The Use of S-Factor of Liver Extract (Kutapressin) in Dermatology*

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It seems that this substance aids in the symptomatic relief of a number of cutaneous diseases. How this is accomplished is as yet unknown.

Introduction

THIS IS A CLINICAL EVALUATION of the use of a cutaneous vasolonstrictor. Kutapressin,** in the treatment of various dermatologic disorders. It contains an active principle obtained from crude liver extract. Lee[1] found that Kutapressin causes contraction of the smooth muscle cells of the peripheral blood vessels and enhances the action of epinephrine on them. It is not a vitamin; some investigators have referred to it as the S-factor.

Holtman[2] using Kutapressin preoperatively in dental extractions reported it to be of value in the prevention of hemorrhage and postoperative pain. Harris and associates[3] reported that it had no effect on bleeding and clotting times. Marshall[4-7] reports favorably on the drug in the management of tissue edema, burns, Raynaud and Buerger's diseases, and in the treatment of keloids and other related skin conditions. Barrock[8] and Poole[9] have reported on its usefulness in the treatment of acne rosacea. Heywood[10] has found that it gives relief and hastens healing in sunburn.

Clinical Studies

This report is based on the use of Kutapressin in 711 patients with dermatologic disorders. It was conducted over a four year period. The drug was administered intramuscularly in doses of 2 cc. The average time interval between injections varied from one day to one week. To obtain the best results injections should be given twice weekly or more frequently. There have been no untoward reactions attributable to the drug. Discomfort at the site of injection, if any, is minimal.

Acne Vulgaris. Kutapressin was used in a series of 178 patients with acne vulgaris of varying degrees of severity. Most of them were over 18 years of age.

Reports of several studies indicate the value of this S-factor of crude liver extract in acne vulgaris. Burke and Knox[11,12] reported a series of 226 cases corroborating previously published clinical reports of its value as adjunctive therapy. Lubowe[13] reported it to be of value in cystic acne. Nierman[14] reported that Kutapressin was an effective drug in treating 22 cases of refractory cystic acne. Pensky and Goldberg[15] reported moderate to good improvement in 63 per cent of 52 private patients with refractory acne. Barksdale and associates,[16] in a preliminary report in 1953, felt it to be a valuable adjunct. Nierman[17] states that in his opinion "Kutapressin, if used in doses that are sufficient both in size and frequency, is an extremely valuable adjunct in acne therapy." He based his opinion on a recent evaluation of over 200 patients who were given 2 cc. injections varying from daily to thrice weekly. He concludes: "Certainly Kutapressin alone is not a cure-all for acne, which is a complex problem in an extremely complex age group; but there is no question in my mind that it is beneficial." Barrock[8] in reporting on a study of 118 patients with acne rosacea states that in conjunction with other indicated procedures Kutapressin appears to accelerate the improvement and reduce the period of treatment required.

In this series of cases Kutapressin was not used alone. It was added to a treatment routine consisting of ultra-violet light, one of the "acne lotions" locally, a low fat diet and vitamin A. Over a period of years I have found this regimen effective.

The patients were started on a schedule of office visits twice weekly. Ultra-violet light

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TABLE 1

ACNE VULGARIS (178 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	89	50.0	16.2	32.4 cc.
Improved	59	33.1	14.9	29.8 cc.
Treatment Failure	30	16.9	14.8	29.6 cc.

and 2 cc. of Kutapressin were given at every visit, and the patients were repeatedly cautioned to continue with their diets and topical applications.

Table 1 shows that after 16 injections 50 per cent of the 178 patients were brought "Under Control" to the extent that they were permitted to discontinue their office visits except in case of recurrence. They were impressed with the necessity of continuing with their diets and general skin care. The 33.1 per cent listed under "Improved" represent an improvement of 50 per cent or better. There was "Treatment Failure" rate of 16.9 per cent.

These were all private patients. For economic reasons, as improvement began, the time interval between office visits was increased to weekly, every two weeks, and then monthly. It is possible that had Kutapressin been given more frequently a considerably greater number of patients would have responded to treatment.

It is interesting to note that the total amount of Kutapressin given in all three groups was approximately the same. Improvement was usually noticeable between the fifth and tenth injection. From this study one can say that if there has been no improvement after fifteen injections, there is not likely to be any even if the injections are continued.

Herpes Zoster. When one begins to study the value of any drug it is fairly easy to form the habit of trying to use it for most, if not every disease. It was probably from such an approach that herpes zoster fell into this evaluation. No report of its use in herpes zoster has been found in the literature, although undoubtedly it has been used.

A total of 24 patients were treated and the series is small. Injections were given daily or on alternate days with the number of injections averaging four or less. It was felt that the severity of discomfort was lessened and the duration of discomfort shortened. Vesicles seemed to dry up more quickly. No other treatment was used in this series.

In such a self-limited condition, a good response in 90 per cent of the patients would be expected. Eighty-three per cent were brought under control with an average of 3.5 injections (Table 2).

Poison Ivy. Kozelka and Marshall[18] reported: "Twenty-eight patients with poison ivy were treated with daily injections of Kutapressin of 2 cc. and every patient responded to this treatment, usually sufficiently improved by the third day to warrant discharge from further care." From their results they concluded that this drug is specific for the relief of symptoms and healing of lesions of poison ivy. White[19] has stated: "It is amazing the number of cases I have had which did not respond to the steroids but did respond to Kutapressin."

In this study there were 50 patients. Kutapressin was given daily or every other day. Adjunctive treatment consisted either of boric acid compresses or starch baths. Discomfort and vesiculation was promptly relieved. When the stage of dryness of the skin developed Kutapressin ointment was occasionally prescribed.

In view of a failure rate of only 2 per cent it is felt that this treatment regimen is at least as specific as any other ever used. It has one other practical advantage,—the physician is given the opportunity of satisfying the public demand for "shots" with an effective and harmless drug (Table 3).

TABLE 2

HERPES ZOSTER (24 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	20	83.33	3.5	7.0 cc.
Improved	3	12.5	4.0	8.0 cc.
Treatment Failure	1	4.16	3.0	6.0 cc.

TABLE 3

POISON IVY (50 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	43	86.0	3.5	7.0 cc.
Improved	6	12.0	3.0	6.0 cc.
Treatment Failure	1	2.0	3.0	6.0 cc.

TABLE 4

PSORIASIS (33 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	6	18.18	36	72.0 cc.
Improved	26	78.78	36	72.0 cc.
Treatment Failure	1	3.03	36	72.0 cc.

Psoriasis. Kutapressin was used experimentally in 36 patients with long-standing psoriasis. Observations were made over a three year period. The study was begun on a definitely controlled basis. There was no doubt of the diagnosis in any case. All other treatment was discontinued. The patients were asked to volunteer for a research study. They were told that there would be no charge for the drug or its administration. A treatment schedule of three injections per week for 3 months was set up. It was understood that if for any reason there was any definite variation of this they would be dropped from the study. Some of the patients were taught to administer the drug themselves. They were impressed and became very enthusiastic. The patients were encouraged to feel that they were making a contribution to medical science. In this way the patients were kept under treatment and observation.

The total prescribed number of 36 injections of 2 cc. was completed by 33 patients. Failure to obtain any response was encountered in only one case. Improvement was manifest by a decrease in itching and cessation of scaling. Spreading was stopped and no new lesions developed. These changes usually appeared about the end of the first month of treatment. The six cases listed "Under Control" relapsed when the drug was discontinued, as had all of the others who were seen later (Table 4).

Kutapressin relieves the symptoms of psoriasis. It is not a cure for psoriasis, but its effect is more than just a psychic effect of new therapy. To be effective it must be used continuously.

TABLE 5

PITYRIASIS ROSEA (19 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	15	78.94	5.9	11.8 cc.
Improved	2	10.52	8.5	17.0 cc.
Treatment Failure	2	10.52	5.0	10.0 cc.

Pityriasis Rosea. Seventy-nine per cent of 19 patients with pityriasis rosea were brought "Under Control" with Kutapressin (Table 5). However because the disease is self-limited, one would hope for a somewhat better response than this.

TABLE 6

SEBORRHEIC DERMATITIS (183 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	126	68.85	9.1	18.2 cc.
Improved	49	26.88	11.8	23.6 cc.
Treatment Failure	8	4.37	9.6	19.2 cc.

Seborrheic Dermatitis. Statements have been made to the effect that Kutapressin reduces oiliness of the skin. Since a large number of patients were available (many seen previously for acne) this study was begun to check the validity of these statements. In addition to Kutapressin they were treated with Selsun, topical steroids and other recognized methods (Table 6).

While patients responded to this treatment, in view of the present ease of controlling seborrhea, the therapeutic advantages obtained from a regimen including an injection twice weekly for four weeks or more does not outweigh the inconveniences.

Urticaria. White[20] stated that he has successfully used Kutapressin in the treatment of giant urticaria. His series at that time included 18 patients. Seventeen of them had received the steroids with no benefit but were benefited by Kutapressin. One patient did not respond to Kutapressin but the steroids did help him considerably.

Our group of 64 cases consisted primarily of urticarial reactions resulting from penicillin and other antibiotics. Injections of 2 cc. were given daily at first, then less frequently.

TABLE 7

URTICARIA (DRUG) (64 CASES)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	48	75.0	6.0	12.0 cc.
Improved	9	14.06	6.0	12.0 cc.
Treatment Failure	7	10.93	9.9	19.8 cc.

TABLE 8

ECZEMA OF THE HANDS (83 CASES)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	24	28.91	11.2	22.4 cc.
Improved	30	36.13	11.6	23.2 cc.
Treatment Failure	29	34.94	11.5	23.0 cc.

The purpose of this investigation was to see whether Kutapressin would be of any value in the control of urticaria of a known etiology when the use of the steroids was not desirable. Ninety per cent of these cases had definite improvement both subjectively and objectively. There was, however, a failure rate of 11 per cent in spite of the fact that the injections were continued (Table 7).

No attempt has been made to see if Kutapressin given in conjunction with the steroids and antihistamines might give more improvement and shorten the duration.

Eczema of the Hands. Kutapressin was used as an adjunct to other forms of therapy in the treatment of 83 patients with eczema of the hands. Since less than 30 per cent of the patients were controlled and approximately another 30 per cent failed to respond satisfactorily, it seems that the drug offers little advantage in treating the difficult problem of eczema of the hands (Table 8).

Diseases Not Responding to Kutapressin. Out of curiosity Kutapressin was tried empirically in several other dermatologic disorders, with no response. The following conditions were treated and resulted in failure:

Mycosis fungoides—1
Stevens-Johnson syndrome—5
Hyperirdosis (palm and soles)—3
Haley and Haley—2
Alopecia areata—4
Lichen planus—5
Neurodermatitis and pruritus ani—16
Pyodermia—13
Fungal infection feet—14 (?)
Tinea versicolor—14 (?)

Comments

1. We need to know more in regard to what this drug is, its mode of action and its optimal dose.
2. It cannot be said that Kutapressin has cured any disease studied in this series.
3. The most dramatic results have been in poison ivy and herpes zoster. These conditions are self-limited.
4. It is felt that Kutapressin is a valuable adjunct to the therapy of acne vulgaris.
5. It does something to psoriasis but has not cured any case and has not prevented relapses.
6. In drug eruptions results are not as dramatic as with the steroids although Kutapressin seems to give a similar but more prolonged response.

Summary

The findings of this study are summarized in table 9. Kutapressin is a valuable adjunct in the treatment of acne vulgaris, herpes zoster, and contact dermatitis from poison ivy.

In acne vulgaris sixteen 2 cc. injections given twice weekly are required to obtain maximum effect. The response of the lesions

TABLE 9

SUMMARY (711 Cases)

			Treatment Success		Treatment Failure	
	Diagnosis	Number	Per Cent Improved	Number of Treatments (Aver.)	Per Cent Failure	Treatments (Aver.)
I	Acne	178	83.14	Aver.—15.5	16.86	14.8
II	Herpes zoster	24	95.83	Aver.— 3.75	4.16	3.0
III	Poison ivy	50	98.0	Aver.— 3.25	2.0	3.0
IV	Psoriasis	33	96.96	No.—36	3.03	No.—36
V	Pityriasis rosea	19	98.46	Aver.— 7.2	10.52	5.0
VI	Seborrhea	183	95.73	Aver.—10.45	4.37	9.6
VII	(Drug)	64	89.06	Aver.— 6.0	10.93	9.9
VIII	Eczema hands	83	65.04	Aver.—11.4	34.94	11.5
IX	Miscellaneous	77	ALL FAILURES			
	Total	711				

in 83 per cent of this series of patients was considered a treatment success.

Herpes zoster responded to an average of four 2 cc. injections, first daily, then less frequently.

Three to four 2 cc. injections relieved discomfort and decreased vesiculation in contact dermatitis due to poison ivy.

Patients with psoriasis obtained symptomatic relief,—freedom from itching, scaling, and spreading as long as they took the medication. When it was discontinued the condition relapsed. It was felt that the effects of Kutapressin were greater than could be expected from the psychic effect of new therapy.

The response in pityriasis rosea was good. However, no definitive statement as to the effectiveness of the medication should be made because of the nature of the disease and the small number of patients treated.

While there was a definite response to the therapeutic regimen for seborrheic dermatitis, the advantages of including injections in the regimen are outweighed by the inconvenience.

Kutapressin was used successfully in treating 89 per cent of 64 patients experiencing urticarial reactions to antibiotics. On the average six injections were required.

References

1. Lee, Richard E.: A Liver Factor(s) "Tonic" to Conjunctival Capillary Bed in Man. (Unpublished paper.)
2. Holtman, David E.: The Use of a New Vasoconstrictor (Kutapressin) in Exodontia, Oral Surg. 7:12, 1954.
3. Harris, S. C., North, W. C., and North, A. B.: The Influence of Kutapressin on the Human Bleeding and Clotting Times, Oral Surg. 7:239, 1954.
4. Marshall, Wallace: Experimental Therapy of Raynaud's and Buerger's Diseases with Kutapressin, Am. J. Surg. 82:448, 1951.
5. Marshall, Wallace: Keloids and Skin Papillomas, M. Times 1951.
6. Marshall, Wallace: Management of Tissue Edema in First and Second Degree Burns, Mississippi Valley M. J. 76:199, 1954.
7. Marshall, Wallace, and Schadeberg, William: A Study of Keloids and Related Conditions, Wisconsin M. J. 49:369, 1950.
8. Barrock, James J.: Rosacea. Paper presented before the Metropolitan Dermatological Society, Chicago, December, 1954. (In press.)
9. Poole, William L.: Effect of Vitamin B Complex and S-Factor on Acne Rosacea, South. M. J. 50:207, 1957.
10. Heywood, H. W.: Use of a Selective Vasoconstrictor in the Treatment of Severe Sunburn, Clin. Med. 3:765, 1956.
11. Burks, James W., Jr.: The Modern Treatment of Acne Vulgaris, J. Louisiana M. Soc. 106:92, 1954.
12. Burks, James W., Jr., and Knox, John M.: S-Factor of Liver Extract in Acne Vulgaris, Arch. Dermat. & Syph. 70:508, 1954.
13. Lubowe, Irwin L.: Modern Treatment of Acne Vulgaris, Clin. Med. 59:8, 1952.
14. Nierman, M. Murray: Treatment of Cystic Acne Vulgaris with a Cutaneous Vasoconstrictor (Kutapressin), J. Indiana S. M. A. 45:497, 1952.
15. Pensky, Nathan, and Goldberg, Natalie D.: Treatment of Refractory Acne with a Fractionated Type of Liver Extract, New York J. Med. 53:2238, 1953.
16. Barksdale, Edwin E., Walters, John D., and Kern, Arthur B.: Some Skin Manifestations of Internal Disorders, Virginia M. Month. 81:321, 1954.
17. Nierman, M. Murray: Personal Communications. (June) 1956.
18. Kozelka, A. William, and Marshall, Wallace: Treatment of Poison Ivy with Kutapressin, Clin. Med. 3:425, 1956.
19. White, C. J.: The Letters of the International Correspondence Society of Allergists, 19:30, 1956.
20. White, C. J.: Personal Communications. (June) 1956.

Discussion (Abstract)

Dr. Joseph Farrington, Jacksonville, Fla. Good research, like a baby, is oftentimes easy to conceive but hard to deliver. Dr. Barksdale is to be commended on his well-documented studies showing, empirically at least, that here is a therapeutic agent effective in a number of dissimilar and apparently unrelated skin conditions. One preparation effective in such a wide range of conditions may have, however, a common therapeutic denominator. This has perhaps been demonstrated by Marshall who reported a drop of 0.3 of a degree in the facial skin temperature in a normal subject after the administration of 1 cc. of Kutapressin, a measurable pharmacologic effect by use of a thermocouple. It was concluded that a vasoconstriction of the skin vessels ensued for the complexion of the subject blanched. Favorable reports in such conditions as Raynaud's phenomenon and Buerger's disease must be viewed with some circumspection, when one realizes he is administering an agent capable of producing further vasoconstriction, unless one postulates some other pharmacologic actions as yet undetermined.

Through the generosity of the Kremers-Urban Company, we have been supplied with considerable amounts of Kutapressin and have, over a period of several years, conducted studies paralleling those of Dr. Barksdale. Our studies have been limited to only three categories of diseases, namely, acne, keloids and allergic reactions.

I believe all investigators are in agreement that Kutapressin is a valuable adjunct in the treatment of acne, as has been substantiated by such able investigators as Burks, Nierman, Pensky and Goldberg.

Our own experiences would indicate that Kutapressin is much more effective in keloids than Dr. Barksdale has stated. In a series of 25 cases in private practice and the clinic, it was felt that at least 10 showed a good response. I am frank to admit that some of these may have been hypertrophic scars rather than true keloids. I recall vividly the first patient I treated. He was a soldier recently returned from Korea with a severe acne keloidalis. His treatment consisted of exposure to ultra-violet light and the intramuscular injection of 2 cc. of Kutapressin every 5 days. At the end of 6 weeks, I would estimate his improvement at about 75 per cent. It is my clinical impression that the keloids in the white race respond more readily to Kutapressin than those in the colored races.

I am not nearly so enthusiastic as Dr. White in his glowing reports about the efficacy of Kutapressin in urticaria and drug eruptions. I will agree with Dr. Barksdale in his comment that in drug eruptions, results are not as dramatic as with steroids but it seems to give a similar but more prolonged response. As a matter of practical management, we have found that treatment for the immediate control may be obtained with corticosteroids and treatment continued with Kutapressin. Dr. Barksdale alluded to it briefly in his paper, but I would like to ask him how effective he

has found Kutapressin used topically, for (as he has pointed out) with Kutapressin, one is given the opportunity of satisfying the public demand for "shots." There is equally as large a number of patients just as adamant about not getting an injection. I know of no reports of allergic reaction to Kutapressin. It is still relatively expensive and is not a panacea but, with such able investigators as Dr. Barksdale, I am sure it will soon settle down into its proper sphere of usefulness.

Dr. James Q. Gant, Jr., Washington, D. C. Dr. Barksdale is to be congratulated on his study of Kutapressin in such a large number of patients having a variety of dermatological disorders. I have used Kutapressin in psoriasis, acne vulgaris, and rosacea over a period of 4 years.

Psoriasis. This is one of the most difficult diseases to evaluate as regards therapy. It is prone to spontaneous remissions and relapses, and the patients are susceptible to the psychic effect of new therapy. I have used Kutapressin in the treatment of 76 such patients, observing them over a period of 18 months. The lesions of 14 patients cleared up completely and have remained so to date under continuous treatment. Another 54 patients responded very well but did not clear up completely. The remaining lesions generally involved the knees and elbows. Still another 5 patients responded fairly well; 3 patients failed to respond at all. Some patients relapsed when treatment was discontinued but responded again when treatment was resumed. With a regimen of 2 cc. intramuscularly, three times weekly, one or two months of treatment was necessary before effects of treatment were evident. I think Kutapressin has a beneficial influence on psoriasis above and beyond the capricious nature of the disease.

Acne Vulgaris. Forty patients in the age range of 18 to 30 were treated during a period of 12 to 18 months. Patients with severe pustular acne did better than the mild indolent cases and about two-thirds of those with the former responded satisfactorily. The dosage schedule was 2 cc. twice weekly.

Rosacea. Eighteen patients with extensive rosacea were treated over a period of 16 months, being given 2 cc. injections twice weekly. Good response was obtained in 11 of 18 patients; the others showed some improvement. The permanence of treatment response is complicated by the effect of emotional stress of the patient; the physician must use every means available to give the patient a new outlook toward his life's problems.

Kutapressin is well tolerated at the site of injection. I have not seen any general or systemic reactions to it.

Dr. William Poole, Birmingham, Ala. Kutapressin has interested me for the past five years in its effect on herpes zoster, having used it in 100 cases, alternating it with either injections of 100 mg. of vitamin B_1 and 1,000 mcg. of B_{12}. The effects was compared with the purpose of preventing post-herpetic neuralgia. Our results were difficult to evaluate since many cases are mild and there is spontaneous recovery without neuralgia.

None of the cases treated with Kutapressin developed post-herpetic neuralgia. On the average the pain improved progressively to be gone by the tenth day,—practically always within two weeks. In 5 cases injection of 2 cc. twice weekly for two months were required before the pain cleared entirely. This compared almost exactly with those who received injections of either vitamins B_1 or B_{12}.

It is theorized that since Kutapressin, in experimental work, reduces intracellular edema, the lessening of swelling within the ganglion is responsible for the cessation of pain.

Five cases of neuralgia which had existed two months without treatment other than local applications, responded in 6 to 12 weeks with Kutapressin twice weekly. Cases of neuralgia lasting for 6 months after herpes zoster have responded only slightly to any treatment we have been able to offer.