated on dried basis (British Pharmacopoeia, 1980; The United States Pharmacopeia, 1980).



Salicylic acid



Acetylsalicylic acid



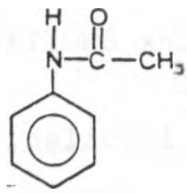
Sodium salicylate

Fig. 1 Chemical structures of some salicylates.

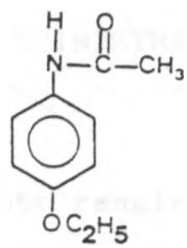
ASA occurs as a white odourless crystalline powder which melts at 135 to 143°C, but the exact melting point varies with conditions of the test. ASA is stable in dry air, but hydrolyzes slowly to acetic and salicylic acid in presence of moisture. The drug is highly soluble in alcohol (1:5), chloroform (1:17) and ether (1:20), and is only slightly soluble in water (1:300) (Swinyard, 1975; Martindale The Extra Pharmacopoeia, 1982).

2.2.2 Paracetamol

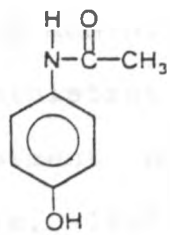
Paracetamol which is also known as acetaminophen, is the major metabolite of acetanilide and phenacetin (Fig. 2). It contains not less than 98% and not more than 101% of $C_8H_9NO_2$ (151.2 mol. wt) calculated on the anhydrous basis (British Pharmacopoeia, 1980; The United States Pharmacopeia, 1980).



Acetanilid



Phenacetin



Paracetamol

Fig. 2 Chemical structures of some para-aminophenol derivatives.

Paracetamol occurs as a odourless, cystalline powder, possessing a slightly bitter taste. It melts between 169 and 172°C. The drug is soluble in alcohol (1:10) and acetone (1:13), slightly soluble in water (1:70) and chloroform, and practically insoluble in ether. The pH of an aqueous solution is between 5.1 and 6.5 (Swinyard, 1975; Martindale The Extra Pharmacopoeia, 1982).

2.3 PREPARATIONS AND ROUTES OF ADMINISTRATION

2.3.1 Acetylsalicylic acid

ASA is available in form of tablets ranging from 65 to 975 mg, capsules and suppositories. Slow-release and liquid preparations are also marketed.

The common route of administration of the drug is per os. Parenteral administration of ASA has been attempted in the treatment of post-operative pain (Blendinger and Eberlein, 1980). The rectal administration of suppositories may be practical in infants or when oral medication is not retained.

2.3.2. Paracetamol

Paracetamol is available in form of tablets ranging

from 160 to 650 mg, capsules, suppositories, elixirs and solutions. The drug is usually administered per os.

2.4 PHARMACOKINETICS

2.4.1 Acetylsalicylic acid

Humans : ASA, a weak organic acid with a pKa of 3.5, is rapidly absorbed from the stomach and upper parts of intestines, and significant plasma levels are attained within 30 min. The amount and rate of absorption is related to the disintegration and dissolution rate of tablets, the gastric emptying times, pH at the mucosal surface and the dosage. Once ASA is dissolved, the un-ionized fraction penetrates the cellular membrane of the mucosal surface by passive diffusion. It is rapidly hydrolyzed to acetic acid and salicylate by esterases in tissues and blood, and only a minor fraction is found in the plasma as ASA.

Approximately 80 to 90% of salicylate in plasma is bound to protein, primarily to albumin. The unbound fraction of drug distributes rapidly through-out all body tissues by passive, pH-dependent processes (Furst et al., 1979). It readily crosses the placental barrier, and is also found in cerebrospinal, synovial and peritoneal fluids.

ASA, is rapidly deacylated to salicylic acid, a pharmacologically active metabolite. Salicylic acid is further metabolized in the liver by oxidation to gentisic acid. Conjugation with glycine to form salicyluric acid, and also with glucuronide to form ether and ester conjugates follows later (Davison, 1971) (Fig. 3).

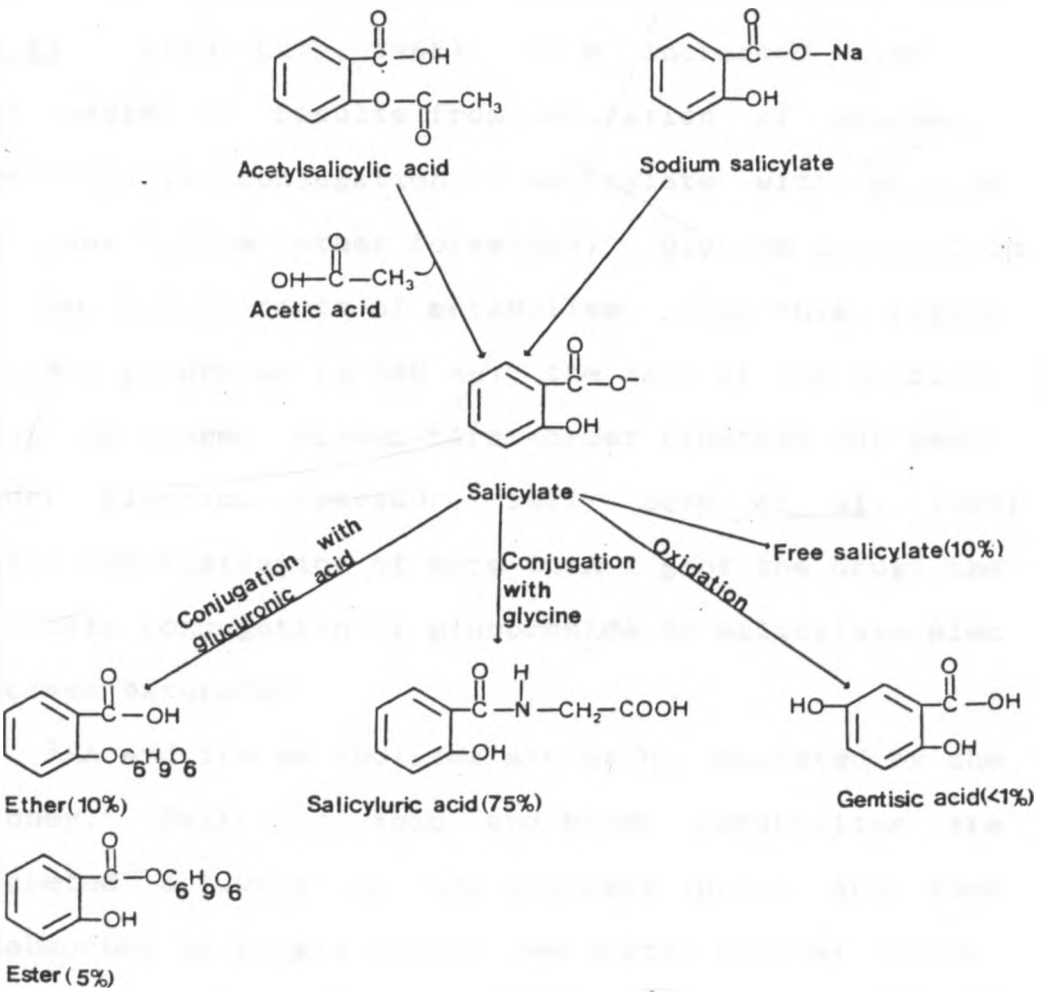


Fig. 3 Metabolism of salicylates (Meyers et al., 1972; Summy-Long, 1984).

Conjugation with glycine results in approximately 75% of salicylate being excreted as salicyluric acid (Davison, 1971; Furst et al., 1979). Approximately 5 to 10% of the dose is metabolized to glucuronide conjugates and 1% as gentisic acid and gentisuric acid. The half-life of salicylate in plasma ranges from 3-6 hrs for low doses, and 15-30 hrs for high doses necessary for the treatment of rheumatoid arthritis (Furst et al., 1979; Levy, 1965). This increased time for excretion results from saturation of enzymes required for conjugation of salicylate with glycine and glucuronide (ether formation). Glycine conjugation is the fastest route of metabolism. When this system becomes saturated ($\geqslant$ 650 mg), the rate of ASA elimination no longer follows first-order kinetics but zero-order kinetics (Davison, 1971; Levy et al., 1969). After administration of more than 1 g of the drug, the phenolic conjugation of glucuronide to salicylate also becomes saturated.

ASA and its metabolites are mainly excreted by the kidney. Salicylic acid and other metabolites are secreted actively by the proximal tubule and then reabsorbed passively across the distal tubular cells. The latter step is markedly dependent on the pH of urine. Additionally; oliguria, renal insufficiency and the presence of other organic acids in urine favour

retention of the drug. The excretion of free gentisic acid and unaltered salicylic acid is also pH-dependent. The glucuronide conjugates of salicylic acid and gentisic acid derivatives are water soluble organic acids, and thus do not readily back-diffuse across the renal tubular cells. Accordingly, in an alkaline urine, upto 85% of the given drug may be eliminated as free salicylate, whereas in the acid range this may drop to only 10% (Cohen, 1976).

Animals : ASA is readily absorbed from the stomach and intestine of dogs, cats and swine. The absorption process in these species is by passive non-ionic diffusion, mainly from the stomach and upper small intestine. In dogs, presystemic elimination (first-pass effect) reduces the systemic availability of ASA to only 45% of the original dose. This can contribute to variations between dogs and cats in the fraction of an oral dose that is available systemically. ASA is slowly absorbed from the gastro-intestinal tract of horses and ruminants. In horses the feeding regimen influences both the shape of plasma concentration-time curve and the area under the curve (Baggot, 1984). When it is administered before feeding, peak plasma level is obtained within a few hours, but if

the drug is administered after feeding, absorption is greatly delayed and variable in extent. In ruminants the contents of the forestomach vary from fluid to semisolid in consistency, and the pH is normally maintained within the range 5.0 to 7.0 (Phillipson, 1977). Accordingly, the ionized, and non-diffusable form of ASA dominates and hence slow absorption.

The distribution pattern of ASA in different animal species is determined by physiological factors and certain physio-chemical properties of the drug. These factors include blood flow to the tissues, the ability of drug to pass through cellular membranes, and drug binding to plasma proteins and extravascular tissue components. In general, the patterns of blood flow per unit of organ weight, is similar for most of the mammals. However, the relative size of some organs varies markedly, especially between ruminants and non-ruminants species, and this can explain why the apparent volume of distribution is similar in all domestic animals, except for ruminants where it is about 75% of that in other animals (Table 1, p. 15). The extent of binding of ASA to serum albumin ranges between 50 and 70% in domestic animals (Davis, 1980).

Table 1 Pharmacokinetic constants for salicylate after intravenous administration of sodium salicylate (44mg/kg) (modified from Davis and Westfall, 1972).

Species	t1/2 hrs	B_1 mg/l	B^{h-1}	V_d l/kg	Cl_r ml.kg^{-1}h^{-1}
Cat	37.60	185	0.018	0.244	4.39
Dog	8.60	200	0.081	0.220	17.80
Swine	5.90	213	0.118	0.207	24.40
Pony	1.03	211	0.673	0.209	140.70
Goat	0.78	293	0.884	0.150	132.60

t1/2 = half-life.

B_1 = intercept of time describing elimination phase with ordinate.

B^{h-1} = apparent first-rate order constant for elimination.

V_d = apparent specific volume of distribution.

Cl_r = total body clearance.

The liver is the principal organ for metabolism of ASA in animals. The hepatic microsomal enzyme systems mediate a variety of oxidative reactions and conjugation. The capacity of the cat for glucuronide conjugation is very limited. Like the cat, neonatal animals of different species perform

glucuronide conjugation at a slow rate. Several species seem to reach adult values at 30 days of age (Davis et al., 1973). The half-life of salicylate in plasma varies from about 1 hr in the goat to approximately 38 hrs in cat (Table 1, p. 15).

The patterns of distribution of metabolites in the urine of neonates are generally similar to those observed in adult animals of the same species (Davis and Westfall, 1972). The foal excretes unchanged salicylate as the principal salicyl compound. The dog excretes salicylate conjugated with glucuronate, goats primarily eliminate the glycine conjugate, and pigs excrete salicyl glucuronide and salicylurate in approximately equal amounts. In adult dog and swine, renal salicylate clearance is low, whereas salicylurate and salicylglucuronide clearance exceed the endogenous creatinine clearance (Davis and Westfall, 1972).

2.4.2 Paracetamol

Humans : Paracetamol is a weak organic acid with a pKa of 9.5. The drug is rapidly and well absorbed from the gastrointestinal tract and peak plasma levels are attained in 30-60 min. The absorption is

related to the dosage form and the rate of gastric emptying. Paracetamol is partly metabolized during absorption, primarily to pharmacologically inactive products. In man, only about 10% is subject to pre-systemic biotransformation at doses of 1g or more, but the fraction may be high (40%) at low doses (Rawlins et al., 1977).

Paracetamol is uniformly distributed throughout most body fluids. It penetrates the blood-brain barrier fairly well. At normal doses only about 10% is bound to plasma proteins, but during acute intoxication as much as 20 to 50% may be bound. These differences in plasma protein binding may partly explain why paracetamol appears to have a larger volume of distribution (1l/kg) than salicylic acid (0.1 to 0.35l/kg) (Levy, 1981).

Paracetamol is metabolized by the hepatic microsomal enzymes and converted primarily to paracetamol sulfate and paracetamol glucuronide, both metabolites being pharmacologically inactive (Fig. 4, p. 18). Mitchell et al. (1973) and Potter et al. (1973) established that a minor, but important metabolic pathway, involves the conversion of paracetamol to a reactive metabolite by the hepatic cytochrome P-450-dependent mixed function oxidase system. The reactive metabolite is thought to be either N-acetyl-p-benzo-

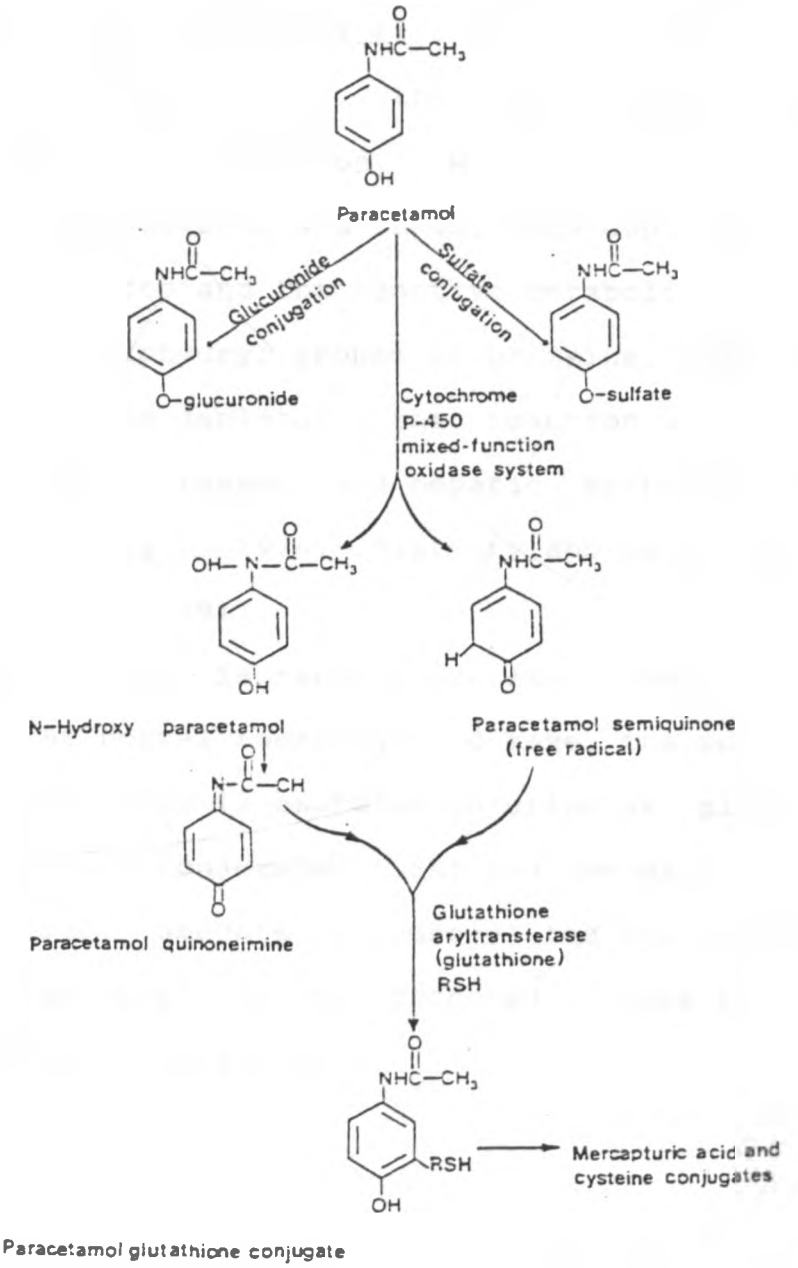


Fig. 4 Metabolism of paracetamol (Summy-Long, 1984).

quinoneimine (Mitchell et al., 1974; Corcoran et al., 1980) or the corresponding semiquinone free radical (DeVries, 1981; Nelson et al., 1981). In the usual therapeutic dose range, the reactive metabolite is inactivated by conjugation. When large single doses (> 5g) of paracetamol are taken, this conjugation capacity may be exceeded and the reactive metabolite may then react with sulphydryl groups in proteins. When hepatic glutathione is depleted, the reaction with hepatic protein is increased and hepatic necrosis results (Mitchell et al., 1974; Slattery and Levy, 1979; Yamada et al., 1981).

Paracetamol is rapidly excreted, mainly by the kidney. At normal therapeutic dosage, the bulk of the administered drug is excreted in urine as glucuronide (60%), sulfate conjugates (35%) and cysteine conjugates (3%). Small amounts of hydroxylated and deacylated metabolites have also been detected. Less than 2% is excreted as unchanged drug.

Animals : The metabolism of paracetamol in domestic animals follows the same pathways as in humans (Fig. 4, p. 18), but quantitative differences of various products exists between different species. At normal therapeutic dosage, most species

(except cat and mouse) excrete a major part of the administered paracetamol in urine as glucuronide and to a lesser extent, as the sulfate conjugate of the parent compound. Less is excreted as unchanged paracetamol, as primary aromatic amines or as an acetylcysteine conjugate (Mercapturic acid) (Welch et al., 1966; Gillette, 1981). In the cat about 12% is excreted as aromatic amines compared with about 4% for dogs and only 0.225% in humans (Welch et al.. 1966).

2.5 PHARMACODYNAMICS

2.5.1 Acetylsalicylic acid

Mechanism of action : Several different hypotheses have been advanced to explain the mode of action of ASA and other NSAID. These include interference with oxidative phosphorylation (Adams and Cobb, 1958; Whitehouse and Haslam, 1962), the displacement of glucucorticoids from protein binding sites (McArthur et al.. 1971; Smith et al., 1971), interference with migration of leukocytes (Di Rosa et al., 1971), inhibition of leukocytic phagocytosis (Chang, 1972), inhibition of generation of lipoperoxides (Sharma et al., 1972) and hyperpolarization of neuronal membranes (Baker and Levitan, 1971). Recently,

much evidence have been found to suggest a major role for prostaglandins in mediation of inflammatory response, irrespective of its aetiology, and that ASA and other NSAID may act by inhibiting the synthesis and release of prostaglandins (Vane, 1971; Ferreira et al., 1971). These drugs inhibit the enzyme cyclo-oxygenase (Fig. 5, p. 22) which catalyzes the synthesis of cyclic endoperoxides important in formation of prostaglandins. Since prostaglandins produce signs of inflammation (erythema, oedema) and potentiates the effect of bradykinin and other allogens on pain receptors, a reduction in prostaglandins result in therapeutic responses, such as anti-inflammatory, antipyretic and analgesic effects.

Anti-inflammatory effects : The anti-inflammatory effects of ASA have been studied extensively. Prostaglandins are associated with the development of oedema that accompanies injury or inflammation. They increase vascular permeability by inducing vascular leakage at the postcapillary and collecting venules resulting in oedema. The effectiveness of ASA as an anti-inflammatory agent is largely due to its capacity to inhibit the eicosanoid synthesis. ASA has different effects according to the dose. At low

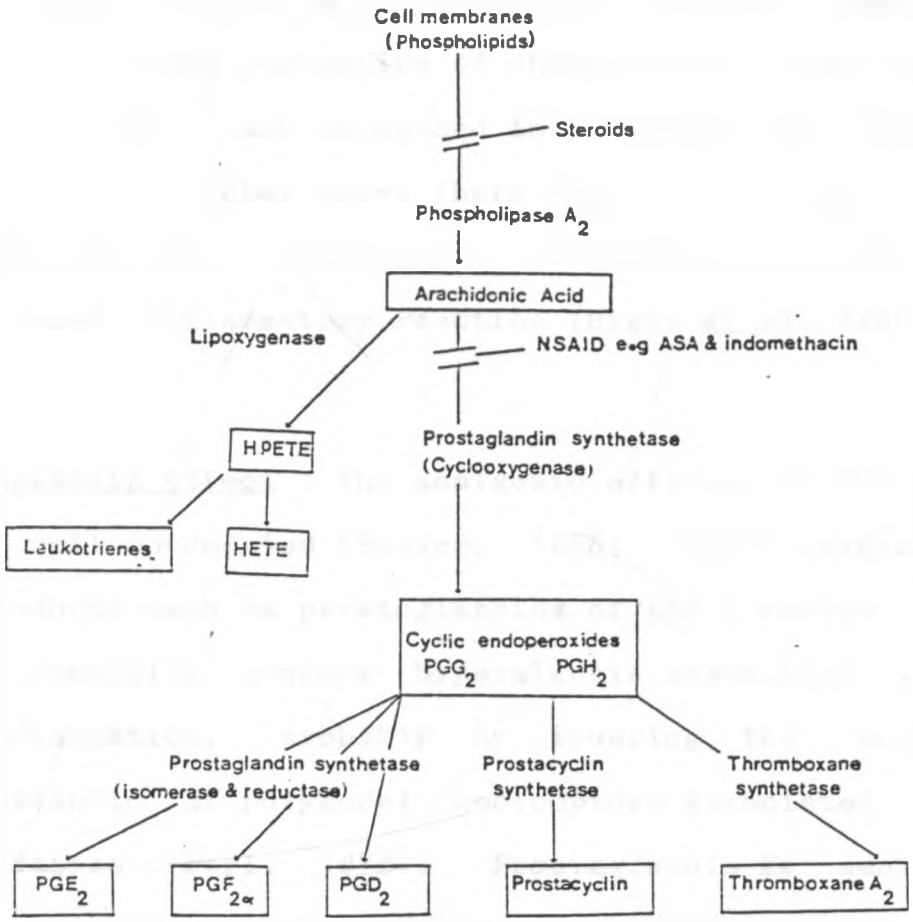


Fig. 5 Metabolism of arachidonic acid and sites of action of anti-inflammatory drugs (Nickander et al., 1979; Summy-Long, 1984).

doses, the drug potentiates the entry of leukocytes in an inflammed area, while leukocyte accumulation is inhibited at higher doses which reduce oedema. ASA at

low doses seems to selectively inhibit the cyclo-oxygenase resulting in a diversion of arachidonic acid substrate through the lipoxygenase pathway, resulting in increased production of chemotactic leukotrienes (e.g. LTB_4) and increased inflammatory reaction, while at higher doses there might be a dual cyclo-oxygenase and lipoxygenase inhibition resulting in reduced inflammatory reaction (Higgs et al.,1980).

Analgesic effect : The analgesic efficacy of ASA is well documented (Beaver, 1965). Cyclo-oxygenase products such as prostaglandins of the E series and prostacyclin produce hyperalgesia associated with inflammation, probably by lowering the normal threshold of polymodal nociceptors associated with C fibres (Perl, 1976). Prostaglandin E_2 sensitizes the chemical receptors of apparent pain endings to other inflammatory mediators such as bradykinin and histamine. ASA and other NSAID which are potent inhibitors of prostaglandins biosynthesis, may exert their analgesic effect through this mechanism. It is also worth noting that NSAID do not affect hyperalgesia or pain caused by direct action of prostaglandins. NSAID have been assumed to exert their analgesic effect locally (Lim et al., 1964). The authors found that

ASA acted at the peripheral pain chemoreceptors. However, Ferreira et al. (1978) have demonstrated that ASA has both a peripheral and central nervous system (CNS) effect.

Antipyretic effect : Fever results from a resetting of the temperature set-point (thermostat) by the action of endogenous pyrogens on the thermoregulatory centre in the preoptic region of the hypothalamus (Dinarello, 1979). NSAID reduce elevated body temperature associated with fever, but it is uncommon for them to reduce the normal body temperature. An elevated body temperature produced by exercise, drugs, hypothalmic lesions, disturbances in monoamine metabolism in CNS, or metabolic disorders, is not lowered by NSAID (Stitt, 1979). ASA lowers the elevated body temperature by altering the reponse of hypothalamus to exogenous pyrogens. In addition, the drug may inhibit the synthesis of pyrogenic prostaglandins, presumably in the neurons of the hypothalamus, and also suppress the release of pyrogens from leukocytes. Toxic doses of ASA have a pyretic effect that results in sweating.

Anti-platelet effect : There is clinical and experimental evidence that ASA affects haemostasis,

resulting in abnormalities in platelet function and prolonged bleeding time (O'Brien, 1968; Stuart, 1970; Mielke et al., 1976). This is not due to hypoprothrombinaemia and can occur with a dose as low as 40 mg/day (Flower et al., 1985). There are, however, conflicting results regarding the effect of various dosage regimens on bleeding time (Godal et al., 1979). In addition to cyclo-oxygenase, the platelet contains thromboxane synthetase which catalyzes the formation of thromboxane (TXA_2) from cyclic endoperoxides (Gorman, 1979). TXA_2 promotes platelet aggregation and vasoconstriction whereas prostacyclin (PGI_2) does the reverse, that is, inhibits platelet aggregation and promotes vasodilation. The anti-platelet effect of ASA is due to acetylation of platelet cyclo-oxygenase and consequent reduced formation of TXA_2 (Roth and Majerus, 1975). Due to its anti-platelet effect ASA should be avoided in patients with severe hepatic damage, hypoprothrombinaemia, vitamin K deficiency, haemophilia and those taking oral anti-coagulants, because the inhibition of platelet haemostasis can result in haemorrhage.

Other effects

Respiration and acid-base balance : Therapeutic doses of ASA generally are without effect on respi-

ration. Large doses (6-10g) increase respiratory rate and depth as a result of direct stimulation of the medulla. This induced hyperventilation results in excess alveolar excretion of carbon dioxide, leading to a respiratory alkalosis. Toxic doses of ASA, on the other hand, depresses the medullary respiratory centres, resulting in increased carbon dioxide accumulation and subsequent development of a metabolic acidosis. Definite changes in the acid-base balance and electrolyte pattern follows. Secondary to depression of the vasomotor centre in the medulla, respiratory paralysis and circulatory collapse occur (Flower et al., 1985).

Metabolic effects : ASA causes uncoupling of oxidative phosphorylation. In both man and animals, large doses of ASA may cause hyperglycaemia and glycosuria and deplete liver and muscle glycogen. These effects are partly explained by the release of adrenaline. ASA in toxic doses causes a significant negative nitrogen balance, characterized by an aminoaciduria. It reduces lipogenesis by partly blocking incorporation of acetate into fatty acid, and it also inhibits adrenaline stimulated lipolysis in fat cells and displace long chain fatty acid from

binding sites on plasma proteins. These leads to the lowering of free fatty acids, phospolipids and cholesterol in plasma (Flower et al., 1985).

Uricosuric effects : ASA has different effects on blood uric acid level depending on the dose, because it affects the reabsorption and secretion of uric acid (Yü and Gutman, 1959). Chronic low doses (1 to 2g daily) may decrease urate excretion and elevate plasma urate concentration, while intermediate doses (2 to 3g daily) usually do not alter urate excretion. Chronic high doses (5g daily), that increase serum concentrations to 20mg/100ml, induce uricosuria and lower plasma urate level. Due to this effect the drug was once used in the treatment of acute and chronic gout. Accordingly, small doses of ASA should not be used concomitantly with probenecid and other uricosuric agents that decrease tubular reabsorption of uric acid, because ASA then abolishes their effects.

Cardiovascular effects : Ordinary therapeutic doses of ASA have no important direct cardiovascular actions. The peripheral vessels tend to dilate after large doses, due to a direct effect on smooth muscles.

In patients given large doses of ASA, such as in the treatment of acute rheumatic fever, the circulating plasma volume increases (about 20%), the haematocrit falls, and cardiac output and stroke work are increased. Consequently, high doses should be avoided in patients with clear evidence of carditis, since they may cause congestive failure and pulmonary oedema (Flower et al., 1985).

Gastrointestinal effects: The ingestion of ASA may result in epigastric distress, nausea and vomiting. Emesis results from stimulation of sites that are accesible from the cerebrospinal fluid, probably in the medullary chemoreceptor trigger zone. In man, centrally induced nausea and vomiting generally appear at plasma salicylate concentration of about 270 µg/ml, but these effects may occur at much lower plasma value as a result of local gastric irritation. ASA may also cause gastric ulcerations and haemorrhage in experimental animals and in man (Kiser, 1963; Phillips, 1973). The ASA induced gastric bleeding leads to blood loss in stool and occasionally an iron deficiency anaemia. In some cases, however, blood loss is not significant.

The occurrence of these effects in man have been demonstrated by many investigators. For example,

ingestion of 4 or 5g of ASA per day for 26 days, a dose that produce plasma salicylate concentration in the usual range for anti-inflammatory therapy (120 to 350 µg/ml), resulted in an average faecal blood loss of about 3 to 8 ml per day as compared with approximately 0.6 ml per day in untreated subjects (Leonards and Levy, 1973). It has also been established by some researchers that repeated administration of ASA may cause major gastrointestinal bleeding. This bleeding may occur on its own, or when the patient has recently been exposed to some drugs, e.g. alcohol, heparin, steroids, ethacrynic acid and warfarin (Jick, 1981).

The mechanisms by which ASA injure gastric mucosal cells are complex. Deleterious effects result from local actions, which cause injury to submucosal capillaries with subsequent necrosis and bleeding, and from effects on the secretion of acid and mucus, which appear to be due to systemic inhibition of the formation of prostaglandins. There may also be an increased bleeding tendency secondary to impaired platelet aggregation.

2.5.2 Paracetamol

Mechanism of action : The mechanism of action of paracetamol is still not well understood. Different

researchers have concluded that the site of action is peripheral, central or a combination of both (Koch-Weser, 1976). Paracetamol has almost the same potency as ASA in inhibiting brain prostaglandin synthetase, but is less effective as an inhibitor of the peripheral enzyme (Flower and Vane, 1972). This marked different sensitivity of enzymes has been used by some researchers to explain why paracetamol has analgesic and antipyretic activity, but should lack anti-inflammatory effect. However, paracetamol has the ability to scavage oxygen-derived free radicals, which are considered to be important mediators of inflammation. During the conversion of PGG_2 to PGH_2, the oxygen radicals released are trapped by paracetamol, thus facilitating rapid turnover of PGG_2, which has a pivotal role in inflammation. This may explain the anti-inflammatory activity observed in some studies (Vinegar et al., 1976; Gleen et al., 1977; Levine et al., 1981). Paracetamol has been reported to be ineffective as a cyclo-oxygenase inhibitor under standard assay conditions in which the peroxide level is high. However, when peroxide level was reduced paracetamol was found to efficiently inhibit the cyclo-oxygenase (Lands, 1981; Warso and Lands, 1983). A reversible interaction between cyclo-oxygenase and paracetamol has also been demonstrated (Mattammal et al., 1979).

Anti-inflammatory effects : The anti-inflammatory activity of paracetamol is still controversial. Although paracetamol has been reported to be without anti-inflammatory activity in patients with rheumatoid arthritis (Boardman and Hart, 1967; Ring et al., 1974; Lee et al., 1976), recent controlled studies with bilateral oral surgery in humans have demonstrated that paracetamol may reduce swelling and other events of an acute inflammatory reaction (Lökken and Skjelbred, 1980; Skjelbred et al., 1984).

The clinical results suggesting anti-inflammatory activity of paracetamol in animals are in accordance with recent findings in rodents (Vinegar et al., 1976; Gleen et al., 1977; Levine et al., 1981). Vinegar et al. (1976) claimed that the analgesia produced by paracetamol in rats is dependent on its anti-inflammatory activity. In another study with rats, oral doses of paracetamol and phenacetin as well as anti-inflammatory steroids were found to inhibit mobilization of inflammatory cells, for example neutrophils, which produce the vasoactive metabolites of arachidonic acid responsible for oedema formation (Vinegar et al., 1978). Kuehl and Egan (1978) have found that paracetamol stimulates the conversion of PGG_2 to PGH_2. PGG_2 seems to have a central role in acute inflammation and to be a prime factor in oedema and pain components (Kuehl et al., 1977).

Analgesic effect : It seems that paracetamol and ASA are equipotent in the relief of pain of almost any cause, and that the drugs have similar dose response and time-effect curves (Cooper, 1981). The site of analgesic action of paracetamol is uncertain (Koch-Weser, 1976). The efficacy of paracetamol is dose related as for ASA (Seymour and Walton, 1984).

Antipyretic effect : Many investigators have found ASA and paracetamol equally effective as antipyretics (Colgan and Mintz, 1957; Eden and Kaufman, 1967; Tarlin et al., 1972; Hunter, 1973; Yaffe, 1981). Paracetamol lowers elevated body temperature as ASA by altering the response of hypothalamus to pyrogens.

Anti-platelet effect : Paracetamol has no significant effect on platelet function and the bleeding time. It also does not influence the coagulation proteins or fibrinolytic mechanism (Mielke, 1981).

Other effects : Single or repeated therapeutic doses of paracetamol have no effect on the cardio-vascular and respiratory systems. The absorption or

secretion of uric acid is not affected by paracetamol.

2.6 THERAPEUTIC USES

2.6.1 Acetylsalicylic acid

Anti-inflammatory/anti-rheumatic : ASA is mainly used in medicine as an anti-inflammatory agent in the treatment of musculoskeletal disorders, such as rheumatoid fever, rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

In acute rheumatic fever, ASA suppresses the acute exudative inflammatory process of the disease but does not affect the progression of the disease or latter phases of granulomatous inflammation or scar tissue formation. Within 24 to 48 hrs after adequate doses of ASA, there is usually considerable or complete relief of pain, swelling, immobility, local heat and redness of involved joints. However, cardiac complications, chorea, encephalopathy, subcutaneous nodules and other features are not prevented. For maximal suppression of rheumatic inflammation, doses that provide a plasma salicylate concentration of 250 to 350 µg/ml should be maintained. Polyarthritis and fever usually respond to smaller amounts.

Despite the development of the newer anti-inflammatory agents, ASA is still regarded as the standard with which other drugs should be compared for the treatment of rheumatoid arthritis. In addition to analgesia, ASA reduces the inflammation in joint tissues and surrounding structures in cases of rheumatoid arthritis. Fairly large doses are advised (4 to 6 g daily), but some patients respond well to less.

In the dog, a dosage regimen of approximately 40 mg/kg every 17 hrs to produce plasma salicylate concentrations between 50-200 mg/l, is recommended for alleviation of inflammation (Table 2).

Table 2 Dosage recommendation for salicylate in various domestic animals (Davis, 1980).

Animal type	Dose (mg/kg) to produce plasma concentration of:			Dosage frequency (hr) to maintain plasma concentration between:		
	50 mg/l	200 mg/l	300 mg/l	20-50 mg/l	50-200 mg/l	50-300 mg/l
Dog	9.5	38	57	12	17	22
Cat	10.5	42	63	52	77	100
Swine	9	36	54	8	12	15
Horse	9	36	54	1.5	2	2.7
Ruminant	6.5	26	39	1	1.6	2

Analgesia/antipyresis : ASA and other NSAID are usually classified as mild analgesics, but this is not altogether true. A consideration of the type of pain as well as its intensity is important in the assessments of analgesic efficacy. In post-operative pain for example, NSAID can be superior to opiod analgesics (Flower et al., 1985), and also in alleviating pain associated with prostaglandins in stimulated smooth muscle contraction (Summy-Long, 1984).

ASA is valuable for the non-specific relief of certain types of pain, for example headache, arthritis, neuralgia and mylgia. For this purpose it is prescribed in the doses and manner as for antipyresis. In humans the analgesic/antipyretic dose of ASA is 325 to 650 mg orally every 4 hours to maintain a plasma salicylate concentration above 60 µg/ml.

To alleviate pain in dogs, a dose of 10 mg/kg every 12 hours, thereby maintaining a plasma salicylate concentration between 20-50 mg/l is recommended (Table 2, p. 34). The antipyretic therapy is reserved for patients with high fever and for those who experience considerable relief when the fever is lowered.

Other uses : Due to the potency and long lasting effect of low doses of ASA on platelet

function, it has been suggested that this drug could be of use in the treatment or prophylaxis of diseases associated with increased platelet aggregation such as coronary artery diseases, myocardial infarction and post-operative deep vein thrombosis (Nickander et al.. 1979; Flower et al.. 1985). Some researchers have concluded that ASA at 1.2 to 1.5 g/day may reduce post-operative thrombosis (Verstraete, 1976; Harris et al.. 1977). The effect of ASA (0.3 - 1.5 g daily) after myocardial infarction have been investigated in various clinical trials. In one trial no statistically significant difference was observed between placebo and 0.3g ASA daily (Elwood et al.. 1974). However, more clinical trials are in progress to assess the effects of low doses of ASA.

ASA and indomethacin promote closure of the patent ductus arteriosus and alleviate the symptoms of cardiac failure in neonate, but drug-induced renal toxicity restricts the use of these drugs to individuals at high risk for surgery. ASA has also been shown to be effective in the treatment of ocular inflammation, acute and chronic glomerulonephritis, Bartter's syndrome and traveller's diarrhoea (Summy-Long, 1984).

2.6.2 Paracetamol

Anti-inflammatory/anti-rheumatic : It is generally assumed that paracetamol has little if any anti-inflammatory effect, and is considered to be inferior in the treatment of rheumatoid arthritis (Boardman and Hart, 1967; Ring et al.. 1974; Lee et al.. 1976). Hence the limitation of its use as an anti-phlogistic agent. It should be kept in mind, however, that the mechanisms and pattern of an acute inflammatory reaction differ from a rheumatoid inflammation. With the recent demonstration of its anti-inflammatory activity in oral surgery (Skjelbred and Lökken, 1979; Lökken and Skjelbred, 1980; Skjelbred et al.. 1984), the authors recommended paracetamol as a useful drug for reducing an excessive acute inflammatory reaction. A total daily dose of 2 g may significantly reduce post-operative swelling.

Paracetamol has not been used as an anti-phlogistic agent in veterinary medicine. However, reduction of inflammatory oedema in laboratory animals has been reported (Vinegar et al.. 1976; Gleen et al.. 1977; Levine et al.. 1981).

Analgesia/antipyresis : Paracetamol is often a suitable alternative to ASA as an analgesic or antipyretic

agent, especially in patients in whom ASA is contra-indicated (e.g. those with peptic ulcers) or when prolongation of bleeding time caused by ASA would be a disadvantage. For relief of acute pain and fever in humans, a dosage of 325-500 mg 4 times daily is adequate to produce a plasma salicylate concentration of 10-20 mg/l. In dogs a dosage of 2-4 mg/kg has been recommended (Bywater, 1982).

2.7 TOXICITY

2.7.1 Acetylsalicylic acid

Fatal dose : The fatal dose varies with the preparations. In humans 10-30 g of ASA has caused death in adults, but much larger amounts (130 g of ASA in one case) have been ingested without fatal outcome (Flower et al., 1985). Children and young animals are more sensitive to ASA. In domestic animals, a dose that produces plasma salicylate concentration greater than 300 mg/l is commonly toxic (Table 2, p. 34).

Symptoms and signs : Mild chronic ASA intoxication is often referred to as salicylism. The condition is

characterized by tinnitus, headache, nausea, dizziness, sweating, reduced hearing and vision, lassitude, drowsiness, sweating, thirst, hyperventilation, vomiting, mental confusion and occasionally diarrhoea.

A more severe degree of ASA intoxication is characterized by CNS disturbances, skin eruptions, fever, acid-base and electrolyte imbalances and at times haemorrhagic phenomena. The salicylate concentration in blood determines the type of toxic effects observed (Fig. 6).

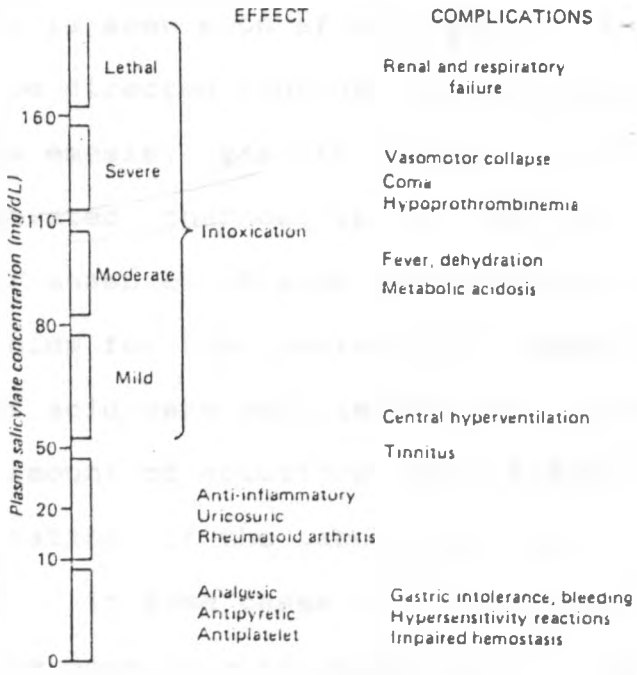


Fig. 6 Approximate relationships of plasma salicylate levels to pharmacodynamics and complications (Shearn, 1984).

Dehydration often occurs as a result of hyperpyrexia, sweating, vomiting, and the loss of water vapour during hyperventilation.

Death suddenly results from complete circulatory collapse and respiratory failure, at times accompanied by terminal pulmonary oedema. Some patients also succumb to uraemia or massive gastrointestinal haemorrhage.

Treatment : There is no specific antidote for ASA poisoning, and treatment is largely symptomatic. If the patient is seen soon after ingestion, treatment should be directed towards reducing absorption of the drug by emesis, gastric lavage, administration of activated charcoal or a combination of these. Other measures include intravenous administration of fluids for the treatment of dehydration, correction of acid-base and electrolyte imbalance. The type and amount of solutions administered depend upon interpretation of the laboratory data on acid-base balance. In some cases forced elimination of the drug can be done by alkalinization of urine. Haemorrhagic phenomena may necessitate whole blood transfusion and vitamin K therapy.

2.7.2. Paracetamol

Fatal dose : In humans, a dose of 10-25 g or more is potentially fatal. In the dog, clinical observations indicate that a single dose of about 250 mg/kg can be toxic (Cullison, 1984). The cat is acutely sensitive to paracetamol and experimental work has shown that a single oral dose of 143 mg/kg bwt can be lethal (Gaunt et al.. 1981).

Symptoms and signs : The most serious effect of acute overdosage of paracetamol is a dose and time-dependent hepatic necrosis. Nausea, vomiting, anorexia and abdominal pain may occur during the initial 24 hrs and persist for a week or more. Renal tubular necrosis, hypoglycaemic coma and thrombocytopenia have also been reported.

The most common signs of paracetamol toxicosis in the dog and cat are cyanosis, dyspnoea, facial oedema, depression, hypothermia and vomiting. Less common clinical signs include coma, generalized weakness and death (Finco et al.. 1975; Cullison, 1984).

Cyanosis is the most striking manifestation of toxicosis in cats, due to the high percentage of

methaemoglobin in the blood, in contrast to humans where the major manifestation of paracetamol overdose is acute centrilobular necrosis.

Treatment : Early diagnosis and vigorous supportive therapy are essential in the treatment of paracetamol overdosage. If the patient is seen within 4 hrs of the ingestion, treatment should be directed . towards reducing absorption of the drug by emesis or gastric lavage followed by administration of activated charcoal.

An established method of treatment is administration of sulphydryl compounds, which probably act in part by replenishing hepatic stores of glutathione. N-acetylcysteine is particularly effective and well tolerated when given orally. The drug is recommended if less than 24 hrs has elapsed since ingestion of paracetamol. In humans, a loading dose of 140 mg/kg followed by a maintenance dose of 70 mg/kg every 4 hrs for 17 doses is recommended (Flower et al., 1985). Intravenous acetylcysteine has also proved successful (Prescott, 1981). The minimum recommended clinical dosing schedule of N-acetylcysteine in the cat and dog is 140 mg/kg orally, repeated at 4

hrs interval for three treatments (St. Omer and McKnight, 1980; St. Omer and Valleroy, 1981).

CHAPTER THREE

AN EVALUATION OF THE EFFECTS OF PARACETAMOL ON SWELLING, PAIN AND OTHER EVENTS AFTER ORTHOPAEDIC SURGERY IN DOGS

3.1 INTRODUCTION

Paracetamol, a widely used non-narcotic analgesic agent has generally been accepted to have the same analgesic and antipyretic efficacy as ASA (Wallenstein and Houde, 1954; Parkhouse and Hallinon, 1967; Yaffe, 1981). In contrast to ASA, paracetamol has traditionally been claimed to have little or no anti-inflammatory effect, and it has been considered to be inferior in the treatment of rheumatic diseases and conditions in which inflammation is a significant factor (Beaver, 1965; Mills, 1974; Koch-Weser, 1976; Ameer and Greenblatt, 1977; Flower et al., 1985).

There is, however, increasing support for the view that paracetamol has anti-inflammatory activity and reduces pain and swelling in inflammatory conditions other than rheumatoid arthritis, sometimes more efficiently than ASA (Lökken and Skjelbred, 1981). Controlled studies with bilateral oral surgery in humans have demonstrated that paracetamol may reduce swelling and other events of an acute inflammatory reaction (Lökken and Skjelbred, 1980; Skjelbred

et al.. 1984). These clinical results agree with some recent findings in models of inflammation in rodents (Vinegar et al.. 1976; Levine et al.. 1981). Although paracetamol offers advantages compared to ASA in oral surgery (Skjelbred et al.. 1977), further controlled studies are needed to evaluate its efficacy and safety in alleviating pain and excessive inflammatory responses after other types of surgical interventions and accidental traumas.

Paracetamol has not been used in veterinary medicine, and information is lacking about its pharmacological properties and potential adverse effects in various animal species. One area where paracetamol might be of value in the veterinary clinic, is in the treatment of post-operative or post-traumatic sequelae.

While therapeutic doses of paracetamol have few adverse effects, acute overdosage may produce severe hepatic necrosis in both man (Prescott et al.. 1971; Clark et al.. 1973; Davis et al.. 1976) and animals (Gazzard et al.. 1975; Cullison, 1984). Renal tubular necrosis and hypoglycaemic coma may also occur (Flower et al.. 1985). Since there are species differences in the pharmacokinetics of paracetamol (Davis et al.. 1974), it is of importance to select an effective and safe dose for each species.

The main aim of the present study was to investi-

gate whether this surgical orthopaedic model in dogs could provide evidence to support the recent claim that paracetamol possesses anti-inflammatory activity and is capable of reducing post-operative swelling. A further aim was to study if the drug would produce any adverse effects at the selected dosage.

3.2 MATERIALS AND METHODS

3.2.1 Experimental design

The trial was carried out as a randomized placebo-controlled crossover study 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.

3.2.2 Animals

Eight mongrel dogs, five males and three females with a mean weight of 19 kg (range 13-24) and an estimated mean age of 8 years (6-10), were used. Individual values are given in Appendix 1, p. 133. The dogs were obtained with assistance of the staff from the Nairobi City Commission's Dog Pound. They were housed individually and provided with commercial dog food (Besbix®

Hound Meal - Proctor and Allan, Nairobi, Kenya) once per day at 4 p.m. and water ad libitum.

Each dog was identified using a collar band (Ident-A-Band® - Hollister Inc., Chicago, U.S.A), and a complete physical examination was done on acquisition. One ml of blood for differential cell count was collected from the cephalic vein using a 1 1/2" x 19 G disposable needle and a plastic syringe (2 ml). It was then transferred into a bijou bottle, containing dried disodium salt of ethylenediaminetetra-acetic acid (EDTA) (BDH Chemicals Ltd., Poole, U.K.), and shaken gently to allow the blood and the anticoagulant to mix. Blood smears from the marginal ear vein were also taken for blood parasites screening. Dogs were only accepted for the study if they were free from verifiable diseases or other abnormalities. A prerequisite was also that they should be easy to handle.

3.2.3 Drop-out

One dog (no. 26) was excluded from the study on the 8th day after the 2nd operation when paracetamol was administered. The dog was euthanized with pentobarbitone sodium (200 mg/ml), (Euthatal® - May and Baker Ltd.,

Dagenham, U.K.), as it became too weak to move and hence difficult in the assessment of various parameters. The post-mortem examination revealed an intestinal obstruction with a pus filled peritoneal cavity accompanied by a severe necrotizing peritonitis. The blood chemistry results indicated no liver or kidney malfunction. This was one of the oldest dogs in the trial and it was excluded from the study for diseases assumed to be unrelated to the medication and trial itself.

3.2.4 Drugs

At one operation a daily dosage of 1.5 g paracetamol (Dawa Pharmaceuticals Ltd., Nairobi, Kenya) was administered and at the other operation matching placebo tablets. The treatments were allocated according to a randomization list, so that half of the dogs received the active drug at the 1st operation. Tablets of 0.5g paracetamol were administered *per os* at 7.30 a.m., 1 p.m. and 6 p.m., starting on the day of surgery and continuing for a total of 4 days. To keep the study blind to the surgeon, the drugs were administered by an assistant who had no other responsibilities in the trial. Two mls of 200,000 I.U. procaine penicillin G and 0.25 g dihydrostreptomycin sulphate (Combiotic®-

Pfizer, Montreal, Canada) was injected intramuscularily immediately after surgery and on each of the following 4 days.

3.2.5 Pre-operative preparations

One week before each operation the dogs were dewormed with 50 mg/kg bwt of nitroscanate (Lopatol® - Ciba Geigy, Basle, Switzertland) and faecal samples were examined for parasitic eggs and segments 48 hrs later. If positive they were dewormed again and another faecal sample tested.

Four days before the surgery, each dog was weighed and sedated with 0.125 mg/kg bwt of acepromazine (ACP® -C-Vet Ltd., Edmunds, U.K.) administered intravenously. The left limb was always operated on first. The preparation of the limb for surgery involved clipping the long hairs with an Oster clipper (Oster Corp., Wisconsin, U.S.A.) from the digits up to a point below the elbow joint. This was followed by shaving using a blade no. 22 (Ailee Co. Ltd., HakJang-Dong, South Korea), after wetting the area with soap (Lifebuoy®- East Africa Industries, Nairobi, Kenya). The area was finally cleaned with 70% (w/v) ethanol (May and Baker Ltd., Dagenham, U.K.) and a superficial horizontal

incision (1-2 cm) was made just below the elbow joint. This incision acted as a standard mark from where pre- and post-operative measurements of the limb volume were made. Finally, all the long nails were clipped to a convenient size.

In the morning of the day of surgery, before the operations, each dog's weight and rectal temperature were recorded.

3.2.6 Operations

The operations were performed on Mondays and Tuesdays, between 8 and 11 a.m. The dogs were pre-medicated with 0.02 mg/kg bwt of atropine sulphate (Veterinary Drug Co. Ltd., York, U.K.) and 0.125 mg/kg bwt of acepromazine (ACP® -C-Vet Ltd., Edmunds, U.K.), both injected subcutaneously. Induction was by thiopentone sodium (Intraval® - May and Baker Ltd., Dagenham, U.K.), at a dose of 10 mg/kg bwt injected intravenously. Thereafter the anaesthesia was maintained by inhalation of a mixture of halothane (Fluothane® - Imperial Chemical Industries, Cheshire, U.K.) and oxygen (East African Oxygen Ltd., Nairobi, Kenya).

Efforts were made to employ the same surgical procedure at both operations, and each pair of opera-

tions were carried out by the same surgeon and assistant. There was no essential difference between the two operations with respect to duration of surgery. The mean duration from incision to last suture was 25 min (range 22-27) with paracetamol versus 26 min (22-29) with placebo. Details of patients, anaesthetic and surgical procedures are presented in Appendix 1, p. 133.

Surgery was carried out by a bilateral orthopaedic surgical technique (Mbugua, 1987). A 3-4cm vertical incision was made through the skin and subcutaneous tissue over the 3rd metacarpus to include most of the bone length. A superficial vein which form an inverted Y over this metacarpus was retracted and a branch of it double ligated with chromic catgut no. 2/0 (Ethicon Ltd., Edinburgh, U.K.). The bone was exposed as much as possible by retracting the tendons of common digital extensor and bluntly dissecting the surrounding tissues. A 6 hole mini dynamic compression plate (DCP) (Synthes®, Waldenburg, Switzerland) was placed in position and the middle two holes were eccentrically drilled using a manual drill with a 1.5 mm bait. The plate was then removed and the holes were tapped with a 2 mm tap which was directed in position by a drill guide. The metacarpus was then

cut transversally at about its mid-point with an oscillating saw (AMSCO Hall Surgical, Santa Barbara, U.S.A.). During transection the surgical site was continuously flushed with a cold aqueous solution containing 2 million I.U. of crystalline benzyl penicillin G in 100 ml sterile water to prevent infection and tissue necrosis. The plate was then placed in position and 2 mm screws (Synthes®, Waldenburg, Switzerland) were placed loosely in the middle holes. The other four holes were then drilled, tapped and screws placed in position. The plate was then fixed by tightening all the six screws. Bleeding was either controlled by digital pressure or ligation with chromic catgut no. 2/0 (Ethicon Ltd., Edinburgh, U.K.). Finally, the skin incision was sutured with nylon no. 2/0 (Ethilon® - Ethicon Ltd., Edinburgh, U.K.) using a simple interrupted pattern.

3.2.7 Assessments

Clinical assessments

Examination and assessments were done between 2 and 4 p.m. on days 1 to 7, and on days 10 and 14 post-operatively. The results were recorded on printed forms (Appendix 2, p. 134).

Swelling : The volume of the limb was measured in millilitres by a water displacement method (Mbugua, 1987). A specially constructed measuring cylinder was filled with water. The limb was then immersed into the cylinder until the mark on the shaved skin reached the top of the cylinder and the water displaced was measured (Fig. 7, p. 62).

The mean of 3 successive measurements was used to represent the volume of the limb. This was done pre- and post-operatively and the difference in volume was recorded as the swelling.

Pain : The pain was estimated by the surgeon who exerted digital pressure on the fracture site. The degree of animal reaction to the pressure was marked on a visual analogue scale that ranged from "no pain" (0 mm) to "pain cannot be worse" (100 mm).

Limping : This was marked on a visual analogue scale as assessed by the surgeon. The scale ranged from "no limping" (0 mm) to "limping cannot be worse" (100 mm).

Surgeon's preference : A global assessment using a visual analogue scale was done after the 2nd operation. The scale ranged from "maximal preference for the 1st course" (0 mm) to "maximal preference for the 2nd course" (100 mm).

Clinical examination : Routine clinical observations were done on each dog daily, and any abnormality, e.g. in the consistency of faeces or occurrence of emesis noted.

Rectal temperature : Measurements of the rectal temperature using a mercury thermometer were recorded. Temperature above 39.3° C was taken as an indicator of hyperthermia.

Wound healing : Any complications in wound healing were recorded daily.

Bone healing : Cranio-caudal and lateral views radiographs of the operation site were taken immediately

post-operatively and bi-weekly until disposal eight weeks after the 2nd operation, when the dogs were euthanized with pentobarbitone sodium (200 mg/ml) (Euthatal® - May and Baker, Dagenham, U.K.). According to the criteria described by Mbugua (1987), a detailed examination was done on each radiograph to assess the degree of union of the fracture, amount of callus formed at the fracture site, the reaction of the bone to implant and/or signs of infection.

Laboratory assessments

A 10 ml blood sample was collected from the jugular vein of each dog pre-operatively and on the 3rd post-operative day using a non-heparinized vacutainer (Becton-Dickinson Vacutainer Systems, New Jersey, U.S.A.).The sample was allowed to stand on a bench at room temperature for 60 min to clot. The serum was pipetted off for the following tests.

Serum alanine amino transferase (ALAT) : The measurements of ALAT were done following the method of Reitman and Frankel (1957), using a commercially available diagnostic kit (Boehringer Mannheim GmbH

Diagnostica, Mannheim, West Germany). Of the test serum 0.2 ml was mixed with 0.5 ml of buffered substrate (alanine-alpha-ketoglutarate) and incubated in a water bath at 37°C for 30 min. A volume of 0.5 ml of the colour reagent was added, mixed gently and incubated at room temperature for 20 min. Ten ml of 0.4 N sodium hydroxide was then added and the tube allowed to stand for 5 min. The optical density was read with a colourimeter (Eppendorf, Hamburg, West Germany) at 546 nanometer (nm), using a water blank reference. The activity of ALAT was obtained from a table of values and expressed in Sigma-Frankel Units (SFU) per ml. Only values above 2 SFU were recorded.

Blood urea nitrogen (BUN) : The measurements were done following the method of Fawcett and Scott (1960), using a commercially available diagnostic kit (Boehringer Mannheim GmbH Diagnostica, Mannheim, West Germany). A 0.1 ml volume of buffered substrate was added into three tubes marked "test", "standard" and "control". Then 0.02 ml of serum was added to the tube labelled "test", 0.2 ml of the standard solution to the "standard" tube, while 0.02 ml re-distilled water was added to the blank. The tubes were incubated at 37°C for 10 min. Five ml of the phenol and 5 ml of the hypochlo-

rite solutions were added into all three tubes, mixed and incubated for further 15 min at 37°C. The tubes were removed and the optical density was read with a colourimeter (Eppendorf, Hamburg, West Germany) at 546 nm, using a water blank reference. The BUN levels were calculated as follows:

$$\text{BUN (mg/100 ml)} = \frac{\text{Optical density test} \times \text{Concentration of standard (mg/100 ml)}}{\text{Optical density standard}}$$

Total serum proteins : The biuret method of Reinhold (1953) was used for determination of the total serum protein levels. A 0.5 ml volume of serum was pipetted into a test tube and 0.9 ml of anhydrous sodium sulphate (May and Baker, Dagenham, U.K.) was added resulting in the formation of a precipitate. Three ml of the precipitate were transferred into a test tube, 5 ml of the biuret reagent was added, and it was then incubated in a waterbath at 22°C for 30 min. The optical density was read with a spectro-photometer (Eppendorf, Hamburg, West Germany) at 546 nm, using a water blank reference. The serum protein levels were read from a standard protein calibration curve and expressed in g/100 ml.

3.2.8 Statistical analyses

The data on various parameters were assessed for normality. A one-sided Wilcoxon signed rank test with correction for ties (Lehmann and d'Abrera, 1975) was found appropriate to use. A significance level of 5% was selected.

3.3 RESULTS

3.3.1 Swelling

With one exception, all dogs exhibited less swelling after the operation when paracetamol was given. The observed differences in swelling in favour of paracetamol were statistically significant from the 2nd post-operative day until the end of the trial (Fig. 8, p. 63; Table 3, p. 66). Individual values are given in Appendix 3, p. 140. On the 3rd post-operative day the mean swelling in paracetamol-treated dogs was 67% of that with placebo (34 versus 51 ml, $p = 0.02$). The largest difference in swelling occurred on the 6th post-operative day, when the mean measured swelling in paracetamol-treated dogs was 61% of that with placebo (27 vs 44 ml, $p = 0.02$).

3.3.2 Pain

Significantly less pain was assessed during the first 4 days after the operation when paracetamol was administered (Fig. 9, p. 64; Table 4, p. 67). Individual values are given in Appendix 4 p. 142. On the 3rd post-operative day the mean pain estimate in paracetamol-treated dogs was 53% of that with placebo (19 vs 36 mm, $p = 0.01$).

3.3.3 Limping

There was no significant difference in limping between paracetamol and placebo treatment periods (Table 5, p. 68). Individual values are presented in Appendix 5, p. 144.

3.3.4 Surgeon's preference

According to the overall assessment after the 2nd operation, the preference scores were clearly in favour of the post-operative course when paracetamol was given (Fig. 10, p. 65).

3.3.5 Clinical examination

The clinical examination revealed no drug-related adverse effects after any of the two operations.

3.3.6 Rectal temperature

There was no consistent difference in the rectal temperature after the two operations (Appendix 6, p. 146).

3.3.7 Wound healing

There was no apparent clinical complication in wound healing, or any evidence of infection after the two operations.

3.3.8 Bone healing

Evaluation of the degree of fracture union, callus formation and bone infection or bone reaction to implant on radiographs taken 2, 4, 6 and 8 weeks after surgery, revealed essentially no difference in the healing process after the two operations (Appendix 7, p. 148).

3.3.9 Laboratory findings

Several dogs showed a certain increase in serum ALAT levels after both operations. This increase was more pronounced after the operation when paracetamol was administered. The mean increase in paracetamol-treated dogs was 23 SFU compared to a mean increase of 5 SFU with placebo. The enzyme levels were, however, within the normal range except for one dog which had levels above normal after the operation when paracetamol was given (Table 6, p. 69).

There was an increase in the serum BUN levels after both operations and the values were above normal in some dogs. The mean BUN levels increased from 26 to 45 mg/100 ml when they received paracetamol and from 22 to 37 mg/100 ml when they received placebo (Table 7, p. 70).

The total serum protein levels remained almost unchanged after the two operations and the mean levels were within the normal range. The mean post-operative value in paracetamol-treated dogs was 6.3 g/100ml while that in placebo was 6.4 g/100 ml (Table 8, p. 71).

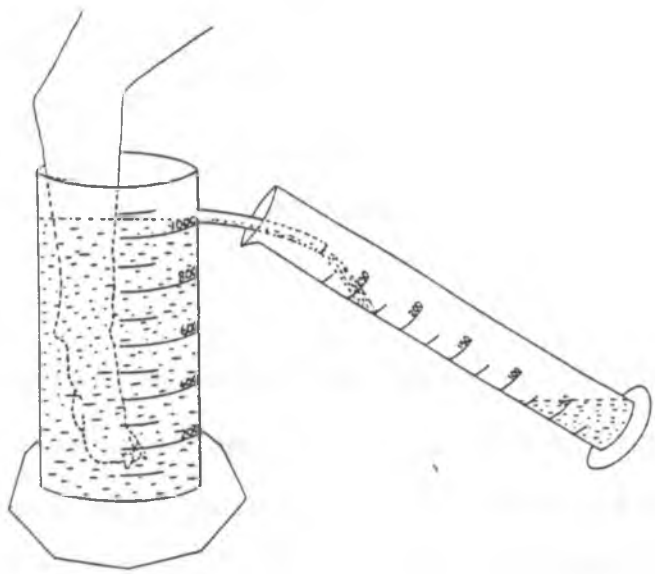


Fig. 7 Device for foot volumetry.

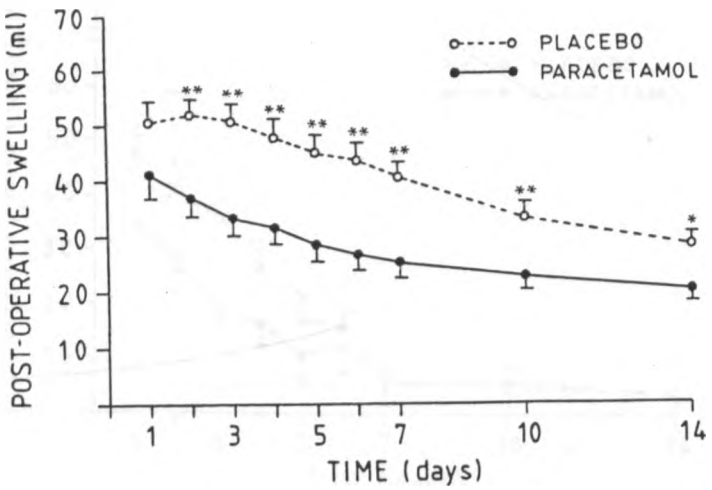


Fig. 8 Post-operative swelling (Mean ± S.E.M.) measured by limb volumetry in a placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given daily dosages of 1.5 g paracetamol. Medication started on the day of surgery and lasted for 4 days.

*p = 0.01, **p = 0.02.

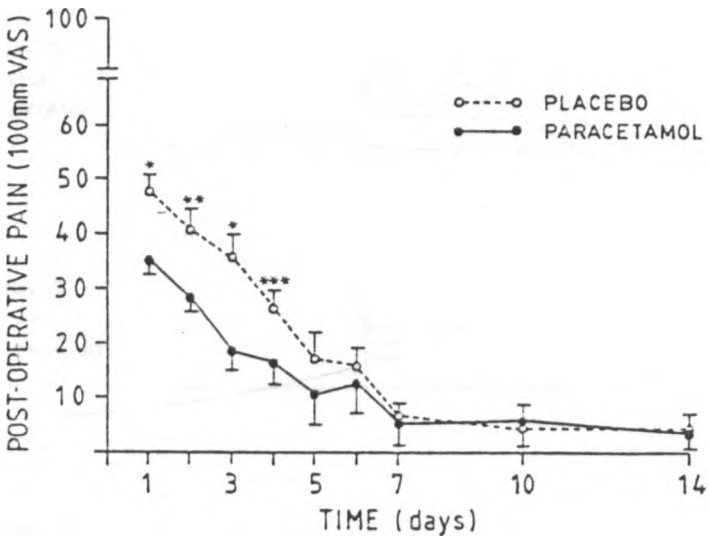


Fig. 9 Post-operative pain (Mean ± S.E.M.) assessed by a visual analogue scale in a placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given daily dosages of 1.5g paracetamol. Medication started on the day of surgery and lasted for 4 days.

*p = 0.01, **p = 0.02, ***p = 0.03.

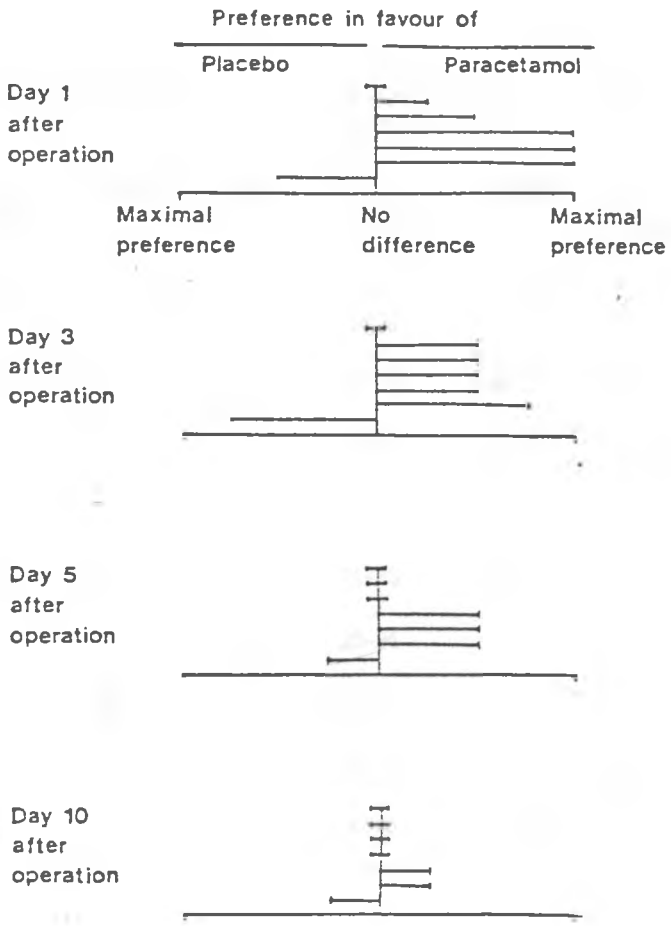


Fig. 10 Surgeon's preference for post-operative course assessed by a visual analogue scale after the 2nd operation in a placebo-controlled crossover trial with 1.5g daily dosages of paracetamol tested against placebo in 7 dogs.

Table 3 Statistical evaluation of post-operative swelling measured by limb volumetry in a randomized placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given daily dosages of 1.5 g paracetamol. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Day after surgery	Mean limb volume (ml)			95% confidence interval		Range		P-values
	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Para-cetamol	Placebo	Paracetamol vs Placebo
1	41	51	-10	39-50	42-60	26-52	37-64	0.08
2	37	52	-15	30-44	45-59	24-48	41-63	0.02
3	34	51	-17	27-41	44-58	22-46	39-63	0.02
4	32	48	-16	25-39	39-57	23-42	35-61	0.02
5	28	45	-17	21-35	38-52	19-39	34-55	0.02
6	27	44	-17	20-34	37-51	18-37	33-54	0.02
7	25	40	-15	18-32	33-47	16-34	31-49	0.02
10	23	33	-10	18-28	26-40	15-33	23-42	0.02
14	20	28	-8	15-25	23-33	13-30	19-36	0.01

Table 4 Statistical evaluation of post-operative pain assessed by a visual analogue scale in a randomized placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given daily dosages of 1.5 g paracetamol. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Day after surgery	Mean pain (mm)			95% confidence interval		Range		P-values
	Paracetamol	Placebo	Diff.	Paracetamol	Placebo	Paracetamol	Placebo	Paracetamol vs Placebo
1	35	48	-13	28-42	41-55	25-45	40-60	0.01
2	29	41	-12	22-36	32-50	20-40	30-55	0.02
3	19	36	-17	10-28	24-48	0-30	25-55	0.01
4	16	26	-10	7-25	19-33	0-35	15-40	0.03
5	11	17	-6	0-25	5-29	0-40	0-35	0.20
6	13	16	-3	0-27	9-23	0-40	0-25	0.29
7	5	6	-1	0-14	1-11	0-30	0-15	0.39
10	6	4	2	0-15	0-13	0-25	0-25	0.50
14	4	4	0	0-13	0-11	0-25	0-20	0.50

Table 5 Statistical evaluation of post-operative limping assessed by a visual analogue scale in a randomized placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given daily dosages of 1.5 g paracetamol. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Day after surgery	Mean limping (mm)			95% confidence interval		Range		P-values
	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Para-cetamol	Placebo	Paracetamol vs Placebo
1	34	36	-2	25-43	29-42	20-55	25-45	0.34
2	28	29	-1	23-33	15-43	15-35	0-45	0.46
3	21	22	-1	16-26	13-31	10-25	0-45	0.47
4	14	19	-5	5-23	12-26	0-30	0-25	0.20
5	14	14	0	0-28	5-23	0-35	0-25	0.50
6	19	14	5	5-33	5-23	0-45	0-25	0.28
7	19	9	10	3-35	0-18	0-50	0-25	0.14
10	9	4	5	0-21	0-13	0-35	0-25	0.21
14	4	0	4	0-13	-	0-30	0-0	0.50

Table 6 Serum alanine amino transferase values (Sigma-Frankel Units above 2) before and on the 3rd post-operative day in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given daily dosages of 1.5 g paracetamol. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Dog no.	Serum alanine amino transferase (SFU/ ml)					
	Paracetamol			Placebo		
	Post-op.	Pre-op.	Diff.	Post-op.	Pre-op.	Diff.
21	35	0	35	0	0	0
22	0	0	0	4	0	4
23	75	2	73	2	0	2
24	2	0	2	31	13	18
25	4	0	4	0	0	0
27	29	2	27	27	21	6
28	25	0	25	15	10	5
Mean	24	1	23	11	6	5

Normal range in dogs: 10 to 50 SFU (Cornelius, 1963).

Table 7 Blood urea nitrogen values before and on the 3rd post-operative day in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given daily dosages of 1.5 g paracetamol. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Dog no.	Blood urea nitrogen (mg/100 ml)					
	Paracetamol			Placebo		
	Post-op.	Pre-op.	Diff.	Post-op.	Pre-op.	Diff.
21	33	21	12	73	28	45
22	103	15	88	25	14	11
23	46	43	3	82	15	67
24	43	20	23	20	25	-5
25	31	41	-10	25	26	-1
27	22	15	7	20	19	-1
28	37	24	13	17	29	-12
Mean	45	26	19	37	22	15

Normal range in dogs: 10 to 30 mg/100 ml (Benjamin, 1974; Coles, 1974).

Table 8 Total serum protein values before and on the 3rd post-operative day in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given daily dosages of 1.5 g paracetamol. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Dog no.	Total serum proteins (g/100 ml)					
	Paracetamol			Placebo		
	Post-op.	Pre-op.	Diff.	Post-op.	Pre-op.	Diff.
21	5.9	5.9	0	5.8	5.8	0
22	7.2	6.9	0.3	7.1	6.8	0.3
23	5.1	6.0	-0.9	6.6	6.4	0.2
24	6.5	6.4	0.1	6.2	6.8	-0.6
25	6.6	7.2	-0.6	7.2	7.6	-0.4
27	5.7	5.1	0.6	5.8	6.6	-0.8
28	6.8	6.8	0	6.4	6.0	-0.4
Mean	6.3	6.3	0	6.4	6.6	-0.2

Normal range in dogs: 4.9 to 7.9 g/100 ml (Benjamin, 1974; Coles, 1974).

3.4 DISCUSSION

Paracetamol significantly reduced the post-operative swelling in this model with bilateral limb surgery. The 33% reduction in swelling recorded on the 3rd day agrees remarkably well with results obtained in oral surgery, where reductions in swelling of 29% (Lökken and Skjelbred, 1980) and 31% (Skjelbred et al., 1984) have been reported on the 3rd post-operative day. In this trial the medication started before surgery, but studies in human oral surgery have demonstrated that there is about the same reductions in pain and swelling, even if the start of anti-inflammatory therapy is delayed for 3 hours after surgery (Skjelbred and Lökken, 1982; Skjelbred et al., 1984).

The common view that paracetamol in contrast to ASA has little or no anti-inflammatory activity, seems to be based on clinical trials in patients with rheumatoid arthritis (Boardman and Hart, 1967; Ring et al., 1974; Lee et al., 1976). However, it should be kept in mind that the mechanisms and pattern of an acute inflammatory reaction differ from a rheumatoid inflammation; consequently anti-inflammatory drug effects are not necessarily the same for these different types of inflammation. The available data from studies of the anti-inflammatory activity of paraceta-

mol in animals are somewhat ambiguous. Using models with experimental inflammation in rodents, some investigations have concluded that paracetamol is devoid of anti-inflammatory activity (Adams, 1960; Brune and Glatt, 1974; Brown and Collins, 1977; Singh et al., 1986), while others have found the drug capable of reducing swelling (Vinegar et al., 1978; Levine et al., 1981).

It appears that drugs which efficiently reduce joint swelling in rheumatoid arthritis, may have little or no effect on post-operative or post-traumatic swelling. For example, oxyphenbutazone did not reduce the oedema after hand surgery (Olesen and Zachariae, 1965), neither did phenylbutazone reduce swelling after ankle sprains (Goldie et al., 1974) or indomethacin reduce swelling after sport injuries (Huskisson et al., 1973). Information on how paracetamol may affect the swelling after such injuries has not been found in the available literature.

There is increasing evidence that the site of surgical intervention and type of operation are important determinants of the post-operative inflammatory response (cited by Tammisto and Tigerstedt, 1980), thus these factors might influence the anti-inflammatory activity of various drugs in different experimental models.

Pappius and Wolfe (1976) noted that several NSAID (indomethacin, ASA, ketoprofen) did not reduce cerebral oedema in cats. These findings were later supported by Levine et al. (1981) who reported failure of some NSAID such as indomethacin, phenylbutazone, piroxicam and salicylic acid to reduce brain oedema in experimental rats, in contrast to the marked reduction observed following dexamethasone treatment, and also a certain reduction with paracetamol. There is still uncertainity as to the mechanism of action of paracetamol (Mattamal et al., 1979; Lands, 1981). A recently established property of paracetamol, which may at least partly explain the anti-inflammatory effect, is its ability to scavenge oxygen-centered radicals which are important mediators of inflammation (Kuehl et al., 1978). Another suggested mechanism is inhibition of mobilization of leukocytes (Vinegar et al., 1978).

The significant pain reduction observed in this study agrees with the common view that paracetamol is an effective analgesic agent (Moertel et al., 1972; Parkhouse, 1975; Flower et al., 1985).

It was difficult to obtain reliable and reproducible assessments of limping, and a significant improvement in the loss of function could not be demonstrated with paracetamol medication. The results in oral surgery

with post-operative mouth opening ability as an indicator of loss of function, have also been inconsistent with regard to paracetamol (Skjelbred and Lökken, 1979; Skjelbred et al., 1984).

The preference scores showed a marked trend in favour of paracetamol. A preference score is a compound assessment which is not necessarily parallel to the pain score (Huskisson, 1974).

In the present study the dogs were given single doses of about 0.025 g paracetamol/kg and daily doses of about 0.075 g/kg. In a study on the toxicity and biotransformation of paracetamol, dogs were given single doses of 0.1, 0.2 and 0.5 g paracetamol/kg. The plasma half-lives remained constant at the two lower doses, but it nearly tripled at the highest dosage. It was found that the dogs required more than 0.1 g/kg before signs of toxicity, such as depression, methaemoglobinaemia and vomiting became apparent (Savides et al., 1984). With repeated doses there might be a risk of cummulative toxicity.

Although there was a slight increase in the serum ALAT levels after the operation when paracetamol was given, all values remained within the normal range except for one dog with 75 SFU. According to Cornelius (1963) normal values in dogs are 10 to 50 Units, moderate liver necrosis 50 to 400 and severe necrosis

more than 400. Elevation above 1000 units is not uncommon in animals with severe hepatic necrosis.

The results on the serum BUN analysis showed a slight increase in the mean BUN levels after both operations. This increase appears not to be suggestive of paracetamol-induced nephrotoxicity, for it was observed in both paracetamol and placebo-treated dogs. Coles (1974) has stated that BUN levels in blood are affected not only by alterations in renal function, but may be altered by certain physiological factors or diseases not primarily of renal origin.

Except for this slight increase in serum ALAT levels, which may indicate a certain liver affection, no signs of toxicity or adverse effects of paracetamol were observed. Accordingly, the present results seem to support the statement recently given in a Leading Article (1981), that paracetamol has very few adverse effects and is very safe when given in therapeutic doses.

In the available literature, not a single report has been found on the therapeutic use of paracetamol in veterinary medicine. According to the present results, paracetamol appears to be a valuable drug in veterinary surgery and traumatology.

CHAPTER FOUR

AN EVALUATION OF THE EFFECTS OF ACETYLSALICYLIC ACID IN "LOW" AND "HIGH" DOSAGE ON SWELLING, PAIN AND OTHER EVENTS AFTER ORTHOPAEDIC SURGERY IN DOGS

4.1 INTRODUCTION

ASA, the prototype of NSAID, is generally accepted to have analgesic, antipyretic and anti-inflammatory activities (Beaver, 1965; Malseed and Malseed, 1978; Yaffe, 1981; Flower et al., 1985). Despite the introduction of many new drugs, ASA is still the most widely used analgesic/antipyretic/anti-inflammatory agent, and is the standard for comparison and evaluation of others (Flower et al., 1985). However, in some countries paracetamol has replaced ASA as the most widely used analgesic/antipyretic agent in human medicine, e.g. in the United Kingdom (Spooner and Harvey, 1976).

ASA has been extensively used in both human and veterinary medicine. In humans, in addition to its common use as an analgesic/antipyretic drug, ASA has since the turn of the century been a corner-stone in the treatment of rheumatoid arthritis (Gall, 1982; Hadler, 1984). In small animals, it is mainly used for

the relief of pain, particularly of musculoskeletal origin and in the treatment of arthritic diseases (Booth, 1982; Pugh, 1982). In dogs, daily dosages of 10 mg/kg bwt every 8 hrs has been recommended for the relief of pain and 25-40 mg/kg bwt every 8 hrs for alleviation of inflammation (Davis, 1980; Johnson, 1983).

It is a common statement, uncritically repeated in text-books of pharmacology, that the analgesic and antipyretic properties of ASA and paracetamol are equivalent, but that ASA in contrast to paracetamol is an effective anti-inflammatory agent. Although ASA is generally accepted to have anti-inflammatory activity, the evidence for this statement is rather limited. In 1945, Murphy stressed the lack of objective studies on the effects of salicylates on swelling of rheumatic joints. However, reduction of swelling was later demonstrated in patients with rheumatoid arthritis, taking ASA in large regular doses (Fremont-Smith and Bayles, 1965). This was also observed by Boardman and Hart (1966) in patients receiving a daily dose of 5.3 g salicylates, while they found that a daily dose of 2.6 g failed to reduce rheumatoid swelling. In other inflammatory conditions, controlled clinical trials which demonstrate anti-inflammatory effect of ASA, at least with swelling as a measure of inflammation, seem to be lacking (Lökken and

Skjelbred, 1981). The only exception is in the field of human oral surgery (Skjelbred et al., 1977; Skjelbred, 1984).

Skjelbred (1984) found that a "high" dose of ASA (4 g daily) reduced the post-operative swelling, while a "low" dose (2 g daily) actually tended to increase swelling.

In the present study with dogs, a daily dose of 0.5 g ASA (about 10 mg/kg bwt three times daily) was selected as a "low" dose, while a daily dose of 1.5 g ASA (about 30 mg/kg bwt three times daily) represented a "high" dose.

The main purpose of the placebo-controlled studies was to evaluate how the two dosages of ASA might modulate the acute post-operative inflammatory reaction.

4.2 MATERIALS AND METHODS

4.2.1 Experimental design

In principle the same placebo-controlled crossover design was used as described in Chapter 3. There were no differences with regard to pre-operative preparations or the surgical procedure, and the pre- and post-operative clinical and laboratory assessments were the same. The times and procedure of drug administration were also similar, as were the housing

and feeding of dogs. As in the study with paracetamol, the various parameters were assessed for normality using a one-sided Wilcoxon signed rank test.

4.2.2 Animals

Sixteen mongrel dogs were allocated to two groups of 8 dogs. Eight dogs (1 male, 7 females) which received 0.5 g ASA daily, had a mean weight of 15 kg (range 11-17) and an estimated mean age of 7 years (5-10). Individual values are given in Appendix 8, p. 150. Another group of 8 dogs (5 males, 3 females) which received 1.5 g ASA daily, had a mean weight of 18 kg (14-22) and an estimated mean age of 8 years (6-9). Individual values are presented in Appendix 9, p. 151. There was no drop-out in the two trials.

4.2.3 Drugs

Acetylsalicylic acid (Aspro® - Nicholas Kiwi Ltd., Nairobi, Kenya) was administered three times daily in doses of 0.17 g and 0.50 g in the "low" and "high" dose groups respectively. Medication started on the day of surgery and continued for a total of 4 days.

4.2.4 Operations

There proved to be no essential difference between the two operations with respect to duration of surgery in any of the two studies. In the study with 0.5 g ASA daily, the mean duration from incision to last suture was 25 min (range 20-28) versus 24 min (22-27) with placebo; and with 1.5 g ASA daily 26 min (20-36) versus 29 min (18-39). The details of patients, anaesthetic and surgical procedures are presented in Appendix 8, p. 150 and Appendix 9, p. 151.

4.3 RESULTS

4.3.1 Swelling

ASA - 0.5 g daily : There were tendencies towards less swelling after the operation when ASA was given, but on no occasion did the difference reach a significant level (Fig. 11, p. 87; Table 9, p. 91). Individual values are given in Appendix 10, p. 152. On the 3rd post-operative day the mean swelling in ASA-treated dogs was 85% of that with placebo (23 versus 27 ml, $p = 0.18$). The largest percentage difference in swelling occurred on the 4th post-operative day, when the mean measured swelling in ASA-treated dogs was 79% of that with placebo (19 vs 24 ml, $p = 0.18$).

ASA - 1.5 g daily : Six of the 8 dogs had less swelling after the operation when ASA was administered and the differences were significant during the 1st week (Fig. 11, p. 87; Table 10, p. 92). Individual values are presented in Appendix 11, p. 154. On the 3rd post-operative day, the mean swelling in ASA-treated dogs was 76% of that with placebo (26 vs 34 ml, p = 0.03). The largest difference in swelling occurred on the 5th post-operative day, when the mean measured swelling in ASA-treated dogs was 65% of that with placebo (20 vs 31 ml, p = 0.02).

4.3.2 Pain

ASA - 0.5 g daily : The pain estimates were somewhat lower after the operation when ASA was administered, but none of the differences were significant (Fig. 12, p. 88; Table 11, p. 93). Individual values are presented in Appendix 12, p. 156. On the 3rd post-operative day the mean pain estimate in ASA-treated dogs was 72% of that with placebo (13 vs 18 mm, p = 0.21).

ASA - 1.5 g daily : Less pain was assessed after the operation when ASA was given, but the difference

was only significant on the 2nd post-operative day (Fig. 12, p. 88; Table 12, p. 94). Individual values are presented in Appendix 13, p. 158. On the 3rd post-operative day the mean pain estimate in ASA-treated dogs was 68% of that with placebo (26 vs 38 mm, p = 0.07).

4.3.3 Limping

ASA - 0.5 g daily : The limping estimates did not reveal any significant difference between ASA and placebo (Table 13, p. 95). Individual values are presented in Appendix 14, p. 160.

ASA - 1.5 g daily : As with the low dose trial, there was no significant difference between the two treatment periods (Table 14, p. 96). Individual values are presented in Appendix 15, p. 162.

4.3.4 Surgeon's preference

ASA - 0.5 g and 1.5 g daily : According to the overall assessment after the 2nd operation, the preference scores were in favour of the post-operative

course when ASA was given in both groups of study (Fig. 13 p. 89; Fig. 14 p. 90).

4.3.5 Clinical examination

ASA - 0.5 g and 1.5 g daily : In both groups of study there were no signs of gastrointestinal toxicity or other potential drug-related adverse effects.

4.3.6 Rectal temperature

ASA - 0.5 g and 1.5 g daily : Post-operative measurements of the rectal temperature revealed no apparent difference to placebo in any of the two treatment groups (Appendix 16, p. 164; Appendix 17, p. 166).

4.3.7 Wound healing

ASA - 0.5 g and 1.5 g daily : The wound healing proceeded uneventful after all operations in both studies.

4.3.8 Bone healing

ASA 0.5 g and 1.5 g : Radiographic evaluation of the degree of fracture union, callus formation and

bone infection or bone reaction to implant on radiographs taken 2, 4, 6 and 8 weeks after surgery, revealed for both studies essentially no difference in the healing process after the two operations (Appendix 18, p. 168; Appendix 19, p. 170).

4.3.9 Laboratory findings

ASA - 0.5 g and 1.5 g daily : There were slight decreases in the mean serum ALAT levels after ASA medication, which were in contrast to the increase observed after placebo administration in both studies. The mean post-operative values in the "low" dose trial for both ASA and placebo-treated dogs were 7 SFU; with the "high" dose trial the values were 13 and 15 SFU for ASA and placebo-treated dogs respectively. All the values were within the normal range, except for one pre-operative value (Table 15, p. 97).

Most of the dogs had serum BUN levels within the normal range, except for three dogs in the "high" dose study that had post-operative values above normal. However, the mean post-operative values were within the normal range. In the "low" dose trial the mean values for both ASA and placebo-treated dogs were 9 mg/100 ml; while those for the "high" dose study were 25 and 23 mg/100 ml respectively for ASA and placebo-treated dogs (Table 16, p. 98).

The serum total protein levels remained almost unchanged in ASA and placebo-treated dogs, either given "low" or "high" dosage of ASA. The values were within the normal range, except for one post-operative and four pre-operative values which were above normal in the "high" dose trial. The mean post-operative values in ASA and placebo-treated dogs ranged from 6-7 g/100 ml (Table 17, p. 99).

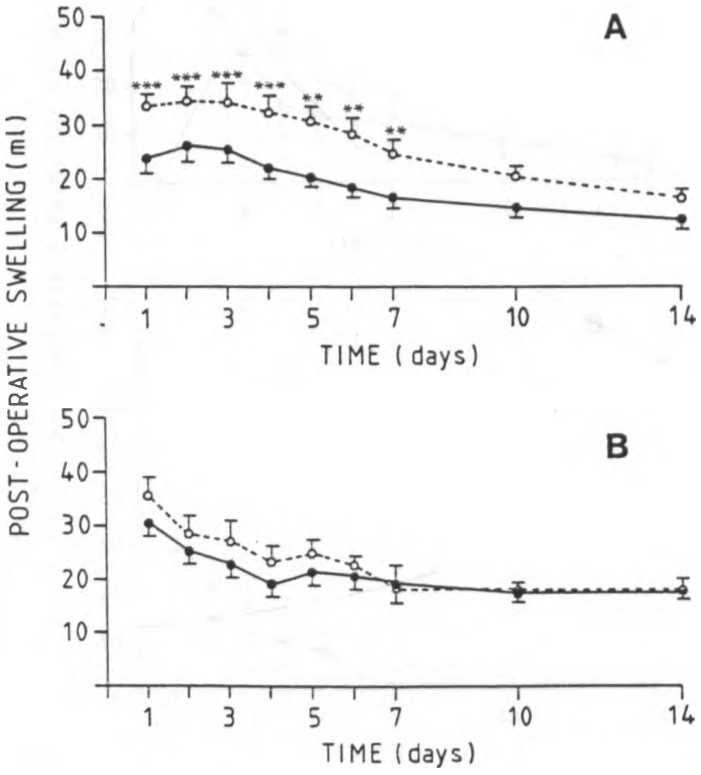


Fig. 11 Post-operative swelling (Mean ± S.E.M.) measured by limb volumetry after orthopaedic surgery on the forelimbs of dogs in placebo-controlled cross-over trials with 1.5 g daily (A) or 0.5 g daily (B) dosages of ASA tested against placebo in two groups of 8 dogs each. Medication started on the day of surgery and lasted for 4 days. **p = 0.02; ***p = 0.03.

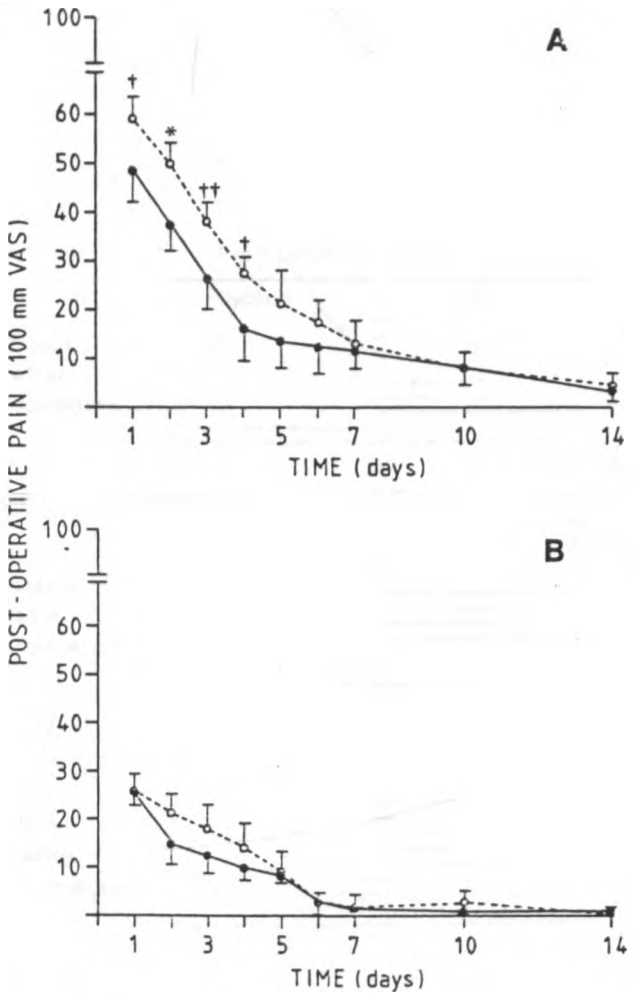


Fig. 12 Post-operative pain (Mean ± S.E.M.) assessed by a visual analogue scale after orthopaedic surgery on the forelimbs of dogs in placebo-controlled crossover trials with 1.5 g daily (A) or 0.5 g daily (B) dosages of ASA tested against placebo in two groups of 8 dogs each. Medication started on the day of surgery and lasted for 4 days. *p = 0.01.

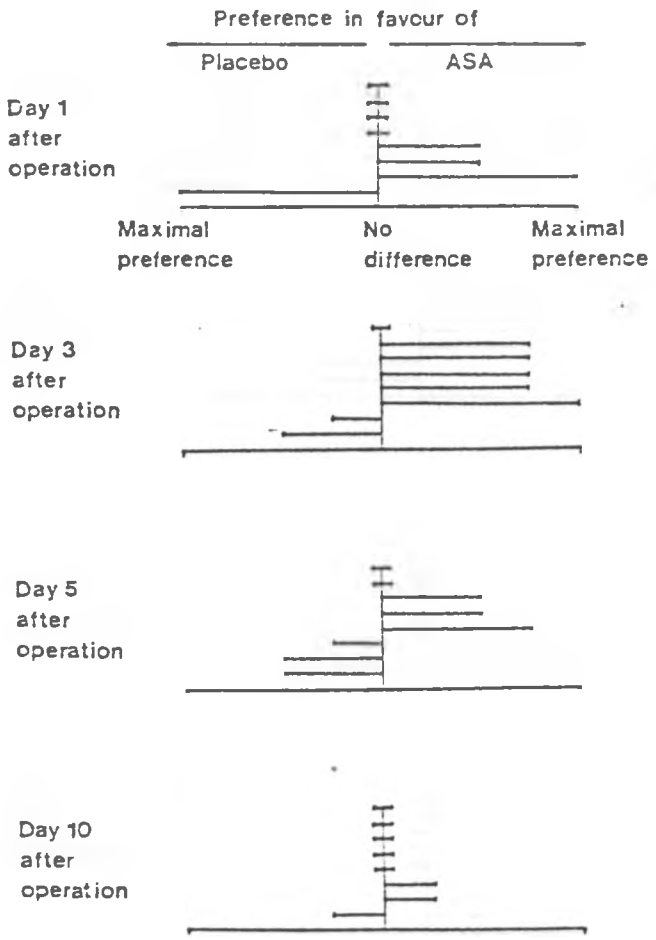


Fig. 13 Surgeon's preference for post-operative course assessed by a visual analogue scale after the 2nd operation in a placebo-controlled crossover trial with 0.5 g daily dosages of ASA tested against placebo in 8 dogs.

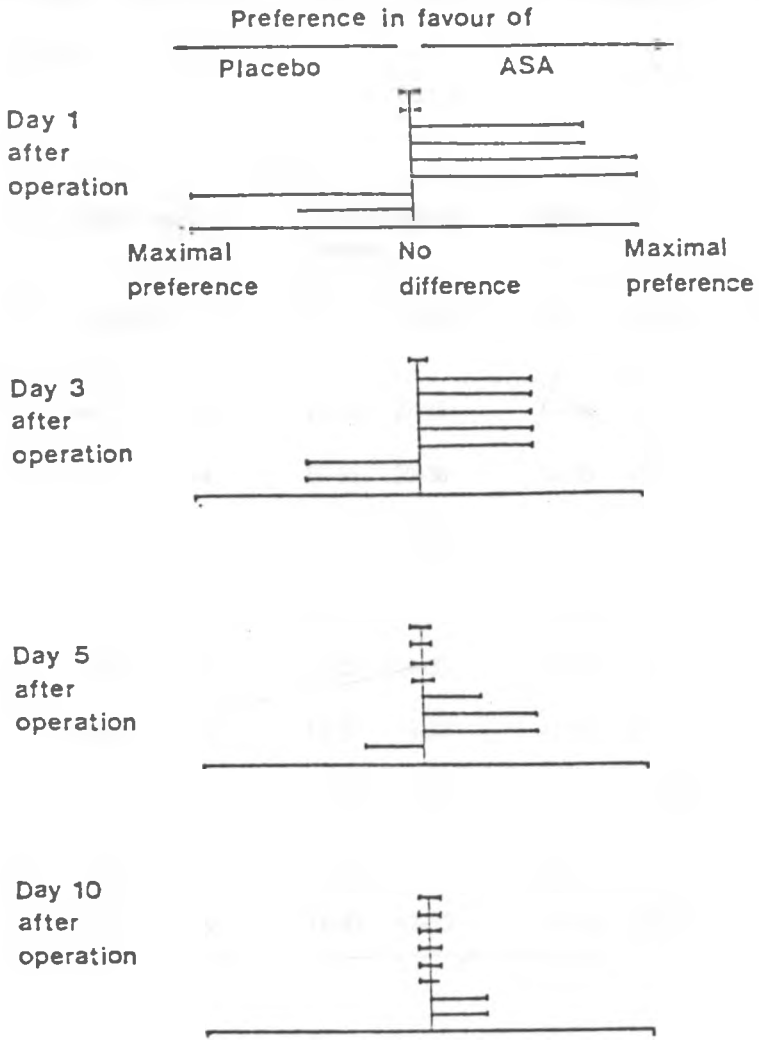


Fig. 14 Surgeon's preference for post-operative course assessed by a visual analogue scale after the 2nd operation in a placebo-controlled crossover trial with 1.5 g daily dosages of ASA tested against placebo in 8 dogs.

Table 9 Statistical evaluation of post-operative swelling measured by limb volumetry in a randomized placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given daily dosages of 0.5 g ASA. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Day after surgery	Mean limb volume (ml)			95% confidence interval		Range		P-values
	ASA	Placebo	Diff.	ASA	Placebo	ASA	Placebo	ASA vs Placebo
1	31	36	-5	25-37	27-45	17-40	21-49	0.18
2	25	29	-4	19-31	20-38	14-39	15-41	0.29
3	23	27	-4	17-29	18-36	13-34	15-47	0.18
4	19	24	-5	13-25	17-31	11-30	13-39	0.18
5	22	25	-3	15-29	19-31	12-35	14-37	0.13
6	21	23	-2	14-28	19-27	11-37	17-31	0.29
7	19	19	0	12-26	12-26	10-36	9-36	0.45
10	18	18	0	14-22	14-22	10-24	11-23	0.34
14	18	18	0	14-22	13-23	11-24	10-29	0.49

Table 10 Statistical evaluation of post-operative swelling measured by limb volumetry in a randomized placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given daily dosages of 1.5 g ASA. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Day after surgery	Mean limb volume (ml)			95% confidence interval		Range		P-values
	ASA	Placebo	Diff.	ASA	Placebo	ASA	Placebo	ASA vs Placebo
1	24	34	-10	17-31	29-39	14-35	24-43	0.03
2	26	35	-9	19-33	28-42	12-42	25-48	0.03
3	26	34	-8	21-31	27-41	16-38	22-46	0.03
4	22	32	-10	18-27	25-39	15-31	19-44	0.03
5	20	31	-11	15-25	24-38	13-29	20-42	0.02
6	19	28	-9	14-24	21-35	13-24	19-44	0.02
7	17	25	-8	12-22	20-30	10-26	17-36	0.02
10	15	21	-6	10-20	16-26	9-24	14-29	0.08
14	13	17	-4	8-18	15-19	6-20	11-23	0.08

Table 11 Statistical evaluation of post-operative pain assessed by a visual analogue scale in a randomized placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given daily dosages of 0.5 g ASA. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Day after surgery	Mean pain (mm)			95% confidence interval		Range		P-values
	ASA	Placebo	Diff.	ASA	Placebo	ASA	Placebo	ASA vs Placebo
1	26	26	0	18-34	16-36	10-35	10-45	0.46
2	15	22	-7	4-26	12-32	0-30	0-35	0.09
3	13	18	-5	4-22	7-29	0-25	0-45	0.21
4	10	14	-4	4-16	2-26	0-20	0-45	0.41
5	4	9	-5	0-9	0-19	0-10	0-30	0.36
6	3	3	0	0-7	0-10	0-15	0-25	0.43
7	2	3	-1	0-6	0-9	0-10	0-20	0.50
10	1	3	-2	0-4	0-8	0-10	0-15	0.30
14	1	0	1	0-3	-	0-5	0-0	0.20

Table 12 Statistical evaluation of post-operative pain assessed by a visual analogue scale in a randomized placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given daily dosages of 1.5 g ASA. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Day after surgery	Mean pain (mm)			95% confidence interval		Range		P-values
	ASA	Placebo	Diff.	ASA	Placebo	ASA	Placebo	ASA vs Placebo
1	49	59	-10	33-65	47-71	25-75	45-75	0.06
2	38	50	-12	24-52	41-59	20-60	35-65	0.01
3	26	38	-12	12-40	29-47	0-55	30-60	0.07
4	16	28	-12	0-32	21-35	0-50	15-40	0.06
5	14	21	-7	0-28	5-37	0-40	0-55	0.15
6	13	18	-5	0-27	6-30	0-45	0-35	0.22
7	12	13	-1	3-21	1-25	0-25	0-35	0.43
10	8	9	-1	0-17	0-18	0-30	0-25	0.39
14	4	4	0	0-11	0-11	0-25	0-20	0.43

Table 13 Statistical evaluation of post-operative limping assessed by a visual analogue scale in a randomized placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given daily dosages of 0.5 g ASA. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Day after surgery	Mean limping (mm)			95% confidence interval		Range		P-values
	ASA	Placebo	Diff.	ASA	Placebo	ASA	Placebo	ASA vs Placebo
1	28	33	-5	20-36	25-40	15-40	25-40	0.12
2	23	22	1	10-36	10-34	0-45	0-45	0.47
3	18	26	-8	3-33	12-40	0-40	0-45	0.15
4	13	17	-4	0-26	2-32	0-45	0-45	0.34
5	7	3	4	0-14	0-15	0-30	0-25	0.50
6	9	7	2	0-22	0-19	0-50	0-30	0.50
7	7	6	1	0-20	0-24	0-45	0-45	0.50
10	0	3	-3	-	0-15	0-0	0-25	0.50
14	0	0	0	-	-	0-0	0-0	-

Table 14 Statistical evaluation of post-operative limping assessed by a visual analogue scale in a randomized placebo-controlled crossover study with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given daily dosages of 1.5 g ASA. Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

Day after surgery	Mean limping (mm)			95% confidence interval		Range		P-values
	ASA	Placebo	Diff.	ASA	Placebo	ASA	Placebo	ASA vs Placebo
1	46	48	-2	23-69	28-68	0-100	15-80	0.39
2	39	43	-4	18-60	29-57	0-90	10-65	0.26
3	32	38	-6	9-55	22-54	0-90	5-70	0.22
4	25	30	-5	2-48	18-42	0-85	0-45	0.17
5	21	21	0	5-37	14-28	0-60	0-30	0.45
6	22	19	3	8-36	12-26	0-45	0-30	0.33
7	11	13	-2	2-20	6-20	0-25	0-25	0.29
10	6	7	-1	0-13	0-14	0-20	0-20	0.50
14	0	1	-1	-	0-3	0-0	0-10	0.50

Table 15 Serum alanine amino transferase values (Sigma-Frankel Units above 2) before and on the 3rd post-operative day in placebo-controlled crossover trials with bilateral orthopaedic surgery on the forelimbs of dogs, given daily dosages of 0.5 g ASA (8 dogs) or 1.5 g ASA (8 dogs). Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

	Serum alanine amino transferase (SFU/ml)												
	ASA 0.5 g			Placebo				ASA 1.5 g			Placebo		
Dog no.	Post-op.	Pre-op.	Diff.	Post-op.	Pre-op.	Diff.	Dog no.	Post-op.	Pre-op.	Diff.	Post-op.	Pre-op.	Diff.
31	6	15	-9	31	0	31	11	35	60	-25	10	13	-3
32	27	10	17	0	0	0	12	0	10	-10	29	10	19
33	0	4	-4	19	0	19	13	0	0	0	35	0	35
34	19	13	6	0	0	0	14	19	8	11	0	0	0
35	0	0	0	2	10	-8	15	10	2	8	0	0	0
36	0	4	-4	0	8	-8	16	31	33	-2	2	13	-11
37	0	19	-19	0	0	0	17	0	0	0	8	10	-2
38	0	8	-8	0	0	0	18	8	2	6	38	2	36
Mean	7	9	-2	7	2	5		13	14	-1	15	6	9

Normal range in dogs: 10 to 50 SFU (Cornelius, 1963).

Table 16 Blood urea nitrogen values before and on the 3rd post-operative day in placebo-controlled crossover trials with bilateral orthopaedic surgery on the forelimbs of dogs, given daily dosages of 0.5 g ASA (8 dogs) or 1.5 g ASA (8 dogs). Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

	Blood urea nitrogen (mg/100 ml)												
	ASA 0.5 g			Placebo				ASA 1.5 g			Placebo		
Dog no.	Post-op.	Pre-op.	Diff.	Post-op.	Pre-op.	Diff.	Dog no.	Post-op.	Pre-op.	Diff.	Post-op.	Pre-op.	Diff.
31	8	8	0	8	13	-5	11	24	12	12	18	32	-14
32	14	20	-6	11	13	-2	12	44	26	18	13	11	2
33	10	6	4	7	7	0	13	10	11	-1	12	12	0
34	5	7	-2	5	9	-4	14	23	15	8	25	23	2
35	7	8	-1	12	9	3	15	14	7	7	44	32	12
36	2	11	-9	7	15	-8	16	16	8	8	28	49	-21
37	11	9	2	13	10	3	17	40	15	25	23	10	13
38	11	7	4	7	8	-1	18	25	49	-24	23	10	13
Mean	9	10	-1	9	11	-2		25	18	7	23	22	1

Normal range in dogs: 10 to 30 mg/100 ml (Benjamin, 1974; Coles, 1974).

Table 17 Total serum protein values before and on the 3rd post-operative day in placebo-controlled crossover trials with bilateral orthopaedic surgery on the forelimbs of dogs, given daily dosages of 0.5 g ASA (8 dogs) or 1.5 g ASA (8 dogs). Medication started on the day of surgery and lasted for 4 days. The two operations were performed in an interval of 28 days.

	Total serum proteins (g/100 ml)												
	ASA 0.5 g			Placebo				ASA 1.5 g			Placebo		
Dog no.	Post-op.	Pre-op.	Diff.	Post-op.	Pre-op.	Diff.	Dog no.	Post-op.	Pre-op.	Diff.	Post-op.	Pre-op.	Diff.
31	5.4	6.0	0.6	5.9	6.2	-0.3	11	7.2	8.5	-1.3	6.5	6.6	-0.1
32	5.5	6.3	-0.8	6.3	7.2	-0.9	12	6.0	6.6	-0.6	7.5	8.5	-1.0
33	6.1	6.6	-0.5	5.8	6.4	-0.6	13	6.0	6.1	-0.1	7.4	7.9	-0.5
34	5.8	5.9	-0.1	6.3	7.5	-1.2	14	7.3	7.4	-0.1	6.4	6.3	0.1
35	7.0	7.0	0	6.0	7.2	-1.2	15	7.0	7.7	-0.7	6.6	6.6	0
36	6.1	6.4	-0.3	7.0	6.7	0.3	16	8.1	8.5	-0.4	7.9	7.8	0.1
37	6.4	6.6	-0.2	5.6	6.3	-0.7	17	5.1	6.2	-1.1	6.8	6.3	0.5
38	5.9	7.0	-1.1	6.8	7.4	-0.6	18	6.7	7.5	-0.8	6.8	8.0	-1.2
Mean	6.0	6.5	-0.5	6.2	6.9	-0.7		6.7	7.3	-0.6	7.0	7.3	-0.3

Normal range in dogs: 4.9 to 7.9 g/100 ml (Benjamin, 1974; Coles, 1974).

4.4 DISCUSSION

A daily dose of about 0.4 to 0.6 g ASA has been recommended for pain relief in dogs (Booth, 1982; Pugh, 1982). With a daily dose of 0.5g ASA it was not possible to demonstrate a significant reduction in either swelling or pain. With a daily dose of 1.5 g ASA, both swelling and pain were significantly reduced.

Skjelbred (1984) found that a "high" dose of ASA (4 g daily) reduced the post-operative swelling in humans, while a "low" dose (2 g daily) tended to increase the swelling. In the present study, it was not possible to demonstrate a pro-inflammatory effect when dogs were given a daily dose of 0.5 g ASA. It might be that this dose was too high to reveal a paradoxical effect of ASA at low doses.

A paradoxical effect of ASA on bleeding time has been described (O'Grady and Moncada, 1978; Rajah et al., 1978), and it is also possible that ASA might modulate an inflammatory reaction according to dose. In experimental inflammation in rats, Higgs et al. (1980), found the entry of leukocytes into inflammed areas to be potentiated by low doses of ASA, while the leukocyte accumulation was inhibited at higher doses which reduced the oedema. They suggested

that ASA at low doses may selectively inhibit the cyclo-oxygenase, thereby causing a diversion of arachidonic acid substrate to lipoxygenase pathway, resulting in increased production of chemotactic leukotrienes and increased inflammatory reaction. At a higher dose of ASA there might be a dual cyclo-oxygenase and lipoxygenase inhibition, and a reduced inflammatory reaction.

Increased swelling after surgery caused by ASA, may also partly depend on ASA-induced bleeding within tissues (Hepsö et al.. 1976; Skjelbred et al.. 1977).

As in the previous study with paracetamol it was difficult to produce a reliable and reproducible assessment of limping. A significant difference in limping compared to placebo could not be demonstrated, neither with the "low" nor with the "high" dose of ASA.

A review of the literature shows extensive studies on the adverse effects of ASA in man and animals (Prescott, 1979; Pugh, 1982; Ruckebusch and Toutain, 1983; Flower et al..1985). However, information on the influence of ASA on soft tissue/bone healing is lacking. According to the present results, 0.5 g or 1.5 g ASA daily, appear to have no significant influence on soft tissue/bone healing in dogs.

The results of the analyses of serum ALAT and

total protein levels on the 3rd post-operative day revealed essentially no difference between ASA and placebo medication. Although a slight increase in the post-operatve BUN levels was observed in 2 ASA-treated dogs in the "high" dose study, this appears not to be indicative of ASA-induced nephrotoxicity, for a similar observation was recorded in one placebo-treated dog. Thus, ASA does not seem to influence the liver and kidney function at the selected doses.

Since no drug-related adverse effects were observed, ASA seems to be a safe drug in dogs even in doses as high as 1.5 g daily.

In conclusion, although the swelling and pain assessments were somewhat lower with the daily dosage of 0.5 g ASA compared to placebo, the differences did not reach a level of significance. At a daily dosage of 1.5 g ASA, both the swelling and pain were significantly reduced. The results reported with paracetamol in Chapter 3, however, indicate that paracetamol is at least as effective as ASA in reducing pain and swelling associated with an acute post-traumatic inflammatory reaction.

CHAPTER FIVE

GENERAL CONCLUSIONS

1. In the model with bilateral limb surgery in dogs, a daily dosage of 1.5 g paracetamol reduced the post-operative swelling significantly. The reduction averaged 33% on the 3rd post-operative day as compared to placebo ($p = 0.02$). This finding agrees well with results obtained in oral surgery, and gives evidence to confirm that paracetamol may exert significant anti-inflammatory activity.

2. The method for pain assessment was rather crude and depended on the subjective assessment of the investigator. Nevertheless, the blind paired comparison to placebo administration, revealed that the mean pain estimate was nearly 50% lower on the 3rd post-operative day when the dogs were given paracetamol. It is noticeable, that with only 7 dogs, the paired comparison provided differences with a significance of 0.01.

3. It was found difficult to obtain reliable and reproducible limping assessments, and the paired comparison showed no consistent difference between paracetamol and placebo.

4. According to clinical examination of wound healing and radiological evaluation of the progress of fracture healing, there appeared to be no difference between paracetamol and placebo. The serum ALAT levels remained within the normal range in all dogs, except for one which had a moderate increase after the operation when paracetamol was given. The elevated level in this dog might indicate a certain liver affection. There were no gross clinical signs of any paracetamol-related toxicity.

5. A daily dosage of 1.5 g ASA, corresponding to the recommended dosage for anti-inflammatory activity in dogs (about 30 mg/kg T.I.D.), reduced the swelling significantly. Compared to placebo, the reduction averaged 24% on the 3rd post-operative day ($p = 0.03$).

6. The daily dose of 1.5 g ASA also resulted in lower pain estimates, but the difference to placebo was only significant on the 2nd post-operative day ($p = 0.01$). As for paracetamol, the limping assessments were inconsistent.

7. With a daily dosage of 0.5 g ASA, the post-operative swelling showed no significant difference to

placebo. It could be that the selected "low" dosage was too high to disclose a potential pro-inflammatory effect of ASA at low doses.

8. With a daily dosage of 0.5 g ASA, corresponding to the dosage recommended for pain relief in dogs (10 mg/kg T.I.D.), no significant pain relief could be demonstrated. Again the limping estimates were inconsistent.

9. The two trials with ASA in "high" and "low" dosage revealed no adverse effects of the drug with regard to wound or fracture healing. There were no gross clinical signs which were indicative of ASA-induced toxicity.

10. Final conclusion. At a daily dosage of 1.5 g, both ASA and paracetamol reduced post-operative swelling and pain significantly, and both drugs appeared to be well tolerated. The results indicate that paracetamol is at least as efficient as ASA in reducing pain and swelling associated with an acute post-traumatic inflammatory reaction.

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APPENDICES

Appendix 1 Details of patients, anaesthetic and surgical procedures in a crossover study with oral administration of 1.5 g paracetamol (PA) tested against placebo (PL) in 7 dogs.

Dog no.	Sex	Age (years)	Weight (kg)	Time (min)					
				Induction to incision		Incision to last suture		Induction to return of swallowing reflex	
				PA	PL	PA	PL	PA	PL
21	F	6	13	5	8	22	29	40	53
22	F	8	18	3	3	22	26	37	33
23	M	8	19	5	15	23	29	35	50
24	F	6	15	5	4	25	22	31	31
25	M	9	23	7	8	26	26	69	51
26	M	9	24	5	7	27	27	32	41
27	M	10	23	5	6	25	23	36	30
28	M	10	19	7	5	26	23	41	48
Mean		8	19	5	7	25	26	40	42

Appendix 2

PRINTED FORMS TO BE FILLED IN DURING THE COLLECTION OF DATA ON DIFFERENT PARAMETERS FOLLOWING BILATERAL ORTHOPAEDIC SURGERY IN DOGS

Dog no. .....

Age ..... Weight ..... Sex .....

Pre-operative blood sample: ..... day, / , ... day, /

Deworming: ..... day, / , ... day, /

Comments - blood/physical examination:

1st operation: ..... day, /

2nd operation: ..... day, /

	1st operation	2nd operation
Min from induction of anaesthesia to incision		
Min from incision to last suture		
Min from induction of anaesthesia to return of swallowing reflex		

Comments - 1st operation:

Comments - 2nd operation:

Post-operative blood sample:..... day, /

Appendix 2 (continued)

Swelling - Measurements

(ml water displaced)

	1st operation					2nd operation				
	Measurement				Diff.	Measurement				Diff.
	1	2	3	Mean	Pre-op.	1	2	3	Mean	Pre-op.
Pre-operatively										
Day 1 after										
Day 2 after										
Day 3 after										
Day 4 after										
Day 5 after										
Day 6 after										
Day 7 after										
Day 10 after										
Day 14 after										

Appendix 2 (continued)

Time	Date		Rectal temperature (°C)		Wound healing/ signs of infection	
	Op.1	Op.2	Op.1	Op.2	Op.1	Op.2
Day of op.						
Day 1 after						
Day 2 after						
Day 3 after						
Day 4 after						
Day 5 after						
Day 6 after						
Day 7 after						
Day 10 after						
Day 14 after						

Signs of infection

0 = no signs of infection

+ = signs of infection

Appendix 2 (continued)

Radiographs - dates

Post-operatively		2 weeks after		4 weeks after		6 weeks after		8 weeks after	
1st op.	2nd op.	1st op.	2nd op.	1st op.	2nd op.	1st op.	2nd op.	1st op.	2nd op.

Overall assessment by the surgeon of the course after the 2nd operation as compared to the 1st course.

Preference - VAS.- assessment

Day 1 after .....

Day 3 after .....

Day 5 after .....

Day 10 after .....

Maximal preference 1st course	No difference	Maximal preference 2nd course

Euthanized: ..... day, /

PAIN ASSESSMENTS - VAS

	1ST OPERATION		2ND OPERATION	
	No pain	Pain cannot be worse	No pain	Pain cannot be worse
Day 1 after	.....		.....	
Day 2 after	.....		.....	
Day 3 after	.....		.....	
Day 4 after	.....		.....	
Day 5 after	.....		.....	
Day 6 after	.....		.....	
Day 7 after	.....		.....	
Day 10 after	.....		.....	
Day 14 after	.....		.....	

LIMPING - VAS

	1ST OPERATION		2ND OPERATION	
	No limping	Limping cannot be worse	No limping	Limping cannot be worse
Day 1 after	.....	.....	.....	.....
Day 2 after	.....	.....	.....	.....
Day 3 after	.....	.....	.....	.....
Day 4 after	.....	.....	.....	.....
Day 5 after	.....	.....	.....	.....
Day 6 after	.....	.....	.....	.....
Day 7 after	.....	.....	.....	.....
Day 10 after	.....	.....	.....	.....
Day 14 after	.....	.....	.....	.....

Appendix 3 Individual values for post-operative swelling (ml) measured by limb volumetry in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given 0.5 g paracetamol per os three times daily for four days, starting in the morning of the day of surgery. The two operations were performed in an interval of 28 days.

Dog no.	Day 1			Day 2			Day 3		
	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	26	64	-38	24	63	-39	22	63	-41
22	36	43	-7	33	41	-8	31	39	-8
23	44	59	-15	39	55	-16	32	53	-21
24	30	37	-7	28	46	-18	26	45	-19
25	52	42	10	48	47	1	46	44	2
27	48	49	-1	40	55	-15	36	52	-16
28	52	61	-9	47	57	-10	42	59	-17

Dog no.	Day 4			Day 5			Day 6		
	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	23	61	-38	19	55	-36	18	54	-36
22	30	38	-8	27	35	-8	26	34	-8
23	27	54	-27	25	52	-27	23	51	-28
24	24	42	-18	21	40	-19	20	37	-17
25	42	35	-7	38	34	4	35	33	2
27	35	49	-14	30	46	-16	28	44	-16
28	41	56	-15	39	53	-14	37	52	-15

Appendix 3 (continued)

Dog no.	Day 7			Day 10			Day 14		
	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	16	49	-33	15	42	-27	13	34	-21
22	22	31	-9	20	23	-3	18	19	-1
23	20	46	-26	19	40	-21	17	32	-15
24	19	35	-16	18	28	-10	16	23	-7
25	34	32	2	28	25	3	24	25	-1
27	31	41	-10	26	34	-8	23	28	-5
28	34	49	-15	33	42	-9	30	36	-6

Appendix 4 Individual values for post-operative pain (mm) assessed by a visual analogue scale in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given 0.5 g paracetamol per os three times daily for four days, starting in the morning of the day of surgery. The two operations were performed in an interval of 28 days.

Dog	Day 1			Day 2			Day 3		
no.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	35	50	-15	25	55	-30	15	45	-30
22	40	45	-5	35	40	-5	25	30	-5
23	40	55	-15	30	30	0	25	55	-30
24	45	60	-15	40	55	-15	30	45	-15
25	30	40	-10	25	35	-10	20	25	-5
27	30	40	-10	25	30	-5	15	25	-10
28	25	45	-20	20	40	-20	0	25	-25

Dog	Day 4			Day 5			Day 6		
no.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	10	30	-20	0	25	-25	0	20	-20
22	20	25	-5	0	25	-25	25	20	5
23	15	30	-15	10	20	-10	5	20	-15
24	25	40	-15	20	35	-15	15	15	0
25	35	25	10	40	0	40	40	25	-15
27	10	20	-10	5	15	-10	5	10	-5
28	0	15	-15	0	0	0	0	0	0

Appendix 4 (continued)

Dog	Day 7			Day 10			Day 14		
no.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	0	10	-10	0	0	0	0	0	0
22	0	10	-10	0	5	-5	0	10	-10
23	0	10	-10	0	0	0	0	0	0
24	5	0	5	15	0	15	0	0	0
25	30	15	15	25	0	25	25	0	25
27	0	0	0	0	0	0	0	0	0
28	0	0	0	0	25	-25	0	20	-20

Appendix 5 Individual values for post-operative limping (mm) assessed by a visual analogue scale in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 7 dogs, given 0.5 g paracetamol per os three times daily for four days, starting in the morning of the day of surgery. The two operations were performed in an interval of 28 days.

Dog	Day 1			Day 2			Day 3		
no.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	35	25	-10	30	0	30	25	0	25
22	35	40	-5	25	35	-10	15	35	-20
23	35	40	-5	30	35	-5	20	25	-5
24	30	30	0	35	20	15	25	15	10
25	20	35	-15	30	45	-15	25	30	-5
27	55	40	15	30	30	0	25	20	5
28	30	45	-15	15	40	-25	10	30	-20

Dog	Day 4			Day 5			Day 6		
no.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	30	0	30	20	0	20	15	0	15
22	10	20	-10	0	25	-25	0	25	-25
23	15	20	-5	30	0	30	25	0	25
24	20	20	0	15	20	-5	20	15	5
25	0	25	-25	0	20	-20	45	15	30
27	20	25	-5	35	15	20	30	20	10
28	0	25	-25	0	20	-20	0	25	-25

Appendix 5 (continued)

Dog	Day 7			Day 10			Day 14		
no.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	25	0	25	10	0	10	0	0	0
22	0	0	0	0	25	-25	0	0	0
23	20	0	20	15	0	15	0	0	0
24	10	0	10	5	0	5	0	0	0
25	50	25	25	35	0	35	30	0	30
27	25	10	15	0	0	0	0	0	0
28	0	25	-25	0	0	0	0	0	0

Appendix 6 Individual and mean values for rectal temperature (°C) before and after two "identical" orthopaedic surgical interventions in a paired crossover trial in 7 dogs treated with 1.5 g daily doses of paracetamol and placebo.

Dog	Pre-operatively			Day 1			Day 2		
no.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	38.5	37.4	1.1	38.9	39.2	-0.3	38.1	38.1	0
22	38.0	37.5	0.5	38.5	38.7	-0.2	38.2	38.7	-0.5
23	37.0	37.6	-0.6	39.6	38.6	1.0	39.0	38.7	0.3
24	37.3	37.2	0.1	38.4	39.2	-0.8	38.9	39.1	-0.2
25	37.0	38.1	-1.1	39.2	38.8	0.4	39.0	39.0	0
27	37.9	37.0	0.9	39.2	39.1	0.1	38.5	39.3	-0.8
28	37.1	38.0	-0.9	39.4	38.0	1.4	38.6	39.3	-0.7
Mean	37.5	37.5	0	39.0	38.8	0.2	38.6	38.9	-0.3

Dog	Day 3			Day 4			Day 5		
no.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	39.1	38.4	0.7	39.3	38.2	1.1	38.1	37.8	0.3
22	37.7	39.1	-1.4	37.8	39.3	-1.5	38.1	38.1	0
23	39.2	38.5	0.7	39.3	38.3	1.0	37.0	37.2	-0.2
24	38.8	39.4	-0.6	38.5	39.3	-0.8	37.5	37.7	-0.2
25	39.1	38.3	0.8	36.0	37.7	-1.7	35.7	37.7	-2.0
27	38.6	39.3	-0.7	37.8	38.4	-0.6	37.7	38.0	-0.3
28	38.9	39.3	-0.4	36.6	39.0	-2.4	35.9	38.3	-2.4
Mean	38.8	38.9	-0.1	37.9	38.6	-0.7	37.1	37.8	-0.7

- temperature $\geq$ 39.3°C.

Appendix 6 (continued)

Dog	Day 6			Day 7		
no.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	38.0	37.9	0.1	39.3	37.3	2.0
22	38.0	37.7	0.3	38.0	39.1	-1.1
23	37.7	37.3	0.4	39.4	36.9	2.5
24	37.6	37.2	0.4	37.6	39.4	-1.8
25	39.3	37.7	1.6	39.5	36.5	3.0
27	37.7	39.4	-1.7	37.5	38.8	-1.3
28	36.4	36.0	0.4	37.3	39.0	-1.7
Mean	37.8	37.6	0.2	38.3	38.1	0.2

Dog	Day 10			Day 14		
no.	Para-cetamol	Placebo	Diff.	Para-cetamol	Placebo	Diff.
21	37.3	38.0	-0.7	39.0	38.6	0.4
22	38.0	37.9	0.1	38.4	38.6	-0.2
23	36.8	37.0	0.2	39.4	37.0	2.4
24	38.0	37.5	0.5	37.8	39.0	-1.2
25	39.4	38.0	1.4	38.9	37.3	1.6
27	37.9	38.8	-0.9	37.8	38.6	-0.8
28	36.0	38.8	2.8	37.3	38.7	-1.4
Mean	37.6	38.0	-0.4	38.4	38.3	0.1

- temperature $\geq$ 39.3°C.

Appendix 7 Radiographic evaluations of bone healing in a crossover trial 2,4,6 and 8 weeks after orthopaedic surgery with oral administration of 1.5 g paracetamol (PA) tested against placebo (PL) in 7 dogs.

Dog no.	Radiographic union		Degree of callus formation		Infection/ reaction to implant	
	PA	PL	PA	PL	PA	PL
2 weeks						
21	++	++	++	0	0	0
22	0	++	0	0	0	0
23	+	++	0	0	0	0
24	++	++	+	+	0	+
25	++	+	0	+	0	0
27	++	0	0	+	0	+
28	++	+	+	0	+	0
4 weeks						
21	++	+++	++	++	0	+
22	+	++	+	0	+	+
23	+	++	+	+	++	+
24	++	+++	++	++	+	+
25	++	++	++	++	+++	++
27	+++	++	++	+	++	++
28	++	+	++	+	++	+

0 = minimum; ++++ = maximum.

Appendix 7 (continued)

Dog no.	Radiographic union		Degree of callus formation		Infection/ reaction to implant	
	PA	PL	PA	PL	PA	PL
6 weeks						
21	+++	+++	++	+++	++	+
22	++	++	+	+	+	++
23	+	++	+	+++	+++	++
24	+++	+++	+++	++	+	+
25	++	++	++	+++	+++	+++
27	+++	++	+++	++	+++	++
28	++	++	++	++	++	++
8 weeks						
21	+++	+++	+++	+++	+++	+++
22	+++	++	+	++	+	++
23	+	++	++	++	+++	++
24	+++	+++	+++	++	+	+
25	++	++	++	+++	+++	+++
27	+++	++	+++	++	+++	++
28	++	++	++	++	+++	++++

0 = minimum; ++++ = maximum.

Appendix 8 Details of patients, anaesthetic and surgical procedures in a crossover study with oral administration of 0.5 g ASA tested against placebo (PL) in 8 dogs.

Dog no.	Sex	Age (years)	Weight (kg)	Time (min)					
				Induction to incision		Incision to last suture		Induction to return of swallowing reflex	
				ASA	PL	ASA	PL	ASA	PL
31	F	6	12	7	10	24	23	38	40
32	M	9	17	10	4	28	27	54	33
33	F	5	13	5	3	26	22	31	40
34	F	8	17	7	5	23	25	35	35
35	F	10	17	5	9	25	22	37	42
36	F	9	17	7	6	24	25	42	44
37	F	6	11	3	6	20	25	41	43
38	F	6	17	7	5	27	25	41	31
Mean		7	15	6	6	25	24	40	39

Appendix 9 Details of patients, anaesthetic and surgical procedures in a crossover study with oral administration of 1.5 g ASA tested against placebo (PL) in 8 dogs.

Dog no.	Sex	Age (years)	Weight (kg)	Time (min)					
				Induction to incision		Incision to last suture		Induction to return of swallowing reflex	
				ASA	PL	ASA	PL	ASA	PL
11	M	9	19	15	7	36	34	58	39
12	M	8	17	7	6	28	28	143	36
13	F	6	16	11	8	20	35	88	51
14	M	8	22	9	10	29	23	85	42
15	F	6	14	11	5	25	21	58	38
16	F	8	19	7	5	24	18	35	37
17	M	9	21	7	7	22	39	37	48
18	M	7	17	4	6	22	36	40	46
Mean		8	18	9	7	26	29	68	42

Appendix 10 Individual values for post-operative swelling (ml) measured by limb volumetry in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given 0.17 g ASA per os three times daily for four days, starting in the morning of the day of surgery. The two operations were performed in an interval of 28 days.

Dog	Day 1			Day 2			Day 3		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	29	43	-14	25	37	-12	19	31	-12
32	23	27	-4	22	23	-1	16	22	-6
33	35	44	-9	23	38	-15	27	47	-20
34	32	36	-4	39	29	10	34	24	10
35	31	49	-18	24	29	-5	22	26	-4
36	39	28	11	24	19	5	21	19	2
37	17	43	-26	14	41	-27	13	35	-22
38	40	21	21	32	15	17	32	15	17

Dog	Day 4			Day 5			Day 6		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	19	24	-5	18	23	-5	20	19	1
32	11	17	-6	12	25	-13	11	25	-14
33	25	39	-14	29	37	-8	23	31	-8
34	30	23	7	35	31	4	37	22	15
35	18	16	2	22	19	3	16	25	-9
36	16	25	-9	18	23	-5	23	17	6
37	11	31	-20	12	29	-17	11	27	-16
38	25	13	12	27	14	13	26	18	8

Appendix 10 (continued)

Dog	Day 7			Day 10			Day 14		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	18	14	4	21	17	4	19	15	4
32	10	17	-7	10	18	-8	11	19	-8
33	17	36	-19	16	23	-7	19	23	-4
34	36	14	22	24	22	2	23	29	-6
35	25	12	13	16	11	5	24	10	14
36	12	22	-10	17	20	3	17	20	-3
37	12	25	13	14	20	-6	12	18	-6
38	25	9	16	23	16	7	19	13	6

Appendix 11 Individual values for post-operative swelling (ml) measured by limb volumetry in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given 0.5 g ASA per os three times daily for four days, starting in the morning of the day of surgery. The two operations were performed in an interval of 28 days.

Dog	Day 1			Day 2			Day 3		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	27	43	-16	29	48	-19	28	45	-17
12	14	29	-15	12	25	-13	16	22	-6
13	16	36	-20	26	38	-12	24	40	-16
14	34	28	-6	31	30	1	29	27	2
15	22	34	-12	19	28	-9	18	30	-12
16	24	27	-3	25	31	-6	23	38	-15
17	20	42	-22	27	43	-16	29	46	-17
18	35	32	3	42	34	8	38	27	11

Dog	Day 4			Day 5			Day 6		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	23	39	-16	21	37	-16	18	32	-14
12	15	19	-4	13	20	-7	2	19	-17
13	19	35	-16	18	31	-13	16	29	-13
14	28	26	2	26	24	2	26	21	5
15	16	34	-18	14	32	-18	13	25	-12
16	20	37	-17	19	36	-17	16	34	-18
17	25	44	-19	23	42	-19	20	44	-24
18	31	25	6	29	24	5	27	22	5

Appendix 11 (continued)

Dog	Day 7			Day 10			Day 14		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	16	29	-13	16	24	-8	15	17	-2
12	10	17	-7	9	16	-7	6	14	-8
13	13	27	-14	12	21	-9	10	20	-10
14	25	19	6	23	14	9	19	11	8
15	11	20	-9	10	17	-7	9	13	-4
16	14	30	-16	11	27	-16	10	20	-10
17	18	36	-18	14	29	-15	12	23	-11
18	26	20	6	24	17	7	20	15	5

Appendix 12 Individual values for post-operative pain (mm) assessed by a visual analogue scale in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given 0.17 g ASA per os three times daily for four days, starting in the morning of the day of surgery. The two operations were performed in an interval of 28 days.

Dog	Day 1			Day 2			Day 3		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	35	25	10	20	25	-5	15	15	0
32	35	25	10	25	30	-5	5	45	-40
33	25	45	-20	30	35	-5	20	25	-5
34	35	25	10	25	25	0	25	0	25
35	25	10	15	20	0	20	15	15	0
36	10	20	-10	0	15	-15	0	10	-10
37	20	35	-15	0	25	-25	20	20	0
38	25	25	0	0	20	-20	0	15	-15

Dog	Day 4			Day 5			Day 6		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	10	15	-5	10	5	5	5	0	5
32	20	25	-5	0	25	-25	0	25	-25
33	10	15	-5	0	5	-5	0	0	0
34	15	0	15	5	0	5	5	0	5
35	10	0	10	10	5	5	15	0	15
36	0	5	-5	0	5	-5	0	0	0
37	15	10	5	10	0	10	0	0	0
38	0	45	-45	0	30	-30	0	0	0

Appendix 12 (continued)

Dog	Day 7			Day 10			Day 14		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	0	0	0	0	15	-15	0	0	0
32	0	20	-20	0	10	-10	0	0	0
33	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0
35	10	0	10	10	0	10	5	0	5
36	0	0	0	0	0	0	0	0	0
37	5	0	5	0	0	0	5	0	5
38	0	0	0	0	0	0	0	0	0

Appendix 13 Individual values for post-operative pain (mm) assessed by a visual analogue scale in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given 0.5 g ASA per os three times daily for four days, starting in the morning of the day of surgery. The two operations were performed in an interval of 28 days.

Dog	Day 1			Day 2			Day 3		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	25	45	-20	20	35	-15	0	30	-30
12	65	50	15	50	45	5	45	30	15
13	50	75	-25	25	50	-25	15	30	-15
14	25	45	-20	20	40	-20	15	35	-20
15	60	70	-10	45	60	-15	35	50	-15
16	55	75	-20	50	65	-15	30	60	-30
17	35	60	-25	30	40	-10	15	35	-20
18	75	55	20	60	65	-5	55	35	20

Dog	Day 4			Day 5			Day 6		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	0	20	-20	0	10	-10	0	15	-15
12	35	15	20	30	10	20	25	0	25
13	10	30	-20	0	35	-35	0	25	-25
14	10	25	-15	0	15	-15	0	20	-20
15	0	30	-30	20	10	10	10	15	-5
16	25	40	-15	20	35	-15	20	30	-10
17	0	20	-20	0	0	0	0	0	0
18	50	40	10	40	55	-15	45	35	10

Appendix 13 (continued)

Dog	Day 7			Day 10			Day 14		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	0	15	-15	0	15	-15	0	10	-10
12	20	0	20	10	0	10	5	0	5
13	0	20	-20	0	15	-15	0	5	-5
14	15	10	5	10	0	10	0	0	0
15	15	0	15	0	0	0	0	0	0
16	20	25	-5	15	15	0	0	0	0
17	0	0	0	0	0	0	0	0	0
18	25	35	-10	30	25	5	25	20	5

Appendix 14 Individual values for post-operative limping (mm) assessed by a visual analogue scale in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given 0.17 g ASA per os three times daily for four days, starting in the morning of the day of surgery. The two operations were performed in an interval of 28 days.

Dog	Day 1			Day 2			Day 3		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	30	25	5	25	15	-10	20	15	5
32	40	25	15	40	20	20	25	45	-20
33	40	40	0	20	20	0	0	25	-25
34	30	40	-10	20	40	-20	25	45	-20
35	20	25	-5	45	0	45	40	15	25
36	15	35	-20	0	10	-10	0	0	0
37	20	35	-15	10	25	-15	0	25	-25
38	25	40	-15	20	45	-25	35	40	-5

Dog	Day 4			Day 5			Day 6		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	0	20	-20	0	0	0	0	0	0
32	35	40	-5	25	25	0	50	30	20
33	0	0	0	0	0	0	0	0	0
34	0	45	-45	0	0	0	0	0	0
35	20	0	20	0	0	0	0	25	-25
36	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0
38	45	30	15	30	0	30	25	0	25

Appendix 14 (continued)

Dog	Day 7			Day 10			Day 14		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	0	0	0	0	0	0	0	0	0
32	45	45	0	0	25	-25	0	0	0
33	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0
37	0	0	0	0	0	0	0	0	0
38	10	0	10	0	0	0	0	0	0

Appendix 15 Individual values for post-operative limping (mm) assessed by a visual analogue scale in a placebo-controlled crossover trial with bilateral orthopaedic surgery on the forelimbs of 8 dogs, given 0.5 g ASA *per os* three times daily for four days, starting in the morning of the day of surgery. The two operations were performed in an interval of 28 days.

Dog	Day 1			Day 2			Day 3		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	60	45	15	50	40	10	40	35	5
12	35	75	-40	25	50	-25	0	70	-70
13	45	60	-15	45	55	-10	40	50	-10
14	0	15	-15	0	10	-10	0	5	-5
15	60	20	40	50	40	10	45	35	10
16	35	80	-45	30	65	-35	25	50	-25
17	30	50	-20	20	45	-25	15	30	-15
18	100	40	60	90	35	55	90	25	65

Dog	Day 4			Day 5			Day 6		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	30	35	-5	30	25	5	40	20	20
12	0	45	-45	0	30	-30	0	20	-20
13	30	40	-10	25	25	0	25	30	-5
14	0	0	0	0	0	0	0	0	0
15	25	25	0	10	20	-10	20	15	5
16	20	30	-10	15	20	-5	25	25	0
17	10	25	-15	25	20	5	20	20	0
18	85	40	45	60	30	30	45	25	20

Appendix 15 (continued)

Dog	Day 7			Day 10			Day 14		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	25	20	5	10	0	10	0	0	0
12	0	0	0	0	0	0	0	0	0
13	10	15	-5	5	10	-5	0	0	0
14	0	0	0	0	0	0	0	0	0
15	20	10	10	10	10	0	0	0	0
16	5	20	-15	0	20	-20	0	0	0
17	0	10	-10	0	0	0	0	0	0
18	25	25	0	20	15	5	0	10	-10

Appendix 16 Individual and mean values for rectal temperature (°C) before and after two "identical" orthopaedic surgical interventions in a paired cross-over trial in 8 dogs treated with 0.5 g daily doses of ASA and placebo.

Dog	Pre-operatively			Day 1			Day 2		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	38.0	37.8	0.2	39.7	38.3	1.4	39.0	38.1	0.9
32	38.4	38.5	-0.1	37.5	40.0	-2.5	37.7	38.5	-0.8
33	37.7	37.5	0.2	39.0	37.8	1.2	38.5	37.8	0.7
34	38.0	38.1	-0.1	37.7	39.2	-1.5	37.6	38.7	-1.1
35	38.2	37.7	0.5	38.4	37.2	1.2	38.2	37.3	0.9
36	37.5	38.0	-0.5	37.7	38.8	-1.1	37.8	38.5	-0.7
37	38.0	38.1	-0.1	38.9	38.8	0.1	38.3	37.8	0.5
38	38.6	38.5	0.1	38.3	39.8	-1.5	38.4	39.5	1.1
Mean	38.1	38.0	0.1	38.4	38.7	-0.3	38.2	38.3	-0.1

Dog	Day 3			Day 4			Day 5		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	39.2	37.7	1.5	38.7	37.8	0.9	38.9	37.5	1.4
32	37.6	38.7	-1.1	36.9	38.0	-1.1	36.7	38.3	-1.6
33	38.5	37.9	0.6	38.9	37.7	1.2	38.4	37.6	0.8
34	37.8	38.7	-0.9	37.9	38.6	-0.7	37.8	38.8	-1.0
35	38.5	36.8	1.7	38.6	37.2	1.4	38.5	37.4	1.1
36	37.7	38.8	-1.1	36.8	38.5	-1.7	36.9	38.6	-1.7
37	39.0	36.9	2.1	39.0	37.6	1.4	38.6	37.4	1.2
38	38.8	39.6	-0.8	37.8	39.7	-1.9	38.5	39.7	1.2
Mean	38.4	38.1	0.3	38.1	38.1	0	38.0	38.2	-0.2

-temperature $\geqslant$ 39.3°C.

Appendix 16 (continued)

Dog	Day 6			Day 7		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	38.0	36.8	-1.2	38.7	38.2	0.5
32	36.2	38.6	-2.4	37.9	38.7	-0.8
33	37.9	37.2	0.7	38.4	38.7	-0.3
34	37.1	38.2	-1.1	38.2	38.4	-0.2
35	38.3	38.1	0.2	37.5	36.4	1.1
36	38.3	38.4	-0.1	37.2	38.2	-1.0
37	39.2	39.6	-0.4	38.6	37.7	0.9
38	39.0	39.0	0	38.5	39.0	-0.5
Mean	38.0	38.2	-0.2	38.1	38.2	-0.1

Dog	Day 10			Day 14		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
31	38.5	37.8	0.7	38.7	36.2	2.5
32	36.0	37.9	-1.9	35.9	38.6	-2.7
33	38.5	37.3	1.2	38.5	37.9	0.6
34	37.9	38.6	-0.7	37.1	37.9	-0.8
35	37.4	36.2	1.2	37.7	37.8	-0.1
36	36.5	38.4	-1.9	37.6	38.6	-1.0
37	38.6	38.2	0.4	38.4	38.8	-0.4
38	38.1	38.1	0	38.8	38.2	0.6
Mean	37.7	37.8	-0.1	37.8	38.0	-0.2

- temperature $\geq$ 39.3°C.

Appendix 17 Individual and mean values for rectal temperature (°C) before and after two "identical" orthopaedic surgical interventions in a paired cross-over trial in 8 dogs treated with 1.5 g daily doses of ASA and placebo.

Dog	Pre-operatively			Day 1			Day 2		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	37.8	37.0	0.8	38.2	37.8	0.4	38.4	37.1	1.3
12	37.4	38.6	-1.2	38.2	39.5	-1.3	37.9	39.0	-1.1
13	37.6	37.9	-0.3	38.4	38.0	0.4	38.0	38.0	0
14	38.0	36.6	1.4	37.9	38.4	-0.5	38.0	37.5	0.5
15	39.3	37.4	1.9	38.5	38.2	0.3	38.6	38.5	0.1
16	37.6	36.5	1.1	38.0	37.6	0.4	38.3	37.5	0.8
17	38.2	37.2	1.0	37.5	38.0	0.5	37.0	38.0	-1.0
18	36.6	37.3	-0.7	37.9	38.2	-0.3	37.4	38.1	-0.7
Mean	37.8	37.3	0.5	38.1	38.2	-0.1	38.0	38.0	0

Dog	Day 3			Day 4			Day 5		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	38.3	37.7	0.6	37.9	37.2	0.7	38.0	37.8	0.2
12	37.6	39.2	-1.6	37.8	39.1	-1.3	37.9	38.5	-0.6
13	38.2	38.5	-0.3	38.5	38.0	0.5	38.3	38.5	-0.2
14	38.2	37.7	0.5	38.2	37.4	0.8	37.8	38.0	-0.2
15	38.4	38.3	0.1	38.9	38.0	0.9	40.1	39.1	1.0
16	38.4	37.4	1.0	38.1	37.5	0.6	38.0	39.0	-1.0
17	36.6	38.0	-1.4	37.8	37.1	0.7	39.0	37.5	1.5
18	37.3	38.2	-0.9	37.7	38.3	-0.6	38.0	38.2	0.2
Mean	37.9	38.1	-0.2	38.1	37.8	0.3	38.4	38.3	0.1

- temperature $\geqslant$ 39.3°C.

Appendix 17 (continued)

Dog	Day 6			Day 7		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	37.6	37.0	0.6	37.3	37.7	-0.4
12	38.0	38.0	0	37.8	38.2	-0.4
13	39.5	38.2	1.3	38.8	38.2	0.6
14	38.3	37.6	0.7	38.3	37.1	1.2
15	40.1	38.7	1.4	39.7	37.6	2.1
16	38.1	38.1	0	38.0	38.2	-0.2
17	37.1	37.7	-0.6	38.2	37.4	0.8
18	37.8	38.3	-0.5	37.5	38.0	-0.5
Mean	38.3	38.0	0.3	38.2	37.8	0.4

Dog	Day 10			Day 14		
no.	ASA	Placebo	Diff.	ASA	Placebo	Diff.
11	37.7	37.0	0.7	38.0	37.6	0.4
12	38.0	38.9	-0.9	38.8	40.3	-1.5
13	38.0	38.5	-0.5	38.4	38.0	0.4
14	39.0	37.4	1.6	38.9	37.5	1.4
15	38.8	37.4	1.4	38.2	38.5	-0.3
16	38.2	37.7	0.5	37.0	38.3	-1.3
17	36.0	37.4	-1.4	37.7	37.6	0.1
18	37.0	38.2	-1.2	37.5	38.3	-0.8
Mean	37.8	37.8	0	38.1	38.3	-0.2

- temperature $\geqslant$ 39.3°C.

Appendix 18 Radiographic evaluations of bone healing in a crossover trial 2,4,6 and 8 weeks after orthopaedic surgery with oral administration of 0.5 g ASA tested against placebo (PL) in 8 dogs.

Dog no.	Radiographic union		Degree of callus formation		Infection/ reaction to implant	
	ASA	PL	ASA	PL	ASA	PL
2 weeks						
31	+++	+++	+	++	0	0
32	++	+	+	0	0	0
33	++	++	+	+	0	0
34	+	++	+	+	0	0
35	+	+	0	0	0	+
36	+	+	0	0	0	0
37	++	+	+	+	+	+
38	++	++	+	+	0	0
4 weeks						
31	+++	+++	+	++	0	0
32	++	++	+	++	+	+
33	++	++	++	+	+	+
34	++	++	++	+	+	++
35	+	+	+	0	+	+
36	+	+	+	+	+	++
37	++	+	+	+	+	+
38	++	++	++	++	++	+

0 = minimum; ++++ = maximum.

Appendix 18 (continued)

Dog no.	Radiographic union		Degree of callus formation		Infection/ reaction to implant	
	ASA	PL	ASA	PL	ASA	PL
6 weeks						
31	+++	+++	++	+++	+	+
32	+++	++	++	++	++	+
33	+++	+++	+++	+	++	+
34	++	+++	++	++	+	+++
35	++	+	++	+	+++	+
36	++	++	++	+	++	+++
37	++	++	+	++	+	+
38	++	++	++	+++	+++	+
8 weeks						
31	+++	+++	+++	+++	++	++
32	+++	++	++	++	+++	++
33	++	++	++	++	++	++
34	+++	+++	+++	+++	++	+++
35	++	++	++	++	+++	+++
36	++	++	++	++	++	+++
37	++	++	++	++	++	++
38	++	++	++	+++	+++	++

0 = minimum; ++++ = maximum.

Appendix 19 Radiographic evaluations of bone healing in a crossover trial 2,4,6, and 8 weeks after orthopaedic surgery with oral administration of 1.5 g ASA tested against placebo (PL) in 8 dogs.

Dog no.	Radiographic union		Degree of callus formation		Infection/ reaction to implant	
	ASA	PL	ASA	PL	ASA	PL
2 weeks						
11	++	++	+	+	+	+
12	+	+	0	0	0	0
13	++	+	0	0	0	0
14	++	+	+	0	0	0
15	++	+	+	+	+	+
16	+	+	+	+	+	0
17	+	+	+	+	+	+
18	++	++	+	+	0	+
4 weeks						
11	++	++	++	+	++	+
12	+	+	+	+	+	+
13	++	++	+	+	+	+
14	++	+	+	+	0	+
15	++	++	++	++	++	++
16	+	+	+	+	++	+
17	+	++	+	+	+	++
18	++	++	+	+	0	+

0 = minimum; ++++ = maximum.

Appendix 19 (continued)

Dog no.	Radiographic union		Degree of callus formation		Infection/ reaction to implant	
	ASA	PL	ASA	PL	ASA	PL
6 weeks						
11	+++	+++	++	+++	+	+
12	+++	++	++	++	++	+
13	+++	+++	+++	+	++	+
14	++	+++	++	++	+	+++
15	++	+	++	+	+++	+
16	++	++	++	+	++	+++
17	++	++	+	++	+	+
18	++	++	++	+++	+++	+
8 weeks						
11	+++	+++	+++	+++	++	++
12	+++	++	++	++	+++	++
13	++	++	++	++	++	++
14	++	+++	+++	+++	++	+++
15	++	++	++	++	+++	+++
16	++	++	++	++	++	+++
17	++	++	++	++	++	++
18	++	++	++	++	+++	++

0 = minimum; ++++ = maximum.