SUNDRY EXPERIENCES IN THE CHEMOTHERAPY OF LEPROSY

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Experience with sulfone treatment of leprosy at Uzuakoli, Nigeria, during the last four years has been described by Davey (1), Lowe and Smith (5), Smith (6, 7) and Lowe (3, 4), and further reports are now ready for publication. There are, however, sundry points which have not been mentioned in these publications, or mentioned only in passing, and which may be of interest to leprosy workers.

In general, sulfone treatment has been found effective in all active forms of leprosy, irrespective of type. The problem of the cost of such treatment has been solved by the use of diaminodiphenyl sulfone (DDS) administered by mouth. The number of patients now being treated with sulfones in Nigeria, here at Uzuakoli and at other centers, is now about 2,500, and this number will rapidly rise when further supplies of DDS are received.

METHODS OF USING DIAMINODIPHENYL SULFONE

In treatment with this form of the drug we have used the highest daily dose that our patients have tolerated well. Heretofore, the standard dose has been 300 mgm. a day attained in the fourth week, although it was realized that further experience might show this dose to be unnecessarily high. We did have some trouble with toxic anemia and sulfone dermatitis, but not appreciably more than with other sulfones. It was noted that any attempt to give larger doses in the early phases of treatment was immediately followed by an increase in the incidence of those conditions. The dermatitis appeared only during the first six weeks of treatment, and it did not occur later if this period was safely passed. Recently we have had a few cases of psychosis developing in sulfone-treated cases, mainly in those receiving DDS but also occasionally in those on sulphetrone. This condition is described later in this paper.

With the widespread extension of sulfone treatment with very limited medical supervision, we have considered it desirable to reduce toxic effects to an absolute minimum. To that end we have been experimenting with slower increase of dosage, lower maxi-

mum or total doses, and less frequent administration. On the basis of present experience we now recommend, especially where medical supervision is limited, that the daily dose should be limited to 200 mgm. for only six days a week. Moreover, the dose of 200 mgm. should be given only at the end of six weeks on 100 mgm. a day. This regimen appears to reduce the incidence of allergic sulfone dermatitis, and it also reduces the anemia often seen in the first few weeks of treatment. Further, we have seen no case of psychosis on this regimen.

We have also had further experience with twice-weekly administration of DDS, with doses increasing to 500 mgm. over several weeks. The drug is so completely absorbed and so slowly excreted that this regimen maintains a reasonable though varying blood level throughout the week. It produces a good therapeutic effect, and, moreover, the incidence of anemia and dermatitis appears to be reduced; psychosis has not been observed at all. We recommend for general use the twice-weekly dosage for use with outpatients, as well as with inpatients under little medical supervision. It is too early to say if this regimen is as effective therapeutically as daily dosage. It does seem to slow down somewhat the response of tuberculoid cases to treatment, although it is producing excellent results.

Workers in some other countries have written saying that their patients do not tolerate 300 mgm. of DDS a day, for they get a progressive anemia, whereas we still normally maintain that dosage for our inpatients here with little trouble. It is good to be able to assure people who meet with such difficulties that lower doses are effective. We have seen good results with only 100 mgm. a day, but recommend 200 mgm. daily for general use. The same recommendation is made by Floch and Destombes (2).

SULFONE DERMATITIS; DESENSITIZATION

We have had considerable experience with the problem of sulfone dermatitis. In a few mild cases, treatment could soon be resumed by giving very small and gradually increasing doses, from one quarter or one half a tablet upwards. In many cases, however, this procedure causes a recurrence of dermatitis. Daily injections of an injectable form of sulfone have been used, starting with very small doses—e. g., 5 mgm. of sulphetrone in solution or 1 or 2 mgm. of DDS in suspension—and increasing slowly and steadily to ordinary therapeutic doses. This procedure also often fails, or succeeds only after several attempts.

Recently we have used the following procedure, which is simple and much more reliable, though slower.

One tablet of sulphetrone (0.5 gm.) is dissolved in 3 ounces of water. The dosage is as follows, given twice weekly:

1st week,	1st dose	1 drachm,	=	20 mgm. sulphetrone
	2nd dose	1½ drachm,	=	30 mgm. sulphetrone
2nd week,	3rd dose	2 drachm,	=	40 mgm. sulphetrone
	4th dose	3 drachm,	=	60 mgm. sulphetrone
3rd week,	5th dose	4 drachm,	=	80 mgm. sulphetrone
	6th dose	6 drachm,	=	120 mgm. sulphetrone
4th week,	7th dose	8 drachm,	=	160 mgm. sulphetrone
	8th dose	10 drachm,	=	200 mgm. sulphetrone
5th week,	9th dose	½ tablet,	=	250 mgm. sulphetrone
	10th dose	½ tablet,	=	250 mgm. sulphetrone
6th week,	11th dose	1 tablet,	=	500 mgm. sulphetrone
	12th dose	1 tablet,	=	500 mgm. sulphetrone
7th week,	13th dose	½ tablet,	=	50 mgm. DDS
	14th dose	½ tablet,	=	50 mgm. DDS
8th week,	15th dose	1 tablet,	=	100 mgm. DDS
	16th dose	1 tablet,	=	100 mgm. DDS

The DDS is then increased at the rate of one tablet a week until the normal dose is reached.

In some cases with a high degree of sensitivity, desensitization must start at even lower doses than those of the above schedule. If at any time dermatitis recurs even in a mild form, desensitization must be stopped for a week, and then be resumed at a dosage level about a quarter of that at which the dermatitis recurred.

SULFONE PSYCHOSIS

During 1948 and 1949, when sulphetrone was the sulfone mainly used, two patients complained of disorientation and other minor psychological disturbance, but no connection between that condition and the sulfone treatment was apparent. Late in 1949 and early in 1950, when DDS was being increasingly used and also when experiments with high doses of DDS were in progress, there occurred several cases of psychosis, some quite marked, and the fact that sulfone can produce that condition became apparent.

CASE 1.—A male adult, an intelligent and educated African, a lepromatous case, was treated with doses of DDS increasing to 300 mgm. a day for eight months, and in the ninth month with 400 mgm. a day. After one month on 400 mgm. he complained of confusion and restlessness and said that the drug was "upsetting his brain." Treatment was stopped and recovery was complete in one month. He has since taken 300 mgm. a day for six days a week for several months, with no further trouble.

There is a reliable history of a previous attack of psychosis while the patient was receiving hydnocarpus oil treatment.

CASE 2.—A male adult African, highly intelligent and educated but highly strung, with some emotional instability accentuated by worry about his disease, was treated with the usual doses of DDS up to 300 mgm. a day, for four months and then, as part of an experiment, with 400 mgm. a day for two months and 500 mgm. a day for two months. No toxic signs appeared. He then reverted to the standard 300 mgm. a day. One month later, in the ninth month of treatment, he became very restless, talkative and finally wildly excited and confused. This state lasted for several weeks, and was later replaced by marked depression and retardation of mental and physical activity. After four months, recovery is not yet complete.

CASE 3.—An adult male with tuberculoid leprosy was given DDS treatment but with the dose increased at twice the usual rate, i.e., 100 mgm. a day for one week only, 200 mgm. a day for one week, and 300 mgm. a day in the third week. In the third week enlargement of the liver and spleen and jaundice occurred, and during the first eight months treatment was temporarily suspended twice for periods totalling several weeks. In the ninth month treatment was being given normally at 300 mgm. a day when the patient developed a psychosis and became restless, talkative and confused. The psychosis had religious manifestations, he being strongly under the influence of a queer and fanatical religious sect. Treatment was stopped and within a month he was normal and has remained so. Treatment has not been resumed, since the disease is inactive.

CASE 4.—An adult female with tuberculoid leprosy, emotionally unstable and worried by her separation from her young baby, was treated with DDS by our usual regimen. In the ninth month she became restless and unmanageable, refused food, and became melancholic and depressed, weeping incessantly. Treatment was stopped. In three weeks she was normal, and treatment was resumed at 100 mgm. a day. In two weeks the psychosis recurred, but again it disappeared on cessation of treatment. One month later treatment was resumed but with sulphetrone, the dose being raised to 3 gm. a day. The psychosis recurred again, and is only now subsiding three weeks after the third cessation of treatment.

CASE 5.—An adult female of psychotic type, a lepromatous case, started DDS treatment on our normal regimen and after three weeks, while on 200 mgm. a day, developed high fever (105°F) of unknown origin and a psychosis which was attributed to the fever. She became restless, talkative and incoherent. Treatment was stopped and the fever and psychosis subsided. One month later treatment was resumed at 100 mgm. a day, and in two days the fever and psychosis recurred. Treatment was stopped for another month. Treatment was then resumed with small doses of sulphetrone (1 gm. a day), and so far there has been no recurrence.

CASE 6.—A young boy, aged 14, was treated with DDS on our usual dosage increasing to 300 mgm. a day. This treatment was continued for four months when he volunteered the information that the drug was affecting his brain, that he was confused and could not remember where he was and what he was doing. Treatment was stopped and the psychosis disappeared in two weeks; treatment has not yet been resumed.

These six cases have occurred among 350 patients at present being treated with DDS here. In 200 cases under my observation elsewhere, and being treated with lower doses, no case has yet occurred. During three years of sulphetrone treatment of over 250 patients, we saw only two mild cases of psychosis, although a few have occurred in other leprosy institutions in Nigeria. It does appear that psychosis is more common and severe during treatment with DDS than with sulphetrone.

Of the six cases here recorded, three occurred after abnormal treatment, either abnormally high dosage or abnormally rapid increase. One other occurred during a high fever of doubtful nature, apparently precipitated by sulfones. Only two occurred in the course of normal treatment, without other factors operating. Furthermore, it is noticed that there is a psychotic background in at least four of the cases. There is a tendency for psychosis to occur in the more highly educated and sensitive patients; it is apparently rare in the ordinary simple Africans.

SULFONES IN NURSING MOTHERS

Because of the importance of the question of the protection of healthy children from infection by leprous mothers, it seemed worth while to study what happened when sulfone is given to such mothers with babies at the breast. Two mothers with newborn babies were given DDS by mouth. The mothers' blood, the mothers' milk and the infants' urine were examined for sulfone content. The blood levels of the mothers were as expected with the dose used. The sulfone content of the breast milk was difficult to estimate accurately because of turbidity, but it appeared to be about the same as in the maternal blood. The infants' urine showed a very definite but variable sulfone content.

The mothers showed no toxic effect, but both of the children became blue, presumably due to methemoglobinemia, when the daily dose of the mother was 100 mgm. in one case and 200 mgm. in the other. Apart from this, the children were not ill, but it was thought advisable to terminate the experiment.

A similar experiment has been made in one case with sulphetrone. On 3 gm. a day mother and child show no ill effects, although sulfone levels are low. It is proposed to try higher doses of sulphetrone.

OTHER DRUGS IN TREATMENT

Para-*aminosalicylate* (PAS). — In view of the beneficial action of this preparation in tuberculosis, a trial in leprosy was carried out in eight patients.[1]

In two lepromatous cases, PAS in solution was injected into leprous nodules and the effect on the number and form of the bacilli was studied. There was no conclusive evidence of reduction in number or of change of morphology.

In six lepromatous cases, 15 gm. a day was given in divided doses by mouth. In three of them the treatment had to be stopped, in one because it was not tolerated and in two because of failure of supplies; but in the remaining three the treatment was continued for six months. There was no definite evidence of subsidence of the leprous lesions, although there was some indication that the number of bacilli was reduced. All of these three cases had prominent lepromatous lesions which, in our experience, would have shown some definite shrinkage after six months of sulfone treatment.

One major tuberculoid case was treated for nine weeks with PAS. The lesions showed no such response as has been seen in every similar case treated for this period with sulfones. Rapid subsidence followed a change to DDS treatment.

The experiment gave no definite evidence of a beneficial effect of PAS in leprosy; there was clear evidence that it was very much less active in leprosy than sulfones. The cost of PAS treatment is fabulously high. There seems little point in studying it further.

Streptomycin.—A few active major tuberculoid cases have recently been treated for 2 to 3 weeks with streptomycin, 1 gm. a day. In some, a definite response was seen within one week, which suggests that streptomycin is more active in leprosy than sulfone. Further work is now in progress and planned with a view to finding out whether short courses of streptomycin are of real value in the treatment of serious complications of leprosy, or in accelerating progress under sulfone treatment. Its cost and toxic effects would severely limit its use as the basic treatment of the disease.

SUMMARY

Experience at Uzuakoli has shown that sulfone treatment is effective in all forms of leprosy, and that such treatment with

[1] The drug for this experiment was provided by Herts Pharmaceuticals, Ltd.

the mother substance, diaminodiphenyl sulfone (DDS), given by mouth is by far the least expensive. A large number of cases is now under treatment with that drug, under varied circumstances.

We have recently found it desirable, in order to lessen the toxic effects, especially where medical supervision is limited, to reduce the maximum dose to 200 mgm. six days a week instead of 300 mgm., and to take six weeks instead of four weeks to attain the maximal level. Furthermore, where conditions make it desirable the dosage may be 500 mgm. given twice a week.

The occurrence of sulfone dermatitis is discussed briefly, and the desensitization routine employed for resuming sulfone treatment is given in some detail.

Descriptions are given of illustrative cases of sulfone psychosis, occurring especially in individuals of unstable nature and especially under the higher dosages of the sulfones.

An attempt at prophylactic treatment of babies of leprous mothers by giving sulfones to the latter was discontinued because the babies turned blue.

Para-aminosalicylate (PAS) has been tried on a small scale, with no indication of promise in leprosy. On the other hand streptomycin, used in a few major tuberculoid cases, seems to be definitely promising.

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