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Double blind study in the use of a new analgesic in musculoskeletal disorders

Larry Richard Evertson
University of Nebraska Medical Center

A DOUBLE BLIND STUDY IN THE USE OF A NEW ANALGESIC IN MUSCULOSKELETAL DISORDERS

Larry R. Evertson

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I. INTRODUCTION

ARTHRITIS IS A DISORDER WITH PAIN AND STIFFNESS REFERABLE TO THE MUSCULOSKELETAL SYSTEM, WITH THE SYMPTOMS BEING DUE TO JOINT ABNORMALITY. ARTHRITIS OCCURS IN A NUMBER OF DIFFERENT FORMS, BUT IS DUE TO ESSENTIALLY TWO FUNDAMENTAL PATHOLOGICAL PROCESSES THAT AFFECT THE JOINT: (A) INFLAMMATION, WHICH MAY BE EXUDATIVE OR PROLIFERATIVE IN TYPE, OR A COMBINATION OF EACH, AND (B) DEGENERATIVE CHANGES WHICH ARE DEPENDENT ON THE LIMITED CAPACITY OF THE ARTICULAR CARTILAGE TO REPAIR ITSELF. ARTHRITIS MAY BE EITHER ACUTE OR CHRONIC AND THE CHRONIC TYPE IS SUBJECT TO ACUTE EXCERBATIONS.

NO CAUSATIVE PROCESS HAS AS YET BEEN ESTABLISHED. THIS MAKES TREATMENT PRIMARILY SYMPTOMATIC. TREATMENT REVOLVES AROUND SEVERAL GENERAL MEASURES: (1) REST, (2) RELIEF OF PAIN, (3) MAINTENANCE OF JOINT FUNCTION, (4) PREVENTION AND CORRECTION OF PHYSICAL DEFORMITIES BY APPLICATION OF ORTHOPEDIC PRINCIPLES AND, (5) CORRECTION OF ANY FACTORS THAT ARE DELETARIOUS TO THE HEALTH OF THE INDIVIDUAL PATIENT.[1]

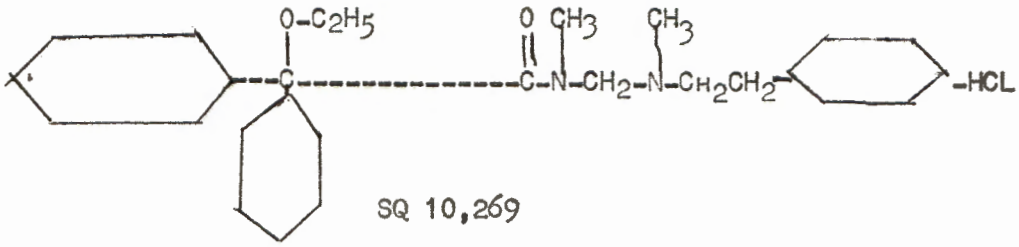
THIS STUDY IS CONCERNED WITH ANALGESIA. THE MOST WIDELY USED ANALGESICS IN ARTHRITIC DISORDERS ARE THE SALICYLATES. OTHERS USED ARE PHENYLBUTAZONE, PROPOXYPHENE (DARVON®) AND VARIOUS SALICYLATE COMPOUNDS. THERE ARE ALSO OTHER MEASURES USED TO ELICIT A REMISSION. THESE INCLUDE THE USE OF STEROIDS AND GOLD SALTS.

GARROD IN HIS BOOK A TREATISE ON RHEUMATISM AND ARTHRITIS PUBLISHED IN 1890, RECOMMENDS TREATMENT OF ARTHRITIS WITH MANY UNUSUAL AND VARIED SUBSTANCES. SALICYLATES HAD BEEN IN USE FOR APPROXIMATELY 15 YEARS FOR ACUTE RHEUMATIC ARTICULAR PAINS, BUT WERE NOT FELT USEFUL IN CHRONIC ARTICULAR INVOLVMENT. GARROD RECOMMENDED THE USE OF LOCAL TREATMENT SUCH AS PAINTING WITH IODINE OR A RUBBING LINAMENT. AS FOR DRUG TREATMENT ONE OF COMPOUNDS WAS COMPOSED OF GUAIACUM COMBINED WITH CITRATE OF POTASH AND BARK AND OCCASIONALLY IODIDE OF POTASSIUM WAS ADDED. ANOTHER SUBSTANCE USED WAS ICHTHYOL- A COAL TAR COMPOUND WHICH WAS TAKEN INTERNALLY OR RUBBED ON THE AFFECTED AREA. OTHER MEASURES IN VOGUE IN 1890 WERE MINERAL WATERS AND BATHS, BUT ONLY AFTER THE ACUTE PROCESS WAS OVER.[2]

WITH THE INABILITY OF MODERN MEDICINE TO GIVE GOOD RELIEF IN PAIN OF ARTHRITIS, IT IS NO WONDER THAT MANY PEOPLE WHO SUFFER FROM THE DISEASE FALL PREY TO ANYONE WHO PROMISES CURE OR RELIEF. THEREFORE, THIS STUDY HAS THE PURPOSE TO AID IN EVALUATING A NEW ANALGESIC-SQ 10,269-WHICH MAY BE OF SOME VALUE IN THE TREATMENT OF ARTHRITIC PAIN. THIS DRUG HAS BEEN SHOWN TO BE OF USE IN HIGHER DOSES, BUT SIDE EFFECTS EXPERIENCED MADE THE DRUG DIFFICULT TO USE. THEREFORE, THIS STUDY IS TO FIND WHETHER OR NOT SQ 10,269 CAN BE USED IN A DOSE OF 37.5 MG. FOUR TIMES DAILY IN RELIEF OF PAIN WITHOUT SIGNIFICANT SIDE EFFECTS.

II. SQ 10,269

A. Technical Data



SQ 10,269

The chemical name for Sq 10,269 is 2-Ethoxy-N-methyl-N-[2-(methylphenethylamine)ethyl]-2, 2-diphenylacetamide, hydrochloride. It is a substituted basic amide derived from benzilic acid. The empirical formula is $C_{28}H_{34}N_2O_2 \cdot HCL$. The molecular weight is 430.60/467.06. It is a white, odorless, tasteless, crystalline powder with a melting point of 168.0-169.5°C (U.S.P.). SQ 10,269 has a solubility of 1.0% in water with slight warming.. The pH of a 1.0% aqueous solution is 3.5. It is very soluble in ethanol, isopropanol, and acetone, but insoluble in ether. SQ 10,269 and its solutions are stable on exposure to air, light and temperatures up to 60°C.. The dry material is nonhygroscopic.

B. Animal Pharmacology, Toxicalogy, and Pathology

SQ 10,269 has been shown to be at least equal to meperidene hydrochloride, codeine sulfate and propoxyphene in analgesic effect in rats and mice. Rats given SQ 10,269 and meperidine hydrochloride both developed a tolerance to

THE DRUGS IN 24 DAYS. THE ANIMALS MADE TOLERANT TO MEPERIDINE WERE ALSO TOLERANT TO SQ 10,269, BUT THE ANIMALS MADE TOLERANT TO SQ 10,269 WERE NOT TOLERANT TO MEPERIDINE. SQ 10,269 DID NOT LESSEN MORPHINE SULFATE WITHDRAWAL SYMPTOMS IN MONKEYS.

SQ 10,269 HAS SHOWN EEG BLOCKAGE OF PAIN AROUSAL IN CATS. ONLY SLIGHT INHIBITION OF CONDITIONED AVOIDANCE RESPONSE IN RATS TO AN ELECTRICAL SHOCK WAS OBSERVED ON HIGH DOSES.

IN UNANESTHETIZED FASTED DOGS GIVEN ORAL DOSES OF 40 AND 80 MG. SQ 10,269/Kg., SIGNS OF DELAYED HYPERNIA, SLIGHT-TO-MODERATE HYPOTENSION, SOMETIMES ACCOMPANIED BY BRADYCARDIA WERE OBERSERVED. THERE WERE ALSO MINOR EKG CHANGES AND MIOSIS. VOMITING OCCURRED 5 TO 7 MINUTES AFTER DOSES OF 160 MG. FIFTY PER CENT OF NONFASTED DOGS RETAINED DOSES UP TO AND INCLUDING 320 MG./Kg., BUT DOSES OF 640 MG./Kg. PRODUCED VOMITING IN ALL THE DOGS STUDIED. NON-FASTED DOGS RETAINING DOSES UP TO 320 MG./Kg. SHOWED NO CHANGES IN RESPIRATORY RATE, HEART RATE, EKG, OR PUPILLARY DIAMETER. THE DOGS THAT VOMITED AFTER DOSES OF 160 OR 320 MG./Kg. SHOWED SYMPTOMS IDENTICAL TO FASTED DOGS GIVEN DOSES OF 40 AND 60 MG. SQ 10,269/Kg.

SQ 10, 269 WHEN GIVEN IN INTRAVENOUS DOSES OF UP TO 16 MG. SQ 10,269/Kg. TO UNANESTHETIZED DOGS HAD NO EFFECT ON RESPIRATORY RATE, BUT DOSE LEVELS FROM 4 TO 60MG./Kg.

REDUCED RESTING BLOOD PRESSURE BY APPROXIMATELY 20 TO 50 PER CENT.. CONVULSIONS DID NOT OCCUR UNTIL CUMULATIVE DOSES OF 32 TO 39 MG./KG. HAD BEEN GIVEN. IN ANESTHETIZED DOGS, INTRAVENOUS DOSES OF 1.0 AND 2.0 MG. SQ 10,269/KG. CARRIED A 25 TO 30 PERCENT REDUCTION IN RESPIRATORY MINUTE VOLUME WITHOUT ALTERING TIDAL VOLUME. RESPIRATORY ARREST WAS PRODUCED IN ANESTHETIZED DOGS AT 4.0 MG. SQ 10,269/KG., BUT WAS REVERSED READILY WITH NALORPHINE.

ORALLY ADMINISTERED DOSES OF 2 AND 8 MG. SQ 10,269/KG. AND EQUIVALENT DOSES OF CODEINE SULFATE GIVEN TO FOUR DOGS SHOWED THAT BOTH MAY EXERT EQUAL ANTITUSSIVE ACTIVITY.

MODERATE IRRITATION OF THE VASTUS LATERALIS MUSCLES OF TWO RABBITS OCCURRED WITHIN TWO DAYS FOLLOWING INTRA-MUSCULAR INJECTION OF A 1.0 PER CENT AQUEOUS SOLUTION OF SQ 10,269, WITH MODERATE TO MARKED CELLLUAR DEGENERATION, BUT NO NECROSIS.. SEVEN DAYS AFTER INJECTION OF THE DRUG FOUR MUSCLES SHOWED DEFINITE AREAS OF NECROSIS.

INSTILLATION INTO THE CONJUNCTIVAL SAC OF RABBITS OF A 0.25 PERCENT SQ 10,269 SOLUTION IN 2.2 PER CENT BORIC ACID PRODUCED CORNEAL ANESTHESIA WITHIN 3 TO 6 MINUTES.

ONE SOLUTION WITH A PH OF 4.36 PRODUCED ANESTHESIA LASTING 30 MINUTES, WHERE AS ANOTHER SOLUTION WITH A PH OF 4.95 PRODUCED ANESTHESIA LASTING 100 MINUTES.

NO SIGNIFICANT SLOWING OF INTESTINAL PERISTALSIS WAS OBSERVED WITH AN INTRAPERITONEAL INJECTION OF AQUEOUS

solutions of 8 mg. SQ 10,269/Kg. into rats. Doses of 16 mg./Kg. slowed intestinal peristalsis 2.2 times as much as comparable doses of codeine sulfate.

SQ 10,269 at concentrations of 0.5 mcg./ml. and higher inhibited normal activity of excised rat's uterus. The spasmogens oxtocin, acetylcholine, and bradykinin were without effect on the excised, estrogen primed, quiescent rat's uterus. SQ 10,269 apparently inhibited the ability of the smooth muscle to respond. Propoxyphene and codiene sulfateinhibited these tissues at concentrations of 2 mcg./ml. and 8 mcg./ml., respectively.

Excretions of SQ 10,269 is apparently via the liver where it is converted to a primary and/or secondary amine. This was observed in vitro with rat liver slices. Other tissues such as kidney, brain, and muscle did not alter SQ 10,269.

Rate of excretion of SQ 10,269 labeled with C^{14} in urine and feces is as below:

C. Excretion

	Per cent of Administered dose excreted			
Specimen	0-24 hrs.	24-48 hrs.	48-72 hrs.	72-96 hrs..
Urine	29.3	3.0	1.1	0.4
Feces	50.0	9.0	2.4	0.6
Total	79.3	12.0	3.5	1.0

Table II-1 Rate of Excretion of C^{14} labeled SQ 10,269 in rats

SQ 10,269 HAS SHOWN NO SIGNIFICANT CHANGES IN FETAL DEVELOPMENT WHEN ADMINISTERED TO RATS.

THE LD_{50} DOSAGES IN MICE VARY FROM 40 MG./KG. FOR 5 DAYS WHEN GIVEN INTRAVENOUSLY TO 20 MG./KG. FOR 5 DAYS WHEN GIVEN INTRAPERITONEALLY TO 740 MG./KG. WHEN GIVEN ORALLY.. THIS STUDY SHOWED THAT A LOWER CONCENTRATION GIVEN ORALLY LED TO A GREATER ABSORPTION. ACUTE ORAL TOXICITY COULD NOT BE DETERMINED IN DOGS DUE TO VOMITING CAUSED BY HIGH DOSES.

ON LARGE DOSES GIVEN OVER 8 WEEKS TO IMMATURE RATS AT 10 TO 165 MG./KG./ DAY, BODY WEIGHT WAS SLIGHTLY TO MODERATELY RETARDED. AT NECROPSY THE RATS GIVEN 165 MG./KG./DAY HAD INCREASED LIVER WEIGHTS AND MILD HISTOLOGICAL LIVER DEGENERATION. IN ANOTHER STUDY ADULT RATS GIVE 50 MG./KG./DAY FOR THE SAME PERIOD HAD ONLY MILD CHANGES AND THOSE GIVEN 15 MG./KG./DAY FOR 26 WEEKS HAD ELEVATED BSP (BROMSULFONPHTHALEIN) AND INCREASED SERUM TRANSAMINASE. NECROPSY SHOWED MODERATE HEPATIC DEGENERATION.[3]

D. Clinical Pharmacology, Use and Indications

Analgesia: SQ 10,269 has been shown to be effective in relief of pain of all types from experimentally produced pain such as electrical stimulation to pathologic pain produced by fractures, herpes zoster and pleuritis. One hundred mg. of SQ 10,269 is approximately equal to 64 mg. of codiene sulfate when both are given orally, but the SQ 10,269 has a more enduring effect. These studies were run with a placebo and significant pain relief was produced.

Toxicity: SQ 10,269 has been given in doses as high as 400 to 900 mg. daily with no pathological changes seen, including white blood cell counts, hematocrit, hemoglobin, SGP-T, fasting blood sugar, alkaline phosphatase, bilirubin, thymol turbidity and complete urinalysis.

In one study SQ 10,269 was given to 25 volunteers in doses of 450 to 600 mg. daily for fourteen weeks with no evidence of chronic toxicity or addiction noted.

Undesirable Side Effects: The most common side effects reported are drowsiness, dizziness, nausea, and vomiting. The Severity of side effects have been directly proportional to the dose of the drug. Others are vertigo (true), excitement abdominal cramps, diarrhea, tremor and constipation.

Indications: SQ 10,269 is an effective analgesic agent indicated for the relief of all types of pain, including post-operative pain and the pain associated with chronic and recurrent disease.

CONTRAINDICATIONS: THERE ARE NO KNOWN CONTRAINDICATIONS TO THE USE OF SQ 10,269.

DOSAGE: DOSAGE SCHEDULES FOR SQ 10,269 ARE EXPLORATORY AT PRESENT, PENDING THE OUTCOME OF FURTHER CLINICAL PHARMACOLOGICAL TRIALS.[3]

III. STUDY PROTOCAL AND METHODS USED

Type of Study The study was a three-way, double-blind, cross-over in 20 patients seen in a medical clinic.

Duration The study lasted three weeks for each patient, one week on SQ 10,269 37.5 mgm.,capsules, one week on propoxyphene (Darvon)32mg. capsules, and one week on Placebo capsules.

Procedure All the subjects selected were between the ages of 31 and 86, and manifested pain due to arthritis--gout, Rheumatoid, or osteo-arthritis. None had a history of drug addiction and none were receiving tranquilizers or sedatives. All the controlled studies were double-blind. The control drugs were: Propoxyphene (Darvon®) 32 mg. and Placebo.

Therapeutic regimen The dosage of drugs given, was one capsule every four hours, not to exceed four capsules each day. The number of capsules taken each day was recorded on a card given the patient for that purpose.

Evaluation of pain relief The patients each kept the record of the number of capsules taken each day and his overall impression of pain relief for the day. The therapeutic response supposedly reflected the relief obtained for the whole day and not the response for an individual dose. The relief was based on a grading scale of 0-4, with the gradation broken down into the following groups:

0= NO RELIEF
1= VERY SLIGHT RELIEF
2= MODERATE RELIEF
3= ALMOST COMPLETE RELIEF
4= COMPLETE RELIEF

A THERAPEUTIC RESULT WAS GIVEN BY EACH PATIENT FOR EACH DAY . CAPSULES WERE TAKEN.

CONCOMITANT ANALGESIA EACH PATIENT WAS INSTRUCTED TO CONTINUE HIS NORMAL ANALGESIA AND MEDICATIONS AS USUAL, JUST ADDING THE CAPSULES FOR THE WEEK TO HIS NORMAL REGIMEN.

EVALUATION OF SIDE EFFECTS SIDE EFFECTS WERE EVALUATED ONLY WHEN SPONTANEOUSLY EXPRESSED BY THE PATIENT. ONCE A SIDE EFFECT WAS OBSERVED, THE PATIENT WAS QUESTIONED CONCERNING THE SEVERITY AND DURATION OF THE SIDE EFFECT. SIDE EFFECTS WERE EVALUATED ON A 0-4 SCALE AS FOLLOWS:

0= NONE
1= MILD
2= MODERATE
3= SEVERE

THE FOLLOWING ARE THE SIDE EFFECT COMMONLY SEEN WITH SQ 10,269:

NAUSEA	ABDOMINAL CRAMPS
VOMITING	DIARRHEA
VERTIGO (TRUE)	TREMOR
EXCITEMENT	DIZZINESS
DROWSINESS	CONSTIPATION 3

Drugs		SQ 10,269					Darvon 32					Placebo				
Days of Pain Relief		0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Patient	#1	5	2		4		3	4				4	3			
	2	7					7					7				
	*3	2	Discontinued					Discontinued					Discontinued			
	4	7					7					7				
	5	7					7					7				
	6	7					7						7			
	7	7					7					3	4			
	8			7			2	1	4					7		
	9				7		7					7				
	10	7								7					7	
	11	1	1	4	1				7			5	2			
	12		2	5				2	5					7		
	13		2	5				7					2	5		
	14	2		5						7					7	
	15		3	5			3	4				2	5			
	16		7				7							7		
	+17	6	2				2	Discontinued				5	2			
	18		2	5					1	6			1		7	
	19	7					7					7	6			
	20			7			4	2	1			7				
Totals		65	20	42	1	7	70	20	18	20	0	55	33	26	20	0

0= no relief
1= very slight relief
2= moderate relief
3= almost complete relief
4= complete relief

Table IV-1

Results of pain relief on a daily basis with 2 capsules on day 1, and 4 on each successive day. *This patient discontinued the study because of a moderately severe rash that developed. +This patient discontinued the study due to an misunderstanding concerning side effects.

THE RESULTS ON THE PREVIOUS PAGE ARE COMPARED A LITTLE MORE READILY WHEN PUT INTO PERCENTAGES AS BELOW:

	SQ 10,269	DARVON	PLACEBO
NO RELIEF	48.1%	54.7%	41.4%
VERY SLIGHT RELIEF	14.8%	15.6%	24.1%
MODERATE RELIEF	31.1%	14.1%	19.5%
ALMOST COMPLETE	0.7%	15.6%	15.0%
COMPLETE	5.2%	0.0%	0.0%

TABLE IV-2

DAYS OF PAIN RELIEF EXPRESSED AS A PERCENTAGE OF THE TOTAL DAYS EACH DRUG WAS TAKEN.

	SQ 10,269	DARVON	PLACEBO
PATIENT # 1	NONE	NONE	NONE
2	NONE	NONE	NONE
3	SKIN RASH MOD. TO SEVERE	- DISCONTINUED STUDY	
4	NONE	NONE	NONE
5	MILD NAUSEA & DROWSINESS	MILD NAUSEA DROWSINESS	MILD NAUSEA DROWSINESS
6	NONE	MILD LIGHTHEADNESS AFTER PILL	NONE
7	NONE	NONE	NONE
8	HEADACHE & NAUSEA FOR THREE DAYS MILD	NONE	MILD HEADACHE AND NAUSEA
9	NONE	MILD CONSTIPATION	NONE
10	MILD DIZZINESS AND NAUSEA	INCREASED ENERGY	MILD DIZZINESS AND NAUSEA
11	NONE	NONE	NONE
12	MILD DROWSINESS	MILD RASH WITH PRURITIS	MILD DROWSINESS
13	MILD ANOREXIA	NONE	MILD ANOREXIA
14	MILD NAUSEA AND AND DIZZINESS	TIRED AND NERVOUS	MILD NAUSEA AND DIZZINESS
15	MILD LIGHTHEADNESS	NONE	MILD LIGHTEADNESS
16	MILD DIZZINESS	NONE	MILD DIZZINESS
17	NONE	MILD NAUSEA	NONE
18	NONE	NONE	NONE
19	RINGING IN EARS	NONE	RINGING IN EARS
20	NONE	NONE	NONE
TOTAL	9 WITH MILD SIDE EFFECTS	7 MILD SIDE EFFECTS	9 MILD SIDE EFFECTS

TABLE IV-3 - SIDE EFFECTS

Discussion

THIS STUDY CONCERNS MANY SUBJECTIVE EVALUATIONS, THEREFORE, EACH PATIENT WAS USED AS HIS OWN CONTROL. THE PATIENTS WERE SELECTED FROM THE ARTHRITIS CLINIC OF THE UNIVERSITY OF NEBRASKA COLLEGE OF MEDICINE. THEY WERE SELECTED ON THE BASIS OF HAVING PAIN AND THEIR RELIABILITY IN BEING ABLE TO EVALUATE THE PAIN AND RELIEF OBTAINED FROM THE DRUGS. THE PATIENTS VARY GREATLY IN AGE AND SEVERITY OF PAIN, THUS MAKING INDIVUAL COMPARISONS MORE DIFFICULT. ALSO THE TYPE OF DISEASE PROCESS VARIED. THERE ARE EXACERBATIONS AND REMISSIONS OF THE ARTHRITIC PROCESS TO CONSIDER, AS WELL AS THE PSYCHOLOGICAL LIFT THAT MAY BE SEEN IN ATTEMPTING A NEW TREATMENT FOR ARTHRITIS. THERE IS VARIATION IN THE GRADING OF PAIN RELIEF BY THE INDIVIDUAL PATIENTS. NO RELIEF AND COMPLETE RELIEF ARE EASILY EVALUATED, BUT THE THREE LEVELS BETWEEN THESE TWO EXTREMES ARE MORE DIFFICULT TO DIFFERENTIATE. POSSIBLE USING FOUR OR THREE GROUPS INSTEAD OF FIVE WOULD MAKE THE VALUES EASIER FOR THE PATIENT TO SELECT, AND THUS INCREASE THE VALIDITY OF THE STUDY. ANOTHER FACTOR LIMITING THE VALIDITY OF THE STUDY IS THE SMALL SIZE OF THE SAMPLE STUDIED. A LARGER SAMPLE WOULD BE MORE EASILY EVALUATED, ESPECIALLY WHEN CONSIDERATION IS GIVEN TO RESULTS SUCH AS THE PATIENT WHO OBTAINED COMPLETE RELIEF FOR ONE WEEK ON SQ 10,269. IN THIS STUDY THE RESULT IS OVER FIVE PER CENT OF THE TOTAL PATIENT DAYS, BUT IF THE SAMPLE WERE 100 INSTEAD OF 20 IN NUMBER, FIVE PER CENT WOULD BE A MUCH MORE VALID RESULT.

If the results are grouped into three groups, with no relief being one group, very slight relief and moderate relief in a second group, and almost complete and complete relief in a third group the results for SQ 10,269 and the placebo are very similar especially if the value for complete relief is disregarded. In fact the placebo gave more overall relief than did SQ 10,269. This is Summarized in table IV-4.

	SQ 10,269	Placebo	Darvon
No relief	48.2%	41.4%	54.7%
Slight & Moderate	47.9%	53.6%	29.7%
Complete & almost complete	5.9%	5.0%	15.6%

Table IV-4 Data regrouped in three groups to show similarity of data.

It is apparent from the above data that the Placebo was as effective as, if not more effective than SQ 10,269 in the relief of Pain. This leads one to feel that with proven pain relief at higher dosage levels, SQ 10,269 at 37.5 mg. taken four times each day is insufficient to produce significant pain relief.[45]

Side effects are summarized in table IV-3. These are subjective in evaluation. Only one Person had anything other than mild side effects from the drugs. This person had a severe skin rash which is apparently previously unreported as an side effect. This leads one to consider the possibilty of another cause for this rash. One other person experienced

SOME MILD SKIN RASH, BUT THIS WAS NOT ON SQ 10,269, BUT ON THE OTHER DRUGS, USED IN THE STUDY. ONE VERY UNEXPECTED FINDING WAS THE SIMILARITY OF THE SIDE EFFECTS OBSERVED WITH SQ 10,269 AND WITH THE PLACEBO. WITH THE EXCEPTION OF THE SKIN RASH, IDENTICAL RESULTS WERE OBTAINED WITH THE TWO DRUGS. THERE WAS NO SUCH RELATIONSHIP BETWEEN DARVON AND EITHER OF THE OTHER DRUGS. ONLY ONE PATIENT EXPERIENCED SIDE EFFECTS ON ALL THREE DRUGS.

V. SUMMARY AND CONCLUSIONS

Twenty patients were given SQ 10,269 37.5 mg. capsules, Darvon 32 mg. capsules, and Placebo capsules, on three successive weeks in a three-way, double-blind, crossover study and evaluated for pain relief and side effects daily. The Placebo gave slightly better relief than SQ 10,269 and both of these drugs gave more relief than Darvon . Side effects were mild with the exception of one patient developing a skin rash on SQ 10,269. With that exception, the side effects were identical for SQ 10,269 and the Placebo.

On the basis of this study, it is felt that SQ 10,269 at the dosage given is not a very effective drug in the treatment of pain due to musculoskeletal disorders such as Rheumatoid and Osteo-Arthritis. With the results obtained, one wonders if the Placebo and SQ 10,269 were not similar or the same drugs. As one person did get complete relief on the drug, the possibility that SQ 10,269 might be helpful in selected patients cannot be ruled out.

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