The Use of Steroids in Tuberculous Patients with Untoward Reactions to Anti-Microbial Therapy

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Introduction

The occurrence of untoward reactions in tuberculous patients receiving chemotherapy is not uncommon. Occasionally, these effects may be so severe or persistent as to jeopardize the continuation and successful administration of drug therapy. In such instances, the usual symptomatic therapy and anti-histaminic agents may be of no avail. The purpose of this study was: (1) To determine the efficacy of a regimen of combined steroid and chemotherapy, in patients exhibiting moderate to severe reactions to anti-tuberculous drugs; (2) to determine the effect of such therapy on the underlying tuberculous process.

Plan of Study

Cases were selected that had both active pulmonary tuberculosis and severe untoward drug reactions to one or more antimicrobial drugs. Baseline studies were obtained, namely, description of the drug reaction, extent of the pulmonary tuberculosis and estimates of liver, kidney and peripheral blood status. Then all chemotherapy was discontinued. Initially, steroid hormones were administered in suppressive doses for three days, ACTH—gel 80—120 units intramuscularly and, if necessary, prednisolone 10—15 units t.i.d. Anti-histaminic medication (oral and/or parenteral) plus steroid ointment (locally) were used as supplements, if required. The severity of the reaction was the criterion used in estimating the dosage of steroid hormone to be employed. Following the initial three days of suppressive hormonal therapy, the anti-tuberculous agents were introduced singly and in progressively increasing doses. After one anti-microbial agent was successfully introduced, the second was started. When the patient could tolerate two or three chemotherapeutic drugs, the dosage of steroid hormone was reduced gradually over a three to five week span. The patient was followed with periodic sputum examinations and chest x-rays to evaluate the effect of therapy on the underlying disease.

Case 1: J. W., a 41 year old white woman, was admitted August 25, 1955 (third admission), in an acutely toxic state, with an intractable harsh cough, positive sputum for tubercle bacilli, hoarseness, high fever, anorexia, gastric intolerance to PAS and pruritic erythematous eruption due to dystricin.** Isoniazid was the sole drug she could accept. On admission, her chest x-ray film revealed a giant antrum with fluid level in the right upper lung field and productive infiltration bilaterally. Her clinical course was one of progressive deterioration. An intradermal test, with 1-1000 streptomycin, revealed a positive immediate and delayed reaction. The past history disclosed allergic perennial vasomotor rhinitis.

Steroid therapy, ACTH-gel 80 units daily, which was the initial minimum dose required to suppress reaction, was instituted on September 16, 1955 and concluded on October 24, 1955. Consequently she could tolerate dystricin 1 gram q. day for 10 days, followed by 2 grams weekly, and PAS 12 grams daily. She also received isoniazid

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**Dystricin: equal parts streptomycin and dihydrostreptomycin (Squibb).
200 mg. t.i.d. Her clinical condition improved impressively. The skin eruption, cough, hoarseness, anorexia, fever, mental apathy, sputum and pulmonary lesion improved promptly. She gained 40 pounds in six months. Due to symptoms of peripheral neuropathy, pyridoxine 50 mg. t.i.d was added to the regimen. The neuropathy manifestations regressed slowly. Dystricin was discontinued after 18 months' administration.
post steroid, due to recurrence of skin reactions. At present she satisfactorily assimilates PAS and isoniazid. The sputum converted from positive to negative on January 1, 1956 and has persisted negative to date, July 3, 1957. The pulmonary lesion which had regressed considerably now remains stable and inactive, without evidence of residual cavitation (Fig. 1 and Chart 1).

**FIGURE 2A**

*Figure 2A, Case 2: Pre-steroid, October 7, 1955.*

**FIGURE 2B**

*Figure 2B: Post-steroid, June 13, 1957.*
Case 1 Summary: This is an allergic patient with an extremely guarded prognosis due to a highly toxic state, the result of far advanced active pulmonary tuberculosis and untoward drug response to dystricin and PAS. Following the combined use of steroids and anti-tuberculocous agents these results became evident: A—Tolerance to...
dystricin and PAS promptly improved; B—Quick subsidence of toxic state; C—Regression of the giant antrum and pulmonary infiltrate; D—Prompt reversal of positive to negative sputum; E—No untoward effect of steroid therapy on the tuberculous pulmonary process.

Case 2: J. W., 47 year old white man was admitted on September 14, 1954 with complaint of weight loss, anorexia, cough and expectoration. The sputum was positive

**FIGURE 4A**

*Figure 4A, Case 4: Pre-steroid, April 27, 1955.—Figure 4B: Post-steroid, May 28, 1957.*
FIGURE 5A

FIGURE 5B

*Figure 5A, Case 5: Pre-steroid, October 25, 1955.—Figure 5B: Post-steroid, June 21, 1957.*
Steroids in Tuberculous Patients

for tubercle bacilli and chest x-ray film showed bilateral exudative, fibro-nodular and cavitary lesion. He was placed on a regimen of dystrin, isoniazid and PAS. In a short time he developed a pruritic eruption, angioedema, fever, anorexia, weight loss and mental apathy. He appeared to have intolerance to many drugs (dystrin, PAS, isoniazid, viomycin, Stokes expectorant, codeine, dromoran, aspirin, pyribenzamine, benadryl and chlor-trimeton.) The most severe reaction occurred 24 hours after an injection of dystrin. He exhibited an acute exfoliative dermatitis that ultimately required six months to subside. As a consequence, exfoliation of the entire skin, scalp hair, finger and toe nails occurred. At this time all chemotherapeutics was suspended for nine months to permit the reaction to subside. In this interval the pulmonary lesion had partially subsided and he regained some weight. On July 12, 1955 he signed a release from the hospital. This untoward reaction to dystrin was interpreted as an accelerated serum sickness type reaction.

J. W. was readmitted August 11, 1955 with complaint of anorexia, dysphagia, weight loss, insomnia, mental depression and the sputum positive for tubercle bacilli. The administration of a teaspoon of Stokes expectorant immediately provoked a pruritic rash, angioedema and fever. After this reaction subsided he ingested a single tablet of isoniazid. This immediately induced fever, angioedema, generalized pruritic eruption and the onset of heavily blood-streaked sputum. His symptoms rapidly became worse, including dysphagia, sore throat, hoarseness, anorexia and thirty-eight pound weight loss in two months.

Steroid therapy was initiated on October 15, 1955 and was terminated on January 25, 1956. His initial minimum dose of steroid hormone required to suppress the reaction consisted of ACTH-gel 120 units q. day and prednisolone 10 mg.m., l.d. by mouth. In addition benadryl 100 mg.m. q.i.d. and 50 mg.m. in the same syringe with the dystrin, and prednisolone were necessary supplements to suppress the untoward reaction. He tolerated dystrin for a few months, then he refused it, due to a phobia of a reaction. He tolerated PAS for three weeks, then he discontinued it, due to gastrointestinal symptoms. Isoniazid 100 mg.m. l.d. was taken with impunity. He had continued to isoniazid as his sole antituberculous agent.

Shortly after steroid therapy was started, his depressed mood had reverted to a cheerful optimistic attitude. His dysphagia and sore throat promptly disappeared. The cough and sputum diminished. His appetite became ravenous and he gained fifty pounds in four months. The fever subsided by lysis and remained normal. The blood pressure rose from the hypotensive level of 90/70 to 140/70 in a short time. The total eosinophil count dropped from 660 to 100 with suppression of his symptoms. The undesirable side effects of steroid therapy were minimal due to careful attention to the sodium and potassium electrolyte balance. He signed a release from the hospital March 1, 1956, but he continued with isoniazid on an outpatient basis. He was readmitted on April 20, 1956 for the evaluation of an episode of blood streaked sputum that occurred subsequent to strenuous exertion. The clinical course during this admission was satisfactory. He was discharged on July 3, 1956 to the outpatient department for follow-up care. The sputum was converted to negative January 1957 and the pulmonary tuberculosis is arrested 21 months post-steroid therapy (July 1957). (Fig. 2 and Chart 2.)

Case 2: Summary: A case of far advanced active pulmonary tuberculosis with untoward drug and symptomatic agents. He is in both antimicrobials and symptomatic agents. He has undergone an acute generalized exfoliative dermatitis due to an injection of dystrin, a bout of fever and pruritic rash due to isoniazid, gastrointestinal reaction due to PAS and toxic reaction due to Stokes expectorant. With the combined use of steroid and antituberculous agents the following results occurred: A—Improved tolerance to dystrin. B—Disease toxicity arrested. C—Improved tolerance to symptomatic drugs. D—Conversion of the sputum from positive to negative on culture, twelve months after steroid therapy. E—Regression of the pulmonary lesion with arrest of the disease. F—With the continued use of a single antimicrobial agent, isoniazid, this patient made an excellent clinical recovery to date.

Case 3: J. A. F., a 66 year white man, was admitted to the hospital on March 3, 1959 with the diagnosis of far advanced active pulmonary tuberculosis. He was given dystrin, isoniazid and PAS. Following six weeks of treatment, he noticed a pruritic eruption on his hands and face. This rash would subside when dystrin was withdrawn and recur when it was resumed. These remissions and relapses of pruritic rash typified his clinical course at the hospital. He later developed a lichenified eruption of his face and an extensive crusting, scaling dermatitis on his scalp. He also endured gastrointestinal symptoms to PAS. As the time of his discharge approached, it was urgent to suppress the drug rash, to enable the maintenance of an adequate chemotherapeutic regimen on an outpatient basis.

Steroid therapy was initiated on June 25, 1955 and was completed on August 4, 1955. Rash suppression was accomplished with ACTH-gel 80 units q. day, as his initial minimum dose, plus pyribenzamine 100 mg.m. q.i.d. and hydrocortisone ointment locally, as supplements. As the eruption subsided he gained five pounds. A peptic ulcer diagnosed thirty years ago was not reactivated by the steroid therapy. Sputum cultures for tubercle bacilli have been negative until the present time, July 1957, except for a single positive culture on September 27, 1956. His last chest x-ray, April 30, 1957, shows a

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residual bilateral productive inactive process with considerable shrinkage of the right upper lobe and associated post-tuberculous bronchiectasis and emphysema. Twenty-four months post steroid therapy, July 1957, the clinical condition of the patient is good. After 13 months treatment with isoniazid 100 mg. i.d. and dystricin 1 gram b.i. weekly, he sustained a reaction thirty minutes after an injection of dystricin. This consisted of ambipoyia for five minutes, generalized aches, malaise and anorexia. Consequently he refused dystricin injections, but has continued with isoniazid as the sole therapeutic agent. (Fig. 3 and Chart 3.)

Case 3 Summary: Case of far advanced pulmonary tuberculosis with a pruritic eruption due to dystricin, gastrointestinal intolerance to PAS and a past history of peptic ulcer which was treated with combined steroid and antimicrobial therapy. The following results were obtained: A—Tolerance to dystricin for thirteen months. B—No re-activation on his peptic ulcer. C—No untoward effect of steroid therapy on the pulmonary lesion. D—Prompt clearing of the drug eruption.

Case 4: P. D. F., a 61 year old white man, was admitted on May 6, 1955 with an infiltration in the left upper lung field. The sputum was negative on culture both on admission and discharge. He was given dystricin and PAS. After several weeks, due to gastrointestinal intolerance, PAS was replaced by isoniazid. On or about June 14, 1955 he had chills and fever succeeded shortly by a severe pruritic maculopapular rash. At this time, all therapy was suspended and an antihistamine was given for symptomatic relief. Nevertheless, the fever persisted and the eruption spread to both ears, both antecubital areas, both inguinal areas and the anterior aspect of the thorax and the abdomen. The regional lymph nodes draining these respective areas were enlarged and tender. The skin and sclera were icteric. At the height of this reaction, ACTH-gel 80 units q. day was started on July 14, 1955. There was a prompt amelioration of this reaction. Subsequently he swallowed a single 0.5 gram tablet of PAS. This caused an immediate rash, fever and jaundice. This reaction was again controlled by steroid medication. Steroid therapy was terminated on November 5, 1955. He was discharged December 23, 1955 to the outpatient department for follow-up care. Here he was continued on dystricin and isoniazid without untoward effects. At the present time, July 1957, twenty-six months post-steroid therapy, his sputum remains negative on culture and the left upper lung infiltrate which has regressed, continues unchanged and inactive. His clinical condition remains good. (See Fig. 4 and Chart 4.)

Case 4 Summary: Case of pulmonary tuberculosis with an untoward reaction to PAS, manifested by rash, fever and hepatitis. The results accomplished were: A—Prompt disappearance of drug reaction. B—Pulmonary lesion promptly receded. C—No adverse effect on the pulmonary tuberculosis, twenty-six months subsequent to the use of steroids. D—Excellent clinical condition.

Case 5: P. C., A 60 year old white man was admitted for the third time on April 27, 1955 with far advanced pulmonary tuberculosis. On admission, he was placed on dystricin and isoniazid. His clinical condition progressed satisfactorily for six months, including resorption of some of the pulmonary infiltration. During October 1955 he noticed the onset of a pruritic vesicular eruption over both hands. This rash became worse after each injection of dystricin and itched more at night. The lesion advanced to a marked exudative state, associated with numerous traumatic linear excoriations and a profuse seropurulent discharge. Simultaneously a quiescent seborrhoeic scalp dermatitis became reactivated.

P. C.'s initial minimum dose required to suppress the reaction with ACTH-gel 80 units q. day started on December 18, 1955. This was supplemented with benadryl 100 mg. q.i.d. and hydrocortisone ointment locally, to maintain the ACTH-gel dose at 80 units q. day. The steroid medication was terminated on January 16, 1956 and the dermatitic reaction was also completely ameliorated at this time. He was discharged from the hospital on July 26, 1956 with a negative sputum on culture, which was also negative on admission to the hospital. His pulmonary tuberculosis has remained unchanged as observed on serial x-ray films and fluoroscopic examinations in the year following hospital discharge. His peptic ulcer, noted thirty years ago, has remained quiescent to date. At the present time, July 1957, his clinical condition remains satisfactory. Dystricin was tolerated for eighteen months post-steroid, but was discontinued July 1957 due to recurrence of untoward skin reaction. Isoniazid is tolerated satisfactorily to date. (Fig. 5 and Chart 5.)

Case 5 Summary: Case of far advanced pulmonary tuberculosis with an untoward reaction to dystricin consisting of a pruritic eruption. The results obtained with the therapy outlined above were: A—Tolerance to injections of dystricin for eighteen months. B—Maintenance of negative sputum cultures. C—No exacerbation of the tuberculous disease on x-ray, but on the contrary, regression and stabilization. D—Quiescence of a peptic ulcer diagnosed thirty years ago.

DISCUSSION

The combined use of steroids (supplemented by antihistamines and hydrocortisone ointment locally in three instances) and antimicrobial agents in four cases of far ad-
vanced and one case of moderately advanced pulmonary tuberculosis appears to have produced a prompt salutary effect in extinguishing the drug reaction (pruritic rash, angioedema, fever and hepatitis) and disease toxicity (cough, expectoration, anorexia, fever and malaise) simultaneously. There was regression of tuberculous exudative and recent infiltrative lesions. The mechanism of the steroid anti-inflammatory action is due to its non-specific interruption of the chain reaction of cell destruction triggered by the injurious stimulus of disease toxicity or untoward drug reaction. The anti-inflammatory effects require high unphysiologic concentrations of circulating hormone. This action occurs at the cell level. Any type of inflammatory cell reaction to injury is modified, irrespective of the cause. It prevents the release and enhances the removal of noxious substance from injured cells. Destructive changes in and around the cell are prevented, and up to the state of necrosis, the damage is reversible. It is noteworthy that a giant antrum in Case 1 was not visualized on x-ray films subsequent to the use of steroid. Positive sputum cultures in Cases 1 and 2 were converted to negative cultures. In the remaining three cases, negative sputum cultures at the onset of the above therapy regimen have remained negative. These cases have now been observed from twenty-one to 26 months subsequent to steroid therapy by serial x-ray films of the chest and sputum cultures. No adverse effect on the pulmonary tuberculous disease has been noted to date.

The undesirable effects of high steroid dosage required to suppress the inflammatory response were of minor significance. The steroids were employed in doses sufficient to reduce the total eosinophils by more than fifty per cent. In two cases with peptic ulcer history, there was no evidence that the use of steroid drugs resulted in any reactivation of the ulcer. In Cases 1 and 2 the use of steroids did result in slight sodium and water retention, easily controlled by low sodium diet and the administration of potassium tablets.

It has been reported that the combined use of steroids and antibacterial agents in unusually severe infections has resulted in significant reduction in morbidity and mortality. The combined use of steroids and isoniazid in tuberculous meningitis decreased the morbidity and the mortality of this complication, according to Shane and Riley. However, documented reports of reactivation of latent tuberculous foci, attributable to the prolonged use of steroids in arthritis, deterred their administration in selected cases.

If one may postulate that tuberculous disease toxicity and untoward drug reaction are both manifested through the common channel of inflammatory response, then the steroid hormones which are notably anti-inflammatory, antitoxic and anti-allergic should be beneficial when employed for this coexistent condition. This has been true in five cases cited here. The observation that untoward drug reactions in these cases were manifested by pruritic dermatitis suggests a hypersensitivity mechanism in their formation. A positive skin test for streptomycin was elicited in Case 1. Skin tests were not performed in the remaining cases. In Cases 1 and 5, it is of interest to note that marked reduction in untoward drug reactions to dystricin permitted usage of dystricin for an additional eighteen months. Case 2 had untoward drug reactions to all antimicrobial agents. After steroids he could take isoniazid and dystricin. Untoward drug reaction to dysstricin in Case 3 was reduced by steroid to permit its further use for thirteen additional months. Case 4 had an untoward response to PAS that subsided on steroids. But the gravity of the hepatic reaction, while under steroid hormones, in response to an oral rest dose, reminded one of an anaphylactic reaction. In this instance, PAS has been avoided for the safety of the patient.

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SUMMARY

This is a report of five cases of active pulmonary tuberculosis with coexistent untoward drug reactions to one or more antituberculous agents, who were treated by combined steroid and antimicrobial therapy. The impressive results obtained were markedly superior to the previous medical regimen. There was no injurious effect on the underlying tuberculous process, as noted on serial x-ray films of the chest and sputum cultures over a period of twenty-one to twenty-six months following steroid treatment. The steroids are a potent of the clinician in treating tuberculous patients who manifest untoward drug reactions to the chemotherapeutic agents. However, one must be alert to the side effects and physiologic effects of the steroids which may be injurious to the patient.

RESUMEN

Esta es una descripción de cinco casos de tuberculosis pulmonar activa con coexistencia de reacciones a una o más de las drogas antituberculosas. Los resultados obtenidos fueron marcadamente superiores a los del régimen médico previo. No hubo mal efecto
en las lesiones tuberculosas subyacentes según se observó a la radiografía y por los cultivos de esputos por un período de 21 a 26 meses después del tratamiento con esteroides.

Los esteroides son un agregado potente al armamentario del clínico que trata tuberculosis con reacciones colaterales a las drogas. Sin embargo hay que estar pendiente de otros efectos así como de los fisiológicos de los esteroides que pueden dañar a los enfermos.

**RESUME**

L’auteur rapporte cinq cas de tuberculose pulmonaire active avec des réactions d’intolérance à l’égard d’un ou de plusieurs agents antituberculeux, qui furent traités par la thérapeutique antimicrobienne et la cortisone associée. Les résultats significatifs obtenus furent notablement supérieurs à ceux du programme médical antérieur. Il n’y eut aucun effet toxique sur l’évolution tuberculeuse sous-jacente, comme il fut noté d’après une série de clichés radiologiques du thorax et des cultures d’expectoration pendant les 21 à 26 mois qui suivirent le traitement par la cortisone. La cortisone représenta un complément puissant de l’armement du clinicien dans le traitement des réactions d’intolérance aux agents thérapeutiques. Cependant, on doit être averti des effets secondaires et des effets physiologiques des corticoides, qui peuvent être toxiques pour le malade.

**ZUSAMMENFASSUNG**


**REFERENCES**