THE EFFICACY OF TOPICAL IBUPROFEN IN AN INFLAMMATORY MODEL; DELAYED ONSET MUSCLE SORENESS

By
Rana L. Mack

B.P.E University of British Columbia. 1992

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE
REQUIREMENTS FOR THE DEGREE OF
MASTER OF HUMAN KINETICS

in

THE FACULTY OF GRADUATE STUDIES
(School of Human Kinetics)

We accept this theses as conforming
to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA

AUGUST, 1995

In presenting this thesis in partial fulfilment of the requirements for an advanced degree at the University of British Columbia, I agree that the Library shall make it freely available for reference and study. I further agree that permission for extensive copying of this thesis for scholarly purposes may be granted by the head of my department or by his or her representatives. It is understood that copying or publication of this thesis for financial gain shall not be allowed without my written permission.

School
~~Department~~ of Human Kinetics

The University of British Columbia
Vancouver, Canada

Date Sept 14, 1995

ABSTRACT

The purpose of this study was two fold: 1) to determine the effectiveness of topical ibuprofen versus oral ibuprofen and a placebo in the treatment of an inflammatory condition, delayed onset muscle soreness and 2) to determine the ibuprofen plasma concentrations following topical administration as compared to orally. Thirty female subjects were randomly assigned to either an oral ibuprofen treatment group, a topical ibuprofen treatment group, or a placebo group. The subjects then underwent an eccentric exercise protocol used to induce delayed onset muscle soreness. Muscle soreness and eccentric torque were quantified before exercise, immediately post exercise, at 24 hours, 48 hours, 72 hours, and 144 hours after the exercise. All groups displayed peak soreness at 48 hours, the placebo group marked the highest average (60.95mm), the oral group had an average of 54.55mm while the topical group had the lowest average at 50.35mm. There was a marked drop in eccentric torque following the exercise which then returned to baseline values at 72 hours. No significant difference was found between groups for either measure. This data indicates that neither oral nor topical ibuprofen were effective in relieving pain or in restoring strength in this model of inflammation, DOMS. However, a significant difference in plasma ibuprofen concentrations between type of drug administration was found ($p=0.033$). To determine plasma concentrations a five subject cross-over design was used. Subjects participated in the eccentric exercise bout with either their right or left arm. Seven days of treatment with either oral or topical ibuprofen was then initiated. A seven day

washout period followed. The exercise protocol was repeated using the other arm and subsequent treatment with the alternative ibuprofen. During both treatment periods four blood samples were taken: prior to the onset of treatment, on day 3, day 5, and day 7of treatment. The fact that minimal amounts of ibuprofen enter the systemic system after topical administration leads researchers to believe associated side effects would be decreased drastically. Research should continue into the efficacy of topical ibuprofen in various other models of inflammation.

TABLE OF CONTENTS

Abstract ii

Table of Contents iv

List of Tables vii

List of Figures viii

Acknowledgements ix

Introduction

Statement of the problem 1

Purpose 3

Hypothesis 3

Review of literature

Inflammation 4

Nonsteroid Anti-inflammatory Drugs 6

Topical Application of NSAIDs 14

Skin 18

Delayed Onset Muscle Soreness 24

Pilot Work 28

Methodology

Part I: Ibuprofen and DOMS 30

Subjects 30

Study Design 31

Exercise Protocol 32

Data Collection Procedures / Measurements 33

Gel Content 35

Hypothesis 36

Statistical Analysis 36

Part II: Blood Ibuprofen Levels 36

Subjects 36

Study Design 36

Data Collection Procedures 37

Blood Analysis 38

Hypothesis 39

Statistical Analysis 39

Limitations and Delimitations 39

Results

Part I: Ibuprofen and DOMS 41

Part II: Blood Ibuprofen Levels 48

Discussion 54

Summary

Summary of Study 60

Conclusions 61

Recommendations 62

References 65

Appendix 73

I Individual Clinical Characteristics of Subjects 73

II Individual Pain Data - Part I 75

III Individual Torque Data - Part I 80

IV Visual Analogue Scale (VAS) 85

V Individual Blood Data - Part II 86

LIST OF TABLES

1. NSAIDs hypothesized treatments 2
2. Concentration of topical ibuprofen 17
3. Ideal drug properties 23
4. Average Clinical Characteristics of Subjects in Part I 41
5. Average Clinical Characteristics of Subjects in Part II 42
6. Summary of Perceived Soreness for the 3 Groups 42
7. Perceived Pain - ANOVA Summary 45
8. Summary of Torque for the 3 Groups 45
9. Torque - ANOVA Summary 48

LIST OF FIGURES

1. Metabolism of Phospholipid and arachidonic acid 7
2. Elevated Intracellular calcium concentrates and its associated effects 27
3. Efficacy of Ibuprofen vs a Placebo in DOMS 29
4. Chemical structure of Ibuprofen 35
5. Time course of Pain for Delayed Onset Muscle Soreness - Average perceived Soreness 44
7. Torque Data - Average Torque 47

ACKNOWLEDGEMENTS

I would like to thank my committee members, Jack Taunton, Don McKenzie, and Doug Clement for all their help with this research. Most especially I would like to thank Doug for his patience and guidance over the past two years.

I would also like to thank: Nancy McLaren for showing me the ins and outs around the clinic; Diana Jespersen for helping with all the blood work; and my friend Nicky Dunlop who preserved my sanity by saving me from computer nightmares and viruses. And finally thanks to my husband, Michael, who put up with me and helped me get through these two years.

Chapter 1

INTRODUCTION

STATEMENT OF PROBLEM

The therapeutic effects of aspirin-like compounds have been utilized for over two thousand years. In the treatments of ailments like cramps, toothaches, and arthritis, willowbark extracts were prescribed. The active components of willowbark, salicin and salicylic acid, were later developed into aspirin by Bayer (1894). From aspirin, a family of drugs now known as non-steroidal anti-inflammatory drugs (NSAIDs) have been developed. Today, these drugs have become one of the most commonly prescribed drugs by physicians.

NSAIDs have become an integral part of the recovery process in sport. NSAIDs are commonly used in combination with other physical modalities such as cryotherapy, rehabilitation exercises, and electrotherapy, with the purpose of returning the athlete to competition as quickly as possible. The hypothesis behind NSAID use is that decreased pain and inflammation will allow earlier movement. In turn, early mobilization is thought to result in earlier restoration of the mechanical properties of the muscle and less necrosis of muscle tissue (Almekinders, 1993). Table 1 lists the goals of NSAID use.

TABLE 1: NSAIDS HYPOTHESIZED EFFECTS.

(Leadbetter, 1989)

1. Positively influence inflammation and repair process.
2. Decrease initial symptoms of the inflammatory process.
(e.g. pain, edema, muscle spasm, joint movement)
3. Return athlete to former activity as soon as possible.
4. Prevent reoccurrence of injury.

Due to the increased participation and involvement in exercise and sports, the medical community is seeing a higher frequency of sport related injuries of both the acute and chronic type. As a result, a sharp rise in NSAID therapy has developed, and spawned scientific interest into the efficacy and risk/benefit ratio of NSAIDs.

The drawback of this medication is the frequently associated side effects. Weler suggests that as many as 50% of patients undergoing oral non-steroidal anti-inflammatory drug therapy will experience side effects (1992). These may range from nausea to peptic ulcers and gastric bleeding, from which an estimated 4000 patients a year may die. Although the risk of side effects increases with age and associated disease, the rate of adverse reactions of these drugs suggests the medical community must take action. Because of the frequent occurrence of side effects and their negative potential alternative modes of administration should be developed. One approach is the investigation into the efficacy of non-steroidal antiinflammatory drugs in as a topical

gel. Effectiveness of the drug may be maintained while the side effects could be minimized. The hypothesis put forth is that the topical administration of an NSAID will be more effective than a placebo in the treatment of muscle soreness.

PURPOSE

The pupose of this study was:

1. To determine if topical ibuprofen gel was more effective than a placebo in reducing muscle soreness.
2. To determine if topical ibuprofen gel was more effective than a placebo in restoring strength.
3. To compare the serum levels of ibuprofen after oral and topical administration.

HYPOTHESIS

It was hypothesized that the percutaneous administration of topical ibuprofen would be more effective in treating delayed onset muscle soreness than a placebo. Subjects in the treatment group would show a faster return of eccentric torque and less muscle soreness. Furthermore, it was hypothesized that the topical ibuprofen would be equally as effective in treating delayed onset muscle soreness as the oral ibuprofen. In addition, it was hypothesized that the administration of oral ibuprofen would result in higher concentrations of ibuprofen in the plasma than the administration of its topical counterpart.

Chapter 2

REVIEW OF LITERATURE

I. INFLAMMATION

Inflammation, the body's normal response to insult, serves two main purposes. The first is to remove the injured tissue and the second is to promote regeneration of normal tissue structure. The process of inflammation is associated with increased sensitivity of nociceptors, increased blood flow in local vessels, increased capillary dilation, increased vascular permeability and increased cellular infiltrates (ie. neutrophils and monocytes) (Larsen, 1983). These clinical alterations, along with loss of function, produce the cardinal signs of inflammation: as reported initially by Cornelius Celsus, " rubor et tumor cum calore et dalore" (redness and swelling with heat and pain) (Leadbetter, 1989). There are considered to be two types of inflammatory reactions, the acute and the chronic responses. This paper will address the acute inflammatory reaction and those events following exercise-induced muscular injury.

A. Acute Inflammation

After injury to the body tissue a complicated interplay of inflammatory mediators will result in the accumulation of leukocytes, increased permeability and the vasodilation of vessels (Larsen, 1983; Malmsten 1986; Smith 1991). Because there are so many mediators, some which seem to have dual affects and others that are not found in all tissues (or in varying concentrations) and because the responses found in vitro may be different than those in vivo it is not yet clear the exact causes and mechanisms leading

to these physiological changes. A general understanding has been formulated, however.

After mechanical insult to tissue, the body responds both on a vascular and a cellular level. The vascular response involves initial vasoconstriction, lasting for 5-10 minutes, followed by an extended period of vasodilation and increased vascular permeability (Smith, 1991). The cellular response which involves mainly neutrophils (PMNs/ polymorphonuclear cells) and monocytes is the result of the interaction of various inflammatory mediators. The net result is described. A few hours following trauma there is a dramatic increase in circulating neutrophils. The neutrophils soon begin to aggregate at the site of injury, reaching peak concentrations between 1-4 hours post injury. Following this peak the concentration of neutrophils declines rapidly. The function of these cells is to aid in the digestion of dead tissue by the release of lysosomal enzymes. Following the decline in neutrophil concentration is the migration of monocytes (Larson et al., 1983). The concentration of monocytes rises quickly and is maintained for 48 hours after the initial trauma. During their migration from the blood to the injured tissue the monocytes mature into adult macrophages. These macrophages then dispose of necrotic tissue and remove foreign bodies (Larson et al., 1983; Smith, 1991).

The process of inflammation, although a normal response to stress, often produces unwanted pain and inhibition of muscle activity. Furthermore, although inflammation is considered part of the healing process, not all inflammation leads to healing: the

response may not always restore the tissue to its normal state. Additionally, pathological inflammation and chronic inflammation may actually delay further healing, eventually producing degenerative changes. Although, injuries will usually heal over time with rest and physical therapy, inflammation and pain will often slow rehabilitation thus lengthening recovery time (Almekinders, 1993). There is evidence that by supressing or controlling inflammation patients' return to activity may be quickened (Almekinders, 1993; Clement, 1975; Clyman, 1986; Weiler, 1994). Athletes are often not able or willing to abstain from participation therefore the control inflammation by NSAID and physical therapy is implemented, hopefully resulting in an earlier return to training and competition.

II. NONSTEROID ANTI-INFLAMMATORY DRUGS (NSAIDS)

A. Pharmokinetics of NSAIDs

NSAIDs may have a rapid onset of action. NSAIDs reach their peak plasma concentration in less than 30 minutes (Abramson, 1989). They accumulate in areas of higher acidity thus accumulating in the stomach, the renal medulla, and areas of inflammation. The interaction of NSAIDs and inflammatory cells depends on; the physiochemical properties of the drug; local environmental conditions; nature of cell membranes; and dosage (Abramson, 1989). At acid pH, NSAIDs have a higher affinity for the lipid bilayer of inflammatory cells. The absorption rate is affected by many factors including drug formation, pH of stomach contents, rate of gastric emptying, volume of food, exercise, and concomitant use of other drugs (Clissold, 1986). Most NSAIDs are metabolized by the liver, with the exception of aspirin and suldinac.

Further, all NSAIDs, except for aspirin, have reversible effects (Abramson, 1989; Buchnan et al., 1989; Clissold, 1986). NSAIDs have three main effects: Analgesic; Antipyretic; and Anti-inflammatory. It should be noted that the extent to which these effects occur is dependant on which drug is used and in what dosage.

B. Mechanisms of Action of NSAIDs

The mode in which NSAIDs propentiate their effects was first put forth by Vane in 1977. Vane found that the primary action of NSAIDs was on the inhibition of prostaglandin (PG) biosynthesis (see FIGURE 1). However, now there is evidence that other mechanisms are at work as well (Brune, 1982; McCormack et al., 1993, 1991).

FIGURE 1: METABOLISM OF A PHOSPHOLIPID AND ARACHIDONIC ACID:

(Clissold, 1986)

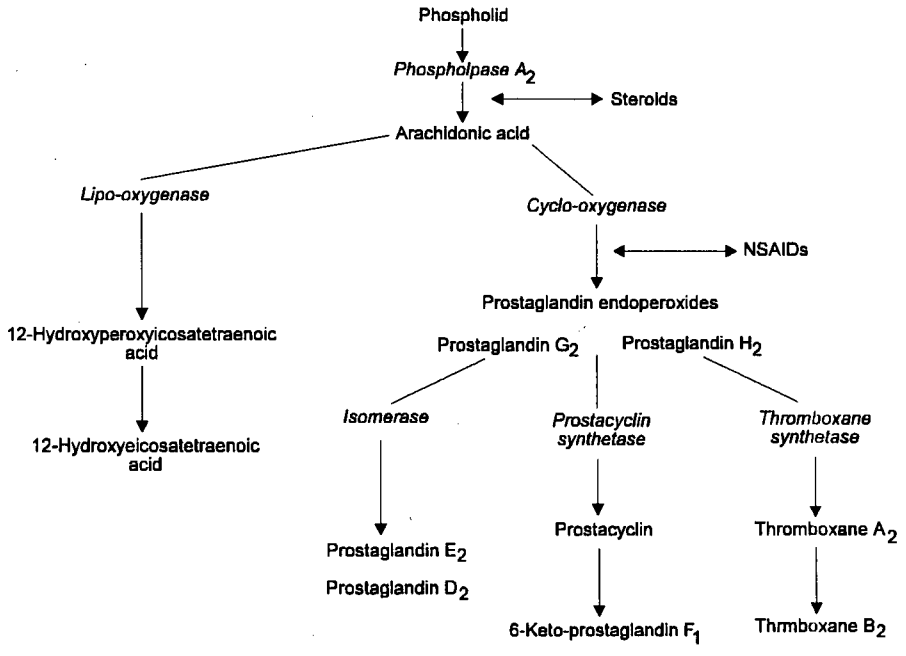


Fig. 1. Enzymes are indicated by italic type. NSAIDs inhibit cyclo-oxygenase and, thereby, supress the suntheses of prostaglandin E2, prostacyclin and thromboxane A2.

1. PROSTAGLANDIN INHIBITION

Prostaglandins (PGs), 20 Carbon unsaturated fatty acids, are metabolites of arachidonic acid produced via the cyclo-oxygenase pathway (FIGURE 1). PGs are autocrine regulatory molecules that exert their effects in the same tissue in which they are produced. Their actions supplement and complement the regulatory effects of the endocrine and nervous system. PGs are classified as autocoid, yet they are often described as local hormones. Some of the many diverse biological effects produced by PGs are: vasodilation of the kidney in pathophysiological conditions; constriction and dilation of pulmonary arterial and venous vessels; effect airway smooth muscle directly; ovulation; regulation of blood vessel diameter; the inflammatory reaction; and GI functioning and activity. Often, antagonistic reactions are also produced by PGs. For example, PGF2 constricts the airway while PGE2 causes dilation (Abramson, 1989; Buchnan et al., 1989; Goldstein, 1988).

The focus of this paper is on the inflammatory reaction and the need for NSAIDs. Prostaglandins contribute significantly to inflammation. Their dilation of blood vessels, production of fever, hyperalgesia, edema, and platelet aggregation are evidence of this. In addition, phagocytic cells (polymorphonuclear/PMN leukocytes, monocytes, and macrophages) produce and release large amounts of PGs at the site of inflammation. Consequently, PGs are found in greater concentrations at inflammation sites.(Abramson, 1989; Buchnan et al., 1989; Goldstein, 1988).

2. OTHER MECHANISMS

It is now believed that the suppression of inflammation by NSAIDs is occurring by additional mechanisms. First a higher dose than that which inhibits cyclo-oxygenase (CO) is needed to inhibit inflammation. Second, drugs that don't effectively inhibit CO still produce anti-inflammatory effects. In addition, some products of the CO pathway have also been found to have anti-inflammatory properties. Finally, every neutrophil function associated with inflammation is inhibited, not all of which are due to inactivating CO.(Abramson et al., 1985; Abramson, 1989; Buchnan et al., 1989; Goldstein, 1988; Leadbetter, 1989).

Since Vane, various other modes of NSAIDs actions have been postulated. Higuchi (1986) found that aspirin has an additional mode of analgesic action. It was found that salicylic acid, from the hydrolysis of aspirin, is also acting on a central mechanism. McCormack and Brune (1993) also believe that the analgesic role of some NSAIDs cannot be due to simply the inhibition of peripherally formed prostaglandins. Investigators have found that some NSAIDs, azapropazone and ketoprofen, can be found in measureable amounts in the cerebrospinal fluid (McCormack et al. 1993). The extent, site and mode of this central action are, however, not yet known.

A study by Vanderheok and Bailey (1984) found that, in vitro, ibuprofen stimulated 15-lipoxygenase while inhibiting the CO and the 15-lipoxygenase pathways in human PMN leukocytes. Hydroperoxyeicosatetraenoic acid (15-HPETE) inhibits prostacyclin (PGI_2)

and platelet aggregation. Both metabolites inhibit lymphocyte mitogenesis and modulate several cellular lipoxygenases. It should be made clear, however, that ibuprofen was used at concentrations of at least an order of a magnitude greater than the normal pharmacological dose.

Many hypotheses have been put forth as to NSAIDs' role in inhibition of neutrophil functioning. One idea is that NSAIDs affect early events that are critical to coupling of stimulation responses (Abramson et al., 1985). This may be caused by an inhibition of calcium movement or enhancement of cyclic adenosine monophosphate (cAMP). Other hypotheses are that NSAIDs have effects on phospholipase A_2 activity, lysomal membrane integrity, cell-surface receptors, or cyclic nucleotide metabolism (Abramson et al., 1985; Abramson, 1989; Buchnan et al., 1989; Goldstein, 1988).

C. Side Effects

NSAID therapy has been shown to correlate highly with adverse side effects. As many as 50% of patients treated with NSAIDs develop adverse effects. Nausea and dyspepsia are the most common problems reported, occurring in approximately 1/3 of those treated (Weiler, 1994).

The toxicity of NSAIDs are related to their ability to inhibit PG biosynthesis. Typically, as dosage and duration of therapy increases, there is an increased susceptibility to adverse reactions. The adverse reactions have been associated with the gastro-

intestinal tract, the kidneys, the liver, the blood, the central nervous system, and allergic reactions.

1. GASTROINTESTINAL EFFECTS (GI)

Occurring in 15-20% of users, GI effects are by far the most common. The symptoms are generally dyspepsia, heartburn, epigastric pain, nausea and vomiting. These symptoms should not be taken lightly for they often infer more serious problems; gastric erythema, haemorrhages, mucosal erosions, occult blood loss, and exacerbation of gastric erosions. An additional concern is that many of these ulcers are asymptomatic (Chlud, 1987;Knodel, 1992; Weiler, 1992). GI effects are due to direct local irritation and/or the inhibition of PGs. PG's have a protective role in the GI tract by inhibiting gastric acid secretion, increasing mucosal blood flow, and stimulating gastric mucus and bicarbonate production (Clissold, 1986; Clyman, 1986; Knodel, 1992; Mather, 1992).

Besides the potency PG synthesis inhibition, the lipophilicity and pKa of the drug are also properties that may determine the degree of ulcerogenic effect the NSAID may have. The lipid soluable weak acids can freely diffuse into mucosal cells where they become ionized, due to the higher pH (pH=7), and trapped. This concentration gradient alter cell permeability causing an influx of hydrogen ions from the lumen which in turns results in decreased mucosal blood flow. Furthermore, the acidic group of the NSAID seems to play a crucial role in the direct irritation of the GI tract (Gyires, 1994).

2. RENAL EFFECTS

Renal effects occur more frequently in high risk patients, chronic users and in abusers rather than in the 'normal' patient. People with congestive heart failure, hypovolemia, cirrhosis or intensive diuretic therapy are high risk subjects (Clissold, 1986; Knodel, 1992). Decreased urine output , body weight gain, rapid increase in serum creatine and rapid increase in blood urea nitrogen levels are signs of underlying renal effects (Knodel, 1992).

There are three main renal effects associated with NSAID therapy. Hyperkalemia occurs due to inhibition of PG-mediated release of renin. Renal insufficiencies are caused by secondary inhibition of vasodilatory PGI_2. Inhibition of PGI_2 results in vasoconstriction thereby causing renal ischemia and acute renal failure (Clissold, 1986; Knodel, 1992). Thirdly, NSAIDs cause sodium and fluid retention. For example, phenylbutazone, an NSAID rarely used now, was associated with a high occurrence of side effects, including an increase in plasma volume up to 50%.

3. HEPATIC EFFECTS

Liver toxicity occurs infrequently and mildly if it does. Phenylbutazone and high doses of aspirin are more related to hepatic side effects (Black, 1980; Knodel, 1992). Although reversible and often mild, nausea, vomiting, fever, rash, anorexia, abdominal pain, liver tenderness, jaundice and bleeding are associated symptoms. Liver effects are more frequent in patients with pre-existing liver impairment but patients with

inflammatory diseases must also be cautious because of the necessity for higher doses (Black, 1980; Knodel, 1992).

4. HAEMATOLOGICAL EFFECTS

NSAIDs block Thromboxane A_2 production which inhibits platelet aggregation resulting in a slight prolongation of bleeding time (~50sec) (Clissold, 1986; Clyman,1986; Hess et al., 1986; Knodel, 1992). The half life of the drug determines the time platelets cannot aggregate. Aspirin binds irreversibly to cyclo-oxygenase therefore producing effects for the platelet life span of 7-12 days. This anti-aggregational effect is an important consideration in patients with ulcers, Vitamin K deficiencies, hemophilia, and those undergoing surgery (Abramson, 1989; Buchnan et al., 1989; Clissold, 1986; Mather, 1992).

Other more rare haematological effects that may occur include agranulocytosis, aplastic anemia, thrombocytopenia, and haemolytic anemia. Phenylbutazone has been the most common cause of fatal drug-related anemia, thus its use has rapidly declined (Black et al., 1980).

5. CENTRAL NERVOUS SYSTEM (CNS) EFFECTS

Drowsiness, dizziness, confusion, disorientation, headaches, depression and/or insomnia may be associated with NSAID therapy. The most common CNS side effects are tinnitus and decreased auditory acuity (Clissold, 1986; Knodel, 1992). Symptoms from CNS effects are reduced with a decrease in dosage or a cessation of therapy.

6. INTOLERANCE REACTIONS/HYPERSENSITIVITY

Like most drugs, there is the chance that some people may develop an allergic reaction to an NSAID. Concurrent drug use and their interactions may also induce a reaction (Clissold, 1986; Knodel, 1992).

Because of the various side effects of NSAIDs, a risk/benefit ratio must be looked at closely for each individual patient. If all that is needed is a relief of pain then an analgesic drug, with fewer risks of side effects, may be optimal. Those susceptible to the problems associated with NSAIDs may need to look towards alternative modes of treatment (e.g. cryotherapy, physical and electrotherapy). However, research into other methods of administering NSAIDs may decrease their side effects.

III. TOPICAL APPLICATION OF NSAIDS

Continuous research is proceeding for NSAIDs in order to decrease side effects. Topical NSAID administration is common practice in Eastern Europe. Chlud (1991) claims that topical percutaneous NSAIDs (gel, cream, or sprays) are effective in their treatment of sports related injuries (Blank, 1964; Chaterjee, 1972; Chlud et al., 1987; Diebschlag et al., 1990; McLatchie et al., 1989; Peters et al., 1987; White, 1991). The advantages of topical administration NSAIDs are:

1. they are applied directly to the painful area
   therefore they reduce GI toxicity;
2. the low plasma concentrations that develop lead
   to decreased side-effects.91

A. Side effects

Minimal side effects have been associated with topical application of NSAIDs. Skin irritations occur in 1-3% of patients applying the cream (Chaterjee, 1972; Chlud et al., 1987; Diebschlag et al.1990; White, 1991). These diminish when therapy is stopped. Photosensitivity has also been seen in 1-2% of users. Because of the low occurrence of side effects from topical application of NSAIDs further research is proceeding into its effectiveness.

B. Topical Ibuprofen

1. ABSORPTION

The absorption of topical ibuprofen is rapid with peak plasma levels occurring in two to four hours. This is comparable to peak plasma levels of oral ibuprofen which are obtained in two to three hours (White, 1991).

2. PHARMOKINETICS

The main concern is whether therapeutic concentrations are achieved following the topical application of non-steroidal anti-inflammatory drugs. Necessary, effective concentrations of ibuprofen in the synovial fluid is 1-5ug/ml. In addition, Cushman et al (1976) found that 1.2ug/ml of ibuprofen is needed to inhibit the syntheses of prostaglandins by 50%. Chlud et al (1987) found that after 350mg of locally applied ibuprofen cream to the knee, maximum drug concentration in the synovial fluid was 2.6ug/ml.

The data shown below (Table 2) illustrates that ibuprofen will penetrate percutaneously through to deeper tissue layers and reach effective therapeutic concentrations.

TABLE 2: CONCENTRATIONS OF TOPICAL IBUPROFEN:

(Chlud et al., 1987; Peters et al., 1987)

1. **subcutaneous - 12.18ug/g**
2. **capsular tissue - 4.4ug/g**
3. **fascia lata - 64.6ug/g**
4. **muscle - 27.95ug/g**

Interestingly the drug plasma levels remain relatively low after topical administration. Maximum plasma levels after oral administration reach 26-40ug/ml whereas after topical application ibuprofen peak plasma levels yield only .15-.64ug/ml. Similar results have been found following the administration of topical NSAIDs by other authors. This leads one to believe that the drugs penetrate the skin and directly reach the deeper, underlying structures.(Chaterjee, 1972; Chlud et al., 1987; Diebschlag et al.1990; Peters et al., 1987; White, 1991)

Conversely, Radermacher et. al. (1991) found that diclofenac, a topical gel, distributed predominantly through the blood while only a small fraction of the drug reached the injury site via direct transport across the skin. Further investigation into this new mode of application of NSAIDs is required.

IV. SKIN

A. Anatomy

Although the skin is only a few millimeters thick it serves a vital role in providing a protective barrier against microorganisms, water, UV light and the environment. There are three main layers of the skin: the superficial epidermis, the dermis, and the inner subcutaneous fat tissue (Blank et al., 1964; Chien, 1992).

1. EPIDERMIS

The outer layer, which is 30-50 cells thick, is composed of stratified squamous epithelial cells. This layer, composed of compact, flattened, dehydrated cells, is considered physiologically "dead" because they have lost their nuclei. The layers of the epidermis are:(Chien, 1992)

1. The stratum corneum is 25-30 cells thick. The flat, scale-like cells are cornified, thus providing the protective, waterproof outer layer.

2. The stratum lucidum only appears in the skin of the soles and palms. This layer has a clear appearance because the nuclei, organelles, and cell membranes are no longer visible.

3. The layer of the stratum granulosum is responsible for the initiation of keratinization. Cells here are flat and contain dark stained granules.

4. The stratum spinosum is composed of stratified layers of polygonal cells. This layer and the stratum basale make up the stratum germinatum.

5. The stratum basale (the innermost layer) is responsible for replenishing the epidermis. The cuboidal cells of this layer are constantly undergoing mitotic activity and migrating upwards. During their upward movement they lose contact with the lower dermis and its associated vascular nutrients and oxygen supply. this causes the degeneration of the nuclei.

2. DERMIS

The dermis contains many vessels that nourish the lower living layer of the epidermis. The many collagenous, elastic and reticular fibers form a tough, flexible meshwork that provides skin support and skin tone. Nerve endings and hair follicles pierce this layer. The dermis itself can be broken into two layers: the upper stratum paillarosum and the stratum reticularosum (Chien, 1992).

3. SUBCUTANEOUS TISSUE

The subcutaneous tissue, often referred to as subcutaneous fat, is mainly composed of loose fibrous connective tissue and adipose cells that bind the dermis to underlying organs. Blood vessels run throughout the layer. This layer stores lipids, provides insulation for temperature regulation and provides a protective cushioning for the body (Chien, 1992).

B. Skin Penetration

The penetration of a drug through the skin depends on the drug's properties and the intact skin. Drugs can penetrate the skin via three routes: across the intact stratum corneum, through hair follicles or through sweat gland ducts. The latter two pathways occupy only 1% of the skin surface and therefore penetration through these routes is considered negligible (Chien, 1992). The primary mode of transport is then across the stratum corneum, the main barrier of the skin. Diffusion across the stratum corneum is followed by diffusion through the viable epidermis and into the papillary layer of dermis. Although substances must diffuse through all the various layers of the skin it is the stratum corneum that regulates the influx of these substances. The diffusion of a drug across this layer is considered the rate limiting step: to increase permeation time one must increase the penetration through the stratum corneum (Chien, 1992). Various properties of the drug and the addition of skin enhancers may be implemented to

increase percutaneous absorption rate. This rate includes the rate of drug delivery to the skin surface and the drug absorption rate by the skin tissue (Guy et al., 1982). Permeation rate will depend on the aqueous solubility of the drug and the oil/water partition coefficient of the drug. The first determines the magnitude of the concentration gradient across the skin tissue while the latter governs the specific skin permeability to that drug. Lipophilicity of the drug has a marked affect on absorption rate: as lipophilicity decreases so does absorption (Chien, 1992; Cooper, 1984; Yano et al., 1986).

1. PATHWAYS

Due to the stratum corneum's affinity for both water-soluble and lipid-soluble penetrants there are two major pathways for molecule transportation across the skin. Water-soluble molecules travel primarily transcellularly through the polar path while lipid-soluble molecules travel via a nonpolar pathway. The polar path is associated with the protein component of the stratum corneum. The "bound" state of Keratin structures inside the cells of the stratum corneum are responsible for the resistance causing the slow diffusion rate of the penetration molecules (Chien, 1992). The pathway for lipid-soluble molecules is not clear, however, it seems to follow endogenous lipids, located both intracellularly and between the keratin filaments of horny cells, within the stratum corneum (Chien, 1992).

Both pathways follow the steps of percutaneous absorption: transport of the penetrant to the skin surface, partitioning of the chemical into the stratum corneum, and molecular diffusion through the multi-layered cells of the stratum corneum (Chien, 1992; Guy et al., 1982).

2. SKIN ALTERATION

To allow for an increased penetration rate techniques are often employed to alter the skin, allowing for easier passage of penetrant molecules. This may be done by physical alterations, by occlusion, or by chemical enhancers.

a. Physical Alteration: Damaging the skin attenuates the barrier properties of the stratum corneum (eg. stripping the stratum corneum) (Squire et al.,1992).

b. Penetration Enhancers: Many vehicles have been found to modify the skin's barrier properties and render the skin more permeable to the drug. Efficiency of enhancers is dependent on the structure of the penetrants (Chien, 1992). Cooper (1984) found that although the individual addition of propylene glycol and oleic acid increased permeation of salicylic acid, a mixture of the two gave a twenty fold increase in transport rate. Ideally, a two-component system,

that contains both a polar and a lipid solvent, should be created (Cooper, 1984).

c. Occlusion: Application of an impermeable dressing will cause increased skin permeability for two reasons: hydration of the stratum corneum and increased skin temperature (34 degrees Celsius to 37 degrees Celsius).

3. DRUG

The ideal properties of a drug to be delivered transcutaneously are shown in Table 3.

TABLE 3: IDEAL DRUG PROPERTIES:

(Squire et al., 1992)

- has both hydrophilic and hydrophobic properties **- has low molecular weight** **- is highly potent (therapeutic dose less than 10mg/24hr)** **- does not stimulate histamine release** **- does not irritate the skin** **- has a suitable preparation available**

V. DELAYED ONSET MUSCLE SORENESS

To test the effectiveness of topically administered ibuprofen, delayed onset muscle soreness (DOMS) will be used as the inflammatory model. DOMS is characterized by the sensation of tender, aching muscles occurring a day or two following unaccustomed exercise (Hasson et al., 1993; Smith, 1991). A decrease in force production also occurrs. DOMS is predominantly associated with exercise that contains the eccentric lengthening of contractions. Mechanical stress is thought to induce muscle damage. It has been suggested that this is then followed by an acute inflammatory reponse. Other theories on the etiology of DOMS have also been postulated (Ciccone et al., 1991; Hasson et al., 1993; MacIntyre et al., 1994; Smith, 1991). These theories include: the lactic acid theory, the spasm theory, connective tissue damage theory, and the muscle damage theory (Cleak et al., 1992).

Although various etiologies have been put forth, experimental evidence points to mechanical stress as the cause for DOMS. Eccentric exercise, the lengthening of muscle while under tension, is the main culprit. In this type of contraction fewer motor units are recruited than in an equal concentric force output. Thus the mechanical stress per fiber is higher in eccentic contractions (Armstrong, 1990 and 1984; Evans et al., 1991; Kuipers, 1994).

It appears that following this structural damage an inflammatory response is then initiated (Kuipers, 1994). Evidence of DOMS being caused by acute inflammation is

shown by the similarities of many indicators occurring in both: cardinal signs and symptoms; loss of function; similar histochemical changes; and cellular infiltrates (Smith, 1991).

Pain and edema, two of the cardinal signs of acute inflammation, are also signs of DOMS. The delayed onset of pain associated with DOMS and acute inflammation is due to the increase in the E series of prostaglandins, especially PGE_2. PGE_2 sensitizes nociceptors (pain receptors) thereby producing hyperalgesia (Kuipers, 1994; Smith, 1991). Both Smith and Bansil have found increases in PGE_2 twenty four hours after eccentric exercise (Smith, 1991). This follows the time line of peak soreness. Macrophage biosysnthesis is probably the main source of PGE_2. Macrophages have been found to be the predominant cell type at 24 and 48 hours after DOMS (Evans et al., 1991; Franklin, 1991; Smith, 1991). In addition, on exposure to inflammation, macrophages are stimulated to synthesize and release large quantities of PGE_2 (Smith, 1991). Swelling or edema, due to the increased permeability of small blood vessels, is common to both inflammation and DOMS. Many prostaglandins contribute to this vasodilation, including PGI_2, PGE_2 and PGD_2 (Abramson, 1989; Buchnan et al., 1989; Clark et al., 1986; Goldstein, 1988). Oxygen free radicals, leukotrienes, serotonin, and histamine also act to effect vasodilation and vascular permeability.

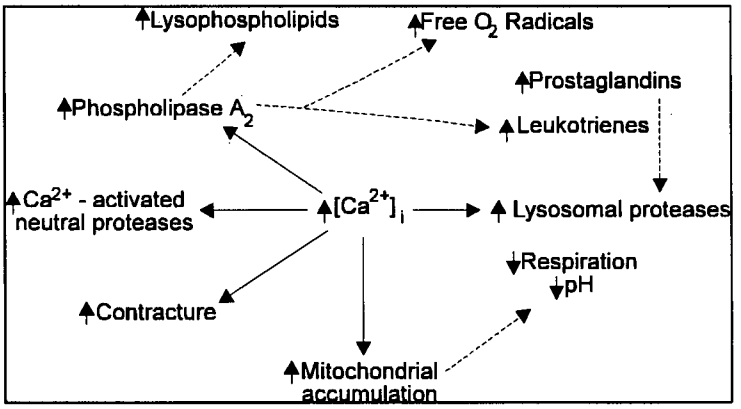
Loss of function or the inability of the affected region to generate force is another common occurrence. DOMS illustrates a decline in force immediately following the

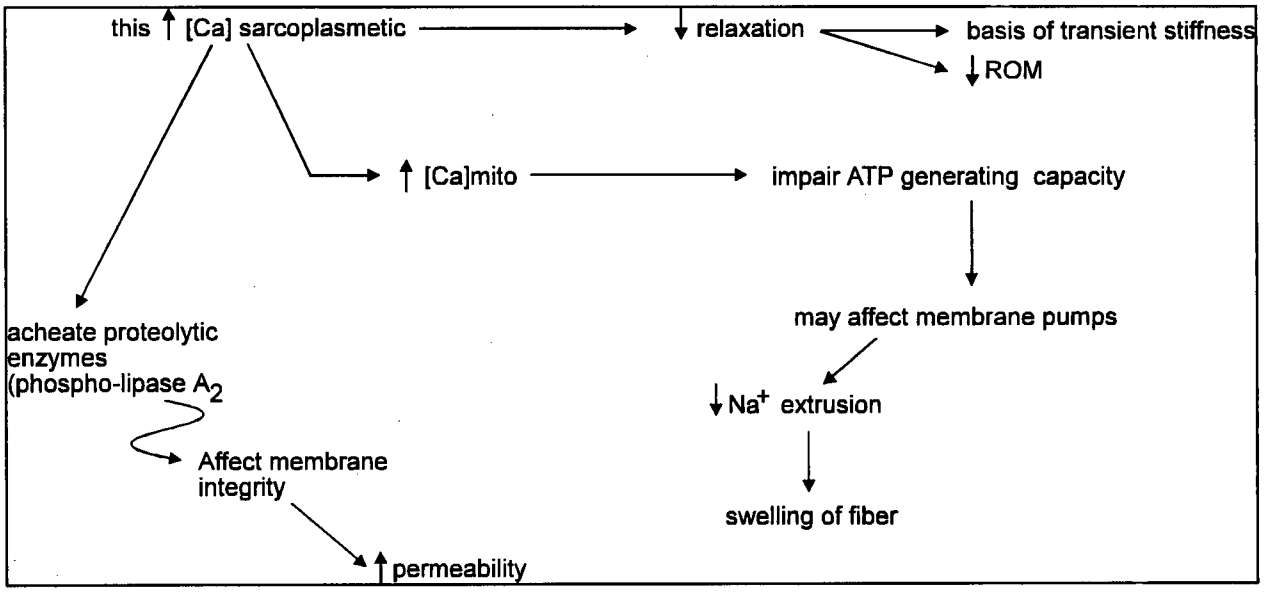
exercise bout (Armstrong, 1984; Evans et al., 1991; MacIntyre et al., 1994; Smith, 1991). In addition to this immediate decline, a recent study by McIntyre and et al. (1994) shows a second drop in eccentric torque occurring 20-24 hours after the exercise.

Finally, similar histochemical changes and cellular infiltrates are common to both DOMS and acute inflammation. Increased fibroblasts, interleukin-I, and macrophages are all found at the injury site in both situations. Furthermore, increased lysosomal activity, activated by neutrophils and platelets, occurs (Smith et al., 1980, 1981, 1994). MacIntrye et al. (1994) labelled white blood cells with technetium-99m and found a significant increase in WBC at the injury site in DOMS. This provides further evidence that acute inflammation is one mechanism underlying delayed onset muscle soreness. In addition, it is believed that the increase in intracellular calcium concentration associated with the mechanical overload of eccentric exercise has a crucial role in the induction of inflammation (Armstrong, 1990; Evans et al.,1991; Duarte et al., 1992; Kuipers, 1994). Increased sarcoplasmic calcium seems to trigger various processes as shown in Figure 2. The activation of phospohlipase A_2 has been found to increase as a function of Ca^{2+}concentration (Armstrong, 1990).

FIGURE 2: ELEVATED INTRACELLULAR CALCIUM CONCENTRATES AND ITS ASSOCIATED EFFECTS:

(Armstrong, 1990; Duarte et al., 1992; Kuipers, 1994) - Elevated intracellular calcium concentrations and its associated effects.



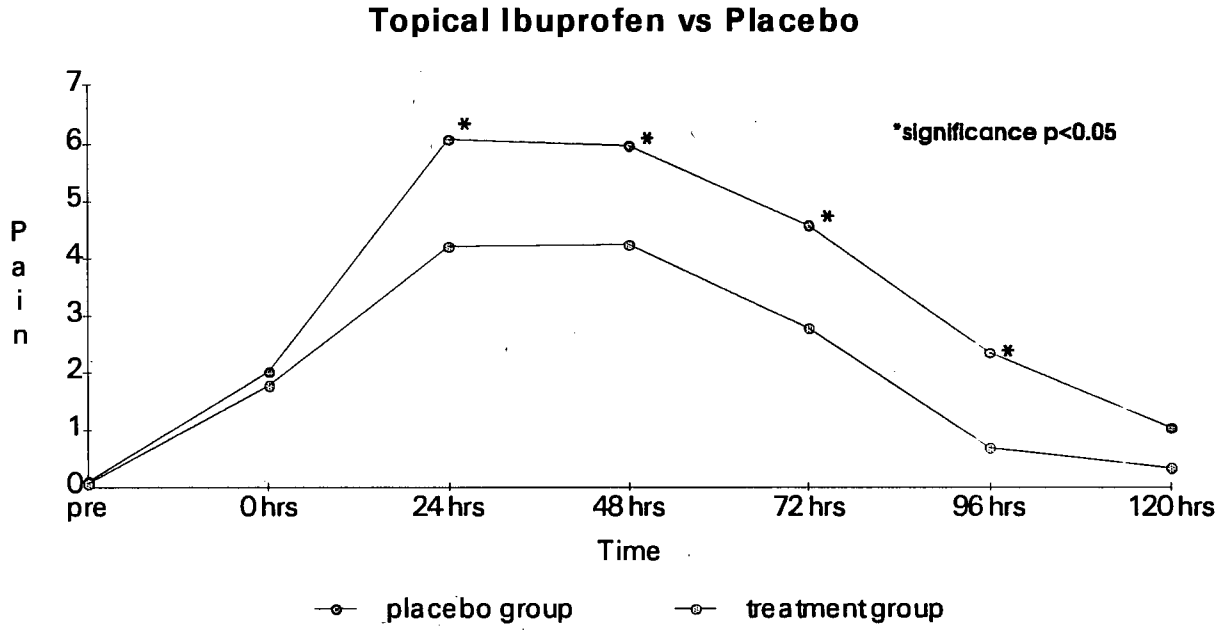


VI. PILOT WORK

A pilot study was conducted to investigate the use of topical ibuprofen in delayed onset muscle soreness. Six subjects, randomly placed into two groups, a placebo or a treatment group, underwent an exercise protocol designed and tested by MacIntyre (1994). The exercise bout consisted of 300 eccentric contractions of the non-dominant quadriceps muscle in a thirty minute time period. There was a 60 degree range of motion, 110 to 50 degrees. The contractions were subdivided into thirty sets of ten with a twenty second rest between sets. The next day subjects started applying the gel and an occlusive dressing (Handy-Wrap). Depending on the group, the gel was either placebo or 5% ibuprofen (400mg). The study was double-blinded. Subjects continued treatment for five days, three times a day. Pain was recorded pre, at 0, 24, 48, 72, 96, and 120 hours post exercise. The results of the study are depicted below (Figure 2).

A 2 (group) x 7 (day) factorial ANOVA was conducted. A significant difference between subjects' soreness in the treatment group and the placebo group was found ($p=.045$).

FIGURE 3: EFFICACY OF IBUPROFEN VS A PLACEBO IN DOMS



Chapter 3

METHODOLOGY

This study was divided into two parts. The first part was concerned with investigating the effectiveness of topical ibuprofen in the treatment of delayed onset muscle soreness while the second part was used to compare blood ibuprofen levels after topical and oral ibuprofen administration.

PART I: IBUPROFEN AND DOMS

SUBJECTS

Thirty healthy, female subjects between the ages of 18 and 45 years were recruited for this study. Those included in the study were not on a weight training program (training their upper body for more than 3 times per week) and were not competitive paddlers (rowers, kayakers etc.). Any subjects who had taken any NSAIDs seven days prior to the testing period, suffer from allergies to aspirin or aspirin related compounds, were undergoing treatment with anticoagulants, hydantoin, or antidiabetic drugs, had a history of severe renal, hepatic or haemopoietic disease; had an active peptic ulcer; were pregnant or lactating, had elbow injuries or biceps muscle strains, or had experienced DOMS three months prior to the testing period were excluded from the study.

STUDY DESIGN

Subjects were randomly assigned to one of three groups: a topical treatment group, an oral treatment group or a placebo group. All three groups applied a topical stick to the musculotendinous junction of the biceps muscle and took an oral tablet starting after the exercise bout. Group A received both the placebo for the oral and topical preparations. Group B received an oral placebo and topical ibuprofen while group C received the opposite, oral ibuprofen and a topical placebo. The gel contained either a placebo or a 7% solution of ibuprofen depending on the group. In addition, a double-blind procedure was used, to prevent any biases. Treatment continued for seven days. Subjects received either a dosage of 400mg of topical gel or oral ibuprofen 3x/day or the placebo 3x/day.

Prior to the study subjects were given standardized instructions of the experimental procedure and an informed consent was then signed.

Subjects were asked to contact us if they experienced any adverse reactions or side effects during the drug therapy. The frequency and type of side effects were then recorded.

Following the exercise bout subjects were carefully instructed on the application of the gel . They were told to refrain from using other analgesic or anti-inflammatory drugs while in the study. This included cough/cold mixtures and over the counter analgesics.

In addition they were instructed to refrain from using ice packs, physiotherapy, stretching, or other forms of self applied therapy.

EXERCISE PROTOCOL

The experimental protocol that was used to induce delayed onset muscle soreness was the protocol used by Smith et. al. (1994). The protocol consists of eccentric isokinetic contractions of the non-dominant elbow flexor muscles (biceps) on the KinCom dynamometer.

Subjects warmed-up by performing 10 submaximal bicep contractions. Following this, subjects performed 4 maximal contractions in the active mode to derive a maximal lift. The exercise protocol then consisted of 5 sets of 35 maximal eccentric muscle contractions performed in the passive mode. A one minute rest period was allowed between each set.

The range of motion for the elbow movement was through an arc of 90 degrees, from 45 to 135 degrees of elbow flexion. The speed was set at 45 degrees per second, non-gravity corrected.

The KinCom dynamometer, or Kinetic Communicator Exercise system, is a hydraulically driven, microcomputer-controlled device that was used to measure maximal strength and to provide resistance in the exercise protocol. The machine has

been found to be highly reliable and valid in the testing and measurement of human joint functioning (Farrell and Richards, 1986).

Each subject was instructed to sit with her back straight against the chair. Her upper body was stabilized by strapping. Both feet were touching the ground. Subjects gripped the arm of the KinCom with their palms facing up.

DATA COLLECTION PROCEDURES / MEASUREMENTS

A. Anthropometric Measures

Prior to subjects' inclusion into the study a skin fold of the non-dominant biceps was taken. Fat calipers were used to evaluate subjects' skinfold. The fold was taken at the mid-biceps point. This was measured anteriorly from the acromion process down to the joint line. To be included in the experiment the subject must have scored in the average norm for females of their age according to the Canadian Fitness data.

B. Soreness Rating

Degree of soreness in the exercised arm was assessed using a visual analogue scale (VAS). A baseline value was taken prior to the eccentric contractions of the biceps and one immediately following it. Subjects were then asked to record their pain level on four days (at 24hrs, 48hrs, 72hrs, 168hrs).

This scale is similar to that used by MacIntyre et al. (1994) and Smith et.al. (1994). The scale is a 10 cm horizontal line with the ends of the continuum closed off. The range is from "no soreness" on the left to "worst soreness possible" on the right end. Subjects will be requested to bend, extend, and palpate their exercised arm and then place a slash mark along the scale that represents the amount of their overall soreness. When analyzing the data the distance will be measured from the left end to the marked slash.

The validity and reliability of the visual analogue scale as a tool in measuring pain has been established by various authors (Downie et al., 1978; Huskisson, 1983; Price et al., 1983; Scorr et al., 1979). This scale has been found to be reliable for experimentally induced pain and chronic clinical pain. Between-session reliability has been found to be high (r=0.97). This is a highly sensitive and reproducible measure. Huskisson (1983) found the correlation coefficient between successive measurements of pain to be 0.99. Furthermore, because the VAS is a ratio scale it becomes a more useful tool to analyze data.

C. Strength

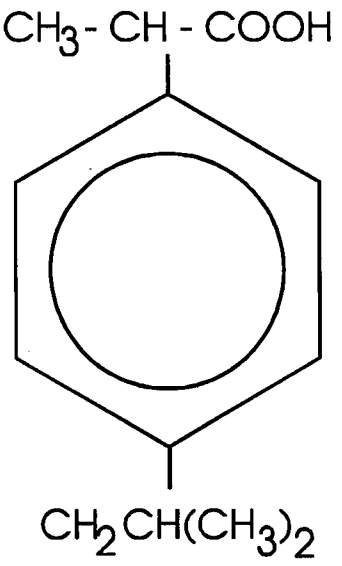
Eccentric torque production was measured throughout the testing period. This was measured on the KinCom dynamometer before the exercise protocol, immediately post exercise (0 hours), and on four separate days following the exercise bout (24 hours, 48 hours, 72 hours, and 144 hours). To determine the subjects' maximal strength they

performed 1 set of 4 maximal contractions in the active mode of the KinCom. The first repetition was discarded and the remaining three were averaged. Ten submaximal contractions were performed prior to the maximal contractions for a warm-up.

GEL CONTENT

The active gel used contained a 7% mixture of ibuprofen. Ibuprofen is a relatively acidic NSAID that is practically insoluble in water. It is readily and almost completely absorbed after oral administration with more than 60% excreted in the urine in 24 hours. Peak plasma levels are reached in approximately 1.5 hours. Figure 4 shows the chemical structure of ibuprofen.

FIGURE 4: CHEMICAL STRUCTURE OF IBUPROFEN:



HYPOTHESIS:

It was hypothesized that the percutaneous administration of topical ibuprofen would be more effective in treating delayed onset muscle soreness than a placebo. Subjects in the treatment group would show a faster return of eccentric torque and less muscle soreness. Furthermore, it was hypothesized that the topical ibuprofen would be as effective in treating delayed onset muscle soreness as the oral ibuprofen.

STATISTICAL ANALYSIS

The dependent measures of eccentric torque and subjects' soreness were analyzed using a 2 (Group) x 6 (Day) factorial ANOVAs with repeated measures on the second factor. Significance was set at $p<0.05$. A Scheffes test was used for post-hoc analysis.

PART II: BLOOD IBUPROFEN LEVELS

SUBJECTS

Five healthy female subjects between the ages of 18 and 25 years were recruited for this portion of the study. The inclusion - exclusion criteria used and the procedures for biceps skinfolds were the same as those used in Part I of this study.

STUDY DESIGN

A cross-over design was implemented for this part of the study. Subjects performed the same exercise protocol describe in Part I. They then used either 400mg of oral or 400mg of topical ibuprofen 3x/day for seven days after the exercise. This was followed

by a ten day wash-out period where no ibuprofen was taken. The exercise protocol was then repeated using the opposite arm and treatment commenced with the other mode of ibuprofen being applied 3x/day for seven days. Treatment times were at 10:00am, 4:00pm and 10:00pm for all subjects. During each drug period four blood tests were taken before 10:00am to determine the blood ibuprofen levels. Ten milliliters of blood were drawn prior to each drug period for a baseline level, on day 3, day 5 and day 7. The initial type of treatment (oral or topical) and arm tested (right or left) was randomly selected for every subject.

Prior to the study a detailed explanation of the experimental procedure was given to each subject and an informed consent was then signed.

No subjects reported any side effects during either treatment period.

Subjects were instructed to refrain from taking any NSAIDs during the entire testing period.

DATA COLLECTION PROCEDURES

Blood samples from the antecubital vein of the un-exercised arm were drawn to assess plasma ibuprofen concentrations. Samples of 10ml were taken on a total of eight separate occasions: four were taken each treatment period. A baseline blood test was taken at the beginning of the study and one after the wash-out period, prior to the start

of the second treatment period. The remaining six samples were taken before the first dose of the day (i.e.. before 10:00am) on day 3, day 5 and day 7.

The blood was spun down immediately following each blood test to yield approximately 4ml of plasma. The plasma was then drawn off and frozen at -20 degrees Celsius.

BLOOD ANALYSIS

Blood was assayed for ibuprofen by Dr. Stewart Huckin and Mahmood Khan of the Riverview Hospital Toxicology Department. The tests were run on gas chromotography - mass spectrometry (GCMS) under the "IBU" method. An OV-1 column was used for detection.

Naproxen was chosen as the internal standard because it behaves the same and has a similar chemical structure to ibuprofen. The internal standard consisted of 100ul of 0.01mg/ml of Naproxen.

To separate ibuprofen into its free form we added 0.5ml of 0.01 N HCL to the 200ul of serum. This increases acidity, thus driving ibuprofen into its free form. 5ml of ethyl acetate was then added to extract the ibuprofen. This was then mixed for 5 minutes, centrifuged and then dried for one hour. BSTFA with 1% TMS and 10ul of pyridine were used to derivatize the drug at 60 degrees Celsius for 1 hour. BSTFA was used to

bind to the acidic portion of ibuprofen (CH_3CHOOH) so the OV column could detect it and trimethylchlorosaline (TMS) was used to catalyze the reaction.

HYPOTHESIS

It was hypothesized that the administration of oral ibuprofen would result in higher concentrations of ibuprofen in the plasma than the administration of its topical counterpart.

STATISTICAL ANALYSIS

Ibuprofen concentrations were analyzed by a 2 (Group) x 3 (Test) factorial ANOVA with repeated measures on the second factor. Significance was set at $p<0.05$. A Scheffes test was used for post-hoc analysis.

LIMITATIONS AND DELIMITATIONS

This study was delimited to:

1. The population of relatively untrained upper-body female UBC students from which the sample will be drawn.
2. The methodology and DOMS protocol applied.

This study was limited to:

1. Homogeneity of the experimental and control groups.
2. The subjects' adherence to the drug administration.
3. The perception of pain experienced by each subject.
4. The ability of the GC-MS "IBU" technique to detect the lower ibuprofen concentrations.

Chapter 4

RESULTS

PART I: IBUPROFEN AND DOMS

Tables 6 shows a summary of the clinical characteristics of the subjects used in each group of Part I of this study. Subjects all fell in the average norm for biceps anthropometric measures.

TABLE 6

Average Clinical Characteristics of Subjects in Part I

	Placebo Group	Topical Tx Group	Oral Tx Group
Subjects (n)	10	10	10
Age	19.8	19.8	21.1
STDEV	2.4	2.18	3.11
Height	160.35	164.68	166.63
STDEV	4.62	6.59	9.31
Weight	55.7	61.68	61.73
STDEV	6.36	6.55	6.13
Bicep Length	25.2	25.6	27.15
STDEV	1.82	1.85	2.26
Bicep Skin Fold	8.3	8.95	10.4
STDEV	2.83	3.05	3.17

Muscle Soreness

Results for subjects' perceived pain can be seen in Table 7. All three groups displayed peak soreness at 48 hours, with the topical ibuprofen group lower than both the placebo and the oral ibuprofen group. The differences between groups was not found to be statistically significant (p=0.302).

TABLE 7

Summary of Perceived Soreness for the 3 Groups

n per group = 10		Pre	Post	24hr	48hr	72hr	144hr
Placebo	**AVG (mm)**	4.5	13.95	49.65	60.95	50.2	16.8
	SD	4.21	9.55	20.83	19.51	27.11	18.24
Topical	**AVG (mm)**	1.70	12.20	43.80	50.35	35.90	6.30
	SD	2.89	13.53	20.08	20.18	23.70	8.30
Oral	**AVG (mm)**	3.75	6.95	50.10	54.55	35.40	4.50
	SD	9.48	8.25	22.80	20.12	15.14	6.69

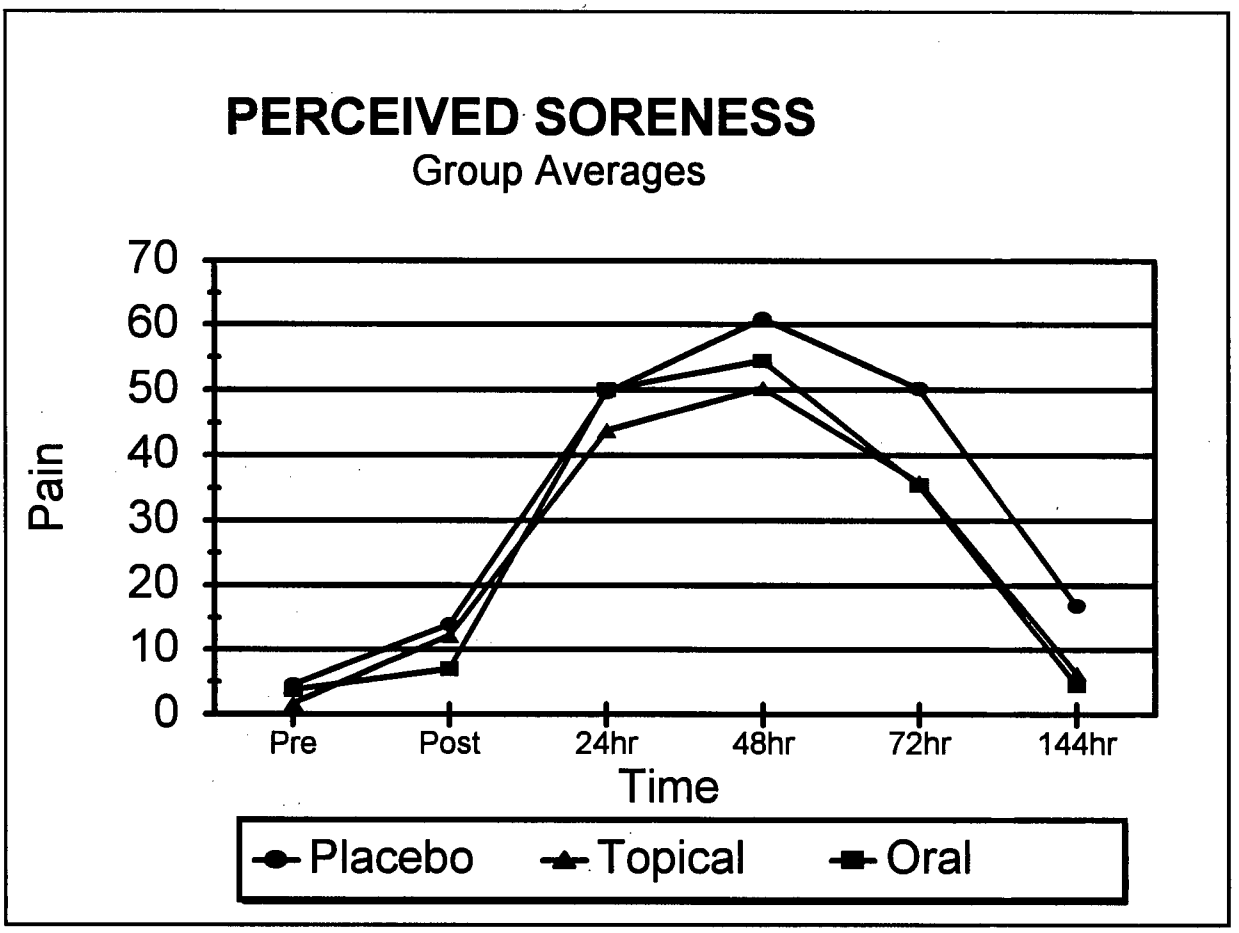
The location of soreness was consistent for all subjects, regardless of group. There was generalized soreness throughout the biceps muscle, however, this was more concentrated at the insertion point / musculo-tendinous junction of the biceps.

As shown in Figure 5 the time course of pain for delayed onset muscle soreness in each group followed a similar pattern. Peak soreness was consistent for all three groups. Both treatment groups had returned to their base line by the end of the seven

day testing period. The placebo group remained slightly elevated above base line at 144 hours. Although this does seem to represent a trend, a t-test was performed and this elevation was not statistically significant ($p=0.055$).

Prior to the exercise protocol subjects' did not mark any soreness. Immediately post exercise there is a slight rise in recorded pain among groups. This is probably because after the exercise subjects sometimes have difficulty differentiating between muscle fatigue or muscle weakness and pain. By 24 hours there was a significant increase in pain $p<0.0005$ from base line pain ratings. Although peak soreness occurred at 48 hours, the placebo group displayed the highest average (60.95mm) and the topical ibuprofen group the lowest (50.35m). At 72 hours pain started to decrease. From the 48 hour pain measurement to the day 7 measurement the placebo group displayed a higher pain rate than the two treatment groups.

FIGURE 5:



In Table 8 the results of the 3(group) x 6(time) randomized group ANOVA with repeated measures on the last factor for perceived pain are summarized. There was no statistical significance between the groups for perceived pain ($p=0.302$). Although the difference was not significant a trend does seem to exist.

TABLE 8

Perceived Pain - ANOVA Summary

SOURCE	SS	DF	MS	F	P
GROUP	2099.236	2	1049.618	1.251	0.302
ERROR	22654.88	27	839.069		

Torque

Table 9 shows the data found from the torque measurements. Due to the Kin Com's computer malfunctions, data from only 29 of the 30 subjects was used for this portion of the study. Post torque data for subject EA was lost and thus her torque data was discarded.

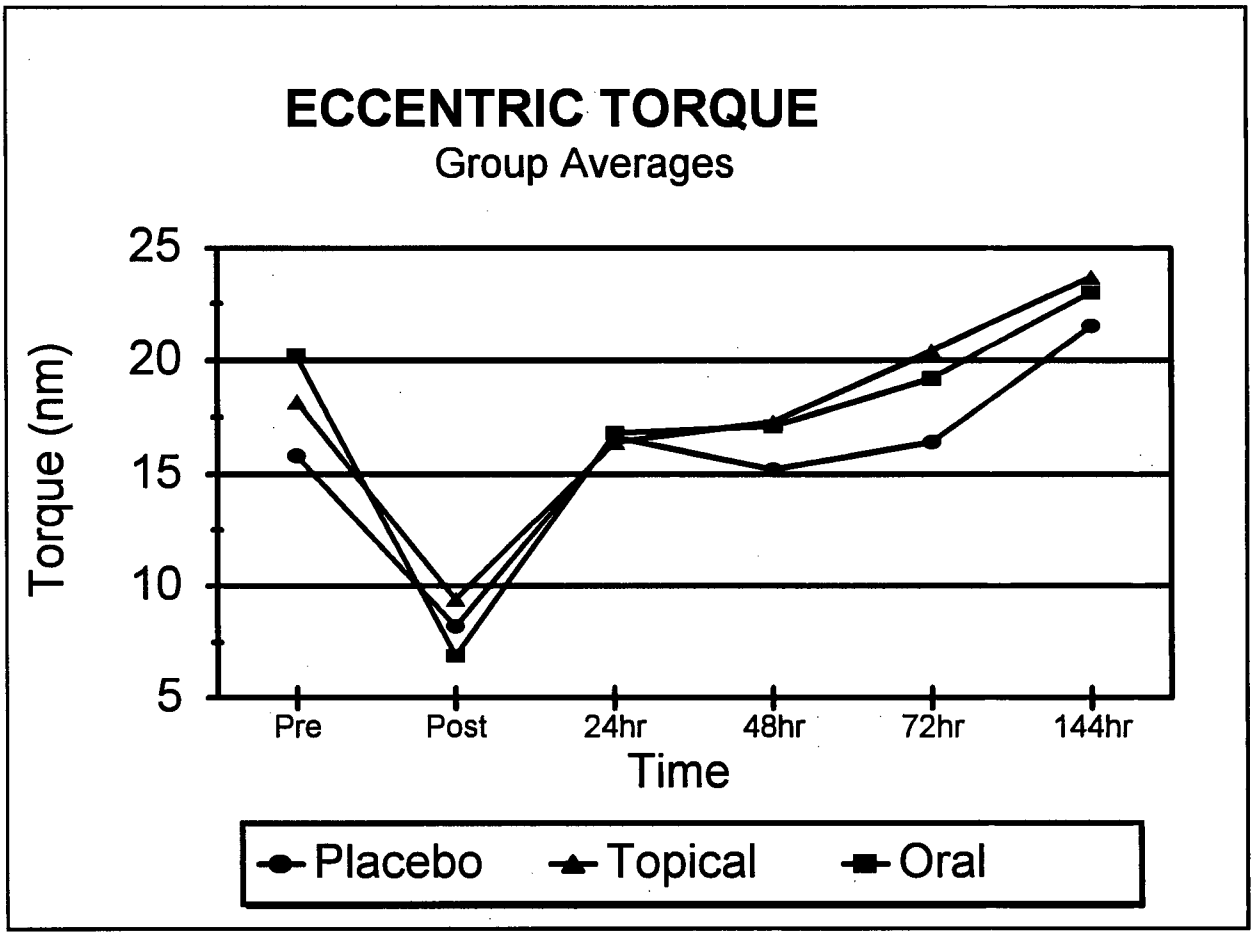
TABLE 9

Summary of Torque for the 3 Groups

		Pre	Post	24hr	48hr	72hr	144hr
Placebo	AVG	15.8	8.2	16.6	15.2	16.4	21.5
n=10	SD	5.92	5.43	6.85	7.22	6.74	7.38
Topical	AVG	18.2	9.4	16.5	17.3	20.4	23.7
n=10	SD	4.64	4.22	6.56	4.52	8.16	6.33
Oral	AVG	20.20	6.89	16.80	17.10	19.20	23.00
n=9	SD	6.21	2.80	7.63	3.96	6.41	6.02

Figure 6 displays the torque data. There is a marked drop in torque from base line to immediately following the exercise ($p<0.0005$). This is to be expected. At 24 hours subjects in all groups are regaining their strength (placebo=16.6, topical=16.5 and the oral=16.80). At 48 hours torque values remained relatively the same as at the 24 hour testing period. All groups had returned to their baseline torque values by 72 hours. At this time the largest difference between groups was also seen with the placebo group having an average torque of 16.4, the oral group an average of 19.2 and the topical group an average of 20.4. A t-test was performed for the placebo and topical treatment group at 72 hours, no statistically significant difference was found ($p=0.263$). By 144 hours the three groups had all surpassed their base line torque values. This elevation from base line to day 7 was found to be statistically significant $p<0.0005$. This is not uncommon because eccentric movement is a learned response, that is, with practice scores can be improved.

FIGURE 6


ECCENTRIC TORQUE
Group Averages
Torque (nm)
25
20
15
10
5
Pre
Post
24hr
48hr
72hr
144hr
Time
Placebo
Topical
Oral

A summary of the 3(group) x 6(time) ANOVA of torque values when compared by groups is shown in Table 10. Statistical analysis revealed there was no statistically significant difference between groups (p=0.616).

TABLE 10

Torque - ANOVA Summary

BETWEEN SUBJECTS					
SOURCE	**SS**	**DF**	**MS**	**F**	**P**
GROUP	129.406	2	64.703	0.493	0.616
ERROR	3406.054	26	131.117		
WITHIN SUBJECTS					
SOURCE	**SS**	**DF**	**MS**	**F**	**P**
torque	3113.411	5	622.682	36.79	0
torque*GROUP	128.813	10	12.881	0.761	0.666
ERROR	2200.313	130	16.925		

PART II: BLOOD IBUPROFEN LEVELS

Subjects' characteristics for this part of the study are shown below in Table 11.

Therapeutic levels of ibuprofen in the Fraser Valley area range from 5-49mg/L. As shown in Tables 12 & 13 ibuprofen concentrations in this study range from 1.74mg/L to 38.8mg/L after oral administration and from 0.0915mg/L to 0.518mg/L after topical administration.

TABLE 11

Average Clinical Characteristics of Subjects in Part II

Subjects	5
Age (years)	20.2
STDEV	1.92
Height (cm)	165.42
STDEV	5.52
Weight (kg)	57.768
STDEV	3.6
Bicep Length (cm)	26.125
STDEV	1.31
Bicep Skin Fold (mm)	5.4
STDEV	1.52

TABLE 12: AVERAGE ORAL BLOOD IBUPROFEN CONCENTRATIONS (mg/L)

	NM	AL	RM	ND	KH	AVG
Pre	0.012	0.01	0.029	0	0	**0.0102**
Day 3	8.69	15.05	4.49	7.65	38.88	**14.952**
Day 5	4.61	14.6	3.46	4.735	24.91	**10.463**
Day 7	*1.74	10.5	**	7.66	29.2	**9.82**
Average	5.013	13.38	3.975	6.6816	30.9966	

NOTE: Averages of the 3 days

*One dosage wasn't taken - for ANOVA data was extrapolated from pattern averages of other subjects.

**Data lost - for ANOVA data was ectrapolated from pattern averages of other subjects.

TABLE 13: AVERAGE TOPICAL BLOOD IBUPROFEN CONCENTRATIONS (mg/L)

	NM	AL	RM	ND	KH	AVG
Pre	0.047		0		0.01	**0.013**
Day 3	0.42	0.267	0.151	0.16	0.148	**0.230**
Day 5	0.51	0.25	0.172	0.091	0.248	**0.256**
Day 7	0.46	0.23	0.095	0.177	0.238	**0.24**
Average	0.46	0.2511	0.1393	0.42	0.2118	

NOTE: Averages of the 3 days

Subjects individual blood results are depicted in the Graphs in Figures 7,8,9,10 & 11. Subject RM data was lost for day 7 oral treatment. Subject NM has high variability during the oral ibuprofen treatment period. One should note however, that when subject NM had an ibuprofen concentration of 1.74mg/L after oral administration she had forgotten to take one dosage of ibuprofen (400mg). This obviously effected her plasma concentration since her other two samples yielded levels of 8.69mg/L and 4.61 mg/L on days 3 and 5 respectively.

FIGURE 7 & 8

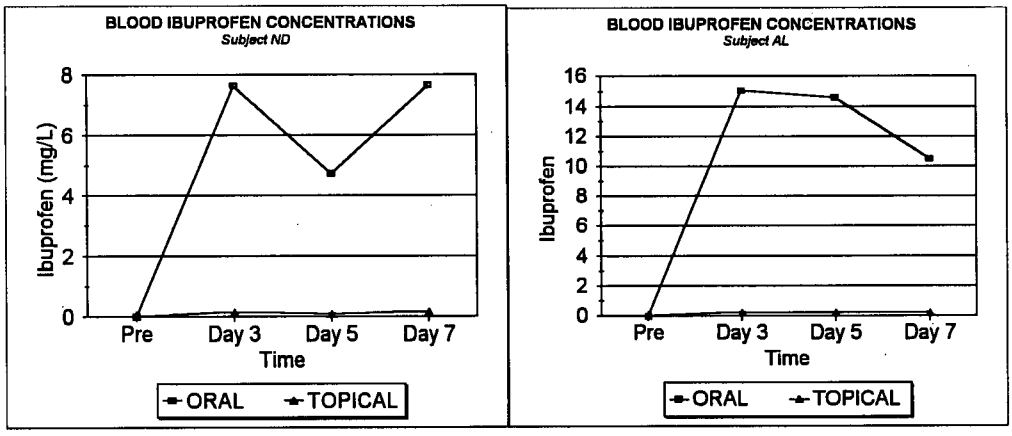


FIGURE 9 & 10

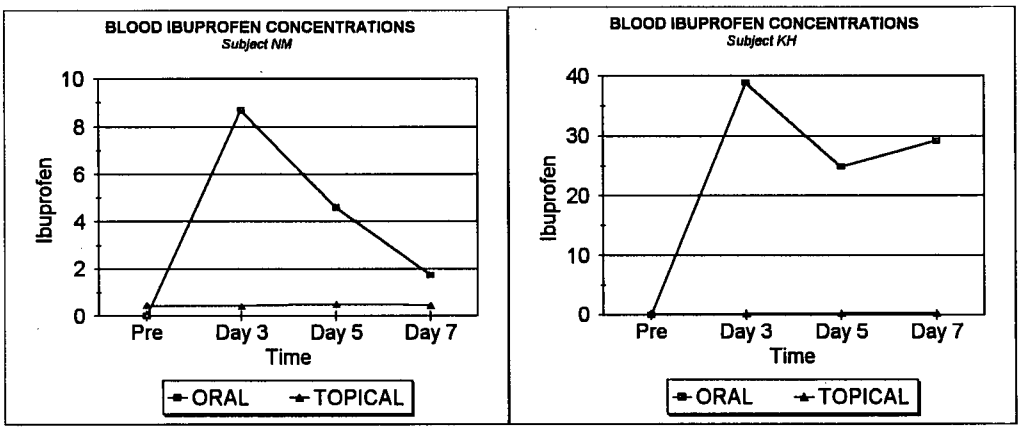
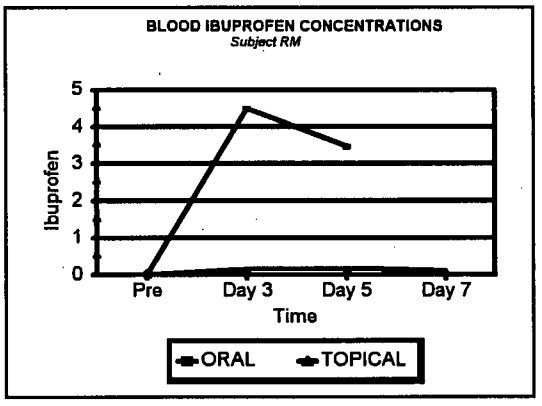
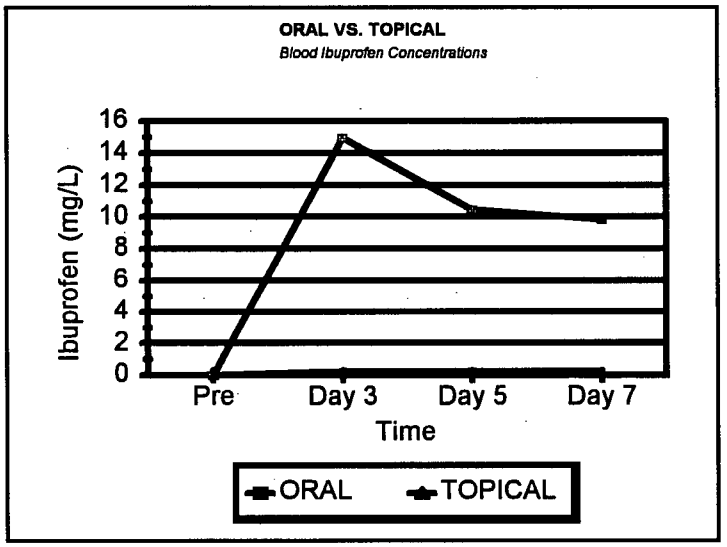


FIGURE 11:



The Graph in Figure 12 shows the pattern of average blood ibuprofen concentrations over the seven day treatment periods after both oral and topical administration. Baseline values, averaging 0.0102mg/L and 0.0133mg/L, show that no ibuprofen was present in the systemic system prior to either treatment period thus any ibuprofen detected later was due to the treatment with ibuprofen either orally or topically. Oral ibuprofen concentrations were the highest on day 3, with an average of 14.952mg/L, while after topical administration concentrations were highest on day 5, with an average of 0.2564mg/L.

FIGURE 12:



Statistical analysis (2 x 3 Repeated Measures ANOVA) shows a statistically significant difference in blood ibuprofen concentrations between the two modes of administration, $p<0.01$ (see Table 14).

TABLE 14: BLOOD IBUPROFEN CONCENTRATIONS - ANOVA SUMMARY

SOURCE	SS	DF	MS	F	P
Between subjects	725.873	4			
Within subjects					
Group	1091.3355	1	1091.3355	27.17	<0.01
Day	27.19	2	13.595	0.3385	
Group x Day	28.1855	2	14.09	0.3509	
Residual	803.19	20	40.16		
Total	2675.74	29			

Chapter 5

DISCUSSION

In the present study a topical ibuprofen gel was analyzed in the treatment of delayed onset muscle soreness. It was compared to an equivalent dose of its oral counterpart and to a placebo. It was hypothesized that topical ibuprofen would be more effective than a placebo and equally as effective as oral ibuprofen in the treatment of delayed onset muscle soreness. Drug effectiveness was analyzed using two measures: perceived pain and eccentric torque. The findings do not show statistically significant differences in either pain scores or torque between the three groups over time. However, following the intense eccentric exercise program subjects did experience delayed onset muscle soreness. There was a significant increase in pain scores from baseline measures and this peaked at 48 hours. In addition, subjects' experienced a significant decline in torque output following the exercise bout. Thus, the lack of siginificant findings was not a result of the exercise used.

Results here support the findings of other researchers who have found that NSAIDs have no effect in treating DOMS. However, as always with research, there are studies that provide conflicting results, including our pilot study. The different results between the findings here and in the pilot study could be a result of the varying application of the topical ibuprofen drug. In the pilot study an occlusive dressing was applied over the gel. This has been shown to enhance skin penetration rates. However, this does not explain the lack of significance in the oral ibuprofen group.

As with most studies involving human subjects, researchers cannot control for every variable. Subject compliance to medication, medication times, and alternative modes of self-induced therpay can all become confounding variables in the study. In addition, although untrained subjects were used, people's past training levels may effect results. Severity of DOMS induced or in their experience of DOMS and what they consider painful may vary considerably with past experience.

Other researchers who have found no effects in DOMS with the treatment of NSAIDs conclude that they are not effective in alleviating DOMS. Furthermore, Kuipers et al. (1985) go as far as stating that prostaglandins are not of importance in exercise-induced inflammation. This may be a premature conclusion due to the designs and group sizes used by some of these researchers and because there is also evidence that finds NSAID therapy to be effective in DOMS. Bansil et al. (1985), and Hasson et al. (1993) have both found aspirin and ibuprofen respectively to decrease pain associated with exercise-induced muscle damage. In addition, Francis and Hoobler (1987) found a significant difference in pain scores between the placebo group and the aspirin group at 48 hours.

Research in the treatment of DOMS with nonsteroidal anti-inflammatory drugs has produced inconclusive results. Findings vary in the effectiveness of these drugs in providing relief of pain and anti-inflammatory effects. Hasson et al. (1993) found that oral ibuprofen taken both prophylactically and post exercise significantly decreased

perceived pain. In addition, the pilot study conducted for this research showed a significant difference in perceived pain between the placebo group and the group treated with a 5% ibuprofen gel. These studies contradict research by Donnelly et al. (1985) and Kuipers et al. (1989) who both found no effects in DOMS after NSAID therapy. One should note, however, that Kuipers et al. bases his findings on a study in which subject dosage of flurbiprofen are minimal, only 50mg 3 times per day. Furthermore, the six subjects participated in a cross-over design that utilized only a 3 week interval between the two tests. Since the efffects of DOMS may last up to ten weeks, the second trial results may be confounded. In the case of Donnelly et al. higher serum creatine kinase and urea levels were found in the ibuprofen group as compared to the placebo group. This may reflect higher levels of muscle damage in the ibuprofen group. Finally, both studies only followed subjects for a three day period. Results from this study show the placebo group maintain an elevation over their baseline pain scores at day 7 therefore it may be necessary to continue treatment and testing for at least a week.

There is extensive documentation in the benefits of NSAID therapy in the inflammatory response. However, to accurately study NSAIDs effects on delayed onset muscle soreness researchers will need to try and decrease some of the variability that seems to be inherent in past DOMS studies, use larger subject sizes, and continue treatment for a minimum period of seven days. Although this study does not reach statistical significance, the hypothesis should not be quickly discarded. One must consider the

possibility that the decreased statistical significance was a function of the high variability between subjects.

Pain is a hard variable to analyze. If someone complains that they are in pain then they are in pain. People rate and tolerate pain differently. It is a subjective measure and commonly, as in this study, yields high variablity. Although, the visual analogue scale is the measure most commonly used in measuring pain associated with DOMS it does have its limitations because it is still a subjective measure. Some researchers suggest trying to take the emotional component out of pain scores by using probes or the DDS questionnaire. MacIntyre et al. (1994) analyzed the DDS and found it to correlate highly with the visual analogue scale, with an r=0.85.

Recorded pain scores do seem to show a slight trend in favor of ibuprofen, both topically and orally. The high standard error of the mean associated with DOMS may have decreased our p value. Other studies that also manage to produce DOMS often show high variability in subjects' perceived pain (Ciccone, 1991; Frankin et al., 1991; Kuipers et al., 1985; Schwane et al., 1983).

Torque values also did not show a difference between groups. The fact that eccentric activity is often a novel activity explains why it can improve with practice. This study used subjects who were untrained in activities of the biceps and thus can partly explain the pattern the torque values followed. That is, by 144 hours, torque had increased significantly over baseline values, suggesting a learning effect did occur. Subjects had

been exposed to the eccentric motion expected in the exercise regime prior to the test but may have needed further exposure.

Researchers have alluded to the concept that muscles will often recruit additional fibers to perform the same movement used to induce DOMS as a protective mechanism for the injured fibers.

The second aim of this thesis was to determine the plasma levels of ibuprofen after oral and after topical treatment with ibuprofen. Statistically significant differences in plasma ibuprofen concentrations were found after the two modes of administration ($p=0.033$). There was a large difference between subjects in blood ibuprofen concentrations after oral administration. Subjects ranged from 1.74 mg/L to 38.88 mg/L. The levels found are, however, similar to the therapeutic plasma concentrations found in the Fraser Valley area, ranging 5 to 49 mg/L. Results show that after topical administration concentrations were minimal, ranging from 0.0915mg/L to 0.518 mg/L. Thus very small amounts of ibuprofen are entering the systemic system after topical administration. This supports fingings by Chaterjee, 1972; Chlud et al., 1987; Diebschlag et al.1990; Peters et al., 1987; and White, 1991.

To explain the large range in concentration differences between subjects one must look at numerous factors: subject age and size; plasma composition; absorption rate; genetics; compliance; drug tolerance; skin composition; and subjects' ability to metabolize the drug. Data showed that subjects NM and RM did not consistently reach

therapeutic levels even after oral administration while subject KH was on the high end of the therapeutic range. It is interesting to note that subjects NM and RM are sisters. Their levels may be lower for any one or for a combination of any of the above mentioned factors.

This decrease in plasma ibuprofen concentrations after topical application is thought to lead to a decrease in the associated side effects. However, because ibuprofen dosages in this study were relatively minimal (400mg 3x/day) and treatment was short (7 days) no side effects were reported with either oral or topical ibuprofen. Therefore, from this study, we cannot directly conclude that topical therapy results in a decrease of side effects. If lower blood levels do correspond to fewer side effects this alternative method of NSAID therapy should be investigated further.

Chapter 6

SUMMARY

SUMMARY

This study was designed to investigate the efficacy of topical ibuprofen in the treatment of delayed onset muscle soreness in relation to pain and torque. Furthermore, blood was analyzed to determine plasma levels of ibuprofen after topical administration as opposed to after oral administration.

An eccentric exercise regime was utilized to induce DOMS in subjects nondominant biceps. Subjects were randomly divided into three groups; a placebo group, a topical ibuprofen treatment group and an oral ibuprofen treatment group. Perceived pain and eccentric torque were monitored and analyzed on six separate occassions over a seven day period.

To examine resulting blood levels after topical and oral administration five subjects participated in a 3 week cross-over design. DOMS was induced as in the first part of the study. During the first treatment period one arm was exercised and one mode of administrating ibuprofen used. This was followed by a seven day washout period and then the second treatment period. The opposite arm and mode of administering ibuprofen was used in the second phase as compared to that in the first treatment phase. Venous blood samples were taken eight times throughout the study. The samples were then assayed for ibuprofen.

It was hypothesized that the percutaneous administration of topical ibuprofen would be more effective than a placebo and as effective as oral ibuprofen in treating delayed onset muscle soreness. Subjects in the treatment groups would show a faster return of eccentric torque and less muscle soreness. Furthermore, it was hypothesized that the administration of oral ibuprofen would result in higher concentrations of ibuprofen in the plasma than the administration of its topical counterpart.

CONCLUSIONS

Based on the findings from this study, we can conclude that:

1. The treatment of delayed onset muscle soreness with topical or oral ibuprofen does not significantly effect pain scores when compared to a placebo.

2. The treatment of delayed onset muscle soreness with topical or oral ibuprofen does not significantly effect return of eccentric torque when compared to a placebo.

3. The mode of administration of ibuprofen does significantly effect the plasma ibuprofen levels. Following oral treatment plasma ibuprofen levels are approximately 58 times greater than after the topical treatment of an equivalent amount. In fact, after topical administration ibuprofen plasma levels are extremely low, often below reported therapeutic levels.

RECOMMENDATIONS

Based on these current findings and those of other researchers, the efficacy of topical nonsteroid anti-inflammatory drugs in the treatment of inflammatory conditions remains inconclusive. The fact that other studies have found the benefits of topical NSAIDs to be statistically significant and that the present study, although not statistically significant, does show a positive trend for topical ibuprofen it would not be prudent to dismiss this alternative mode for NSAID therapy. Because this study does show the low levels of systemic ibuprofen attained after topical ibuprofen therapy the side effects would be greatly reduced. The study of this mode should continue because this may be a plausible alternative to oral NSAIDs if it is found to be effective. The following are some reccommendations that may be utilized for future studies:

1. If possible, a more stringent control of variables should be taken. This may include: investigators applying the drug themselves to control for time of application and adherance to each dose and stricter subject inclusion-exclusion criteria to control intersubject variability.

2. The effectiveness of topical NSAIDs should be examined under various other models of inflammation. The fact that in this study neither oral nor topical ibuprofen was effective in the treatment of DOMS suggests that maybe an alternative inflammatory model should be investigated.

3. Similarly because neither treatments were effective in treating DOMS the dosage of treatment could be increased. In the present study, minimal dosages were used (400mg 3x/day). If doses were increased a statistcally significant difference may be found.

4. In order to look directly at the anti-inflammatory effects of the topically applied NSAID researchers must analyze inflammatory markers: WBC infiltration (monocytes and neutrophils), prostaglandin concentrations and CPK.

5. In order to minimize any learning effect that may occur subjects could have more than one introductory period to the eccentric exercise prior to the exercise bout. Researchers should use caution so as not to 'train' the muscle group under investigation and thus potentially diminish the desired effect of delayed onset muscle soreness.

6. Analysis of ibuprofen concentrations in underlying tissue after topical therapy would provide necessary information regarding the penetration ability of the percutaneous drug. This would show whether or not effective therapeutic levels are being reached in underlying structures. Studies that followed similar procedures as utilized by Peters et al. (1987) may be more effective than traditional biopsies.

7. To further analyze the effectiveness of topical ibuprofen in the treatment of delayed onset muscle soreness researchers should utilize the design used in this pilot study. That is, the 300 eccentric quadriceps contractions used to induce DOMS and the occlusive dressing applied on the gels. Data from this study dictates an N=46 to achieve a power of 0.81.

Because NSIAD therpay is so widespread and associated side effects are so frequent it would be premature to discard this mode of administration so quickly. If the effects of topical treatment is found to be statistically significant the benefits may be tremendous. Further investigation is therefore needed before any conclusive statements are made.

REFERENCES

Abramson, Steven. et.al. Modes of action of aspirin-like drugs. *Proc. National Acad. Sci USA* 82:7227-7231, 1985.

Abramson, Steven B. Non-steroidal Anti-inflammatory Drugs: Mechanisms of action and therapeudic considerations. *Sports-Induced Inflammation*: 421-429, 1989.

Almekinders, Louis C. Anti-inflammatory treatment of muscular injuries in sports. *Sports Med* 15(3): 139-145, 1993.

Almekinders, Louis C. and Gilbert, J.A. Healing of experimental muscle strains and the effects of nonsteroidal anti-inflammatory medication. *Am J Sports Med* 14(4): 303-308, 1986.

Armstrong, R.B. Mechanisms of exercise-induced delayed onset muscular soreness: a brief review. *Med Sci Sports Excerc.* 16(6): 529-538, 1984.

Armstrong, R.B. Initial events in exercise-induced muscular injury. *Med Sci Sports Excerc.* 22(4): 429-435, 1990.

Black, Howard M., et. al. Use of Phenylbutazone in sports medecine: understanding the risks. *Am J Sports Med.* 8(4): 270-272, 1980.

Blank, IH., and RJ. Scheuplein The Epidermal Barrier. *Progress in the Biological Sciences in Relation to Dermatology.* 2: 245-261, 1964.

Bobbert, MF., Hollander, AP., and PA. Huijing. Factors in Delayed Onset Muscular Soreness of Man. *Med Sci Sports Excerc* 18(1): 75-81, 1986.

Bouchier-Hayes, T.A., Rotman, H. and B.S. Darekar. Comparison of the Efficacy and Tolerability of Diclofenac gel (Voltarol Emulgel) and Felbinac gel (Troxam) in the Treatment of Soft Tissue Injuries. *BJCP* 44(8):319-320, 1990

Bourne. The effect on healing of analgesic anti-inflammatory therapy. *Br J Sports Med* 14: 26-27, 1980.

Brune, K. Prostaglandins, Inflammation, and Anti-inflammatory Drugs. *Eur J of Rheum Inflam.* 5: 335-349, 1982.

Buchnan, et. al. Aspirin and nonacetylated salicylates: use in inflammatory Injuries incurred during sporting activities. *Sports-Induced Inflammation* 431-439, 1989.

Camu, Frederick. et. al. Cardiovascular Risks and Benefits of Perioperative Nonsteroidal Anti-inflammatory Treatment. *Drugs* 44(supp.5):42-47, 1992

Camus, J. et. al. Plasma Levels of Polymorphonuclear Elastase and Myeloperoxidase after Uphill Walking and Downhill Running at Similar Energy Cost. *Int J Sports Med* 13: 443-446, 1992.

Chatterjee, D.S. A Double Blind Clinical Study in Benzydamine 3% Cream on Soft Tissue Injuries in an Occupational Health Center. *J Int Med Res* 5: 450-458, 1972

Chavez, Edmundo. et. al. Ianophoretic-like action of Diflunisal. *Life Sciences* 37: 1491-1498, 1985.

Chien, Y.W. Transdermal Drug Delivery and Delivery Systems. *Drugs and Pharmaceutical Sciences 2nd Ed.* Marcel Dekker Inc., New York, 50: 301-380, 1992

Chlud, K., and H.H. Wagnener. Percutaneous Non-Steroidal Anti-inflammatory (NSAID) Therapy With Particular Reference to Pharmacokinetic Factors. *EULAR Bulletin* 2: 40-43, 1987

Chlud, K. Perkutane therapie der schmerzhaften arthrose. *Therapeutische umschau* 48:42-45, 1991

Ciccone, C.D., Leggin, B.G., and J.J. Caliamaro. Effects of Ultrasound and Trolamine Salicylate Phonophoresis on Delayed Onset Muscle Soreness. *Physical Therapy* 71(9): 666-675, Sept. 1991

Clark, A. et. al. Differential effects of aspirin and dexamethasone on phospholipase A2 and C activities and arachidonic acid release from endothelial cells in response to bradykinin and leikotriene D4. *Prostaglandins* 32(5): 703-707, 1986.

Cleak, M.J., and R.J. Eston. Delayed onset muscle soreness: Mechanisms and management. *J Sports Sci* 10:325-341, 1992.

Clement, Douglas B. New agent may help in soft tissue therapy. *Phys Sports Med* Sept: 45-47, 1975.

Clissold, Stephen P. Aspirin and related derivatives of salicylic acid. *Drugs* 32(supp 4): 8-26, 1986

Clyman, Bill. Role of non-steroidal anti-inflammatory drugs in sports medicine. *Sports Med* 3:242-246, 1986

Cooper ER. Increased Skin Permeability for Lipophilic Molecules. J *Pharm Sci* 73(8): 1153-1156, 1984

Cooper, ER., Merritt, EW, and RL Smith. Effect of Fatty Acids and Alcohols on the Penetration of Acyclovir Across Human Skin In Vitro. J *Pharm Sci* 74: 688-689, 1985.

Dahners, Laurence. et. al. The effects of nonsteroidal anti-inflammatory drugs on the healing of ligaments. *J Sports Med* 16(6): 641-646, 1988.

Diebschlag, W., Nocker, W., and R. Bullingham. A Double-Blind Study of the Efficacy of Topical Ketorolac Tromethamine Gel in the Treatment of Ankle Sprains, in Comparison to Placebo and Etofenamate. *J Clin Pharmacol* 30: 82-89, 1990.

Donnelly, A.E., Maughan, R.J., and P.H. Whiting. Effects of ibuprofen on exercise-induced muscle soreness and indices of muscle damage. *Br J Sports Med* 24(3): 191-195, 1985.

Duarte, J.A., Soares, J.M., and H.J. Appell. Nifedipine diminishes exercise-induced muscle damage in mouse. *Int J Sports Med.* 13:274-277, 1992.

Downie, W.W. et. al. Studies with Pain Rating Scales. *Annals of the Rheamatic Diseases.* 37: 378-381, 1978.

Duncan, John and Farr, James. Comparison of diclofenae sodium and aspirin in the treatment of acute sports injuries. *Am J Sports Med* 16(6): 656-659, 1988.

Ebert , CD, Heiber, W., Andriola, R., and P. Williams. Development of a Novel Transdermal System Design. *J Controlled Release.* 6: 107-111, 1987.

Evans, WJ. Exercise-Induced Skeletal Muscle Damage. *Phys Sports Med* 15(1): 89-100, 1987.

Evans, W.J. and J.G. Cannon. The metabolic effects of exercise-induced muscle damage. *Exercise Sport Sci Reviews.* p.99-119. Edited by J.O. Holloszy. Williams & Wilkins Co., Baltimore, 1991.

Fantano, S. and M. DeGregorio. Clinical Evaluation of Topical Benzydamine in Traumatology. *Arzneim-Forsch.* 21(10): 1530-1533, 1971.

Farrell, M., and J.G. Richards. Analysis of the Reliability and Validity of th Kinetic Communicator Exercise Device. *Med Sci Sport Exerc* 18(1): 44-49, 1986.

Fitch, Kennneth and Gray, Stuart. Idomethacin in soft tissue sports injuries. *Med J Aus* 1:260-263, 1974.

Fitzgerald, G.K. et. al. Exercise-Induced Muscle Soreness After Concentric and Eccentric Isokinetic Contractions. *Physical Therapy* 71(7): 505-513, 1991 July.

Francis, KT. and T. Hobbler. Effects of Aspirin on Delayed Muscle Soreness. *J Sports Med 27:* 333-337, 1987.

Franklin, ME. et. al. The Effect of One Session of Muscle Soreness-Inducing Weight Lifting Exercise on WBC Count, Serum CK, and Plasma Volume. *J Orthopaedic and Sports Physical Therapy* 13(6): 316-321, 1991.

Fred, Herbert L. Reflections on a 100-mile run: effects of aspirin therapy. *Med Sci Sports Exerc* 12(3): 212-215, 1980.

Fredburg, Ulrich et. al. Ibuprofen in the treatment of acute ankle joint injuries. *Am J Sports Med* 6: 336-339, 1985

Friden, J., Sjostrom, M., and Ekblom, B. Myofibrillar damage following intense eccentric exercise in man. *Int J Sports Med.* 4:170-176, 1983.

Giese, U. Absorption and distribution of ibuprofen from a cream formulation after dermal administration to guinea pigs. *Arzneim-Forrsch.* 40(I): 1990.

Goldstein, Ira M. Agents that interfere with arachidonic acid metabolism. Inflammation: *Basic Principles and Clinical Correlates.* 935-946, 1988.

Guy, RH., Hadgraft, J., and HI Maibach. A Pharmokinetic Model for Percutaneous Absorption. *Int J Pharmaceutics.* 70: 119-129, 1982.

Guy, RH., Hadgraft, J., and HI Maibach. Percutaneous Absorption in Man: A Kinetic Approach. *Toxicology and Applied Pharmacology.* 78: 123-129, 1985.

Gyires, K. Some of the factors that may mediate or modify the gastrointestinal mucosal damage induced by non-steroidal anti-inflammatory drugs. *Agents Actions.* 41: 73-79, 1994.

Hasson, S.M. et. al. Effect of Ibuprofen use on Muscle Soreness, Damage and Performance: A Peliminary Investigation. *Med Sci Sports Exerc* 25(1): 9-17,1993.

Hatherill, J.R., Till, G.O., and P.A. Ward. Mechanisms of oxidant-induced changes in erythrocytes. *Agents and Actions.* 32(3/4): 351-357, 1991.

Hess, Evelyn V. et. al. A rational approach to NSAID therapy. *Rational Drug Therapy.* 20(6): 1-6, 1986.

Higuchi, S. et. al. Two modes of analgesic action of aspirin, and the site of analgesic action of salicylic acid. *Int J Tissue Reactivity.* 8(4): 327-331, 1986.

Hill, DW., and JD. Richardson. Effectiveness of 10% Trolamine Salicylate Cream on Muscular Soreness Induced by a Reproducible Program of Weight Training. *JOSPT.* July: 19-23, 1989.

Holden, Scott C. et. al. The effect of over-the-counter analgesics on physiological responses to rest and exercise. *Sports Med, Training and Rehab.* 3: 29-36, 1991.

Huskisson, E.C. Visual Analogue Scales. *Pain Measurement and Assessment*, edited by Melzak, R., Raven press, New York, 33-37: 1983.

Izumomoto, Taneno et. al. Relationship between the Transference of a Drug from a Transdermal Patch and the Physiochemical Properties. *Chem Pharm Bull* 40(2): 456-458, 1992.

Jenkins, R.R. Free Radical Chemistry Relationship to Exercise. *Sports Med.* 5:156-170, 1988.

Johnson A.G. et. al. Non-steroidal anti-inflammatory drugs and hypertension in the elderly: a community-based cross-sectional study. *BJCP,* 35: 455-459, 1993.

Jones, DA. et.al. Experimental Human Muscle Damage: Morphological Changes in Relation to Other Indices of Damage. *J Physiol* 375: 435-448, 1986.

Kenny, Gavin. Potential Renal, Haematological and Allergic Adverse Effects Associated with NSAIDs. *Drugs* 44(Suppl.5): 31-37, 1992.

Knodel, Leory C. NSAIDs adverse effects and interactions: Who is at risk? *Amer Pharm* 32(3), 1992.

Kuipers et. al. Influence of prostaglandin inhibiting drug on muscle soreness after eccentric work. *Int J Sports Med* 17(4): 564-566, 1989.

Kuipers, H. Exercise-induced muscle damage. *Int j Sports Med.* 15: 132-135, 1994.

Kuna, Samuel T. and Levine, Sanford. Relationship between cyclooxygenase activity (COA) inhibition and stimulation of ventilation by salicyclate. *J Pharm Exper Ther.* 219(3): 723730, 1981.

Larsen, G.L., and P.M. Henson. Mediators of Inflammation. *Immunology.* 1: 335-359, 1983

Leadbetter, Wayne B. An introduction to sports induced soft tissue inflammation. *Sports-Induced Inflammation.*: 3-23, 1989.

Lovlin, R. et al. Are indices of free radical damage related to exercise intensity. *Eur J Appl Physiol.* 56:313-316, 1987.

McCormack, K., and K. Brune. Dissociation between the antinociceptive and anti-inflammatory effects of the nonsteroidal anti-inflammatory drugs: a survey of their analgesic efficacy. *Drugs.* 41(4): 533-547, 1991.

MacIntyre, D., Reid, W.D., and D. McKenzie. Acute inflammation in exercise-induced muscle injury. In Press, 1994.

McLatchie, G.R. et. al. Soft tissue trauma: A randomized controlled trial of the topical application of Felbinac, a new NSAID. *BJCP.* 43(8): 277-280, 1989, Aug.

Malmsten, C.L. Prostaglandins, Thromboxanes, and Leukotrienes in Inflammation. *Am J Med* 80 (suppl 4B): 11-15,1986.

Mather, Lawrence E. Pharmodynamics of NSAIDs in post-operative pain. *Drugs* 44(supp 5): 1-11, 1992.

Miescher, P.A. andP. Wolfgang. Haematological Effects of Non-Narcotic Analgesics. *Drugs* 32(Suppl.4): 90-108, 1986.

Muckle, David. Comparitive study of ibuprofen and aspirin in soft tissue injuries. *Rheumatol rehab* 13: 141-147, 1974

O'Connor, TP. et. al. A Novel Sustained-Release Formulation of Ibuprofen Provides Effective Once-Daily Therapy in the Treatment of Rheumatoid Arthritis and Osteoarthritis. *BCJP.* 47(1), 1993.

Peters, H. et. al. Zur perkutanen kinetik von Ibuprofen. *Akt. Rheumatol.* 12: 208-211, 1987

Poelman, M.C. et. al. Assessment of topical non-steroidal anti-inflammatory drugs. *J Pharm Pharmacol* 41: 720-722, 1989.

Priborsky, J. et.al. Influence of Limonene and Laurocapram on Percutaneous Absorption of Nonsteroidal Anti-inflammatory Drugs. *Arzneim-Forsch* 42(I-21): 116-119, 1992.

Price, D.D. et. al. The Validation of Visual Analogue Scales and Ratio Scale Measures for Chronic and Experimental Pain. *Pain.* 17: 45-56, 1983.

Rabinowitz, J.L. et. al. Comparatize Tissue Absorption of Oral 14C- Aspirin and Topical Triethanolamine 14C-Salicylate in Human and Canine Knee Joints. *J Clin Pharm* 22: 42-48, 1982.

Radermacher, et. al. Diclofenac concentrations in synovial fluids and plasma after cutaneous application in inflammatory and degenerative joint disease. *BJCP* 31: 537-541, 1991.

Riess, V.W. et. al. Die perkutane Resorption von Diclofenac. *Arzneim.-Forsch* 36(II-7): 1092-1096, 1986.

Rodenburg, J.B. et. al. Relationships Between Muscle Soreness and Biochemical and Functional Outcomes of Eccentric Exercise. J *Appl Physiol* 74(6); 2976-2983, 1993 June.

Roderick, P.J., Wilkes, H.C., and T.W. Meade. The gastrointestinal toxicity of aspirin: an overview of randomised controlled trials. *BJCP* 35: 219-226, 1993.

Saurez-Kurtz et. al. Inhibitory effects of Salicylate on contractility in skeletal muscle. *J Pharm Exper Therapeutics*. 230(2): 478-482, 1984.

Schwane, J.A. et. al. Delayed-onset Muscular Soreness and Plasma CPK and LDH Activities After Downhill Running. *Med Sci Sports Exerc* 15(1): 51-56, 1983.

Scott, J. and E.C. Huskisson. Accuracy of subjective measurements made with or without previous scores: An important source of error in serial measurement of subjective states. *Annals of the Rheumatic Diseases* 38: 558-559, 1979.

Scott, J. and E.C. Huskisson. Vertical or Horizontal Visual Analogue Scales. *Annals of the Rheumatic Diseases* 38: 560, 1979.

Seth, P.L. Percutaneous absorption of Ibuprofen from different formulations: Comparitive study with gel, hydrophilic ointment and emulsion cream. *Arzneimittel-Forschung* 43(8): 919-921, 1993 Aug.

Sjodin, B., Westing, Y.H., and F.S. Apple. Biochemical mechanisms for oxygen free radical formation during exercise. *Sports Med.* 10(4): 236-254, 1990.

Smith, L.L. Acute Inflammation: The Underlying Mechanism in Delayed Onset Muscle Soreness? *Med Sci Sports Exerc* 23(5): 542-551, 1991 May.

Smith, LL. et.al. White Blood Cell Response to Uphill Walking and Downhill Jogging at Similar Metabolic Loads. *Eur J Appl Physiol* 58: 833-837, 1989.

Smith, LL. et.al. The Effects of Athletic Massage on Delayed Onset Muscle Soreness, Creatine kinase, and Neutrophil Count: A Preliminary Report. *JOSPT*. 19(2): 93-99, 1994.

Squire, I. and K. Lees. Topical Drug Delivery. *Practitioner* 236: 203-206, 1992.

Sturrock, N., and A.D. Struthers. NSAIDs and Angiotension coverting enzyme inhibitors: a commonly prescribed combination with variable effects on renal function. *BJCP* 35: 343-348, 1993.

Swarbrick, J. et al. Drug permeation through human skin II: Permeability of ionizable compounds. *J Pharm Sci.* 73(10): 1352-1353, 1984.

Swift, G.L. and Rhodes, J. Are non-steroidal anti-inflammatory drugs always necessary? A general practice survey. *BJCP* 46(2), 1992

Tenney, S.M. and Miller, R.M. The respiratory and circulatory actions of salycylate. *Am J Sports Med* 19: 498-508, 1955.

Vanderhoek, Jack Y. and Bailey, J. Marten. Activation of a 15-Lipoxygenase / Leukotriene pathway in human polymorphonuclear leukocytes by the anti-inflammatory agent ibuprofen. *J Biol Chem* 259(11): 6752-6756, 1984.

Vogel, H.G. Mechanical and chemical properties of various connective tissue organs in rats as influenced by non-steroidal anti-rheumatic drugs. *Connective Tissue Research.* 5: 91-95, 1977.

Weiler, John M. Medical modifiers of sports injury: the use of NSAIDs in sports soft tissue injury. *Clin Sports Med* 11(3): 625-642, 1992

Wessel, J. and A. Wan. Effect of Stretching on the Intensity of Delayed-Onset Muscle Soreness. *Clin J Sports Med* 4: 83-87, 1994.

White, S. Topical Non-steriodal Anti-inflammatory Drugs (NSAIDs) in the Treatment of Inflammatory Musculoskeletal Disorders. *Prostaglandins, Leukotrienes and Essential Fatty Acids.* 43: 209-222, 1991.

Yano, T. et. al. Skin Permeability of Various Non-Steroidal Anti-inflammatory Drugs in Man. *Life Science.* 39: 1043-1050, 1986.

Zambraski, Edward J. et. al. Effects of aspirin treatment on kidney function in exercising man. *Med Sci Sports Exerc* 14(6): 419-423, 1982.

APPENDIX I

INDIVIDUAL CLINICAL CHARACTERISTICS OF SUBJECTS

Individual Clinical Characteristics of the Placebo Group Subjects

	TN	CB	SP	MB	SY	TK	AL	SP	AW	SW	Average	Standard Deviation
Age (Years)	20	18	22	20	18	19	18	26	19	18	19.8	2.4
Height (cm)	157.5	160	172.7	157.5	157.5	159.5	160	162.6	161.3	154.9	160.35	4.62087654
Weight (kg)	45	54.4	65.8	52.2	49.9	67	54.4	58.1	53.5	56.7	55.7	6.364432418
B. Length (cm)	23	28	28.5	25	25	23	24	24	26.5	25	25.2	1.81934054
B. Skin Fold (mm)	6	6	9	10	9	13	6	3	10	11	8.3	2.83019434

Individual Clinical Characteristics of the Topical Group Subjects

	JK	AB	CD	AG	KK	EW	MH	RM	KD	JT	Average	Standard Deviation
Age (Years)	19	19	25	18	19	19	18	19	19	23	19.8	2.181742423
Height (cm)	162.6	172.7	172.7	167.6	170	157.5	152.4	170	160	161.3	164.68	6.586167323
Weight (kg)	68	63.5	70.3	61.2	61.2	49.9	52.2	58.96	61.2	70.3	61.676	6.5466926
B. Length (cm)	28	27	26	27	25	25	21	25	25	27	25.6	1.854723699
B. Skin Fold (mm)	6	12	6	8	11.5	5	9	6	12	14	8.95	3.053276928

Individual Clinical Characteristics of the Oral Treatment Subjects

	SS	NS	EA	MD	MA	HB	JL	SA	AM	KM	Average	Standard Deviation
Age (Years)	20	19	20	18	28	26	21	19	21	19	21.1	3.112876483
Height (cm)	172.7	175.3	172.7	167.6	154.9	177.8	149.9	175.3	162.6	157.5	166.63	9.310322229
Weight (kg)	66.7	74.8	61.2	58.1	65.8	62.6	56.7	63.5	53.5	54.4	61.73	6.133522642
B. Length (cm)	30	27	29	27	26	31.5	24	25	25	27	27.15	2.2588714
B. Skin Fold (mm)	11	18	11	8	12	6	10	12	8	8	10.4	3.168595904

APPENDIX I

INDIVIDUAL CLINICAL CHARACTERISTICS OF SUBJECTS

Individual Clinical Characteristics of Subjects in Part II

	ND	KH	AL	RM	NM
Age	20	19	21	23	18
Height	174	162.9	160	162.6	167.6
Weight	60.78	58.96	54.4	53.5	61.2
Biceps Length	28	26	25		25.5
Biceps Skin Fold	8	4	5	5	5

APPENDIX II

INDIVIDUAL PAIN DATA - PART I

Individual Pain Data for the Placebo Group

	Pre	Post	24hr	48hr	72hr	144hr
TN	9	21	42	53.5	21.5	2
CB	7.5	26.5	50	64.5	77.5	55
SP	1	6.5	43.5	46	34	10.5
MB	1	1	77.5	51.5	31.5	1
SY	5	0	25	21.5	7	0
TK	2	23	76.5	98	77	35
AL	6.5	22	57	64	63.5	15.5
SCP	13	6.5	63.5	82	63.5	38
AW	0	10.5	6.5	67.5	94	10
SW	0	22.5	55	61	32.5	1

Individual Pain Data for the Topical Treatment Group

	Pre	Post	24hr	48hr	72hr	144hr
JK	1	2	27.5	25	32	2
AB	3	6	32	49	35	18
CD	0	6	28	43.5	15	2
AG	0	8	61	70	50.5	1.5
KK	0	41.5	51	28.5	4.5	0
EW	9.5	18.5	85	95	74.5	5
MH	0	33	45	55.5	63.5	26
RM	0	0	13	39	8	0
KD	0	3	34.5	35.5	16.5	1.5
JT	3.5	4	61	62.5	59.5	7

APPENDIX II

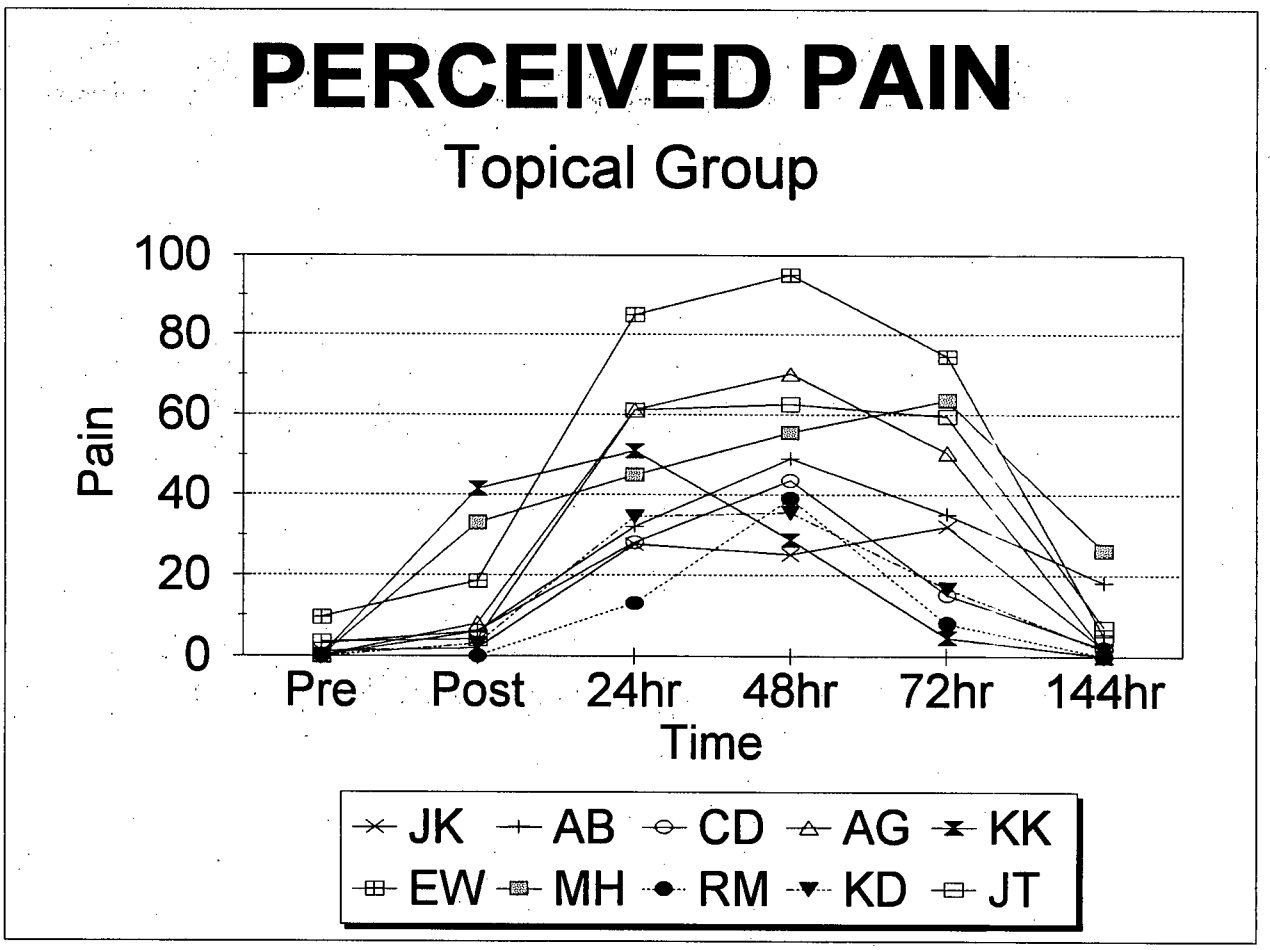
INDIVIDUAL PAIN DATA - PART I

Individual Pain Data for the Oral Treatment Group

	Pre	Post	24hr	48hr	72hr	144hr
SS	32	0	38	43.5	45	4
NS	0	0	13.5	13.5	4	0
EA	0	24	54	74.5	60	10.5
MD	0	8.5	40	39	27	0
MA	3	9	81	55.5	49	3
HB	0	0	32	64	21	0
JL	2.5	20	82	89.5	37.5	22
SA	0	3	61	41.5	30	0
AM	0	0	74	62	46	0
KM	0	5	25.5	62.5	34.5	5.5

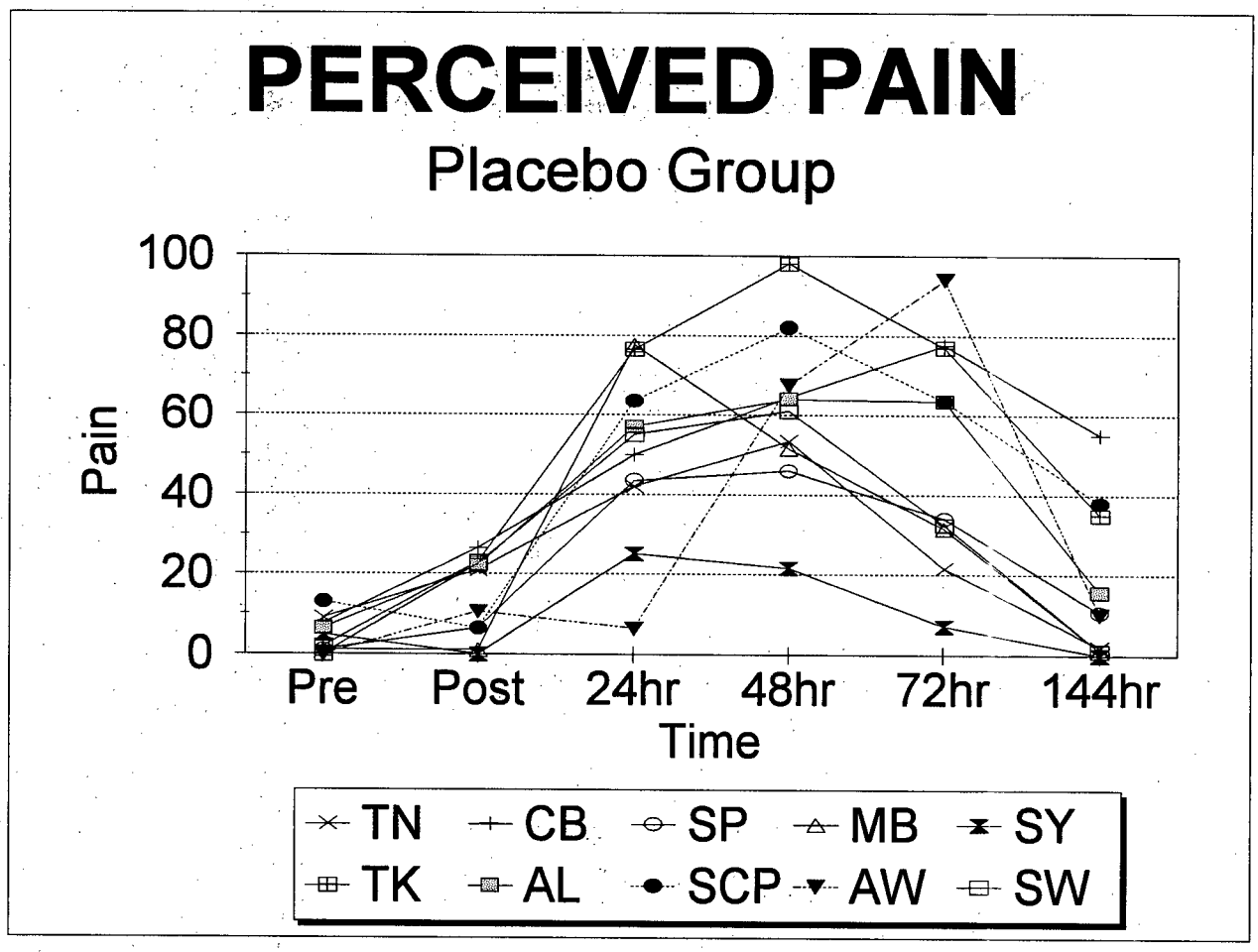
APPENDIX II

INDIVIDUAL PAIN DATA - PART I



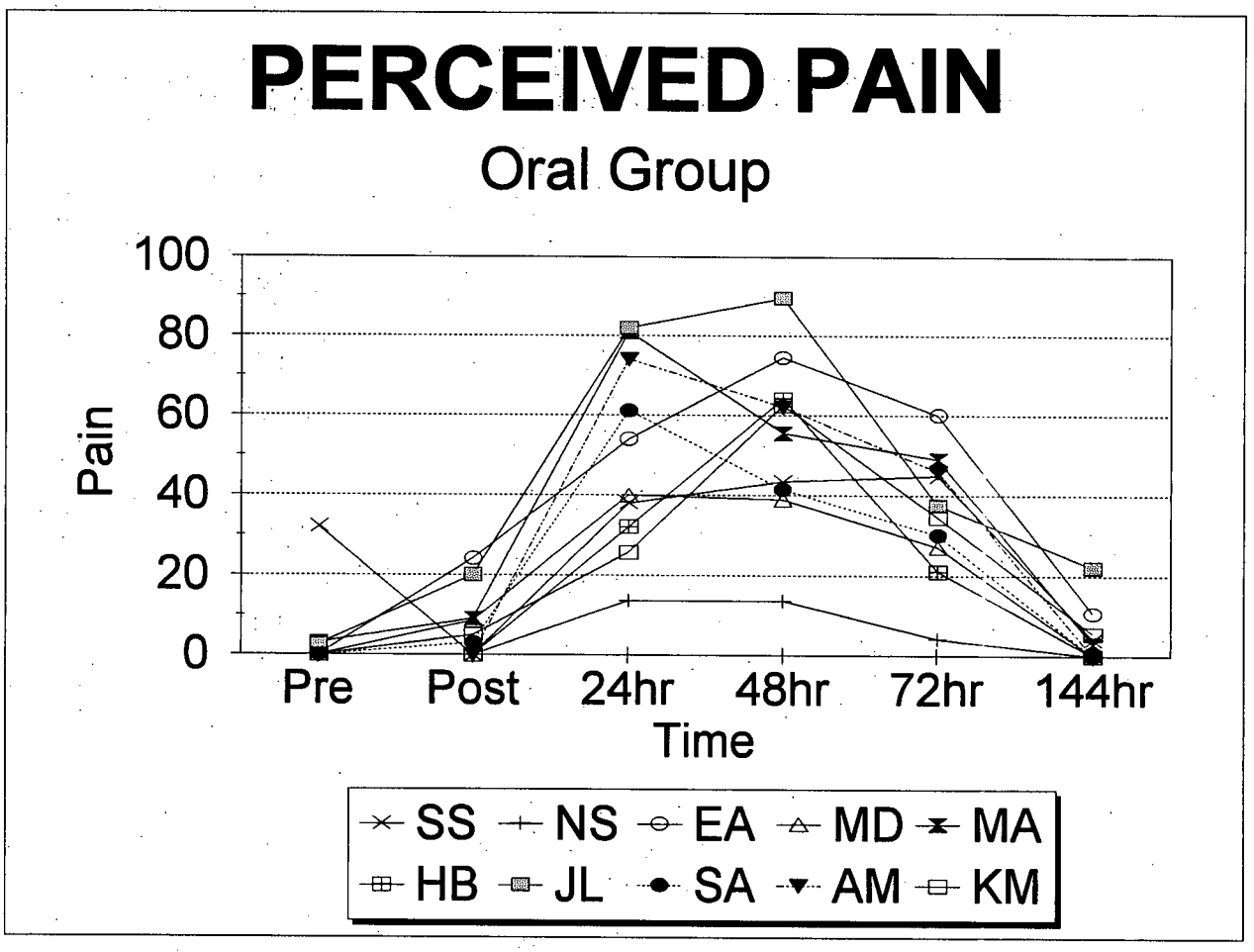
APPENDIX II

INDIVIDUAL PAIN DATA - PART I



APPENDIX II

INDIVIDUAL PAIN DATA - PART I



APPENDIX III

INDIVIDUAL TORQUE DATA - PART I

Individual Torque Data for the Placebo Group

Subject	Pre	Post	24hr	48hr	72hr	144hr
TN	12	10	26	19	22	20
CB	7	3	21	7	6	9
SP	15	8	17	19	27	33
MB	19	7	12	9	14	23
SY	12	12	13	17	17	27
TK	18	4	13	15	13	21
AL	18	6	13	14	12	21
SCP	22	18	23	19	23	21
AW	9	0	4	4	9	11
SW	26	14	24	29	21	29

Individual Torque Data for the Oral Group

Subject	Pre	Post	24hr	48hr	72hr	144hr
SS	15	7	30	19	17	23
NS	30	10	15	21	28	29
EA	25	-	32	21	32	36
MD	18	4	13	16	15	17
MA	27	4	14	18	22	27
HB	24	4	15	22	20	22
JL	10	6	11	9	15	20
SA	15	8	13	14	12	20
AM	18	7	14	16	16	18
KM	20	12	11	15	15	18

APPENDIX III

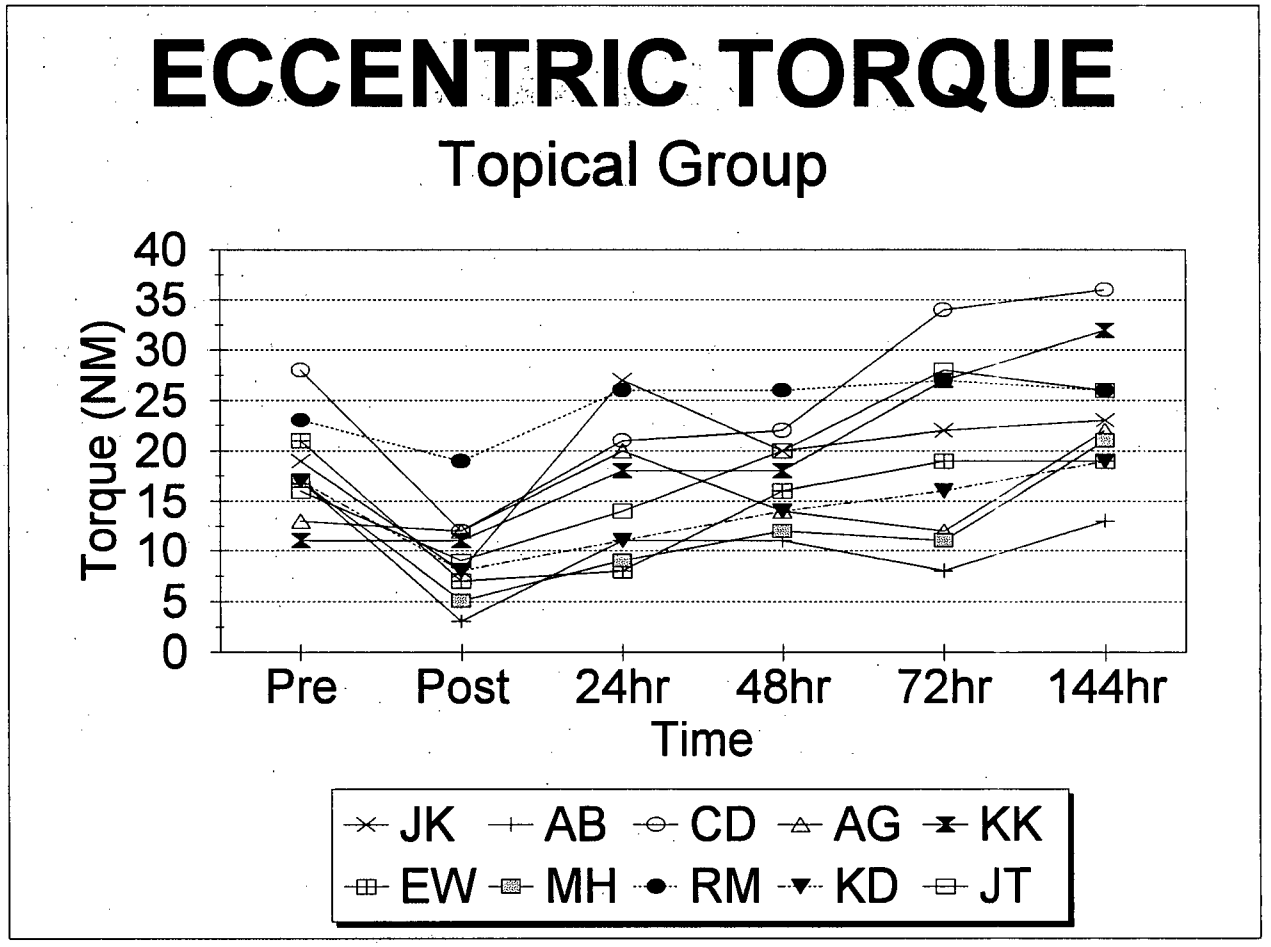
INDIVIDUAL TORQUE DATA - PART I

Individual Torque Data for the Topical Group

Subject	Pre	Post	24hr	48hr	72hr	144hr
JK	19	8	27	20	22	23
AB	17	3	11	11	8	13
CD	28	12	21	22	34	36
AG	13	12	20	14	12	22
KK	11	11	18	18	27	32
EW	21	7	8	16	19	19
MH	17	5	9	12	11	21
RM	23	19	25	26	27	26
KD	17	8	11	14	16	19
JT	16	9	14	20	28	26

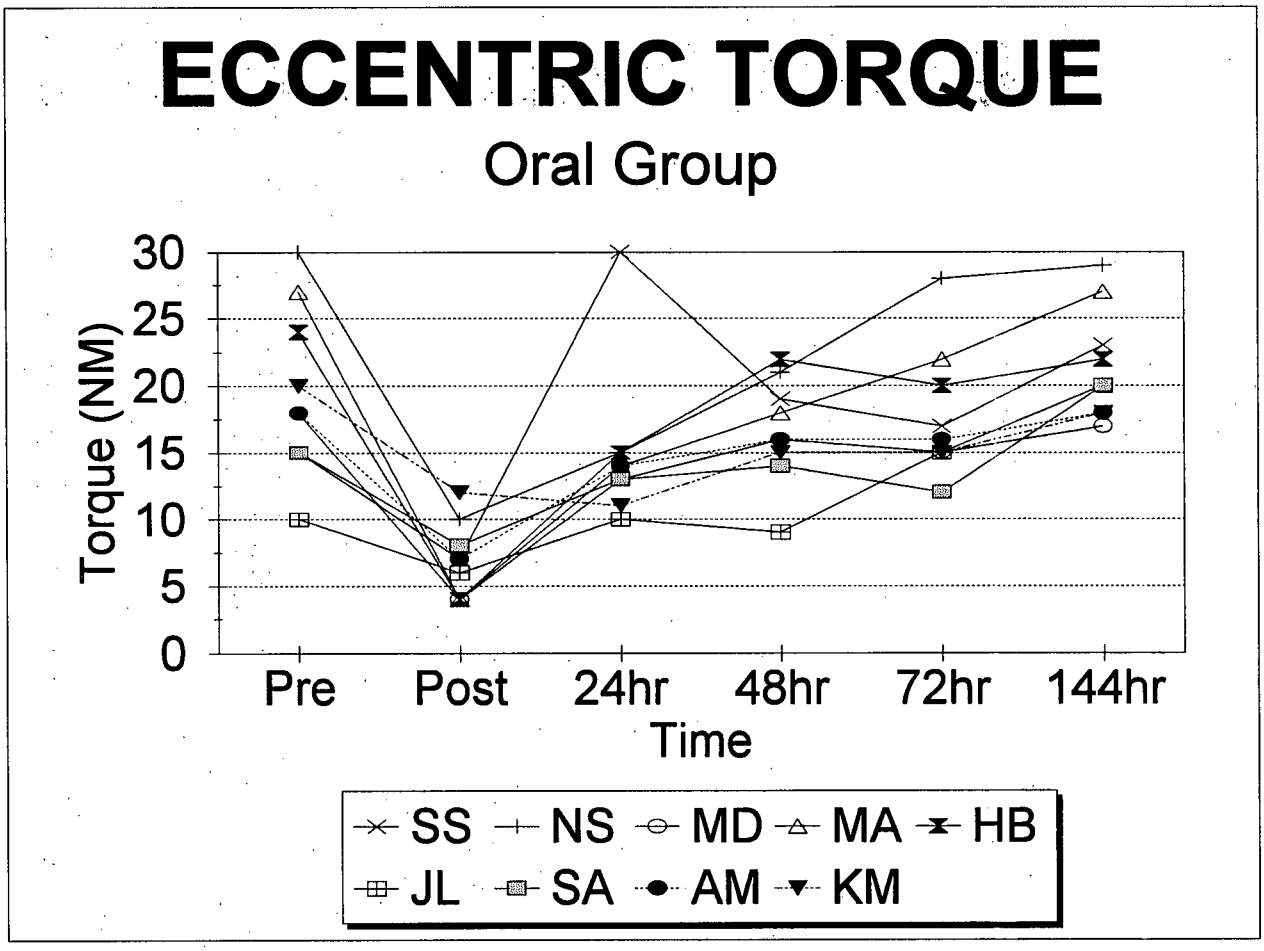
APPENDIX III

INDIVIDUAL TORQUE DATA - PART I



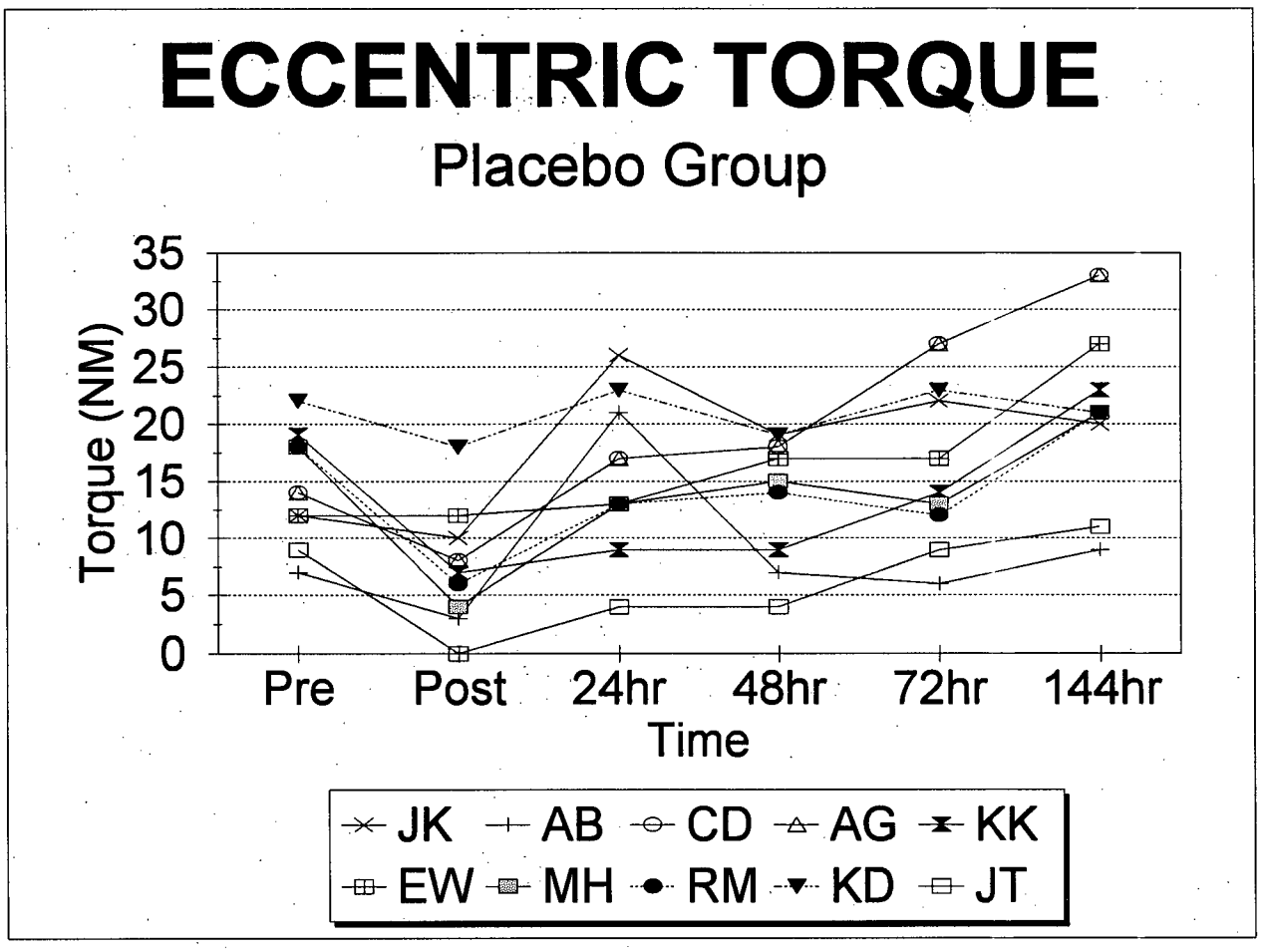
APPENDIX III

INDIVIDUAL TORQUE DATA - PART I



APPENDIX III

INDIVIDUAL TORQUE DATA - PART I



APPENDIX IV

VAS - VISUAL ANALOGUE SCALE

NAME:
DATE:
TEST:

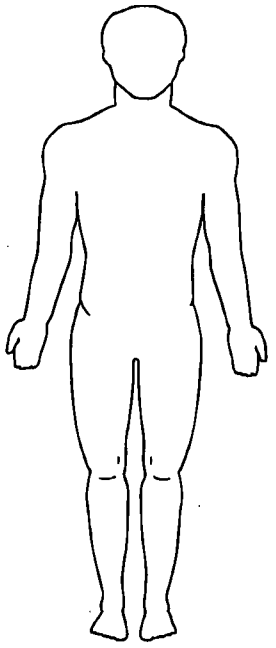
Have you experienced any discomforts or adverse effects from the treatment? _____

If so please specify _____

No soreness

Worst soreness

Where is the soreness:



APPENDIX V

INDIVIDUAL BLOOD DATA - PART II

	ORAL (mg/L)				TOPICAL (mg/L)			
Subject	ND				ND			
	Pre	**Day 3**	**Day 5**	**Day 7**	**Pre**	**Day 3**	**Day 5**	**Day 7**
RUN 1	0	7.88	4.86	8.38	0	0.152	0.063	0.179
RUN 2	0	7.42	4.61	6.94	0	0.154	0.12	0.176
Average	0	7.65	4.73	7.66	0	0.153	0.0915	0.1775

	ORAL (mg/L)				TOPICAL (mg/L)			
Subject	AL				AL			
	Pre	**Day 3**	**Day 5**	**Day 7**	**Pre**	**Day 3**	**Day 5**	**Day 7**
RUN 1	0	16.7	15.2	14.02	0	0.136	0.139	0.17
RUN 2	0.02	13.4	14	*9.44	0	*0.283	*0.247	*0.247
RUN 3				*11.56		*0.252	*0.257	*0.221
Average	0.01	15.05	14.6	10.5	0	0.2675	0.252	0.234

	ORAL (mg/L)				TOPICAL (mg/L)			
Subject	NM				NM			
	Pre	**Day 3**	**Day 5**	**Day**	**Pre**	**Day 3**	**Day 5**	**Day 7**
RUN 1	0	*7.88	4.43	1.85	0.062	0.268	0.34	0.492
RUN 2	0.024	4.83	4.79	1.63	0.033	*0.378	0.475	0.438
RUN 3		*9.5				*0.464	0.561	
Average	0.012	8.69	4.61	1.74	0.475	0.421	0.518	0.465

** Runs used to calculate average.*

APPENDIX V

INDIVIDUAL BLOOD DATA - PART II

	ORAL (mg/L)				TOPICAL (mg/L)			
Subject	KH				KH			
	Pre	**Day 3**	**Day 5**	**Day 7**	**Pre**	**Day 3**	**Day 5**	**Day 7**
RUN 1	0	42.85	22.06	31.94	0	0.148	*0.226	0.207
RUN 2	0	34.91	27.76	26.46	0.038	0.149	0.341	0.27
							*0.271	
Average	0	38.88	24.91	29.2	0.019	0.1485	0.2485	0.238

	ORAL (mg/L)				TOPICAL (mg/L)			
Subject	RM				RM			
	Pre	**Day 3**	**Day 5**	**Day 7****	**Pre**	**Day 3**	**Day 5**	**Day 7**
RUN 1	0.0	3.16	3.74		0	0.085	0.119	0.08
RUN 2	0.1	*4.23	3.18		0	*0.14	*0.187	0.11
RUN 3		*4.75				*0.162	*0.157	
Average	0.02	4.49	3.46		0	0.13	0.15	0.095

** Runs used to calculate average.*

*** Data lost.*