IBUPROFEN (BRUFEN) AS AN ANALGESIC AFTER ORAL SURGERY - A CLINICAL TRIAL

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DECLARATION

I, Anthony John Garwood, hereby declare that this dissertation is my own work and has not been presented for any degree of another University.

The work reported in this dissertation was performed in the Division of Maxillo-Facial and Oral Surgery, University of the Witwatersrand, Johannesburg, and the Medical Research Council/University of the Witwatersrand Dental Research Institute and the Witwatersrand University, Johannesburg.

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To

Rus, Christine and Dennis

ABSTRACT

Pain, swelling and trismus are common features after oral surgery, particularly after the surgical removal of impacted third molar teeth. The Maxillo-Facial and Oral Surgeon has a vast array of drugs at his disposal to combat post-operative pain, but none of these are perfect in terms of efficacy and side effects. Recently, the non-steroidal anti-inflammatory drugs have been receiving much attention as post-operative analgesics.

The purpose of this study was to assess the efficacy and side effects of Ibuprofen (Brufen ^{R}), a non-steroidal anti-inflammatory agent, with that of a control analgesic in a double blind clinical trial following the removal of impacted third molar teeth. The operative procedure was carried out on 100 patients by one surgeon using a standarised surgical technique while the survey was carried out by an indepedant observer. The Ibuprofen, as well as the control analgesic, were placed in unmarked packets, and the patients were instructed on how to take them post-operatively. Ibuprofen was administered to 52, and the control analgesic to 48 randomly selected patients.

The results showed that Ibuprofen compared favourably with the control analgesic, producing acceptable analgesia in 80% or more of patients. Although similar analgesia was obtained with the control analgesic, Ibuprofen appeared superior in the post-operative ambulatory phase in that the side effects of dizziness and drowsiness were significantly less with the drug than with the control analgesic.

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CHAPTER 1
INTRODUCTION

1.1 HISTORICAL BACKGROUND

One of the first drugs used by man to alleviate pain was Opium. This is a crude mixture of related alkaloids derived from the dried poppy seed (Papaver somniferum) and has been known to medicine since the times of the ancient Egyptians (Wilkin and Davidson 1979). It was also used extensively by the ancient Chinese. Purification of the alkaloids yielded the narcotic group of analgesics, and a number of synthetic drugs of this type are still manufactured at present. (Wilkin and Davidson 1979). Some of the better known narcotic analgesics in use at the present time are Morphine, Methyl Morphine (Codeine), Papavaretum (Omnopon), and Meperidine (Pethidine).

A historical review also reveals that willow bark, which contains Salicin, was used to treat fever in the 18th Century. It was used "because willow trees and agues occurred in marshy places, and according to the 'Doctrine of Signatures', where a disease was found, so there would be a remedy nearby" (Laurence 1973).

During the latter half of the 19th Century Sodium Salicylate and Acetylsalacylic acid (Aspirin) were introduced to medicine (Laurence 1973). The British are now known to consume about 2 million kg. of Aspirin annually (Laurence 1973).

Today there is a vast array of analgesics available, but the search still goes to manufacture drugs with greater efficacy, but with fewer side effects.

1.2 REVIEW OF THE LITERATURE

Oral surgery, and particularly the surgical removal of impacted third molar teeth, is generally accompanied by pain and discomfort due to post-operative swelling and trismus. The Maxillo-Facial and Oral Surgeon frequently prescribes an analgesic or analgesic combination for the post-operative relief of pain. (Forbes et al, 1981).

A classification of common analgesics which may be used in Oral Surgery is shown in Table 1.1

Table 1.1

Classification of Analgesics in use at the present time

1. Narcotic Analgesics

   eg. Papaveretum (Omnopon), Meperidine (Pethidine).

2. Non-narcotic Analgesics

   a. Salicylates eg. Acetylsalicylic Acid (Aspirin)
   b. Aniline derivities eg. Acetophenetidin (Phenacetin), Acetaminophen (Paracetamol).

3. Non-steroidal anti-inflamatory agents

   eg. 1. Ibuprofen (Brufen)
   2. Phenylbutazone (Butazolidin)
   3. Indomethacin (Indocid)
   4. Oxyphenbutazone (Tanderil)

NOTE: As far as possible in this paper, generic names of drugs will be used in preference to Trade Names.

These drugs are well known and frequently prescribed but none are free from unwanted side effects. Laurence (1973) notes some of the side effects of narcotic analgesics as:

(i) Drug dependance.
(ii) The withdrawal syndrome.
(iii) Respiratory despression from overdose.
(iv) Depression of the cough reflex.
(v) Responsible for inducing hypotension.
(vi) Constipation.

Of the non-narcotic analgesics, Acetophenetidin (Phenacetin) is well known for its role in the causation of analgesic nephropathy.

Najjar and Newark (1977) have described the harmful effects of Acetylsalicylic acid (Aspirin) in some detail. The tissues affected by Aspirin include the gastro-intestinal tract, the renal system, the auditory system, the blood and coagulation systems and certain homeostatic mechanisms.

They describe the effects on the gastro-intestinal tract as varying from epigastric discomfort to frank bleeding, depending on the susceptibility of the individual, dosage, the duration of intake, and contents of the stomach. Gastritis may be observed after oral and even after intra-venous administration. The irritation is initiated by the release of histamine, resulting in stimulation of the gastric mucosa, which further results in the release of hydrochloric acid.

These authors further report that Aspirin compounds containing Acetophenetidin can lead to renal damage, (eg. necrotising papillitis or acute necrosis of renal papillae).

Relatively low doses of salicylates may also inhibit the response of platelets to adenosine-di-phosphate, causing a decrease in coagulability, and chronic use may lead to thrombocytopenia or even pancytopenia. (Najjar and Newark, 1977).

These workers have also reported that Aspirin has been known to cause hypersensitization of the respiratory centre to carbon dioxide leading to an increase in circulating carbonic acid, thus lowering the pH of the plasma. In addition to this, the use of Aspirin for the control of fever is not completely safe as high doses of salicylates can cause hyperthermia, especially in children.

1.2.1 Non-steroidal Anti-inflammatory Agents

In recent times the non-steriodal anti-inflammatory agents have been receiving much attention as short term analgesics after surgery. The majority of these drugs have anti-inflammatory, analgesic and antipyretic properties and many have been considered particularly good in reducing pain in the post-operative phase, probably by reducing inflammation and by inhibiting the chemicals of the inflammatory process, mainly prostaglandins. (Laurence 1973). It is also thought that by reducing the inflammatory process, improved tissue viability can be maintained in inflamed tissues.

Petersen (1975) tested the analgesic and anti-inflammatory effects of Indomethacin following third molar tooth removal. His study comprised fifty patients who were each to have one mandibular third molar tooth removed. The patients were divided into two groups: one group received Indomethacin post operatively and the other group an unspecified placebo. This study demonstrated Indomethacin to be a significantly better analgesic than the placebo,and furthermore seemed to reduce post-operative trismus. In this study 28% of patients taking the Indomethacin complained of side effects. These included dizziness, headache, nausea and/or gastric upset.

Breytenbach (1976) compared the effects of Oxphenbutazone, Chymoral (proteolytic enzymes), and an unspecified placebo in the control of swelling, trismus, and pain after the removal of impacted third molar teeth. He found that Oxphenbutazone significantly improved pain, discomfort, wound appearance, and oedema when compared to the placebo and Chymoral when measured subjectively on "point scales". Oxyphenbutazone was also significantly superior to Chymoral and the placebo in improving intermaxillary opening. The side effects encountered were all mild and transient in nature. These were unspecified, but thought by the operator to be mainly related to the operation.

Album, Olsen and Lokken (1977) compared the effects of Oxyphenbutazone and a placebo in 24 patients who underwent the surgical removal of third molar teeth on opposite sides of the jaws at successive operations. After the first procedure, the patients were given either Oxyphenbutazone or an unspecified placebo and after the following procedure 2 weeks later the opposite drug was given. The analgesic effect of the Oxyphenbutazone was found to be adequate, but these workers found that it did not reduce swelling significantly in all patients. Side effects of the drug however were minimal.

1.2.2 Ibuprofen (Brufen^{R}) as an analgesic

Lokken et al (1975) studied the efficacy of Ibuprofen following the removal of third molar teeth. Their study comprised 24 healthy patients who had two separate operations for the removal of an impacted third molar tooth from either left or right side in the lower jaw. These patients were given Ibuprofen (400mg. three times daily) or an unspecified placebo for 5 days, commencing the day prior to surgery. The drugs were reversed at the second operation, carried out approximately 26 days later. A number of measurements were made, including swelling, trismus and pain. The measurements for swelling were made with a mechanical device developed for the study. For each patient a bite block was made at the first pre-operative visit using a thermo-plastic impression of the patients dentition in occlusion. This was then fixed to a face bow with 8 adjustable plastic screws on each side. Each time the patient bit into the bite block the face bow became fixed in the same position. The plastic screws could then be adjusted to touch the skin. Measurement of the remaining length of the screws outside the holding plate would give exact values, which could easily be related to the degree of swelling. Mouth opening was measured with a Vernier Gauge.

These authors noted that the Ibuprofen significantly reduced pain on the day of operation, and also reduced trismus. The patients expressed their preference for Ibuprofen in the post-operative phase, and swelling was also somewhat reduced post-operatively although not immediately after surgery.

The drug was well tolerated and subjective assessments indicated that neither wound healing nor bleeding during or after the operation was affected by the drug.

Muckle (1975) undertook a double blind trial on 22 professional footballers to compare the effectiveness of 1200 mg, Ibuprofen and 3,0 g Aspirin daily in the treatment of soft tissue injuries. The duration and severity of pain were significantly reduced in those patients to whom Ibuprofen had been administered, compared to those to whom Aspirin had been administered.

The time between injury and the players returning to training or match play was reduced. Muckle (1975) also stressed that the reduction in pain due to the Ibuprofen has a practical value because it allows an earlier application of remedial therapy and helps to combat muscle atrophy.

Cooper, Needle and Kruger (1977) attempted to evaluate the efficacy of Ibuprofen for the relief of dental pain. They compared the efficacy of Aspirin, Ibuprofen and placebo after the removal of third molar teeth. A minimum of 37 patients in each of five treatment groups were assessed for pain relief after the surgical removal of impacted third molar teeth under local anaesthesia. Usually the mandibular tooth, or the mandibular and maxillary teeth on one side were removed at one visit.

The results of this study showed that Ibuprofen 400 mg. was the most effective drug, followed by Ibuprofen 200 mg., Aspirin 650 mg., Aspirin 325 mg., and lastly the unspecified placebo. There was no significant difference in the side effects of these drugs. In summary these workers note that considering the cause of most types of dental pain it is not unreasonable to expect peripherally acting analgesics, such as Aspirin to be especially effective. However, there is no single peripherally acting drug or combination of such drugs that has sufficient efficacy to consistently relieve moderate or severe post-operative pain, so the usefulness of this class of analgesic has been limited.

To enhance efficacy of the peripherally acting analgesics, they are commonly combined with centrally acting analgesics such as Methyl Morphine (Codeine)(Cooper et al, 1977). These authors suggested that for relief of dental pain, the peripherally acting analgesics provided the most analgesia, whereas the centrally acting drugs provided a relatively small additive effect. In addition, there was a notable increase in the incidence of side effects as the dosage of the centrally acting drug was increased. Cooper et al (1977) were the first to show that any other peripherally acting analgesic i.e. Ibuprofen, was significantly more effective than Aspirin. Their results showed that Ibuprofen was not only more potent than Aspirin but had greater efficacy without any notable increase in adverse effects. They concluded by stating that a comparison of Ibuprofen to a combination analgesic, eg. Aspirin and Methyl Morphine (Codeine) would seem an appropriate next step.

Dionne and Cooper (1978) undertook a study to assess whether Ibuprofen administered pre-operatively would have any effect on post-operative pain and swelling. Seventy three patients were used in their analysis of post-operative pain following removal of impacted third molar teeth. Ibuprofen 400 mg., Aspirin 650 mg. and an unspecified placebo were the drugs used in this study and one of the drugs was given to the specific patient 30 minutes pre-operatively. The patients were then given the same drug post-operatively when the pain became moderate to severe. It was noted that patients who received Ibuprofen pre-operatively had a significantly delayed onset and decreased severity of post operative pain. The incidence of side effects was negligable.

1.2.2.1 Pharmacology and metabolism of Ibuprofen

Adams (1960) stated that to be clinically effective, potential non-steriodal antirheumatic compounds should possess anti-inflammatory, analgesic and antipyretic properties. After carrying out laboratory tests on over 600 compounds, 4 were finally put on clinical trial. One of these was Ibuprofen.

The first three compounds were acetic acid derivatives (R.D. 10335, R.D. 10499 and Ibuferal) and clinical results were most disappointing. It was then decided to abandon the acetic acid derivatives, which tend to accumulate in tissues, and to proceed with the propionic acid. Ibuprofen was selected to undergo further clinical trials (Adams et al, 1970). These workers further tested the efficacy of Ibuprofen by means of a number of recognised animal tests, among them the mouse writhing test and the inflamed rat foot test. As a result of these studies they found the potency of Ibuprofen to be 16-32 times greater than that of Aspirin. They also noted that the similarity of the analgesic potencies for the mouse writhing test and inflamed rat foot test, two different analgesic techniques in two different species, suggests that the high analgesic potency is genuine and they felt that the drug was a peripheral and not a central analgesic. They also found that a dose of 200 mg. would give levels of Ibuprofen in man which would produce a significant anti-inflammatory, analgesic and anti-pyretic effect.

The pharmacology of Ibuprofen can further be discussed under the following headings:

(a) **Mode of Action**

Glenn and Bowman (1969) have shown that Ibuprofen, like the other non-steroidal agents, Aspirin, Phenyl-butazone, Indomethocin, etc., inhibits various in vitro systems such as the release of lactic dehydrogenase and acid phosphates from thrombin. It also results in the aggregation of platelets and the hypotonic-hyperthermic lysis of erythrocytes. They nevertheless describe definite qualitative differences between the various non-steroidal anti-inflammatory compounds in vivo. Ibuprofen has the same spectrum of activity in terms of the balance of anti-inflammatory, analgesic and antipyretic potencies as Aspirin, whereas Phenyl-butazone has weaker analgesic and antipyretic activity relative to its anti-inmflammatory properties.

In order to assess the chemical mode of action of Ibuprofen, it is important to summarize the work of Piper and Vane (1969). It is well known that pain and inflammation may be produced by certain endogenous substances eg. Kinins, SRS-A (slow reacting substance of anaphylaxis) and adenosine-tri-phosphate (A.T.P.). This reaction was thought to be antagonised by Aspirin and similar compounds (Adams et al 1970).

Piper and Vane (1969) however showed that Aspirin did not directly antagonise bradykinin and SRS-A, but rather blocked the release by bradykinin and SRS-A of another smooth muscle stimulant RCS (Rabbit aorta contracting substance), which is thought to be released at the end of a complex sequence of events. This may well be the final mediator for pain and inflammation. Adams et al (1970) stated that there is circumstantial evidence to suggest that the inhibition of RCS release may play an important role in the mode of action of Brufen/Ibuprofen.

(b) **Absorption**

Ibuprofen is well absorbed after oral administration. Absorption occurs from both the stomach and intestine, but is greater and more rapid from the intestines (Adams et al, 1969).

The manufacturers state that an oral dose taken on an empty stomach by human volunteers produced peak serum levels after 45 minutes (Manufacturers prescribing leaflet). Absorption is slower and peak serum levels lower after meals.

(c) **Excretion**

Two major metabolites have been isolated in human urine. They are (+)2-4'-(2-Hydroxy-2-Methylpropyl) Proprionic acid (Metabolite A) and (+)2-4'-(2 Cardoxy-propyl) phenylpropionic acid (Metabolite B).

The levels of both metabolites in human serum have been measured after single and repeated doses (Adams et al 1970). About 60% of the dose is excreted in the urine and the excretory products are in the form of either free or conjugated Metabolites A or B. Adams et al (1970) have stated that after multiple doses there is a tendency for metabolites to persist slightly longer than for single doses, but that all compounds have completely disappeared 24 hours after the administration of the final dose.

These results indicate that Ibuprofen is a drug with a short half life in man, and Adams and co-workers (1970) believe that this rapid excretion may well contribute to the lack of toxicity of the drug. It does however mean that many patients have found the originally recommended dose of 200 mg. 8 hourly inadequate, and that many clinicians now recommend a dosage of 400 mg. 8 hourly.

(d) **Effect on the Liver**

Adams et al (1970) state that since 1962 they have investigated the toxicity of Ibuprofen in a series of wide ranging studies. From these studies they concluded that Ibuprofen is a drug of relatively low toxicity.

Several studies were performed to determine whether Ibuprofen could induce signs of liver dysfunction and liver injury in mice, rats and dogs. Plasma glutamic pyruvic transaminase (GPT) activity was measured in mice and rats at the end of the treatment, while in dogs the plasma GPT, glutamate oxaloacetate transaminase, bilirubin and alkaline phosphatase concentrations were measured at intermediate times as well as terminally. The livers of all animals were weighed at autopsy and subjected to microscopic examination. No significant alteration in blood biochemical parameters was observed in the mouse, rat or dog.

The livers of mice and rats increased in weight, but not in dogs. The rat liver returned to normal weight after withdrawal of treatment. There were no histological signs of liver damage in any of the experimental animals. They further stated that liver hypertrophy in the rat and mouse is a common response to high doses of drugs. When liver enlargement is reversible and occurs in the absence of liver lesions it probably represents a functional hypertrophy increasing the work capacity of the organ. In these circumstances liver enlargement is not usually regarded as a toxic manifestation. A fairly high concentrate of drug was found in the biliary tract of the experimental animals showing that this is an important route of excretion. (Adams et al 1970).

(e) **Gastrointestinal Irritation**

Gastric irritation has been a problem with all non-steroidal anti-inflammatory agents. Adams et al (1970) demonstrated that although Ibuprofen does have ulcerogenic potential, this appears to be less marked with Ibuprofen than with most other agents. In a series of experiments on mice, rats and dogs, the dog was found to be the most susceptible to ulceration and the rat the least. In the dogs the ulcers occurred in the gastric antrum and pylorus, while in the rats they occurred in the small intestine. It is interesting to note that they also found that Ibuprofen injected intraperitoneally was equally ulcerogenic in the mouse which suggests that the stimulus for ulcer formation is systemic and not dependant on a local action of the drug. It was further observed that there was a greater susceptibility to ulceration in pregnant rats, thought possibly to be due to raised histamine production and higher levels of circulating adrenal corticosteroids.

Parry and Wood (1963) showed that in respect of Aspirin products, their liability to produce major gastro-duodenal lesions is apparently independent of their liability to cause mucosal erosions with occult bleeding. Thompson and Anderson (1970) undertook a study on humans to determine whether Ibuprofen could cause occult bleeding from the alimentary tract similar to that noted with many Aspirin preparations. Studies of blood loss from the alimentary tract were undertaken on 18 patients. All the patients remained in hospital for the duration of the study and all were receiving analgesics for musculo-skeletal symptoms. None of the patients were suffering from any active gastro-intestinal disorder. The drugs used in the study were Ibuprofen, Calcium Aspirin and Lactose. The results of this study demonstrated that, while an apparent increase in blood loss occurred during the administration of Calcium Aspirin in comparison with the blood loss noted during the administration of a placebo, there was no such increase when Ibuprofen was administered. Increasing the dosage of Ibuprofen did not lead to any increase in the amount of average daily blood loss which remained below 2ml. irrespective of dosage.

Cardoe (1970) reviewed his long term experience with Ibuprofen with special reference to gastric tolerance and found the drug to be well tolerated by the gastro-intestinal tract, even in the presence of peptic ulceration. In his group of 179 patients, 42 had a history of peptic ulceration. Of these patients 34 showed excellent tolerance with no indigestion at all, 3 showed good tolerance, having mild indigestion controlled by alkalis, but not bad enough to stop treatment, and in 5 patients the result was poor, with the patients experiencing an exacerbation of ulcer symptoms. Twenty seven patients tolerated continuous therapy for at least 6 months.

Rejholec (1975) also studied long-term Ibuprofen therapy in patients with a past history of peptic ulceration. In 24 of the 30 patients studied, Ibuprofen was administered for 12 months in a dose of 600 mg. to 1200 mg. daily in divided doses. As verified by a gastro-intestinal examination, including fibroscopy in 16 patients, this therapy did not cause activation of the pre-existing lesion or occurrence of new ulceration.

(f) **Carcinogenic potential**

Adams et al (1970) tested Ibuprofen for carcinogenic potential by administering it to rats and mice for their entire life span. Normal animals were used as controls. In the study involving mice, mortality of dosed males was no different to the control males. The proportion of mice with tumours of all types among those examined did not differ between the dosed and control groups. A similar result was obtained with rats. These 2 studies show that Ibuprofen does not induce tumours of the liver or any other organ.

In reviewing the literature it has become clear that the non-steroidal anti-inflammatory drugs, and Ibuprofen in particular, have great potential for use as analgesics in Maxillo-Facial and Oral Surgery.

However, on reviewing the literature of the past decade there appears to be a paucity of reports related to clinical trials using these drugs. The majority of the research appears to have been undertaken by Japanese and Russian researchers, which is unavailable in this country.

A criticism of the available literature, is that many of the trials have been undertaken on small numbers of patients, and none have compared Ibuprofen to a commonly used and clinically tested combination analgesic.

1.3 AIMS OF THIS STUDY

The aims of this study are:-

1. To undertake a double blind clinical trial to assess the analgesic effects of Ibuprofen compared with a standard analgesic compound.

2. To note any adverse effects resulting from the use of the drug.

CHAPTER 2
MATERIALS AND METHODS

2.1 Source of the material

Prior to beginning this experiment, the protocol was submitted for approval to the Committee for Research on Human Subjects of the University of the Witwatersrand, Johannesburg, and permission was granted.

All the patients in this survey were undergoing surgery for the removal of impacted third molar teeth in a Johannesburg Maxillo-Facial and Oral Surgery practice. The methods and reasons for the clinical trial were explained to the patients and informed consent was obtained in all cases.

2.2 Experimental Design

This survey took the form of a double blind clinical trial. The control analgesic chosen for this study was Syndol*. This analgesic was chosen as a study on Syndol was undertaken by Reitzik and Lownie (1976), and it was found to provide complete or satisfactory analgesic response in 80% or more of patients who had undergone surgical removal of impacted third molar teeth.

The composition of Syndol is:

Paracetamol	450mg.
Codeine Phosphate	10mg.
Doxylamine Succinate	5mg.
Caffeine	30mg.

Both the Ibuprofen and the Syndol were packed in unlabelled plastic containers, marked only with the batch number (1 or 2) and the instructions to the patient on how the drug should be taken. Enough analgesic was dispensed for 5 days use, and the packets were given to the patients randomly by the sister in charge of the ward on discharge.

* Syndol - Mer National Laboratories.
P.O. Box 9170, Johannesburg, 2000

2.3 Selection of Patients

This study comprised 100 patients who underwent surgery for the removal of impacted third molar teeth, confirmed on panoramic X-Ray. The patients were selected on the basis that they required the removal of at least two impacted third molars, one of which had to be a mandibular tooth, and none of which could be extracted by the normal forceps technique.

Pregnant patients, or patients with a previous history of gastro-intestinal tract ulceration were excluded from the survey. No distinction was made on behalf of the sex of the patients.

2.4 Anaesthetic and Operative Technique

All procedures were carried out under general anasthesia with naso-endotracheal intubation. All the anaesthetics were given by two specialist anaesthetists. The patients were premedicated with atropine 0,6mg. and Omnopon (Papaveretum) 10mg. by intra-muscular injection. Induction of anaesthesia was by means of Fabantal (Propanidid) and Scoline (Succinylcholine), and maintenance of anaesthesia was by means of nitrous oxide, Halothane (Fluothane), and oxygen in dosages adequate for the patients' clinical needs.

A standardised surgical technique was used with one surgeon carrying out all the operations. This was not the same person responsible for the survey. The reason for this was to minimise all bias in the study.

In all the procedures a mucoperiosteal flap was raised to expose the underlying bone. Bone was removed to expose the tooth by means of surgical burs under saline coolant and the teeth removed either whole or after having been sectioned. The sockets were then irrigated with saline, and the mucoperiosteal flap sutured with 2/0 plain catgut.

2.5 Administration of drugs

Immediately post-operatively all patients were given 10mg. of Omnopon (Papaveretum) by intra-muscular injection. Any patients complaining of nausea were given 50mg. of Valoid (Cyclizine Hydrochloride) by intra-muscular injection.

Either the Ibuprofen or the control analgesic were then randomly administered to the patients both in unmarked containers. The patients were instructed to take the tablets according to the instructions on the containers. The dosage of Ibuprofen being 400mg.(1 tablet) 8 hourly and the dosage of Syndol 2 tablets 8 hourly.

2.6 Recording of Data

On discharge the patients were given a questionnaire prepared for this survey, and were asked to note their observations on the specific analgesic they were taking. At the end of the survey 52 patients had filled in a questionnaire regarding Ibuprofen and 48 patients had completed the same form for Syndol. The answers on the questionnaires were then transferred to specially prepared computer forms for analysis. A copy of the questionnaire and the computer form appear in the Appendix at the end of this Chapter.

2.7 Data Processing

The information on the computer forms was transferred to computer punch cards, and these were analysed using an IBM 370/148 computer with the Statistical Package for the Social Sciences. (Nie et al, 1975). The statistical test used was the Chi-square test without Yate's correction and the critical level of statistical significance chosen was P=0,05.

APPENDIX TO CHAPTER 2

PATIENT QUESTIONNAIRE

CASE NUMBER:
BATCH NUMBER:

NAME:
AGE:
SEX:

ANTIBIOTICS
PROCEDURE

2. Mark with an X whether the analgesics prescribed were taken:
   (a) according to prescription
   (b) more than prescription
   (c) less than prescription

3. If the answer to the above is b or c state number taken:

4. Thinking back over the past few days, in general what was the average time taken for the pain to improve:
   0-15 minutes
   15-30 minutes
   more than 30 minutes
   no improvement

5. If the pain was relieved, state the duration of relief:
   Less than 2 hours
   2-3 hours
   3-4 hours
   more than 4 hours

6. Was pain relief:
   Total
   Moderate
   No relief

7. Was it necessary to take analgesics for:
   2 days
   3 days
   4 days
   more than 4 days

8. Did you suffer from any of the following whilst taking the analgesics:
   Nausea/vomiting
   Allergies
   Constipation
   Diarrhoea
   Dizziness/Drowsiness

   Other - state

9. During the period of analgesia was your jaw movement:
   Mildly improved
   Markedly improved
   Not improved at all

10. Pain rating: After three days please assess the average amount of pain you have experienced on a scale of 0 to 10:
    0 = total pain relief 10 = unbearable pain

COMPUTER FORM - PAGE 1

DIVISION OF MAXILLO FACIAL AND ORAL SURGERY AND THE DENTAL RESEARCH UNIT OF THE SOUTH AFRICAN MEDICAL RESEARCH COUNCIL AND THE UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG.

USE OF BRUFEN AS AN ANALGESIC IN ORAL SURGERY: A CLINICAL TRIAL.

A. GARWOOD

Code numbers in blocks as follows.

1		1
1	0	1
10	0	1	0

FOR KEYPUNCH USE ONLY
1. Valid punch codes
   1. Numeric ... everywhere
   2. Blanks .... everywhere

Note 1: If information is missing or not known leave blank

1. General details — Card No. 1
   Case number — 2–5
   Age of patient — 5–7
   Sex 1=female, 2=male — 7

2. Preoperative assessment
   Jaw 1=maxilla 2=mandible
   3=maxilla and mandible — 8

   No. of teeth removed
   1=one 2=two
   3=three 4=four
   5-more than four — 9

3. Operative procedure
   Type of anaesthetic
   1=local anaesthesia 2=general anaesthesia — 10

   Antibiotics
   1=Pen VK 2=Amoxil 3=Erythrocin
   4=Tetracycline 5=Other 6=None — 11

4. Post-operative assessment
   Type of Analgesia

   i. Immediate post-operative
      1=I.M.I. given
      2=I.M.I. not given
      3=Oral Syndol
      4=Oral Brufen
      5=I.M.I. and Syndol
      6=I.M.I. and Brufen — 12

   ii. Analgesia given on discharge (T.T.O.)
      1=Syndol
      2=Brufen — 13

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5. Effect of analgesia
Quantity of analgesic taken:
1=according to schedule
2=more than prescribed
3=less than prescribed 14 ☐

i. Time of onset of
1= 0-15 minutes
2= 15-30 minutes
3= more than 30 minutes
4= none 15 ☐

ii. Duration of analgesia
1= less than two hours
2= 2-3 hours
3= 3-4 hours
4= more than 4 hours 16 ☐

iii. Depth of analgesia
1= no relief
2= moderate relief
3= total relief 17 ☐

iv. Length of time analgesic taken (in days)
1= 2 days
2= 3 days
3= 4 days
4= more than 4 days 18 ☐

6. Side effects
1= none
2= nausea/vomiting
3= allergies
4= constipation
5= diarrhoea
6= dizziness
7= other 19 ☐

7. Effect on mandibular function
1= no improvement
2= moderate improvement
3= marked improvement 20 ☐

8. Pain rating
0= 10 21 ☐

Columns 23 - 80 not used.

CHAPTER 3
RESULTS AND DISCUSSION

For clarity, the results and discussion are presented in a single chapter.

3.1 Age Distribution of Cases

The age distribution of cases, recorded in decades, is listed in Table 3.1

Table 3.1 - Frequency distribution of post-operative analgesic given by age (in decades)

Age in years	Decades	Syndol		Ibuprofen	
		n	%	n	%
10-19	2nd	13	27	10	19,2
20-29	3rd	26	54,1	27	51,9
30-39	4th	6	12,5	10	19,2
40-49	5th	2	4,2	3	5,8
50-59	6th	0	0	1	1,9
60-69	7th	1	2	1	1,9
TOTAL		48	99,8	52	99,9

n = number of cases in all tables.

Chi square = 2,58 Degrees of Freedom = 5 p = 0,10

Mean Age - Syndol 24,2 yrs s.d. = 8,7
Ibuprofen 26,3 yrs s.d. = 9,5

Table 3.1 shows that the majority of patients in this trial were in the age group 10-39, with a peak in the third decade. This correlates well with the fact that the majority of patients presenting for removal of third molar teeth are first seen in the second or third decades. Petersen (1975) in his study, showed a mean age distribution in the two groups of 27,1 years and 28,2 years. Lokken et al (1975) had a mean age of 20 years in their survey.

3.2 Sex distribution of Patients

The sex distribution of all cases treated in this survey was as follows:-

Female - 64 Male - 36

The ratio Female : Male was 1,7:1

The total number of females taking Syndol was 28, and the number of females taking Ibuprofen was 36.

The total number of males taking Syndol was 20, and the number of males taking Ibuprofen was 16.

After discussion with colleagues, it appears that this slight female predominance in removal of third molar teeth is a normal characteristic in Johannesburg. The ratio of both sexes taking the analgesics was however very similar and of no significance.

3.3 Site of Extraction

In all cases treated, 19 patients had only mandibular teeth removed, and 81 patients had mandibular and maxillary teeth removed. Of those patients taking Syndol, 7 had mandibular teeth extracted, and 41 had mandibular and maxillary teeth extracted. In the group of patients taking Ibuprofen, 12 had mandibular teeth only removed, and 40 cases required the removal of mandibular and maxillary teeth. There was no significant difference between the two groups.

Chi square = 1,17 Degrees of Freedom = 1 p = 0,35

3.4 Number of teeth extracted

The number of teeth extracted appears in Table 3.2

Table 3.2 Frequency distribution of the number of teeth extracted by the post-operative analgesic given

Teeth Removed	Syndol		Ibuprofen	
No.	n	%	n	%
2	13	27	16	30,8
3	8	16,7	13	25
4	27	56,2	23	42,2
Total	48	99,9	52	100

Chi square = 1,66 Degrees of Freedom = 2 p = 0,44

Both groups of patients had a similar number of teeth extracted, with no significant difference between them.

3.5 Choice of Antibiotic used

The types of antibiotics used in the trial are shown in Table 3.3

Table 3.3 Frequency distribution of Antibiotics used by post-operative analgesic given

Antibiotic	Syndol		Ibuprofen	
	n	%	n	%
Penicillin V K	0	0	2	3,8
Amoxil^{R}	39	81,3	34	65,4
Erythromycin	4	8,3	8	15,4
Tetracycline	5	10,4	7	13,5
Other	0	0	1	1,9
Total	48	100	52	100

Chi square = 4,86 Degrees of Freedom = 4 p = 0,3

Amoxil^{R} (Amoxycillin) was the standard antibiotic prescribed post-operatively in all cases. Only if patients were allergic to penicillen was the antibiotic changed. Both groups of patients in this study shared a similar antibiotic spectrum, with no significant differences.

3.6 Amount of analgesic prescribed

Table 3.4 shows the amount of analgesic taken in relation to the amount of analgesic prescribed.

Table 3.4 Frequency distribution of amount of analgesic prescribed by type of analgesic given

Analgesic taken	Syndol		Ibuprofen	
	n	%	n	%
Less than prescribed	9	18,8	8	15,4
As scheduled	39	81,3	35	67,3
More than prescribed	0	0	9	17,3
Total	48	100,1	52	100

Chi square = 9,78 Degrees of Freedom = 2 p = 0,008

It is significant to note in Table 3.4 that 9 patients (17,3%) taking the Ibuprofen had to take more tablets than prescribed. The dosage prescribed was 400mg. 8 hourly. This could possibly be explained by the fact that Ibuprofen has a very short half life in man (Adams et al 1970) and it seems possible that an 8 hour gap between administrations of the drug may be too large in certain patients with serum levels of the drug dropping too low for adequate analgesia.

Of the 43 other patients (82,7%) taking the Ibuprofen, the drug was taken as prescribed or less than prescribed. All the patients to whom Syndol was given either took it as prescribed or less than the prescribed dose.

3.7 Time of onset of pain relief

The time of onset of pain relief is shown in Table 3.5

Table 3.5 Frequency distribution of time of onset of analgesia by type of analgesic given

Onset time (in minutes)	Syndol n	Syndol %	Ibuprofen n	Ibuprofen %
0-15	25	52,1	22	42,3
15-30	20	41,7	21	40,4
More than 30	3	6,3	5	9,6
No analgesia	0	0,0	4	7,7
Total	48	100,1	52	100

Chi square = 4,56 Degrees of Freedom = 3 p = 0,21

From Table 3.5 one notes that both groups of patients had very similar times of onset of analgesia, except for 4 patients (7,7%) in the group taking Ibuprofen who did not experience any analgesia at all. However 97% of patients taking Syndol and 82,7% of patients taking Ibuprofen experienced adequate analgesia within 30 minutes of taking the drug,

In their study on Syndol, Reitzik and Lownie (1976) found the average time for analgesia to occur was 20,8 minutes.

Results of this study showed that both groups showed adeqate time of onset of analgesia. p = 0,21 which is not significant.

3.8 Duration Period of Pain Relief

The duration period of pain relief related to the type of analgesic taken is shown in Table 3.6.

Table 3.6 Frequency distribution of duration of pain relief by type of analgesic given

Duration (in hours)	Syndol		Ibuprofen	
	n	%	n	%
Less than 2	6	12,5	12	23,1
2-3	15	31,3	7	13,5
3-4	24	50,0	25	48,1
More than 4	3	6,3	8	15,4

Chi square = 7,1 Degrees of Freedom = 3 p = 0,07

Table 3.6 again shows similarities between the 2 groups, but it is interesting to note that the patients taking Syndol are grouped mainly in the 2-4 hour period, whereas the patients taking the Ibuprofen tend to be more spread out in the 4 hour period of analgesia. Of particular note is the fact that 15,4% of patients taking Ibuprofen had adequate analgesia after 4 hours whereas only 6,3% of patients taking Syndol had adequate analgesia after a similar period. Reitzik and Lownie (1976) found the average duration of analgesia of patients taking Syndol was 5,2 hours. Cooper et al 1977 found Ibuprofen 400mg. and Ibuprofen 200mg. gave adequate analgesia for up to 4 hours, but they did not record data over 4 hours.

From these figures in Table 3.6 it may be interesting to postulate that Ibuprofen may possibly show more patient specificity than Syndol, with more patients at both ends of the analgesic spectrum.

There is however no significant difference between the two groups.

3.9 Depth of Analgesia

The depth of analgesia as related to the type of analgesic given is shown in Table 3.7.

Table 3.7 Frequency distribution of depth of analgesia by type of analgesic given.

Depth of analgesia	Syndol		Ibuprofen	
	n	%	n	%
No relief	0	0,0	4	7,7
Moderate relief	24	50	25	48,1
Total relief	24	50	23	44,2

Chi square = 3,89 Degrees of Freedom = 2 p = 0,14 NS

Once again both groups show similarity, related to depth of analgesia, except that 4 patients taking Ibuprofen did not experience any analgesia. Differences between the two groups are not significant.

3.10 Length of Time the Drug was taken

The length of time it was necessary for the patients to take the analgesic is shown in Table 3.8

Table 3.8 Frequency distribution of the length of time the analgesics were taken by the type of analgesic taken

Length of Time (in Days)	Syndol		Ibuprofen	
	n	%	n	%
2	10	20,8	6	11,5
3	13	27,1	4	7,7
4	13	27,1	23	44,2
More than 4	12	25,0	19	36,5
Total	48	100	52	99,9

Chi square = 10,60 Degrees of Freedom = 3 p = 0,03

In both groups, no patients took the analgesic for less than 2 days, and the majority of patients required analgesia for 3-5 days. There was a tendency for the patients on Ibuprofen to take analgesics for slightly longer than the group taking Syndol. p = 0,03 which is significant.

3.11 Effect of Jaw Function

The effect of the type of analgesic taken on the improvement in Mandibular function is shown in Table 3.9

Table 3.9 Frequency distribution of Mandibular function by type of analgesic given

Function	Syndol		Ibuprofen	
	n	%	n	%
No improvement	6	12,5	6	11,5
Moderate improvement	28	58,3	34	65,4
Marked improvement	14	29,2	12	23,1
Total	48	100	52	100

Chi square = 0,47 Degrees of Freedom = 2 p = 0,79

Lokken et al (1975) found significantly better mouth opening in their group of patients given Ibuprofen post-operatively as compared to the group given an unspecified placebo.

This table shows however remarkable similarity between the two groups of analgesics and seems to suggest that it is pain that is mainly responsible for the lack of jaw movement post-operatively. The majority of patients experienced improvement of function with both analgesics that it seems possible to postulate the improvement in jaw function is not the direct result of the anti-inflammatory component of the Ibuprofen but its analgesic effect.

3.12 Side Effects

The side effects of each analgesic related to the type of analgesic taken is shown in Tables 3.10 and 3.11

Table 3.10 Frequency distribution of overall side effects by type of analgesic given

Side Effect	Syndol		Ibuprofen	
	n	%	n	%
No side effects	30	62,5	34	65,4
Side effects	18	37,5	18	34,5
Total	48	100	52	100

Chi square = 0,09 Degrees of Freedom = 1 p = 0,10

Table 3.11 Frequency distribution of specific side effects by type of analgesic given

Side Effects	Syndol		Ibuprofen	
	n	%	n	%
Nausea	0	0,0	5	9,6
Constipation	1	2,1	11	21,2
Diarrhoea	1	2,1	0	0,0
Dizziness/Drowsiness	16	33,3	2	3,8
Total	18	37,5	18	34,6

When considering side effects in general, both groups of patients showed a similar number with adverse effects to the particular analgesic taken with no significant difference being noted.

However, when relating this to the specific side effects the difference between the two groups is significant.

In the group taking Ibuprofen, the side effects were mainly gastro-intestinal in nature, with 9,6% of patients complaining of nausea, and 21,2% of patients complaining of constipation. In all cases these effects were mild and transient in nature.

Cooper et al (1977) reported that a few of the patients in their study experienced nausea and drowsiness, but again this was mild and transient. Dionne and Cooper (1978) reported drowsiness to be the most common side effect, but also found some patients to complain of nausea and headaches. They make the point that all 3 symptoms are frequently encountered after surgical removal of third molar teeth.

In the group taking Syndol 33,3% of patients complained of drowsiness or dizziness. A few patients felt that this was severe enough to prevent them from driving. This is a significantly larger group of patients complaining of drowsiness than in the series of Reitzik and Lownie (1976) where only 1 patient complained of this side effect.

3.13 Pain Rating

The pain rating for each analgesic related to the type of analgesic given is shown in Table 3.12.

Table 3.12 Frequency distribution of the Pain rating by the type of analgesic given

Pain Rating Given	Syndol		Ibuprofen	
	n	%	n	%
0	3	6,3	3	5,8
1	10	20,8	6	11,5
2	2	4,2	2	3,8
3	7	14,6	5	9,6
4	12	25,0	14	26,9
5	3	6,3	9	17,3
6	3	6,3	1	1,9
7	5	10,4	4	7,7
8	3	6,3	7	13,5
9	0	0,0	1	1,9
Total	48	100,2	52	100,00
	Mean=3.6 (sd = 2,3)		Mean=4.3 (sd = 2,4)	

Chi square = 8,05 Degrees of Freedom = 9 p = 0,53

All the patients taking part in the study were asked to assess the average amount of pain experienced over the first 5 post-operative days, and to relate this to a scale of 0-10, with 0 being no pain at all and 10 being unbearable pain.

Both groups of patients gave a fairly similiar pain rating with the patients on Ibuprofen indicating they had slightly more pain than the patients on Syndol.

The mean pain rating for the patients of Syndol was 3,6, and for the patients on Ibuprofen 4,3. These figures are similar enough not to be significant.

CHAPTER 4
CONCLUSION

This study has involved a double blind clinical trial, using Ibuprofen as an analgesic after surgery and comparing it to a standard combination analgesic, Syndol®.

In most respects, both analgesics have proved to be adequate in that over 80% of patients experienced moderate to total analgesia within 30 minutes of taking the particular drug they were prescribed. The majority of patients also had adequate analgesia for the desired length of time.

The Syndol did however appear superior in certain respects. A small group of patients (17,3%) taking the Ibuprofen were forced to increase the prescribed dose to obtain adequate analgesia over the 5 day period. As has been suggested previously, this is possibly due to the high excretion rate of the drug, and it may be worth considering a regime of prescribing the drug on a 6 hourly and not an 8 hourly basis. Levernieux (1975) has also shown that a daily dosage of 1800mg. is not only effective in the treatment of acute rheumatoid conditions, but is also well tolerated. In his series of 100 patients treated with this dose, only 11 patients were withdrawn due to side effects. Seven developed gastric pain, 2 developed urticaria, 1 developed a rubella type rash and 1 developed facial oedema. No serious side effects were considered. One may therefore also postulate increasing the dosage in the immediate post-operative state.

There were also however 4 patients who experienced no analgesia and one could also postulate that there appears to be a higher degree of patients specificity with Ibuprofen compared to Syndol.

In general, in most other facets of the trial, both groups compared favourably with Syndol appearing slightly better as an all-round analgesic, but with over 80% of patients in both groups signifying that analgesia was adequate.

The Ibuprofen did however seem to be superior in the aspect of side effects. The adverse effects due to the Ibuprofen were mainly gastro-intestinal in nature, these being mild and transient. The side effects due to the Syndol were mainly that the patients were drowsy or dizzy. This is not problematic, and may in fact be advantageous in the immediate post-operative phase, but is not desirable in the ambulant patient.

In conclusion therefore, the Ibuprofen appears to be an adequate analgesic for mild to moderate post-operative oral surgical trauma, with minimal side effects. The drug appears particularly useful in the ambulant patient, where sedation is not required.

REFERENCES

Adams, S.S., Bough R.G., Cliffe, E.E., et al. Some aspects of the Pharmacology, Metabolism and Toxicity of Ibuprofen. Symposium on Ibuprofen. Supp.Rheum. and Phys.Med. March 1970, 9-22

Album, B., Olsen, I. and Lokken, p. Bilatteral surgical removal of impacted mandibular third molar teeth as a model for drug evaluation: A test with Oxythenbutazone (Tanderil). Int.J.Oral.Surg. 1977: 6: 177-189

Breytenbach, H.S. Effects of Tanderil (Oxyphenbutazone). Chymoral (Proeolytic enzymes), and Placebo in the control of swelling, trismus, and pain after removal of impacted wisdom teeth. J.Dent,Ass,S.Afr.Vol 31, No.2, 61-63

Cardoe, N. A review of Long Term experience with Ibuprofen, with special reference to gastric tolerance. Symposium on Ibuprofen - Supp. to Rheum. and Phys.Med. March 1970. 28-31

Cooper, S.A., Needle, S.A., Kruger, G.O. Comparative analgesic potency of Aspirin and Ibuprofen. J.Oral.Surg.1977: 35:898-903

Dionne, R.A., Cooper, S.A. Evaluation of pre-operative Ibuprofen for post-operative pain after removal of third molars. Oral.Surg. 1978: 45: 851-856

Forbes, J.A., Bowser. M.A., Calderazzo, J.P., Foor, V.M. An evaluation of the analgesic efficacy of three opiod-analgesic combinations in post-operative oral surgery pain. J.Oral.Surg. 1981: 39: 198-112

Hellem, S., Persson, G., Nord, P.G. Gustafsson, B., and Huitfeldt B. A model for evaluating the analgesic effect of a new fixed ratio combination analgesic in patients undergoing oral surgery. Int.J.Oral.Surg.1979: 8: 435-442

Lawrence, D.R. Clinical Pharmacology, 4th Ed. Churchill-Livingstone, 1973.

Levernieux, M.D. Ibuprofen at high dosage. Curr.Med.Res.Opin. 1975: 3: 485-487

Lokken, P., Norman-Pedersen, K., Brauset, I. and Olsen I. Ibuprofen (Brufen) tested with bilateral oral surgery as a model for evaluation of anti-inflammatory effects. Curr.Med.Res.Opin. 1975: 3: 493-501

Muckle, D.S. Ibuprofen (Brufen) in soft tissue injuries. Curr.Med.Res.Opin. 1975: 3: 488-492

Najjar, T.A. and Newark, N.J. Harmfull effects of "Aspirin Compounds". Oral Surg. 1977: 44: 64-70

Nie, H., Hull, C.H., Jenkins, J.G., Steinbreme, K. and Brent, D.H. Statistical Package for the Social Sciences: 2nd Ed. New York, McGraw Hill, 1975

Petersen, J.K. Anti-inflammatory and analgesic effects of Indomethacin following removal of impacted mandibular third molars. Int.J.Oral Surg. 1975: 4: 267-276

Peterson, J.K. Diflunsial, a new analgesic, in the treatment of post-operative pain following removal of impacted mandibular third molars. Int.J. Oral Surg. 1979: 8: 102-113

Prescribing Leaflet DL 01/4. Brufen^{R} 400. The Boots Company (SA)(Pty) Ltd.

Rejholec, T. Long term Ibuprofen therapy of Rheumatic disease in patients with a past-history of peptic ulceration. Curr.Med.Res.Opin. 1975: 3: 522-524

Rietzik, M., Lownie, J.F. The analgesic effects of Syndol following surgical removal of impacted wisdom teeth. J.Dent.Ass.S.Afr. 1976: 31: 295-297

Thompson, M. and Anderson, M. Studies of gastrointestinal blood loss during Ibuprofen therapy. Symposium of Ibuprofen. Supplement to Rheum. and Phys.Med. March 13. 1970. 104-107

Wilkin, T.J. and Davidson, P.N. Lecture notes on drugs for dental students. Blackwell Scientific Publications 1979.