1958

Clinical evaluation of zacterin in arthritis

Leroy Richard Smith
University of Nebraska Medical Center

THE CLINICAL EVALUATION OF ZACTIRIN IN ARTHRITIS

Leroy R. Smith

Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

College of Medicine, University of Nebraska

April 1, 1958

Omaha, Nebraska

TABLE OF CONTENTS

THE CLINICAL EVALUATION OF ZACTIRIN IN ARTHRITIS

Arthritis, a potentially crippling disease of unknown etiology and of variable and unpredictable course, demands individualized management if treatment is to be effective. As in all therapy, accuracy of diagnosis is fundamental. Before treatment is undertaken, a complete study of the patient is made, including a detailed history and physical examination, necessary laboratory tests and roentgen studies to provide a comprehensive picture of the patient's general health status. This is the first step in following the axiom "Treat the entire patient, not just his joints."

While the details of treatment will vary with the individual patient, certain fundamental principles govern the management of every case. Many of these are simple, but no apology for their mention is necessary because they are so frequently overlooked in practice. No single measure of therapy suffices. Too often the older, time-tested principles of general treatment are neglected in the enthusiasm engendered by the latest product of the pharmaceutical houses. A substantial number of patients can be controlled by the basic program alone which includes:

1. Orientation of Patient and Family
2. Symptomatic Therapy
3. General Measures
   a. emotional factors
   b. diet
   c. elimination
   d. focal infections
   e. rest
4. Local Measures
   a. heat
   b. exercise
   c. massage

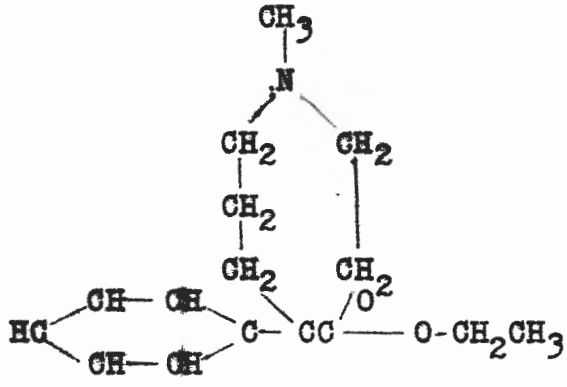
Without faithful adherence to this basic program, the supplemental program, which includes medications, would be relatively ineffective.

The supplemental program for the past several years has centered around time-tested aspirin, chrysotherapy, steroids and hormones, and phenylbutazone. The limitations and serious side effects are well known to all students in the study of arthritis. It is, therefore, the purpose of this thesis to evaluate the clinical effectiveness of a new analgesic agent in the treatment of osteo-arthritis and rheumatoid arthritis. A major portion of this thesis is concerned with a series of patients receiving varying doses of adrenal steroids who were able to be taken off the steroids with the use of this new analgesic agent.

This supplementary analgesic agent is called Zactirin.

Chemistry and Pharmacology

Each Zactirin tablet contains 75 mgm. ethoheptazine citrate and 324 mgm. acetylsalicylic acid. Ethoheptazine is a racemic mixture of the d and l isomers of 1-methyl-4-carbethoxy-4-phenyl hexamethylenimine. This compound was first synthesized by Diamond and Bruce at the Wyeth Institute for Medical Research. The structural formula appears below and it will be noted that it contains a seven membered heterocyclic ring. The active ingredients are separated by an inert buffer layer.



The general pharmacological properties and analgesic potency of ethoheptazine in animals have been reported (1,5). This group of investigators found that the acute toxicity determinations in mice and rats by all routes of administration indicate that ethoheptazine is less toxic than meperidine hydrochloride. When deaths did occur from toxic doses the respiratory and

cardiac action appeared to cease simultaneously whereas respiration is immediately depressed by toxic doses of meperidine and respiratory failure precedes cardiac failure by a long period. Studies in dogs and cats by means of acute intravenous toxicity experiments also indicated that ethoheptazine caused less respiratory and cardiovascular depression than meperidine. The LD_{50} for mice was 318 mgm/kg by oral, 167 mgm/kg by intramuscular, and 53 mgm/kg by intravenous administration.

Chronic administration to animals for six months did not result in untoward effects on general behavior. The typical excitement produced by the potent and addicting analgesic agents was strikingly lacking in all cases, as were changes in the body weight, bone marrow, hemoglobin, red cells and leukocytes. Animals sacrificed in the course of acute and chronic toxicity studies showed no pathological changes on gross and microscopic examination of the heart, lung, liver, kidney, spleen, pancreas, salivary glands, adrenals, genitalia, bone marrow and brain.

The analgesic potency of ethoheptazine as determined in rats by the usual testing procedures indicates that this compound is approximately 1/3 as active as meperidine (1,5) and in the appropriate dosage has been found

to be equivalent to codeine and aspirin in analgesic potency (9). At the time of these studies it was found that if ethoheptazine was administered to mice just before or at the time of the administration of barbiturates, the action of the barbiturates was potentiated. The above analgesic properties were able to be duplicated by this author and will be described later. Seifter, et al (1), also found that monkeys could not become addicted to ethoheptazine and when this compound was administered to monkeys already addicted to morphine or meperidine, it would not prevent the development of the typical withdrawal syndrome.

Seifter, et al (1), found in their complete study of the aza-acycloheptane analgesics, which includes ethoheptazine, that the use of these compounds was not attended by any serious untoward side effects. Having observed individuals receiving ethoheptazine for several months, in amounts exceeding the daily recommended dosage, no changes in pupil size, dryness of the mouth, constipation, significant sedation, addiction, habituation, effects on pulse, blood pressure, or the formed elements of the blood have been noted.

Zactirin, as this new analgesic agent is called, has been studied quite extensively by Batterman, et al

(10), Grossman (6) and Golbey (7) concerning its clinical effectiveness, tolerance, and safety. Batterman, et al (10), in their report of the effectiveness, tolerance and safety of ethoheptazine combined with aspirin, found that the overall response for the combination and for ethoheptazine alone for the treatment of musculoskeletal conditions was identical. There was, however, a striking change in the group of patients with rheumatoid arthritis. Ethoheptazine alone, lacking any anti-inflammatory properties was not as satisfactory as when combined with salicylate. This result reflects the principles of combined analgesic therapy in that unless a specific type of pain is present, the overall potency of the mixture is dependent upon the most potent of the analgesic agents. Batterman (10), in his study, used patients with arthritis, menopausal arthralgia, bursitis, post laminectomy, gout, sciatica, fibrositis, ligament strain, calcific bursitis and coccodynia. Grossman (6) and Golbey (7) have reported that the drug is an effective and well tolerated analgesic and is intended for the relief of moderate or moderately severe pain. Cass, Frederik and Bartholomay (9), in their series of 71 patients, used it for all types of arthritis, metastatic carcinoma, neurological disorders with deform-

ity, amyotrophic lateral sclerosis, progressive muscular disease, cerebro-vascular accident, hypertension and non-union fractures. In their study the following evaluations and statements were made:

1. Ethoheptazine, 100mgm., plus aspirin, 600 mgm., is as active a pain reliever as codeine, 30 mgm., plus aspirin, 600 mgm.
2. Aspirin alone (600 mgm.) has a definite pain-relieving action as compared with a placebo.
3. Ethoheptazine, 100 mgm., is more efficient than aspirin alone, 600 mgm.
4. Addition of 600 mgm. of aspirin to ethoheptazine provides a significant increase in efficiency.
5. Addition of codeine, 30 mgm., to aspirin, 600 mgm., causes a significant improvement in pain relief.
6. Ethoheptazine, 100 mgm., has a highly significant analgesic effect as compared with a placebo.
7. Codeine, 30 mgm., plus aspirin, 600 mgm., is significantly more effective than ethoheptazine, 100 mgm.
8. Ethoheptazine, 100 mgm., plus aspirin, 600 mgm., is more effective than aspirin alone.

The recommended dosage at the present time is one or two Zactirin tablets, depending on the severity of pain, three or four times daily. According to recommendations of the company the total daily dosage was not to exceed eight tablets. Cass, Frederik and Bartholomay (9) in their series of 71 patients used two tablets four times daily. At the present time this drug is only obtainable in tablet form and must be taken orally. There are no known contraindications to the use of Zactirin with exception of those persons with a history of sensitivity or severe intolerance to aspirin. Since this drug has been under clinical investigation for the past two years with no reports of addiction, it is not subject to the regulations of the Federal Bureau of Narcotics and does not come under the regulations of the Harrison Narcotic Act.

Method of Study

The group of patients selected for this study were generally classified as moderate to severe arthritics. All patients were either located at the Rehabilitation Center of Douglas County Hospital, Omaha, Nebraska, or seen as out-patients in the Arthritic Clinic of the University of Nebraska College of Medicine. Those located at Douglas County Hospital were seen every day whereas

TABLE 1
Weekly Record of Results

Name_____ Diagnosis_____ Case No._____

Sex_____ Age_____ Medications_____

Type of Pain_____ (Classify as to slight, moderate, or severe)

Date	Degree of relief	Side effects							Remarks
		N	V	C	E	D	S	OTHERS	
	1 2 3 4 5								
	1 2 3 4 5								
	1 2 3 4 5								
	1 2 3 4 5								
	1 2 3 4 5								
	1 2 3 4 5								
	1 2 3 4 5								
Total									

1--No relief
2--Slight relief
3--Moderate relief
4--Almost complete relief
5--Complete relief

N--Nausea
V--Vomiting
C--Constipation
E--Excitement
D--Dizziness
S--Sedation

those who attended the Arthritic Clinic were seen once every week. Those patients seen in the clinic were given a chart and required to keep their own records whereas those located at Douglas County were recorded each day by the author. These 30 patients were each asked to volunteer side effects and were specifically asked about nausea, vomiting, constipation, excitement, drowsiness, dizziness, and sedation. For the type of record used refer to table 1. In our small series of 30 patients we used predominately arthritic pain for evaluation which included both osteo-arthritis and rheumatoid. Twenty-six of the thirty were arthritic patients. The type of condition was that encountered in any arthritis service and consisted of 14 patients with osteo-arthritis and 12 patients with rheumatoid arthritis who were receiving adrenal steroid derivatives in doses ranging from 5 to 15 mgm/day. The remaining four patients in our series consisted of two traumatic cord lesions with paralysis and two with traumatic bursitis. Most of the patients were ambulatory and presented varying degrees of pain due to these types of musculoskeletal conditions. In each case the patient suffered pain of sufficient severity to require analgesics. The age of the patients varied between 22 and

81 years and included 17 females and 9 males. The data for each patient is summarized in Table 11. Of the 14 osteo-arthritic patients, 10 had previously used aspirin with codeine for relief and their apparent relief was recorded prior to starting this experiment. So, therefore the four medications used in this clinical evaluation were:

1. Aspirin 10 grains qid
2. Aspirin 10 grains plus codeine ½ grain tid
3. Placebo (lactose) tabs 2 tid
4. Zactirin tabs 2 tid (each tablet consisting of 75 mgm. ethoheptazine citrate and 324 mgm. acetylsalicylic acid)

It might be noted that the placebo supplied looked identical to the Zactirin tablet and that all aspirin used was in disguised form. All patients received each of the test medications in different order. The test period was seven days for each medication. The random rotation of administration was considered adequate to compensate for any carryover of analgesic action (9). During the complete examination of the drugs the examiner did know the drug being used, but the patient did not know the name of the medications, but was aware that it was an experimental test. All patients, with the exception of two, received two tablets three times a day, whereas the other two were prescribed two tablets four times a day.

TABLE 11

No.	Pt.	Age	Diag-nosis	Status	No.wks. therapy	Degree relief	Reac-tions	Remarks
1	RP	63	Mixed	MS	1	mod.	none	more relief than with any previous medication
2	NT	71	Osteo.	MS	12	com.	none	
3	JS	22	Rheum.	S	12	almost com.	none	as much relief as when on cortisone 15 mgm/day
4	EC	33	Rheum.	S	1	none	none	no relief from any analgesics
5	GM	54	Rheum.	MS	1	slight	none	
6	EB	70	Rheum.	M	6	almost com.	none	more relief than with any previous medication
7	MS	44	Rheum.	M	12	mod.	naus. once	
8	NW	67	Osteo.	S	12	mod.	none	
9	DA	81	Osteo.	MS	1	slight	none	better relief; swelling of knees went down
10	OH	56	Rheum.	S	1	slight	none	
11	RH	28	Rheum.	S	1	mod.	none	as much relief as from cortisone 10 mgm/day
12	CB	71	Osteo.	MS	1	slight	none	
13	AS	63	Osteo.	M	1	almost com.	none	
14	HB	48	Osteo.	M	12	mod.	none	

TABLE 11 (continued)

No.	Pt.	Age	Diagnosis	Status	No.wks. therapy	Degree relief	Reactions	Remarks
15	LR	45	Osteo.	MS	1	com.	none	more relief than with any other analgesic
16	MP	56	Rheum.	S	1	none	naus. vom.	
17	ER	49	Osteo.	M	2	com.	none	
18	VD	72	Osteo.	MS	1	almost com.	none	
19	RM	66	Osteo.	M	1	slight	none	
20	BV	61	Rheum.	M	8	almost com.	none	
21	AF	50	Osteo.	M	12	mod.	none	
22	NS	66	Osteo.	S	1	mod.	none	
23	JS	36	Rheum.	MS	6	almost com.	none	as much relief as with cortisone 5 mgm/day
24	RL	41	Rheum.	M	7	mod.	none	as much relief as with cortisone 1 mgm/day
25	DE	74	Osteo.	M	12	slight	none	
26	PP	45	Rheum.	MS	9	slight	none	

M---Moderate
MS--Moderately severe
S---Severe

com.---complete
mod.---moderate

During the study, fifteen of the thirty patients had blood evaluations which consisted of WBC with differential, RBC, and Hb. After the experimental project was finished, 7 patients who continued on Zactirin had repeat blood studies for evaluation after 3 months for possible long term changes. These 7 were also followed for latent undesirable side-effects.

Evaluation of Results

In this study involving three drugs, Zactirin, placebo and aspirin with associated comparison of aspirin and codeine, all 26 patients were started within a one and one-half month period and the medication was changed every seven days until the study was completed as described previously. Twenty-six patients completed the study. The total number of observations, therefore, was 26 x 7 x 3 or approximately 516. Since only ten patients had previously received codeine and aspirin, seventy observations were recorded. Table 3 gives the rating of effectiveness as recorded in the 586 observations.

Table 3 shows placebo received the lowest total score by virtue of the fact that 112 observations showed a rating of 1 or no effectiveness. Zactirin, percentage-wise, gave more total effectiveness than any of the

other drugs. But it must be noted that aspirin with codeine in comparison with Zactirin showed the least number of observations with "no effectiveness" (rating 1) percentage wise.

Table 3

	Effectiveness					
Drug	1	2	3	4	5	Total
Placebo	112	39	27	4	0	182
Aspirin	54	80	26	15	7	182
Zactirin	25	38	52	40	27	182
Aspirin with codeine	4	20	22	17	7	70

In order to interpret the data in table 3, the author calculated the average effectiveness for each drug by the method used by Cass, Frederik and Bartholomay (9). This was done by using the following formula:

$$\frac{\text{No. of observations x rating}}{\text{total no. of observations}} \quad \text{(either 1,2,3,4 or 5)}$$

For example using the placebo rating from table 3, the average effectiveness would be as follows,

$$\frac{112 \times 1 + 39 \times 2 + 27 \times 3 + 4 \times + 5 \times 0}{182} = 1.576$$

The average effectiveness of each drug is rated in table 4. As the table shows the placebo is the least effective, whereas aspirin and codeine were the most effective. It should be noted, however, that aspirin with codeine exceeded Zactirin only slightly in aver-

age effectiveness.

Table 4

Drug and order of rank	Average effectiveness
1. Placebo (least effective)	1.576
2. Aspirin	2.126
3. Zactirin	3.087
4. Aspirin with codeine (most effective)	3.185

In order for a comparison, the weighted average was calculated for each drug, in our study, by the method of Cass, et al (9). This was done by multiplying the number of patients times their rating number for a specific drug. Each of these answers were then added together as above and the sum was divided by the number of patients. Table 5 shows the number of times each rating by a patient was recorded for each of the four drugs used in the study.

Table 5

Drug	1	2	3	4	5	Total patients
Placebo	16	6	4	0	0	26
Aspirin	8	14	0	4	0	26
Zactirin	2	7	8	6	3	26
Aspirin with codeine	1	3	2	3	1	10

Table 6 shows the wieghted average for the four drugs. An example of the calculation is below for the placebo.

$$\frac{16 \times 1 \quad 6 \times 2 \quad 4 \times 3 \quad 0 \times 4 \quad 0 \times 5}{26} = 1.538$$

Table 6

Drug and order of rank		Weighted average
Placebo (1) least effective		1.538
Aspirin (2)		1.846
Zactirin	>Equally effective	3.000
Aspirin with codeine		3.000

From the results of table 4 and 6, it can be seen that we found for all practical purposes, that Zactirin is as effective an analgesic agent in the treatment of arthritis as is aspirin with codeine. Therefore, this author is in complete agreement with the clinical effectiveness as found by Cass, et al (9), Grossman (6) and Golbey (7).

Another special portion of the study concerned the twelve rheumatoid arthritic patients who were being given adrenal cortex derivatives ranging from 5 to 15 mgm/day. The criteria used for their original placement on these derivatives is unknown, but it is known that in one-half of the patients the adrenal cortical steroids were used as last resort. The number of times each rating by a patient was recorded is shown in table 7 with the weighted average being calculated as in table 6. The weighted average, for Zactirin, as figured previously for the total 26 patients which included the 12 rheumatoid arthritics on adrenal ster-

oid derivatives was 3.000, whereas in the 12 rheumatoids alone the weighted average is 3.3.

Table 7

Drug	1	2	3	4	5	Total patients
Zactirin	2	3	3	4	0	12
Adrenal steroid derivatives	0	6	2	3	1	12

Subjectively the patients stated, with the exception of two, that they obtained as much relief with the Zactirin as with the adrenal steroid derivatives and felt considerably better. But as far as the weighted average is concerned the adrenal steroid derivatives was 3.5 compared to 3.3 for Zactirin. It is the opinion of this author that Zactirin has considerable use in arthritic patients in place of low doses of adrenal steroid derivatives without the potential hazards of undesirable side-effects and possible adrenal insufficiency.

Side effects were minimal throughout the study as indicated in table 2. Throughout our series only 2 side reactions were recorded. One patient complained of nausea, but which was not severe enough for the removal of the Zactirin. One patient's medication was discontinued because of severe nausea and vomiting.

This patient was one of the rheumatoid arthritics on 15 mgm/day of adrenal steroid derivatives. She was being seen as an out-patient and it cannot be said for certain if this was due to Zactirin or due to a concurrent infectious process such as flu which was so prevalent at that time. The nausea and vomiting stopped within 24 hours after the medication was discontinued. Seven patients seen regularly have reported no undesirable side-effects after 3 months of continuous therapy. During the experiment fifteen of the thirty patients had blood evaluations which consisted of WBC with differential, RBC and Hb and no changes were noted in comparison with pre-treatment blood studies. The seven patients followed for 3 months on continous therapy also showed no change in comparison with pre-treatment blood studies.

As a side line in this research two patients with traumatic cord lesions were placed on Zactirin. During their trial period they received barbituates and the action of these drugs definitely seemed potentiated by the associated administration of Zactirin. This finding is in full agreement with Cass, et al, (9), who noted that if ethoheptazine was administered to mice just before or at the time of the administration of

barbiturates, the action of the barbiturates was potentiated.

Summary and Conclusions

Zactirin, a new analgesic agent, contains 75 mgm. ethoheptazine citrate and 324 mgm. acetylsalicylic acid. It is an effective and well tolerated analgesic and is indicated for the relief of moderate or moderately severe pain. Chronic administration for six months did not result in untoward effects on general behavior such as those produced by the potent and addicting analgesic agents and no serious untoward side effects have been observed in the use of Zactirin. In 26 arthritic patients it was found that Zactirin was as effective an analgesic agent as the combination of aspirin with codeine. In 10 patients on adrenal steroid derivatives it was found that Zactirin gave excellent subjective relief without evidence of exacerbation of the disease process. Only two patients had side effects which consisted of nausea and vomiting and in only one patient was it necessary to discontinue the drug. Also, in the study, it was found that Zactirin apparently potentiates the action of barbituates.

In conclusion, it appears that Zactirin may be used in moderate to severe arthritic patients requiring an

analgesic as strong as aspirin with codeine, but without the well known side effects. Finally, Zactirin may be used in place of low doses of adrenal steroid derivatives without the potential danger of adrenal insufficiency and their specific untoward side effects.

Acknowledgements

Acknowledgement and thanks to the Wyeth Company for the supply of Zactirin which made this thesis possible. Deepest regards and thanks to Dr. Mary J. Henn for her instruction and guidance throughout this project. Thanks to Dr. Dwight M. Frost and the personnel of the Rehabilitation Center at Douglas County Hospital and the University of Nebraska College of Medicine Clinics for their cooperation throughout this research project.

Bibliography

1. Seifter, J.; Eckfeld, D. K.; Letchack, I.; Gore, E. M., and Glassman, J. M.: Pharmacological properties of some azacycloheptane analgesics.
   Fed. Proc. 13:403, 1954.

2. Glassman, J. M.; Letchack, I.; Walkenstein, S., and Seifter, J.: Chemical structure and action in meperidine type analgesics.
   Am. J. M. Sc. 230:226, 1955.

3. Glassman, J. M., and Seifter, J.: The effects of analgesic agents on barbiturate responses in mice.
   J. Pharmacol. and Exper. T herap. 115:21, 1955.

4. Glassman, J. M., and Seifter, J.: The analgesic activity of some phenylhexamethylenimine derivatives.
   J. Pharmacol. and Exper. Therap. 116:23, (Jan.) 1956.

5. Walkenstein, S.; MacMullen, J. A.; Knebel, C., and Seifter, J.: The metabolic fate of a hexamethylenimine analgesic.
   J. Pharmacol. and Exper. Therap. (To be published).

6. Grossman, A. J., et al.: Clinical effectiveness and safety of a new series of analgesic compounds.
   J. Am. Geriatrics Soc. 4:187, 1956.

7. Golbey, Maurice; Leifer, Paul; Grossman, Arthur J., and Batterman, Robert C.: Analgesic effectiveness of orally administered heptacyclazine in man.
   Federation Proc. 15:428, (March) 1956.

8. Minutes of the 17th Meeting of the Committee on Drug Addiction and Narcotics, 1956, Addendum, Page 3.

9. Cass, L. J.; Frederik, W . S., and Bartholomay, A. F.: Refport of the clinical evaluation of ethoheptazine and ethoheptazine combined with aspirin. (To be published).

10. Batterman, Robert C., et al.: Report on the effectiveness, tolerance, and safety of the administration of combined ethoheptazine and aspirin. (To be published).

11. Armitage, P.: Sequential tests in prophylactic and therapeutic trials.
Quarterly J. Med. 23:255, 1954.