

CLINICAL CONFERENCE

The Role of Adrenal Steroids in the Treatment of Tuberculosis

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DR. MARGARET H. D. SMITH: We have been using adrenal steroids in the treatment of tuberculosis in children. We have a relatively small number of cases, not enough to set up a controlled, randomized, case study. We decided a couple of years ago, when we embarked on this study, to treat consecutive cases for certain indications, and see where we got, hoping to find out in the first place whether steroids seemed to do good or whether they seemed to do harm; in the second place, if they did seem to do good, to try and find out what sort of treatment dosage, what treatment schedule, and so forth, might be indicated. We thought then that, if we actually ended up with some sort of positive experience and data, that perhaps we might, under other circumstances, be able to do a properly controlled study. Our observations on the use of steroids in the treatment of tuberculosis have really been patterned on the experience of various European investigators, who started us on our way.

I am not going to say very much about the use of steroids in *tuberculous meningitis* because that is an indication for the use of steroids which is fairly generally accepted. I think that the data which have been gathered in Italy, in South Africa, and in many other parts of the world, as well as in the few cases that we have had occasion to treat here, make one realize that steroids are a very valuable adjunct in the treatment of tuberculous meningitis. The reason for the better results obtained with steroids is perhaps not simply the one usually given, namely prevention of block.

I think that perhaps the mode of action of steroids in tuberculous meningitis is that they bring down increased intracranial pressure very dramatically, and this not only in tuberculous meningitis but apparently in other forms of meningitis also. Of course, the main reason for death from any kind of meningitis is increased intracranial pressure. If you have something which will bring down this pressure rather quickly and satisfactorily, then you can take your time, so to speak, to go about curing the meningitis.

Steroids have been used also in the treatment of *miliary tuberculosis*, and we can add nothing to the information which is presently available from other clinics. We can say that in other people's experience, and also in ours, there seems to be no danger attendant upon utilization of steroids in any form of tuberculosis, provided the tubercle bacillus involved is drug susceptible, and we have no fear at all of using steroids in miliary tuberculosis.

However we have not been able to show, in our few cases, with the difficulties attendant upon reading chest films in small children, that the lesions of miliary tuberculosis clear faster. Drs. McClement and Cournand on the Adult Chest Service of Bellevue Hospital were able to show, some years ago, that some adult patients with marked dyspnea from miliary tuberculosis seemed to benefit considerably from the use of steroids. If we had a small child, as we had 2 or 3 years ago, with marked dyspnea from miliary tuberculosis, I would not hesitate to try the steroids. I would not hesitate because I am sure that they do

Presented at a Clinic Session, Dr. L. E. Holt, Jr. presiding, for the Spring Session of the Academy, April 23, 1958.

ADDRESS: 550 First Avenue, New York 16, New York.

PEDIATRICS, October 1958

not promote the spread of the disease, although I am not sure that they are always beneficial.

The third clinical form of tuberculosis in which we have used steroids, and where we feel rather happy about our results, is *tuberculous pleural effusion*. Here I feel we can recommend the use of steroids quite heartily. We have now treated seven consecutive patients.

In a series of over 100 consecutive cases of pleural effusion treated on this service, Dr. Edith Lincoln showed that the duration of clinical symptoms was approximately 21 days in patients treated without steroids, while the mean duration of the effusion itself was 48 days. These were patients, some of whom were treated with nothing, and some with antimicrobial therapy.

It is proper to ask what is the course of tuberculous pleural effusion in children where antimicrobial therapy alone is given. The only answer is that, so far as we know, there are no data concerning children, but there is a very good series on young adults from the Veterans Administration showing that antimicrobial therapy, while it does lower the incidence of later complications of the pleural effusion, does nothing to the actual course of the pleural effusion itself as regards symptoms or duration of fluid.

On the other hand, in the cases treated with antimicrobial therapy plus steroids, the course becomes a very favorable one indeed. The first six patients in this consecutive series treated with steroids were all children with pleural effusions which were proved by laboratory diagnosis to be tuberculous, either on the basis of positive gastric cultures or on the basis of pleural biopsy or both. In the cases that form this group, we found that, if the duration of the effusion had been very short prior to admission, the response was extremely good. The symptoms cleared immediately, and the x-ray would clear in a period of 4 to 14 days. In the one patient in this group of seven, in whom the effusion had been

present for 4 months prior to admission, the course was not notably influenced.

In tuberculous pleural effusion, we feel that steroids are definitely indicated, and while it would be nice to have a randomized series of cases, I think seven consecutive ones, with six who did well, and the seventh a rather anomalous one, is probably fairly adequate proof in itself that the steroids are useful. Steroids are always used under cover of antimicrobial therapy and never without antimicrobial therapy.

As to the dosage of steroids, Professor Cocchi and his co-workers in Florence, who were among the first people to use steroids systematically in the treatment of children with tuberculosis, are very emphatic that the dose should not be large. I think that he is probably right. Our dosage of prednisone at the present time is 1 mg/kg/24 hr. We continue this for a period of 6 weeks, and then we reduce this to 0.5 mg/kg/24 hr for 2 weeks. Then for the last 2-week period we reduce the dosage to 0.25 mg/kg/24 hr. I think if one is going to use steroids, one should use adequate antimicrobial therapy consisting of isoniazid of at least 20 mg/kg/24 hr, and sodium p-aminosalicylic acid, in a dosage of 300 to 500 mg/kg/24 hr, simultaneously.

There is still another form of tuberculosis in children, in which we have been doing quite a lot of work on the use of steroids, and that is in the treatment of *tuberculous adenitis*, both cervical and mediastinal. Here I cannot yet recommend the steroids heartily. I think that we still have to do some more work.

The French have done a good deal more work than we have, and their studies concur almost exactly with ours. The results of our respective studies are something like this: In about a third of the patients who are treated with enlarged nodes, either cervical, hilar or axillary, the response is rather dramatic. If the patient is suffering, for instance, from enlarged mediastinal glands which are pressing on the trachea, actually causing respiratory obstruction with wheezing, the result is indeed dra-

matic. In a third of the patients the result seems to be good, and the patients get better quite quickly after you institute treatment. You think that you have a good result, but there is always lurking in the back of your mind the feeling that this might just have been a case which would have done well anyway. Then there is another group, approximately a third of the cases that seem to be uninfluenced by the use of steroids. There are, however, no patients that we have seen or that others have seen who went on and got worse after they were given steroids. In the case of enlarged mediastinal nodes, we have followed not only the size of the nodes on x-ray films and the clinical symptoms, but we have followed the endobronchial lesions also. Our bronchoscopists have been able to watch the bulging into the tracheobronchial tree disappear very quickly, and they have been able to watch the tuberculous granuloma within the lumen of the bronchus disappear very quickly. Like the radiologists, they have seen no evidence of an enlargement of these nodes during use of steroids.

I think in summary we can say a good deal more work needs to be done, but that if one has a child who is in dire straits from enlarged nodes pressing on the tracheobronchial tree, it is certainly worth trying the steroids.

We have used prednisone in all cases, whether of meningitis, tuberculous pleural effusion, or glandular lesions, in the same dosage already mentioned, except in a couple of cases of meningitis and one of adenitis where it seemed to be an emergency; and there we used intravenous hydrocortisone.

This I think fairly well sums up our experience and our attitude at the present time. I think we can only re-emphasize that fear of the use of steroids in tuberculosis

is justified only if the patient is not receiving effective antimicrobial therapy. But so long as the patient is receiving effective, appropriate antimicrobial therapy for the particular strain of organism which is plaguing him, it seems to be perfectly safe to add steroids.

We have not added other types of antimicrobial drugs; unless the patient has some other reason for adding penicillin or something of that sort, we do not add it.

CHAIRMAN HOLT: We have a short time for questions.

DR. COLEMAN (Washington, D.C.): We had occasion recently to see a small child about 1½ years old, on high dosage, develop a convulsive disorder. I wonder if you are giving extra pyridoxine?

DR. SMITH: We have not seen any difficulty. We have had 150 children receiving dosage of isoniazid of 20 mg/kg/24 hr, and we have run into no trouble nor have the clinics in Europe that I was able to visit year before last, where 30 mg/kg/24 hr was used in many children. A study was done here about 2 years ago on the effect of isoniazid on pyridoxine metabolism in children, and it suggested that supplemental pyridoxine is not necessary in those children. If we had such an occurrence on our service, we would probably look elsewhere for the cause of the convulsions because we feel so very secure now about the use of large doses of isoniazid. As a matter of fact, in one of our patients in the outpatient department, where, as many of you know, our population is almost entirely Spanish-speaking, there was a mistake made between teaspoons and tablespoons. The patient had been receiving 60 mg/kg/24 hr for a month when I saw her in the outpatient department and was doing very well. There was no difficulty at all. I think there is a fairly good margin of safety, as far as our experience goes.

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Pediatrics 1958;22;774

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