SULPHANILAMIDE IN THE TREATMENT OF ERYSIPELAS

A CONTROLLED SERIES OF 270 CASES*

BY

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A report to the Therapeutic Trials Committee of the Medical Research Council on the effect of prontosil "red" in the treatment of erysipelas was recently published by us (Snodgrass and Anderson, 1937). Using ultra-violet light as the method of treatment in the control group, it was concluded that those cases which received prontosil "red" showed better results in respect of the curtailment of (1) the duration of the spread of the local lesion; (2) the duration of primary pyrexia; (3) the duration of toxaemia. The evidence supporting these statements was assessed statistically.

Tréfouel, Nitti, and Bovet (1935) showed that *p*-aminobenzene sulphonamide was as effective as prontosil "red" in controlling streptococcal infection in the mouse. Colebrook, Buttle, and O'Meara (1936) and later Fuller (1937) produced evidence to show that the red dye was itself inactive but was reduced in the body to a colourless active substance, and that this substance was *p*-aminobenzene sulphonamide, now commonly called sulphanilamide. The present report has as its main objectives the following three points: (1) the investigation of the therapeutic benefits of sulphanilamide in erysipelas; (2) the investigation of the effects of a larger and more prolonged dosage in respect of the therapeutic criteria mentioned above and also in respect of the prevention of recurrence; (3) the investigation of the effect of varying dosage of sulphanilamide during the first twelve hours.

The material consists of all cases diagnosed as erysipelas after admission to Ruchill Hospital, Glasgow, from the middle of February to the middle of August, 1937. Ruchill Hospital receives all notified cases of erysipelas admitted to hospital in Glasgow, so that the material is thoroughly representative of the incidence of the disease in this district during the period reviewed. All patients were under the clinical control of one of us (T. A.).

Plan of Investigation

Apart from the specific treatment shortly to be described all cases were treated under strictly comparable conditions. The wards to which they were admitted and the personnel of the nursing staff were common to all cases. On admission each patient was given a soap-and-water enema, repeated when necessary. Thereafter the same laxative—liquid paraffin—was used when required. A standard diet was adopted, which, in view of its importance when cases are being treated by sulphanilamide or its congeners, we give in full.

(*a*) During the stage of pyrexia the patients receive a fluid diet which may contain any of the following: barley water, Imperial drink, milk, glucose in water, Horlick's malted milk, chicken tea, arrowroot, cornflour, and junket. Most patients receive bovril at night, and in addition are encouraged to eat oranges and grapes.

(*b*) About the second to fourth day the diet begins to become more solid, and may contain porridge, fish, chicken, chicken cream, custards, jellies, and fruits. This diet is continued until the end of the first week.

(*c*) During the second and any subsequent week ordinary diet is resumed—for example, mince, stew, vegetables such as potatoes, cabbage, and turnip, steamed puddings, and milk puddings.

No eggs or onions have been included during the first week in hospital.

An enema is given before treatment is begun, and is repeated in some cases on the second and third mornings.

No local treatment was given. As in the first series of cases, ultra-violet light was used as a control method of treatment. The cases were, in the order of their admission, assigned to two treatment groups. Cases in Group 1 received treatment in the first instance only with ultra-violet light. Cases in Group 2 received treatment only with sulphanilamide. There were 270 cases in all, 135 in each group. The series remained complete, as after further observation the original diagnosis of erysipelas was considered to be correct.

Since our first report showed that prontosil "red" was of greater therapeutic effect than ultra-violet light, it was felt that seriously ill patients who were not improving under ultra-violet light therapy should receive sulphanilamide. Accordingly twelve of the cases originally placed in the ultra-violet light group ultimately received treatment with sulphanilamide.

Details of Treatment

Ultra-violet Light.—A portable mercury-vapour lamp (Messrs. Kelvin, Bottomley, and Baird) was used at a distance of twelve inches from the margin of the lesion. For female cases the exposure was of eight minutes' duration, equal to one and a half erythema doses; for male cases the exposure was for ten minutes—in each case once daily. Exposures were repeated at intervals of twenty-four hours when considered necessary. The average number of exposures was 1.4 per case.

Sulphanilamide.—The preparation used was that marketed under the trade name of "streptocide" by Messrs. Evans Sons Lescher and Webb Ltd., to whom our thanks are due for the generous quantities provided for the tests. Treatment was begun immediately on admission, and in all cases the drug was given by mouth. It was administered in 1-, 2-, or 3-gramme doses at four-hourly intervals, and such dosage was continued until the temperature of the patient became normal. The average duration of this period of treatment was 2.5 days, during which the average case dosage of sulphanilamide was 14.64 grammes. Thereafter 0.75 gramme was given thrice daily until the patient left hospital. The average stay in hospital was 14.4 days, with an average total case dosage of 41.6 grammes of sulphanilamide.

The form in which the drug is given seems to us worthy of comment. In some of the earlier cases undissolved tablets were evacuated by the bowel. It was found, too, that with the larger doses the patient had difficulty in swallowing the required number of tablets. In the majority of the present cases, therefore, the drug was administered in powder form.

* A report to the Therapeutic Trials Committee of the Medical Research Council.

Records of Results

The following data were noted in each case: sex, age, duration of illness before admission, and whether the disease was primary or recurrent, idiopathic or traumatic. The local lesion was considered with regard to its site, extent, swelling, painfulness, and tenderness. The patient's temperature and pulse rate were recorded four-hourly; and toxaemia was estimated under the following headings —prostration, headache, state of tongue, insomnia, vomiting, abdominal distension, and delirium. The urine was examined daily. Intercurrent diseases or degenerations were described; complications, relapses, and recurrences were noted. Each case was reviewed daily. In short, a careful attempt was made to record similar observations on each case in a comparative manner.

Assessment of Results

1. The distribution of the individual cases in the two treatment groups must be considered in respect of certain factors known to influence the course of the disease. Those regarded of greatest importance are: (*a*) the duration of the disease before admission to hospital; (*b*) the age of the patient; (*c*) the severity of the infection; (*d*) associated diseases. Tables constructed to show the relation of these factors to the types of treatment indicate an even distribution. A statistician who has examined them is satisfied that there was no weighting of any one line of treatment by any of these factors.

2. The question when "cure" is achieved has to be determined. The fatality rate in erysipelas is so low that it cannot be used in a small series of cases to assess the value of a therapeutic measure. There is no single clinical feature which can be regarded as a satisfactory criterion of recovery. Cases are seen where the lesion continues to spread after the temperature has become normal; and, again, it is not uncommon for the local lesion to cease spreading while the temperature is still elevated and the patient continues in a toxic condition. In order to arrive at a conclusion in this series of cases attention was paid to the following points from the commencement of treatment: (i) the duration in days of spread of the local lesion; (ii) the duration in days of the primary pyrexia; (iii) the time in days which elapsed until the patient was free from the toxic symptoms. These are the criteria which were used in our previous report.

Results of Treatment

The total number of cases in each treatment group is 135. In compiling the following tables we have adhered to our previous decision to exclude from them all patients who died. In addition there are in this series a number of cases responding so badly to ultra-violet light therapy that in the interest of the patient sulphanilamide was given. It is difficult to assign those twelve cases, which may be termed "failed ultra-violet light," to either treatment group. In our clinical judgement all of these patients were seriously ill when sulphanilamide was given, and yet nine recovered. Clinical judgement, however, is not statistically assessable, and as the following tables have been subjected to statistical analysis the "failed ultra-violet light" cases must be excluded. They will be dealt with in a separate paragraph. The exclusion of five deaths from the sulphanilamide group reduces it to a total of 130 cases; and the exclusion of the twelve "failed ultra-violet light" cases and one death in the ultra-violet light group leaves 122 cases in that group.

TABLE I.—*Spread of Lesion*

Method of Treatment	Duration of Spread in Days						Total Cases
	0	1	2	3	4	5 and over	
Sulphanilamide	78 (60.0)	48 (36.9)	3 (2.3)	1 (0.77)	—	—	130
Ultra-violet Light	48 (39.3)	24 (19.7)	17 (14)	12 (9.9)	14 (11.5)	7 (5.7)	122

The figures in parentheses are percentages.

Table I shows a decidedly more favourable result as regards cessation of spread in those cases which received sulphanilamide. Thus the proportions of cases which showed no spread of the lesion after the end of the first day are: ultra-violet light, 59 per cent.; sulphanilamide, 96.9 per cent. After two days in hospital the lesion continued to spread in only 0.77 per cent. of cases receiving sulphanilamide, but with ultra-violet light the lesion continued to spread in 27.1 per cent. (The corresponding percentages for ultra-violet light in our first report were 59.1 per cent. for the end of the first day and 23.4 per cent. after two days.)

TABLE II.—*Duration of Primary Pyrexia*

Method of Treatment	Duration of Pyrexia in Days								Total Cases
	0	1	2	3	4	5	6	More than 6	
Sulphanilamide	5	48 (38.4)	46 (36.8)	19 (15.2)	9 (7.2)	2 1.6)	1 (0.8)	—	130
Ultra-violet Light	10	28 (25)	25 (22.3)	14 (12.5)	10 (8.9)	15 (13.4)	11 (9.8)	9 (7.9)	122

The figures in parentheses are percentages given after deducting those cases which were apyrexial.

Table II shows a more favourable result as regards duration of pyrexia in those cases receiving sulphanilamide. Thus, after deducting the cases which were apyrexial the percentages of those with no fever after forty-eight hours' treatment are: ultra-violet light, 47.3; sulphanilamide, 75.2. Pyrexia continued for more than three days in only 9.6 per cent. of cases receiving sulphanilamide, but with ultra-violet light the equivalent percentage was 40. (In the first report the corresponding percentages for ultra-violet light were 49 and 38.1 respectively.)

TABLE III.—*Duration of Toxaemia*

Method of Treatment	Duration of Toxaemia in Days								Total Cases
	0	1	2	3	4	5	6	More than 6	
Sulphanilamide	2	22 (17.2)	38 (29.7)	38 (29.7)	18 (14.1)	8 (6.25)	3 (2.34)	1 (0.78)	130
Ultra-violet Light	6	17 (14.6)	27 (23.3)	22 (18.9)	17 (14.6)	15 (13)	10 (8.8)	8 (6.9)	122

The figures in parentheses are percentages given after those cases in which there was no toxaemia have been deducted.

Table III shows a slightly more favourable outcome as regards duration of toxaemia in those cases which received sulphanilamide. Thus, after deducting the cases with no assessable degree of toxaemia, the percentages of those free from signs of toxaemia at the end of forty-eight hours' treatment were: ultra-violet light, 37.9; sulphanilamide, 46.9. After three days in hospital 23.47 per cent. of all cases receiving sulphanilamide remained toxic; the equivalent percentage with ultra-violet light was 43.3. (The corresponding percentages for ultra-violet light in the first report were 39.08 per cent. at the end of forty-eight hours and 39.07 per cent. after three days.)

For ease of comparison the main results of the three preceding tables are presented in Table IV along with the standard errors of the differences.

In this table the standard errors of the differences in I and II render the percentage differences significant.

TABLE IV

		Ultra-violet Light	Sulphanilamide	Standard Error of the Difference
		%	%	
I	Ceased spread by end of first day	59.0	96.9	±4.7
II	No fever after 48 hours ..	47.2	75.2	±6.1
III	No toxaemia after 48 hours	37.9	46.9	±6.3

With regard to III (duration of toxaemia), although the difference is not statistically significant many of the cases (35.5 per cent.) showed toxic effects from the administration of sulphanilamide. This makes comparison more difficult.

Recurrence

Recurrence took place in eight cases in the ultra-violet light group, a percentage incidence of 5.9; in the sulphanilamide group two cases were seen, a percentage incidence of 1.5. The difference is suggestive (S.E. ± 2.4). In our first report the recurrence rates were 11.5 per cent. for ultra-violet light and 8.5 per cent. for prontosil "red." It will be noted that there is a decided fall in both percentages in this second series of cases. While the evidence is not conclusive, the repetition of the lower percentage in the group receiving sulphanilamide strongly suggests that these drugs are of value in preventing recurrence.

Complications

Here are included the septic complications directly attributable to infection with erysipelas. Among such conditions are abscess formation, septicaemia, thrombosis, and nephritis. There were eleven cases in the sulphanilamide series, a percentage incidence of 8.1. There were twenty-eight cases in the ultra-violet light series, a percentage incidence of 20.7. The difference between these percentages is almost three times the standard error, which affords further evidence indicating the superiority of sulphanilamide over ultra-violet light.

Cases Transferred from Ultra-violet Light Therapy to Sulphanilamide

The twelve cases which received sulphanilamide in addition to ultra-violet light are shown in detail in Table V. The three deaths occurred in elderly patients suffering from heart disease. Several of the others were extremely ill indeed, and made remarkable recoveries, notably Cases 3670, 2766, and 1574. It is recalled that these twelve cases have been removed from Tables I, II, and III to allow of such tables being dealt with statistically. Here, however, it can definitely be stated that, in our clinical opinion, sulphanilamide contributed to the recovery of many of them.

TABLE V.—*"Failed Ultra-violet Light" Cases*

Case No.	Sex	Age in Years	Day of Illness on Admission	No. of Doses of U.V. Light	Day of Illness when Sulphanilamide begun	Dose given (Total) Grammes	Day of Illness on which Cessation occurred of— Spread	Toxaemia	Pyrexia	Remarks
3670	F.	9/12	3rd	2	5th	15	6th	9th	6th	
3664	M.	65	3rd	4	7th	31	8th	12th	9th	Myocarditis with auricular fibrillation when sulphanilamide started. Remarkable recovery
2436	M.	74	3rd	2	5th	27	6th	9th	7th	Slight cyanosis. Blepharitis with abscess
2766	M.	48	2nd	2	3rd	11	4th	10th	6th	Admitted after decompression operation with cerebral hernia. Cyanosis. Remarkable recovery
2865	M.	59	2nd	4	7th	10	7th	9th	8th	Slight cyanosis
1468	M.	40	7th	5	14th	13	12th	?	?	Bilateral venous thrombosis of legs
3108	F.	55	2nd	2	3rd	24	4th	9th	6th	Myocarditis with auricular fibrillation. Slight cyanosis
1574	M.	63	3rd	1	3rd	19	5th	6th	6th	Excision of rectum before admission. Remarkable recovery
1411	F.	19	1st	5	9th	8	6th	9th	11th	—
2079	F.	69	2nd	3	7th	9	6th	8th	8th	Died 8th day. Operation for cataract before admission. Chronic myocarditis
1029	M.	70	2nd	5	9th	25	9th	15th	10th	Died 15th day. Auricular fibrillation
2167	M.	80	2nd	2	4th	37	4th	9th	9th	Died 9th day. Auricular fibrillation. Epithelioma of tongue. Retro-orbital cellulitis

Deaths

There were nine deaths in this series—a fatality rate of 3.4 per cent. Table VI gives the relevant information.

TABLE VI.—*Details of Fatal Cases*

Case No.	Sex and Age	Method of Treatment	Dosage	No. of Days in Hospital	Remarks
2167	M. 80	U.V. light (failed)	2 doses U.V.L. + 37 grammes sulphanilamide	7	Epithelioma of tongue
1029	M. 70	„ „	5 doses U.V.L. + 25 grammes sulphanilamide	13	Admitted as senile. Erysipelas quite subsided at death
2079	F. 69	„ „	3 doses U.V.L. + 9 grammes sulphanilamide	6	Operation for cataract prior to admission. Myocarditis with auricular fibrillation
3081	F. 7 days	U.V. light	1	1	Premature marasmic baby
3474	F. 87	Sulphanilamide	21 grammes	13	Admitted as senile. Erysipelas quite subsided at death
3487	F. 41	„	12 grammes	15 hrs.	Bronchopneumonia and septicaemia on admission
3616	F. 69	„	9 grammes	3	Intertrochanteric fracture of femur on admission. Bronchopneumonia
1828	M. 55		4 grammes	8 hrs.	Dying on admission
3539	M. 58	„	14 grammes	2	Admitted with bronchopneumonia. Myocarditis and failing heart

Deaths are mainly due to associated disease, often in elderly people. One fatal case was that of a premature marasmic baby, aged 7 days, who died within twenty-four hours of being admitted to hospital. The majority of the fatal cases in the ultra-violet light group received treatment with sulphanilamide owing to their severely ill condition. Comparative figures are therefore impossible.

Toxicity

In our last report only two cases of mild and transient cyanosis were noted. There the average dose of prontosil "red" was 5 grammes and the maximum dosage received by any case was 15 grammes. In the present series the average dosage of sulphanilamide during the first two days was 14.64 grammes and the average total dosage per case 41.6 grammes given in 14.4 days. There was a considerable incidence of toxic phenomena.

Cyanosis was present, lasting from one to five days in thirty-five cases and for more than five days in five cases; two of the latter were proved to be due to sulphaemoglobinaemia, the estimations for which were made by Dr. Eaton, biochemist, of Victoria Infirmary. There was a total percentage incidence of 29.6. Severe vomiting necessitating stoppage of the drug occurred in two cases (1.5 per cent.), toxic eruptions in three cases (2.2 per cent.), and drug fever in three cases (2.2 per cent.). (Drug fever is noted by Hageman and Blake (1937), and implies fever associated with the giving of sulphanilamide, which stops when the drug is stopped and starts when the drug is resumed.) Two of the three cases had received only a moderate dosage of sulphanilamide. In no case was any toxic effect seen which could be described as alarming.

Effect of Varied Dosage of Sulphanilamide

Analysis of the previous report showed that the effect of prontosil "red" treatment was most marked in limiting the spread of the local condition. It was hoped that if the body were flooded with sulphanilamide during the first twelve hours dramatic results might be achieved. Accordingly three ranges of dosage were adopted for this period: (i) 1 to 3 grammes, (ii) from 3 to 6 grammes, (iii) over 6 grammes. Table VII shows the results obtained.

TABLE VII.—*Spread of Lesion with Different Doses of Sulphanilamide*

Dosage of Sulphanilamide in First 12 Hours	Duration in Days of Spread				Percentage of Cases showing Toxic Effects	Total Cases
	0	1	2	3		
1-3 grammes..	34 (60.7%)	21	1	–	19.6	56
3-6 grammes..	21 (60.0%)	13	–	1	40.0	35
More than 6 grammes	23 (58.9%)	14	2	–	48.7	39

No evidence is forthcoming in this small series to show that greater therapeutic benefit follows the increase of sulphanilamide beyond 1 gramme given at four-hourly intervals, but, on the other hand, an increase in toxaemia follows the raising of this dosage.

Discussion

Further proof is afforded of the value of sulphanilamide in the treatment of erysipelas. We would again lay stress on the difficulties attendant on drawing conclusions from the treatment of a disease so variable in its severity as erysipelas. We would once more emphasize that, so far as we can detect, the cases in the two groups are reasonably comparable. There is no weighting of either group through duration of disease before admission to hospital, age, severity of infection, or associated diseases. Both groups were closely controlled in respect of diet, nursing, and laxatives. Our conclusions are based on statistical evidence, but we feel that the expression of clinical opinion is also relevant. The results achieved in some of the cases transferred from ultra-violet light treatment to sulphanilamide were most impressive. It is felt that such cases, which are not included in our statistical analysis, helped to demonstrate the undoubted value of the drug.

As the percentages of the ultra-violet light cases so closely correspond in the two reports, comparison of sulphanilamide with prontosil "red" might seem permissible. This, however, is invalidated by the fact that the amounts used of the two drugs are not comparable. The increased incidence of cyanosis in this series as compared with the original one is noteworthy, and is probably associated with the increased dosage used.

While the question of the optimum dosage cannot at present be considered as settled, we suggest that the general practitioner adopts the following regime in the treatment of erysipelas.

(*a*) As a preliminary to treatment a soap-and-water enema should be administered and thereafter the bowels kept open by the use of liquid paraffin.

(*b*) One gramme of sulphanilamide should be given at four-hourly intervals until the temperature becomes normal, provided no toxic symptoms appear.

(*c*) 0.75 gramme of sulphanilamide should then be given thrice daily for a further period of ten days.

Conclusions

1. A series of 270 cases of erysipelas was treated under controlled conditions with (*a*) ultra-violet light, (*b*) sulphanilamide.

2. There was an even distribution of the individual cases in the treatment groups in respect of factors known to influence the course of the disease, such as (*a*) the duration of the disease before admission to hospital; (*b*) the age of the patient; (*c*) the severity of the infection; (*d*) associated diseases.

3. The average total case dosage of sulphanilamide was 41.6 grammes, given in 14.4 days. The drug was administered in 1-, 2-, or 3-gramme doses four-hourly until the cessation of primary pyrexia, with an average case dosage of 14.64 grammes; thereafter 0.75 gramme was given thrice daily until the case was dismissed.

4. Cyanosis occurred in 29.6 per cent. of cases: it was more frequent when the larger doses of sulphanilamide were given.

5. Sulphanilamide is of benefit in securing curtailment of (i) the duration of the spread of the lesion; (ii) the duration of primary pyrexia; (iii) the duration of toxaemia.

6. The administration of sulphanilamide reduced the incidence of complications and diminished the tendency to recurrence.

7. An effective method of treatment is to give 1 gramme of sulphanilamide by mouth at four-hourly intervals until the cessation of primary pyrexia, and thereafter 0.75 gramme by mouth thrice daily until final cure is determined.

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