1964

Clinical evaluation of SQ 1,069 as an analgesic agent in arthritis

James R. Mouer
University of Nebraska Medical Center

The Clinical Evaluation of SQ 10,269 as an Analgesic Agent in Arthritis

James R. Mouer

Submitted in Partial Fulfillment for the Degree of Doctor of Medicine

College of Medicine, University of Nebraska
February 1, 1964
Omaha, Nebraska

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INTRODUCTION

Arthritis, which is a chronic joint disease, has been known for years as a potentially crippling disease; but in the main, it has remained of unknown etiology. In most cases the treatment is symptomatic and must be tailored to each individual's needs.

It is for this reason that a complete evaluation is necessary including a history, physical examination, appropriate laboratory studies, and roentgenograms. This affords a knowledge of the patients's general condition, as well as any associated or complicating disorders. The entire patient must be considered when initiating therapy.

Treatment of arthritis is primarily symptomatic, aimed at reduction of pain, reduction of inflammation, adequate rest, and physical therapy. If pain and inflammation reduction can be maintained, the rest and physical therapy might naturally follow. Such local measures as splintage, heat, rest, and counter-irritation, all play their part in this reduction of pain and inflammation.

Aspirin has remained the most important drug in the treatment of arthritis for the past 25 years. There are, however, about 25% of arthritis patients

who cannot tolerate aspirin, at least not in analgesic doses. Intolerance to aspirin is usually due to gastric irritation or hypersensitivity.(6)

When aspirin has failed, phenylbutazone compounds, also having both analgesic and antiphlogistic effects, may be used. There are many more untoward effects, however, including salt retention, gastric irritation, reduction of bleeding time, allergic rashes, and agranulocytosis. Phenylbutazone compounds are usually given for a trial period of one week, if none of the preceding symptoms have been present with less toxic analgesics. If, at the end of one week, improvement is not marked, the drug is discontinued.(6)

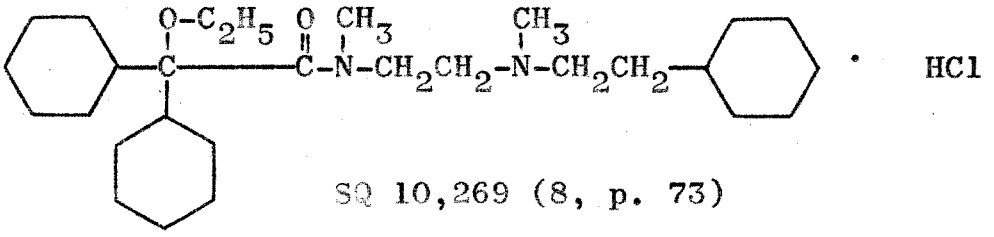
Steroids, primarily prednisone and prednisolone, may be indicated in severe or difficult arthritis. They should not be used intermittently or alternated with aspirin or phenylbutazone, according to Dr. Kersley.(6) Side effects of steroids, of course, include salt retention, hypertension and Cushinoid appearance. Steroids are contraindicated in patients with associated peptic ulcer, severe hypertension, diabetes mellitus, or recent psychoses. In cases such as these, gold therapy may be considered. The

effects of gold therapy are less certain and slower but the benefits are usually longer and side effects less disturbing.(4)

The majority of this paper will be concerned with a double-blind clinical evaluation of a new analgesic agent and its effect on the chronic pain of arthritis. The new drug is known only by the code name of SQ 10,269.

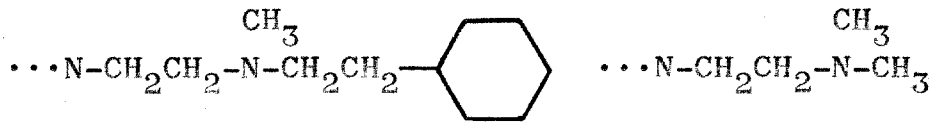
CHEMISTRY AND PHARMACOLOGY

Chemically, SQ 10,269 is 2-Ethoxy-N-methyl-N-[2-(methylphenethylamino)ethyl]-2,2-diphenylacetamide hydrochloride. The structural formula is as follows:



SQ 10,269 (8, p. 73)

It is classed as a basic amide of diphenylacetic acid. The parent compound, with similar analgesic properties, is SQ 4773. As an analgesic agent, SQ 10,269 is considered to be about 1.5 times as effective as SQ 4773. Chemically, SQ 4773 has a methyl group in place of the phenylethyl group on the amino nitrogen, as shown at top of following page.(7)



SQ 10,269 SQ 4773

SQ 10,269 is a white, odorless, tasteless, crystalline powder, which dissolves about 1.0% in water, forming a solution with a pH of 3.5. It is very soluble in methanol and chloroform, and is insoluble in ether. It is stable on exposure to air, light, and temperatures up to 60°C.(8p.73)

In a series of experiments using mice, SQ 10,269 was found to be about 1.3 times as potent as meperidine and about equal to codeine sulfate and propoxylene. Clinically, SQ 10,269 was compared to codeine sulfate. The experimental pain threshhold produced by the electrical stimulation of a metallic filling in a vital tooth was the basis for the comparison. It was found that 100 mg. of SQ 10,269 had the equivalent analgesic effect of 64 mg. of codeine and produced a more enduring response. The degree of pain relief with SQ 10,269 has been directly proportional to the dose. The higher the dose, however, the higher the incidence of side effects. Drowsiness, vertigo, nausea, and vomiting have been the most prominently reported side effects

thus far. No untoward effects on the liver, kidneys, or hematopoietic system have been noted clinically. Patients, who have been placed on the drug for as long as fourteen weeks have shown no evidence of toxicity or physical dependence.

Vomiting has been noted in dogs with high doses of SQ 10,269. All dogs vomited within a few minutes when in the fasting state and given a dosage of 160 mg./Kg. However, in the non-fasting state, fifty per cent of the animals retained doses as large as 320 mg./Kg. After retained doses of this magnitude, no effects were observed on the respiratory rate, blood pressure, heart rate, electrocardiogram, or pupillary diameter.

The spontaneous motor activity decreased in mice when given either SQ 10,269 or codeine sulfate. The decrease was inversely related to the dose. The smaller doses caused a greater decrease in activity.

SQ 10,269 tolerance has been demonstrated to occur at about the same rate as that of meperidine. Rats developed tolerance to either drug after about 15-20 days. Tolerance to SQ 10,269 did not show cross tolerance to meperidine, whereas tolerance to meperidine did show reciprocal tolerance to SQ 10,269.

Complete withdrawal for 21 days restored the original effect with either drug.

The median lethal dose (LD_{50}) of SQ 10,269 varied with the concentration of the drug. The lower concentrations were more lethal than the higher concentrations, indicating that the lower concentrations were more rapidly or completely absorbed from the gastrointestinal tract. The median lethal oral dose was estimated to be 325 mg./Kg. Two of three rats died when given 350 mg./Kg. as a 2% solution, whereas only one of three died when given 500 mg./Kg. as a 4% solution. The LD_{50} of intravenously administered SQ 10,269 was 40 $\pm$ 1.7 mg./Kg.

The effect of chronic ingestion of the drug was demonstrated by giving three groups of dogs 4.5, 14 and 40 mg./Kg., respectfully, for 26 weeks. All three groups appeared alert and healthy throughout the 26 week period. In the 40 mg./Kg. group, there were Bromsulfalein changes and an elevation of the Serum Glutamic Pyruvic Transaminase levels suggestive of depressed liver function. The intermediate and low dose groups demonstrated no abnormal laboratory values. Only the dogs that received 40

mg./Kg. showed any pathological changes when sacrificed. In these dogs the liver showed moderate degeneration evidenced by the following: numerous homogeneous eosinophilic bodies in liver cells, a few acidophilic bodies, and an increased number of double nucleated cells.

SQ 10,269 is considered to be a non-addicting analgesic agent indicated for the relief of all types of pain, including post-operative pain and pain associated with chronic and recurrent diseases. There are no known contraindications to its use. At present the dosage is exploratory, pending the outcome of further clinical pharmacological trials. The dosage originally recommended for this study was 150 mg. four times daily, but was changed to 150 mg. twice daily. The change was requested by the manufacturer, apparently due to side effects with the higher dosage.

PURPOSE AND METHOD OF STUDY

The purpose of this study was to evaluate the following: the extent of pain relief, the presence and severity of side effects, and the toxicity of SQ 10,269.

The patients selected were moderate to severe arthritics, and were seen weekly by the author in

the Arthritis Clinic of the University of Nebraska College of Medicine. There were five patients classified with osteoarthritis, seven classified with rheumatoid arthritis, and one with mixed rheumatoid and osteoarthritis. There were two men and eleven women, and their ages varied from 33 to 84. Of the total of thirteen patients selected, eleven completed the study. Two patients dropped out due to intolerence to the drug.

The medications were supplied as buff colored gelatin capsules by the Squibb Institute for Medical Research. They were labeled only with the codes of JEX and JEV. After the study was completed, the code was broken and revealed that:

JEX was SQ 10,269--150 mg. per capsule

JEV was aspirin----600 mg. per capsule

Each patient served as his own control in this double-blind study. The two codes were alternated every week for a total of one month. The patients were given a weeks supply of medication and instructed to take one capsule twice daily with breakfast and supper. They were to keep a daily record of the degree of analgesia, side effects, and necessary concomitant analgesia. No patient was

asked specifically about side effects, and those recorded were spontaneously expressed by the patient.

At the beginning of the study and at two week intervals during the study, the following laboratory values were checked: complete blood count, urinalysis, blood urea nitrogen, cephalin cholesterol flocculation, alkaline phosphatase, and serum glutamic pyruvic transaminase. All prior analgesic medication was discontinued. All other medications, such as steroids, gold, cardiovascular and renal medications, were left unchanged. At the conclusion of each patient's test series, the original analgesic medication was again reinstated.

EVALUATION OF RESULTS

The patient recorded his own daily report on a form similar to the one reproduced in Fig. 1. Table 1 is a composite of all the patient report forms.

Degree of relief	0	1	2	3	4	Total
SQ 10,269	3	7	60	41	42	153
Aspirin	33	41	49	39	0	162

Table 1

The code for the degree of relief is as follows:

Patient's Name					Study Week Number		
Day of the Week	First	Second	Third	Fourth	Fifth	Sixth	Seventh
Daily Capsule Number							
Pain Relief: None							
Slight							
Moderate							
Almost Complete							
Complete							
Other Drugs For Pain Relief: Name							
Amount							
Remarks							

(10)

Fig. 1

0 = None

1 = Slight

2 = Moderate

3 = Almost complete

4 = Complete

The total number of SQ 10,269 observations should have equaled the total number of aspirin observations; however, a few of the patients were unable to complete their entire weekly dosage due to intolerence of one kind or another.

The effectiveness was compared by using the method of Cass, Frederik and Bartholomay.(2) This was done by employing the following formula:

$$\frac{\text{Number of observations times rating}}{\text{Total number of observations}}$$

The average effectiveness of SQ 10,269 would then be as follows:

$$\frac{3x0 + 7x1 + 60x2 + 41x3 + 42x4}{153} = 2.7$$

And the average effectiveness of aspirin would be:

$$\frac{33x0 + 41x1 + 49x2 + 39x3 + 0x4}{162} = 1.6$$

The means obtained above were compared statistically. The standard deviation for SQ 10,269 was 0.9975 and that for aspirin was 1.0643. The standard error of the difference between the two

means was 0.115. This figure divided by the observed difference of 1.1 produced a relative deviate of 9.5. This is to say that the possibility of the difference between the two means being due to chance alone is a figure 9.5 deviations from the mean. The p value then is considerably less than 0.001.(1)

The duration of pain relief with SQ 10,269 was reported by most patients to be between five and eight hours.

In compiling the list of side effects, it should be remembered that these were spontaneous observations of the patient. None of the symptoms were asked about or suggested. The following table shows the comparison of side effects elicited in this study with SQ 10,269 and aspirin.

The most common side effects were vertigo, drowsiness, and nausea, in that order. These are the same side effects mentioned as most prominent in the literature received from the manufacturer. The relative incidence, however, appears to be greater in this study. No instances of constipation were reported; but in experimental studies, SQ 10,269 was shown to be more effective than codeine in slowing peristalsis.

Side effects	SQ 10,269	aspirin
Nausea	35	1
Vertigo	66	0
Vomiting	10	0
Constipation	0	0
Drowsiness	45	7
Excitement	1	0
Headache	7	1
Abdominal cramps	1	0
Weakness	2	0

Table 2

No significant toxic effects were noted from the laboratory studies done. Two patients showed a rise from normal in the cephalin flocculation; however, an equal number returned to normal after an abnormal control. The SGPT rose above normal in one patient on one occasion, and rose above the control values in several others. The significance of these few values is difficult to ascertain, but the author feels it is small.

SUMMARY

SQ 10,269 is a basic amide derivative of diphenylacetic acid. It is a new non-narcotic analgesic which has been evaluated in animal experiments and is presently being studied clinically. It is an effective analgesic with a potency equivalent to that of codeine. No toxic effects on hepatic, renal

or hematopoietic systems have been noted. While tolerance has been demonstrated to occur, no indications of addiction have been shown.

This investigative study was conducted in a double-blind manner using 150 mg. of SQ 10,269 and 600 mg. of aspirin. The analgesic activity was compared in thirteen moderately severe arthritis patients. Each of the medications had the same appearance and were alternated weekly in each patient for a total of four weeks. In this way, each patient acted as his own control.

The composite results showed that SQ 10,269 was significantly superior to aspirin in the dosages used.(p 0.001) The incidence of side effects was also significantly higher with SQ 10,269. The most frequently noted in this and also in previous studies, have been vertigo, drowsiness, nausea, and vomiting.

CONCLUSION

In conclusion, SQ 10,269 appears to be an effective analgesic agent in relieving the pain due to moderate to severe arthritis. The side effects noted, however, might preclude its popularity. It may be that a smaller single dose at more frequent

intervals, may be as effective an analgesic without the incidence of side effects.

ACKNOWLEDGEMENTS

Most sincere thanks to Dr. Mary J. Henn for guidance and assistance throughout this project. Acknowledgement and thanks to Dr. L. Lizbeth Monroe and the Squibb Research Institute for their cooperation in supplying the SQ 10,269 and aspirin preparations. Also, for the use of their experimental material in preparing this paper. Thanks to the personnel of the Medicine Clinics of the University of Nebraska College of Medicine for their cooperation.

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