The Treatment of Erythema Nodosum Leprosum with B.663

A Controlled Study[1]

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Among his original studies of a riminophenazine compound at present known under the name B.663, Browne ([1]) published an article concerning its possible anti-inflammatory action in lepromatous leprosy. He reported that of 26 patients whom he had treated (21 for six months and five for 12 months) only two developed erythema nodosum leprosum (ENL) while receiving B.663. When this treatment was stopped, however, 14 of them later developed ENL. Browne suggested, therefore, that B.663 may exert a suppressive effect on the development of "acute exacerbations in lepromatous leprosy"; it is understood that this phase includes the whole of the ENL clinical spectrum. Although this claim was not believed to be completely logical, the problem of treatment of ENL is so pressing that it was decided to investigate whether or not the use of B.663 had any effect on the progress of patients with severe ENL. As it had been shown ([5]) already that high doses of B.663 are unacceptable to patients in Malaysia because of the pigmentation produced, the dose that was used was 100 mgm. daily for six days per week. After this work had been initiated, Williams *et al.* ([8]) reported the treatment of three cases of leprosy with B.663 and claimed that in two cases such treatment was associated with "near or complete disappearance" of ENL, but they, too, were using a dosage schedule that was higher (up to 600 mgm. per day) than was used in this study.

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METHODS

It is always difficult to come to any conclusions on therapy in a disease with a fluctuating clinical course, and this is particularly true of ENL, which can last for several years, occasionally being severe while at other times it is almost, if not completely, quiescent. In devising a method to assess the progress of treatment in such a condition one must indicate both the severity of the disease and its progress over a long period. This paper concerns an attempt to develop a method of study that not only ensures that the ENL in all cases is of comparable severity but also allows the patients' progress to be assessed.

Waters ([7]) classified ENL as follows:

1+ mild, causing little discomfort, and responding to standard therapy.

2+ moderate, usually persistent, and not easily controlled by standard therapy; where corticosteroids are given, the reaction is easily controlled by 5-15 mgm. prednisolone daily.

3+ severe, persistent, causing very considerable discomfort, unaffected by standard therapy, and requiring 20-35 mgm. prednisolone daily for adequate control.

4+ very severe, usually of the necrotic type, difficult to control, even with 35-45 mgm. prednisolone daily.

Using this classification we limited the present study to patients whose disease was of 3+ or 4+ severity.

It is well known, however, that even severe ENL may occasionally disappear unexpectedly and completely within a surprisingly short time, and so it is necessary not only to grade the severity of the disease but to find some way of marking its progress. As all cases in this series were inpatients who had been under treatment for a long time, it was thought that progress could be assessed by totalling the dose of anti-inflammatory hormones needed each month to suppress symptoms and keep the patient comfortable. An attempt was made to treat all patients with aqueous solution of adrenocorticotropic hormone (ACTH, 25 IU per ml.), as it was believed that the use of ACTH would give a more accurate reflection of the patients' day-to-day condition since this therapy can be reduced more quickly than steroids. It is thought that if a patient is treated only with ACTH, the number of units used each month will be a fair reflection of his progress, provided that at all times the same criteria are used for treatment. As far as possible, therefore, all the patients with ENL who were considered to be potential candidates for study, were treated with ACTH injections, and as soon as possible the steroids they had been receiving previously were diminished and stopped. The administration of ACTH followed fairly rigid rules; it was not given unless the patient was in pain that could not be alleviated by analgesics, or if the temperature rose above 99°F. It had been hoped that a simple index of ACTH treatment could be reached that would show the number of multiples of 25 units given to an individual in the course of a month, but, since in the early days of the introductory studies patients were receiving some prednisolone also, the marking that was actually used was 1 point for 25 units of ACTH or for 20 mgm. of prednisolone.

In order to establish an individual base line, only those patients were accepted who had been treated for severe ENL for at least six months. Treatment at first consisted simply of the usual therapy for severe cases, with an attempt to reduce steroids and establish the patient on ACTH. After the patients had been under treatment in the Research Unit for a minimum of three months, B.663 was given in a dosage of 100 mgm. daily for six days each week. It is not our habit to diminish the dose of sulfones when a patient develops ENL ([3]), but, as many workers believe that this should be done, we divided the group into two, half of whom (Group A) continued their sulfone therapy while the others (Group B) did not. Those who stopped sulfone treatment were of course not stopping antileprosy treatment, as experience ([2, 4, 5]) shows that B.663 itself is a satisfactory treatment for leprosy. This drug was given throughout the study, but the two groups were interchanged after seven months, and those who had stopped sulfone therapy restarted it while the others were taken off the drug. As will be seen, there was some disparity in the findings of Groups A and B, and an additional five patients were therefore studied, designated Group C. The results have been included in an attempt to clarify one of the points we wish to make.

RESULTS

Table 1 contains two sets of figures concerning Groups A and B and shows the number of ACTH equivalents needed by the first ten patients during the prestudy control period and during a further 14-month period, for half of which time the patients received sulfone treatment. In Group A the amount of anti-inflammatory hormone needed by three of the five patients (A1, A2 and A5), diminished with surprising speed, and, although A3 did not show any change, even A4 showed some improvement over the seven-month period. If we had not incorporated the second period as a control, the results would have suggested strongly that either treatment with B.663, or cessation of sulfone treatment, or a combination of the two, was markedly successful in aiding the

TABLE 1. *The number of ACTH equivalents needed by two groups (A and B) of patients under treatment.*

Treatment	Month	Group and hospital number A1 14324	A2 14335	A3 14564	A4 14719	A5 14817	Treatment	Month	Group and hospital number B1 13703	B2 13864	B3 14273	B4 14360	B5 14683
Prestudy	1	7½	15	27½	15	32	Prestudy	1	18	7	10	21½	32
control	2	30	25	14½	17	20½	control	2	34	15	38½	26½	17
sulfone	3	16	18½	9	26	9	sulfone	3	28	11	14½	19½	10
B.663 started	4	15½	14	22½	14	31	B.663	4	13½	7½	17½	17	14
	5	26	32½	19	13	5½	started	5	14½	10	12½	15½	10½
	6	8½	4½	12½	9½	—		6	7	12	12½	12½	13
	7	—	2½	11	13½	—		7	5½	12½	17	21	15½
Sulfone stopped	8	—	—	12	10½	—	Sulfone	8	9	13	21	15½	15
	9	—	—	12	7	—	con-	9	7	15	15½	21½	17½
	10	—	—	15	½	—	tinued	10	9½	13	23½	23½	23
B.663	11	—	—	20	2	—	B.663	11	14	12	37	16½	19
continued	12	—	—	21	5½	—	con-	12	14	9½	18½	20	14½
	13	—	—	18	3	—	tinued	13	9½	8½	20½	22½	17½
	14	—	—	20	11½	—		14	18	11	8½	21½	14
	15	—	—	19½	—	—		15	13	10	4	10½	13
Sulfone	16	—	—	15½	—	—	Sulfone	16	3	8	1	13	?*
restarted	17	—	—	14½	—	—	stopped	17	½	19	—	6	16

*This dosage is unknown, as the patient was away from hospital but later returned.

TABLE 2. *Number of ACTH equivalents needed by one group (C) of patients under treatment.*

Treatment	Month	Group and hospital number				
		C1 14177	C2 14268	C3 14925	C4 15157	C5 15267
Prestudy	1	16	19½	13½	12½	41
control	2	13	18	15½	18	41
sulfone	3	13	13	9	20	53½
B.663	4	24½	28	14	14	27½
started	5	29½	20½	15	2	19
	6	29	25	15½	—	45½
	7	32	29½	18	18	27½
Sulfone	8	24	18	10½	23½	42½
continued	9	26	16½	5	—	45
	10	16½	15½	—	—	45
B.663	11	16	9½	—	—	36
continued	12	17	4	—	—	29
	13	18½	—	—	—	23½
	14	9	—	11	—	20
Sulfone	15	11½	—	7	—	19
stopped	16	9	—	—	—	19½
	17	1	—	—	—	

patients. Turning to the first seven-month period of Group B we find what seems to be convincing evidence that patients who continued sulfone treatment showed less satisfactory progress. Fortunately, however, we continued the study for seven more months, with the sulfone treatments reversed, and, returning to Group A, it now becomes obvious that restarting sulfone therapy did not induce any exacerbation of the disease in any of the patients, and, while it may be claimed that this was due to the suppressive effect of B.663, we have seen already from the first seven months in Group B, that B.663 in this dosage has no anti-inflammatory effect. Perhaps the most instructive part of these two tables, however, is the lower part of the Group B study, where B.663 was continued while the sulfone was stopped. If the findings in Group A were produced by anything more than chance, it would have been expected that sometime during the 12th or 13th month some of the Group B cases would have improved. This did not happen, and it is believed that the dramatic improvement that occurred in cases A1, A2 and A5 was not connected with any change in treatment but was due simply to the natural history of the disease.

Table 2 shows the progress of Group C cases, and it is believed that this group is more representative than those in the previous table. It can be seen that two of the patients improved while sulfone therapy was continued (one of these relapsed for a short time in the middle of the "no sulfone" period), and another one cleared on the "no sulfone" dosage. An overall examination of this table, however, shows no more than the steady improvement that would be expected even in a chronic disease over a period of more than a year.

DISCUSSION

Although Sheskin ([6]), in his work on thalidomide, attempted to use "the patient as his own control," in a fairly widespread search we have failed to discover any other reports concerning controlled trials of therapy in leprosy reactions. It is of course realized that in diseases of a fluctuant nature, such trials are difficult to formulate and carry through; it is believed, however, that until such studies are attempted the literature will be full of presumptions which, based on uncontrolled investigations, have been published, ac-

cepted, and promulgated with much faith but little knowledge.

It is essential in an analytic study of such reactions that not only should the *type* be carefully selected but the *progress* also should be watched over a long enough period to ensure that daily or weekly fluctuations do not bias the findings. It is hoped that the trial reported here may go some way toward encouraging studies of an accurate and controlled nature. In all probability it will be found that the paired method of trial is not of value in this form of disease. For example, patients B3 and C2 were admitted to hospital with the same type of disease at almost the same time, and have had a somewhat similar course of reaction, while patient C1, who was admitted to hospital earlier, has so far failed to show any signs of improvement. If C1 and C2 had been paired, it is obvious that the findings would have been weighted in favor of the latter.

Methods of drug trial must, therefore, be developed that use the patient as his own control, and in order to claim any credence for findings based on this form of study it is necessary not only to establish the severity of the disease for a reasonably long period before the study starts, but also to use a "crossover technic" at the halfway mark to establish whether or not the improvement is due to time or therapy. Such a study is necessarily limited to the more chronic diseases and, as far as ENL is concerned, can be used only in the more severe types of reactions (Waters' grades 3+ and 4+).

Our findings show conclusively that B.663, when given in a dosage of 100 mgm. per day for six days per week over a period of 14 months, has no anti-inflammatory effect in ENL. At the same time we believe that this study has shown, albeit in a rather small number of patients, that the cessation of sulfone treatment is not necessarily associated with improvement of the disease. Of the 13 patients (A1 to A5, B1 to B5, C 1, C2 and C5) who had active ENL at the time the sulfone was stopped, only four showed such a degree of clinical improvement over the following six months that no further anti-inflammatory hormones were necessary. It was rather unexpected that an investigation that was conceived as a study of B.663 should produce not only a firm answer concerning this new therapy but should also disprove the much repeated misconception concerning the cessation of sulfones in ENL. In another paper ([3]), which is of a more theoretic nature and concerns the etiology of ENL, an attempt is made to show that these findings are neither unusual nor surprising.

As far as B.663 is concerned, it must be remembered that Browne was using three times the dosage that was used in Malaysia. We believe, however, that the average patient here will not accept a high dosage and, although a number of resistant patients ([4]) have accepted the therapy *faut-de-mieux*, it was simply because they were well aware that their own condition was not improving with routine antileprosy measures. It is not considered probable that a higher dose will give more satisfactory results. Browne's findings, viz., that the 14 out of 21 patients who had been treated with B.663 for six months later developed ENL when this was stopped, are not considered evidence that B.663 has an anti-inflammatory effect nor that dapsone is liable to precipitate ENL; they show simply that as a rule ENL does not start during the first six months of the antileprosy treatment, and confirm his previous findings ([2]) that B.663 is of value in the treatment of leprosy.

SUMMARY

An attempt has been made to establish a method whereby controlled investigations may be used to assess the value of a treatment in erythema nodosum leprosum. Limiting the study to severe cases, all of which needed a high dosage of anti-inflammatory hormones, we found evidence that the riminophenazine derivative B.663, in a dosage of 100 mgm. daily for six days a week over a 14-month period, had no dramatic effect on the alleviation of ENL.

It was shown also that the cessation of sulfone therapy does not demonstrably speed the diminution of the reaction.

RESUMEN

Se ha hecho un ensayo para establecer un método por medio del cual investigaciones controladas puedan ser usadas para determinar el valor de un tratamiento en erythema nodosum leprosum. Limitando el estudio a casos severos, todos los cuales necesitan una alta dosis de hormonas anti-inflamatorias, encontramos evidencia que la riminophenazine derivado B.663, en dosis de 100 mgm. diarios por seis días a la semana en un período de 14 meses, no tuvo efectos dramáticos en el alivio del ENL.

Se demostró también que la suspención del tratamiento con sulfona no apresuraba demostrablemente la disminución de la reacción.

RÉSUMÉ

Un essai est ici tenté pour établir une méthode qui pourrait être utilisée pour estimer la valeur d'un traitement dans l'erythème noueux lépreux. Limitant cette étude aux cas graves, lesquels, nécessitaient tous de hautes doses d'hormones anti-inflammatoires, les auteurs ont trouvé des élements permettant de dire que le B.663, un dérivé de la riminophenazine, administré à la dose de 100 mgm. par jour, six jours par semaine, durant 14 mois, n'avait pas un effet considérable pour diminuer l'ENL.

Il a aussi été montré que l'interruption de la thérapeutique sulfonée n'accélérait pas de façon nette la diminution de la réaction.

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REFERENCES

1. Browne, S. G. "B.663" Possible anti-inflammatory action in lepromatous leprosy. Leprosy Rev. **36** (1965) 9-11.
2. Browne, S. G. and Hogerzeil, L. M. "B.663" in the treatment of leprosy. Supplementary report of the pilot trial. Leprosy Rev. **33** (1962) 182-184.
3. Pettit, J. H. S. The etiology of erythema nodosum leprosum. Internat. J. Leprosy **35** (1967) 1-10.
4. Pettit, J. H. S. and Rees, R. J. W. Studies on sulfone resistance in leprosy. 2. Treatment with a riminophenazine derivative (B.663). Internat. J. Leprosy **34** (1966) 391-397.
5. Pettit, J. H. S., Ridley, D. S. and Rees, R. J. W. Chemotherapeutic trials in leprosy. 3. Pilot trial of a riminophenazine derivative, B.663, in the treatment of lepromatous leprosy. Internat. J. Leprosy **35** (1967) 25-33.
6. Sheskin, J. Further observation with thalidomide in lepra reactions. Leprosy Rev. **36** (1965) 183-187.
7. Waters, M. F. R. Chemotherapeutic trials in leprosy. 1. Comparative trial of Macrocyclon plus dapsone and dapsone alone in the treatment of lepromatous leprosy. Leprosy Rev. **34** (1963) 173-192.
8. Williams, T. W., Jr., Mott, P. D., Wertlake, P. T., Barba Rubio, J., Adler, R. C., Hill, G. J. II, Perez Suarez, G. and Knight, V. Leprosy research at the National Institutes of Health. Experience with B.663 in the treatment of leprosy. Internat. J. Leprosy **33** (1965) 767-775. (Part 2)