

DR. ROY W. SCOTT, Cleveland: Are there any advantages of sulfadiazine over sulfathiazole?

COLONEL W. PAUL HOLBROOK, M. C., A. U. S.: Dr. Jones asked about what is being done to determine the question of sensitivity. The possibility of individuals becoming sensitized to the drug has been considered. As yet, evidence for an increasing sensitivity in individuals who are on the prophylactic program is not available. Repeated periods of prophylaxis on the same groups have shown in each instance a decreased number of reactors for the second or third prophylactic period rather than an increase. Once the known positive reactors are eliminated, no further difficulty is encountered during subsequent periods of prophylaxis. We also now have a rather large number of troops who have had prophylactic sulfadiazine and who have subsequently developed an acute illness requiring the administration of sulfadiazine therapeutically. These patients have responded as well as those not having had a prophylactic period. These experiences do not appear compatible with an increasing sensitivity. A long range study is planned by means of recording each individual's prophylactic record on his immunization register, so that in six months or a year a rather large accumulation of information should be available on this subject. I have not used sulfathiazole, largely because of the general reports in the literature as to its increased toxicity, but I have no experience in its use for this type of prophylaxis.

THE TREATMENT OF TONSILLITIS WITH SMALL DOSES OF SULFONAMIDES

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From both military and economic aspects, any relatively nontoxic therapy which will shorten the course of a prevalent disease, if even for a few days, is worthy of application. Since it is generally acknowledged that tonsillitis is responsible for a significant number of the total man hours lost to industry and the armed forces, the advisability of treating acute follicular tonsillitis with sulfonamides has been the subject of a variety of studies. From the medical point of view, chemotherapy would be desirable because of the possibility that such complications as peritonsillar abscess and such sequelae of tonsillitis as nephritis and rheumatic fever might be prevented or at least minimized.

The advisability of using large doses of sulfonamides (2 Gm. or more per day) in the treatment of tonsillitis remains controversial. Some believe that, since this disease is relatively benign and self limited, chemotherapy is unnecessary and even dangerous.¹ This view is supported by the number of serious toxic reactions that have resulted from the indiscriminate use of the sulfonamides. Others believe with Gettelman and Kaiz² that early treatment with sulfonamides (2 Gm. per day) appreciably shortens the course of the disease.

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Lieut. Col. Robert King, M. C., and Dr. Chester S. Keefer cooperated with suggestions and criticisms.

From the Medical and Laboratory Services, AAF Regional Station Hospital, U. S. Army Air Field, Lincoln, Neb.

1. Rhoads, P. S., and Afremow, M. I.: Sulfanilamide in the Treatment of Sore Throat Due to Hemolytic Streptococci, with Controls, *J. A. M. A.* **114**: 942 (March 16) 1940. Richards, L. G.: Treatment of Diseases of the Throat, *ibid.* **115**: 501 (Aug. 17) 1940. Hughes, L. W.: Diseases of the Nasopharynx, *Mississippi Doctor* **18**: 261 (Oct.) 1940. Kernan, J. D.: Infections of the Mouth, Pharynx, and Respiratory Tract, *Bull. New York Acad. Med.* **17**: 674 (Sept.) 1941. Beckman, H.: Treatment in General Practice, ed. 4, Philadelphia, W. B. Saunders Company, 1942.

2. Gettelman, E., and Kaiz, S. P.: The Treatment of Severe Tonsillitis in a Naval Dispensary, *U. S. Nav. M. Bull.* **42**: 399 (Feb.) 1944.

A middle of the road point of view is taken by Janeway,³ who prescribes chemotherapy only for those patients whose temperature exceeds 102 F.

In addition to systemic therapy, the local treatment with sulfonamide sprays has become popular. Many investigators have reported effective therapeutic results and an absence of drug reactions following the use of local sprays in the treatment of various upper respiratory infections.⁴

In order to establish the relative efficacy of the local and systemic administration of sulfonamides in the treatment of acute follicular tonsillitis we considered it necessary to study this question under controlled conditions using hospitalized patients.

METHOD

During the winters of 1943 and 1944 a series of 405 young men of military age who had definite clinical evidence of acute follicular tonsillitis were hospitalized to a separate ward devoted to their care. During the first year of the study the patients were divided into two groups, alternate patients being treated by one of two methods. One group (1) of 100 patients were given only hot saline irrigations every four hours and received no chemotherapy. The other group (2) of 100 patients were treated with hot saline irrigations every four hours and in addition received sulfanilamide spray to the tonsils and pharynx every two hours except while asleep. Powdered sulfanilamide was sprayed into the throat until an even white coating of the mucous membranes was produced, the patient being then instructed to swallow, following which the throat was again sprayed.⁵ The amount of sulfanilamide used per dose varied from 75 to 100 mg. and, as eight applications were administered daily, the total daily dosage varied from 500 to 800 mg. With this dosage blood sulfanilamide levels were never found to be above 1 mg. per hundred cubic centimeters and usually were too low to be read by standard methods.

During the second year group 3, consisting of 115 patients, received saline irrigations every four hours and, in addition, 125 mg. of sulfadiazine by mouth four times a day (500 mg. daily). The sulfadiazine was in tablet form and was swallowed immediately. Another group (4) of 90 cases was treated in the same way as group 2 except that "microform crystals" of sulfadiazine⁶ were substituted for sulfanilamide powder.

On admission a throat culture and white blood count were obtained. Patients who showed peritonsillar abscess, fusospirochetal ulcers of the tonsil, scarlet fever, acute glomerulonephritis or rheumatic fever on admission were not included in this study. Similarly excluded were patients who had the common cold with nasopharyngitis and tonsillar swelling without pronounced redness or follicles.

As indicated in the table, the four groups were essentially similar in regard to admission temperature, infecting organism and average admission leukocyte counts.

3. Janeway, C. A.: *Medical Progress: The Sulfonamides*, New England J. Med. **227**: 1029 (Dec. 31) 1942.

4. Freeman, M. S.: Local Use of Sulfathiazole Powder for Acute Pharyngeal Infections, *Arch. Otolaryng.* **37**: 496 (April) 1943. Silcox, L. E., and Schenck, H. P.: Use in Otolaryngology of Microcrystals of Drugs of the Sulfanilamide Group, *ibid.* **36**: 171 (Aug.) 1942. Dolowitz, D. A.; Loch, W. E.; Haines, H. L.; Ward, A. T., and Pickrell, K. L.: The Prevention of Ear and Nasal Sinus Complications of the Common Cold, *J. A. M. A.* **123**: 534 (Oct. 30) 1943. Turnbull, F. M.; Hamilton, W. F.; Simon, E., and George, M. F.: Sinusitis and Infections Secondary to the Common Cold, *ibid.* **123**: 536 (Oct. 30) 1943.

5. The DeVilbiss standard atomizer-type powder blower No. 175 was used.

6. Smith, Kline and French laboratories supplied the sulfadiazine microform crystals.

RESULTS

The groups which received sulfonamides (2, 3 and 4) either locally or systemically showed a return to normal temperature and "clinical recovery" in an appreciably shorter period of time than the control group (1) treated with irrigations alone (as shown in the table). Statistical examination of our data reveals that a reliable difference exists between group 1 and the other (sulfonamide treated) groups, since the reliability of the differences of the control group as compared with each of the sulfonamide treated groups is greater than three.

The criteria for "clinical recovery" were complete subjective relief of symptoms and complete disappearance of erythema, edema and follicles. Many of the patients, particularly in the sulfonamide treated groups, were subjectively well before the signs of inflammation had completely subsided. Hence it is probable that in other hands this period of "to clinical recovery" might be shorter or longer. Obviously this interim has not the same objectivity as "return to normal temperature" and therefore is not equally significant.

4 and group 2 can be attributed to the well known fact that sulfadiazine is more effective in infections caused by the hemolytic streptococcus than is sulfanilamide.

The fact that the patients in group 3, who received 0.5 Gm. of sulfadiazine daily in tablet form, showed a rate of recovery comparable to the groups receiving local spray raises the question of the advisability of using topical therapy in the treatment of tonsillitis. As tablets are more easily administered than local spray, there is no clinical reason for the use of the latter in the treatment of this condition.

The saving of even one day in hospitalization has much economic and military importance, since, when the incidence of tonsillitis is considered, this saving can be translated into terms of thousands of man-days salvaged. In view of the fact that the patients receiving sulfonamides experienced subjective relief even though some residual signs of subsiding inflammation remained, it is possible that such patients can be discharged to military duty or to industry as soon as the temperature becomes normal, with the stipulation that they con-

Summary of Data

Groups	No. of Cases	Temperature on Admission	White Blood Cells on Admission, Thousands	Positive Hemolytic Streptococcus	Days to Normal Temperature				Days to Clinical Recovery				Complicating Peritonsillar Abscess
					Mean	S. D.	S. E. M.	Reliability of Difference	Mean	S. D.	S. E. M.	Reliability of Difference	
1	100	101.6 (98.8-104.2)	13.7 (5-24)	83	3.3	1.68	0.168	...	4.7	1.95	0.195	...	6
2	100	101.7 (98.6-104.6)	13.6 (5-23)	85	2.3	1.07	0.107	5.0	3.5	1.44	0.144	5.0	1
3	115	101.7 (99.2-104.8)	12.5 (5-23)	86	1.6	0.88	0.082	9.1	3.6	1.24	0.116	4.9	1
4	90	101.4 (98.6-104.5)	12.6 (5-26)	78	1.4	0.73	0.077	10.2	3.0	1.15	0.121	7.4	0

$$\text{S. D. (standard deviation)} = \sqrt{\frac{\sum d^2}{n}}$$

$$\text{S. E. M. (standard error of mean)} = \text{S. D.}/\sqrt{n}$$

$$\text{Reliability of difference} = \frac{\text{Difference between means}}{\sqrt{(\text{S. E. M.}_1)^2 + (\text{S. E. M.}_2)^2}} \text{ (all comparisons made between group 1 and the other groups).}$$

The control group (1) showed an incidence of 6 cases of peritonsillar abscess, which developed as a complication during the period of hospitalization. In both the sulfanilamide spray treated group (2) and in the group receiving sulfadiazine tablets (3) one complicating peritonsillar abscess developed, while none occurred in the group receiving microform crystals of sulfadiazine as a local spray.

The data reveal that the temperature returned to normal more rapidly in the sulfadiazine treated groups (3 and 4) than in the sulfanilamide spray treated group (2). The group receiving sulfadiazine microform crystals locally (4) seemed to be the most benefited. However, the differences between the various sulfonamide treated groups are not of sufficient significance to merit separate discussion.

None of the patients who received sulfonamides developed either toxic reactions or evidences of sensitization.

COMMENT

Our data demonstrate that small, nontoxic doses of sulfonamides will appreciably reduce the period of illness associated with tonsillitis, irrespective of the route of administration of the drug. That the difference between the sulfonamide treated groups and the control group is real is indicated by statistical examination of the data. The small difference between groups 3 and

4 and group 2 can be attributed to the well known fact that sulfadiazine is more effective in infections caused by the hemolytic streptococcus than is sulfanilamide.

It is possible that the use of more than 500 mg. of sulfadiazine daily would have further hastened recovery. However, when dealing with a potentially harmful drug, a balance must be struck between effective and toxic dosage. The complete absence of sulfonamide reactions in the treated groups favors the use of small dosage in the treatment of tonsillitis. This does not imply that these small doses of sulfonamides necessarily are effective in other infections.

CONCLUSIONS

1. The administration of small doses of sulfonamides appreciably shortens the course of acute follicular tonsillitis and minimizes the complication of peritonsillar abscess.

2. Small doses (500 mg. per day) of sulfadiazine administered by mouth in tablet form are as effective as the local application of sulfonamides to the tonsillar area in the form of a powder spray. The ease of administration makes the systemic route the ideal therapeutic procedure.

3. There were no toxic or sensitization reactions observed in any of the 305 patients receiving sulfonamides in the doses given.