Long Term (Five or More Years) Administration of Corticosteroids in Pulmonary Diseases*

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Experiences all over the world have proved the value of corticosteroids in the treatment of pulmonary diseases, including tuberculosis. In 1958, having reported extensively on our work with these drugs, we recommended using corticosteroids for the shortest period necessary to obtain the desired effects. These are potent metabolic agents, and this recommendation still is a good one. However, a number of patients have clinical remissions when the corticoids are reduced too much or are discontinued. This group included patients with pulmonary tuberculosis, chronic, severe, allergic bronchitis, pulmonary fibrosis (specific and non-specific), lupus erythematosus, and pulmonary emphysema. In view of these relapses, it was necessary to resume corticoid therapy, in an attempt to control the patient’s symptoms.

Purpose of Study
The opportunity of following 47 patients on 4 to 12 mg. triamcinolone for five to eight years allowed us to evaluate long term clinical effects, both beneficial and undesirable side reactions.*

Plan of Study
This report is of a group of 47 patients, including 24 pulmonary tuberculosis, 11 chronic allergic bronchitis, three men with pulmonary fibrosis (two Hamman-Rich syndrome and one Loeffler’s syndrome), one lupus erythematosus, and eight patients with chronic pulmonary emphysema. There were 34 men and 13 women, varying in age from 37 years to 73 years; 34 Caucasians, 11 Negroes, and two Orientals.

All of these patients had been hospitalized during their acute illness, at which time, in addition to chemotherapy, they received corticosteroids (in this series triamcinolone [Kenacort]). Initially, dosage varied from 32 to 40 mg., gradually reduced to maintenance dose of 2 to 8 mg. daily. When this maintenance dose was reduced or the triamcinolone was discontinued, a clinical relapse was noted within two to eight days in these 47 patients. One hundred forty-three other patients of the original 190 patients in this study group were able to discontinue their corticosteroid therapy completely without adverse reactions.

All of the 47 patients had had beneficial clinical effects from the corticosteroids—since any who had undesirable side effects or no clinical improvement had been eliminated from this study. These patients served as their own double controls, since they had been followed before receiving corticoids, when they received larger doses of these drugs, and in this study on long term maintenance therapy. The long term maintenance dose of 2 to 8 mg. was administered once daily after breakfast to 41 of the 47 patients.*

Results
Pulmonary Tuberculosis—There were 24 patients with chronic disease, who were not getting any better, nor any worse—who had intermittent positive sputa, and x-ray evidence of active tuberculosis—on triamcinolone and antituberculosis chemotherapy. There had been a definite weight gain, improved mental outlook, and x-ray evidence of improvement. These beneficial effects continued in all but two patients, who died. One had a massive pulmonary hemorrhage after five years and three months,
and the other had an acute anterior coronary infarction as he began his sixth year of corticosteroid therapy.

Chronic Severe Allergic Bronchitis—The 11 patients studied all had multiple perennial allergies. They had had desensitization regimens and antihistamines, prior to being treated with corticosteroids. This group had beneficial effects with control of acute symptoms, but as the dosage of triamcinolone was reduced, attacks of wheezing and dyspnea recurred. A number of patients, not included in this study, were controlled with corticosteroids during their attacks, and did not require long term therapy. On maintenance dosage, 2 to 8 mg. daily, they were generally controlled. When the patient was exposed to a high concentration of the offending allergen, there was an exacerbation, relieved with increased dosage for two to three days. Then the drug was decreased to maintenance dose. One of the patients moved to Arizona after five years of triamcinolone therapy.

Pulmonary Fibrosis, including Lupus Erythematosus—Among the three patients with pulmonary fibrosis and one with lupus erythematosus with pulmonary involvement, there had been marked x-ray clearing and symptomatic improvement with triamcinolone (plus “prophylactic” isoniazid). As the corticosteroid was reduced, within one week cough returned, dyspnea recurred and in one patient who was without triamcinolone for three weeks, there was evidence of pulmonary infiltration. All four patients have been maintained on 2 to 6 mg. triamcinolone daily for five years and six months to seven years (Fig. 1).

Pulmonary Emphysema—Although the value of corticosteroids alone in the treat-
ment of pulmonary emphysema is equivocal, when combined with other measures, it is often excellent adjunct therapy. Among a group of 47 patients who had bronchoscopic drainage, autogenous vaccines, intermittent positive pressure breathing, antibiotics, breathing exercises, with triamcinolone, there was subjective and objective improvement. There were eight patients in this group who showed evidence of relapse when triamcinolone was discontinued although other therapy was maintained. These patients were supported on 2 to 8 mg. triamcinolone daily for five to eight years, with good symptomatic control.

The following chart (Table 1) compares side effects on short term (60 day) and long term (five to eight years) treatment with corticosteroids. Of greatest interest is the large number of patients exhibiting moon faces (Cushingoid syndrome), the one fatal pulmonary hemorrhage and the one almost silent coronary infarction.

In view of the reported high incidence of osteoporosis with chronic corticoid therapy, all patients were maintained on a high protein diet with adequate fluid intake. At the onset of this study, 20 patients served as controls while 27 others received anabolic steroids\(^*\) (combination of androgen and estrogen). Twelve of the 20 controls showed clinical and/or x-ray evidence of osteoporosis while only one of the 27 receiving anabolic steroids had evidence of osteoporosis. One patient, not included in this study, who was taking corticosteroids without supervision, developed marked osteoporosis (Fig. 2).

**Conclusion**

Long term, maintenance or supportive (2 to 12 mg. daily) treatment with corticosteroids is often necessary to maintain symptomatic improvement. In this study, we found the same clinical action whether the corticoid was given once daily, or in divided doses. This tends to confirm the recent report of Demos, et al.\(^*\) on once daily therapy.

The beneficial effects can be complicated by undesirable side reactions. For supportive and prophylactic care, all patients were on high protein diets (re: osteoporosis); in between feedings, milk, etc. (re: ulcer); adequate water intake (avoiding a concentrated urine with hypercalciuria); isoniazid 100 mg. three times a day (against reactivating tuberculosis) with regular complete examinations, including laboratory evaluation. The concurrent administration of anabolic steroids (androgen and estrogen) has been shown to control osteoporosis. Unfortunately, the moon faces often appear early in the course of treatment and persist in a large group of patients.

Finally, the corticosteroids are potent, effective drugs for acute and chronic pulmonary diseases. They should be used with discretion, when indicated, under close clinical supervision.

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**Table 1—Summary of Side Effects with Corticosteroid Therapy**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>30 Patients</th>
<th>47 Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moon face</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td>Hirsutism</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Acne</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anorexia</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Emotional disturbance</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Weakness</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Edema</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Glycosuria</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gastro-intestinal symptoms</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Weight loss</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Ecchymoses and/or purpura</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>0</td>
<td>12*</td>
</tr>
<tr>
<td>Peripheral neuritis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reactivated tuberculosis</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

\(^*\)out of 20 patients.

\(^*\)out of 27 patients, also received anabolic hormones.
ACREMKNOWLEDGMENT: I wish to acknowledge the cooperation of E. C. Reifenstein, Sr. and C. H. Demos of the Squibb Institute for Medical Research.

CONCLUSION

El tratamiento a largo plazo con dosis de mantenimiento de corticoestroides (2 a 12 mg. diarios) es frecuentemente necesario para mantener la mejoría sintomática. En nuestra experiencia hemos observado idéntico efecto clínico con dosis unicas o fraccionadas, lo que tiende a confirmar los observaciones de Demos et al. con el método de dosis unica diaria.

Los efectos beneficiosos pueden aparecer acompañados de efectos secundarios indeseables. Todos nuestros casos en curso de tratamiento profilático o de mantenimiento recibían una dieta hipoproteínica (para contrarrestar la tendencia a la osteoporosis) tomas de alimento leche etc. entre comidas (ulceras) y adecuada cantidad de líquidos (para evitar la concentración urinaria con hipercalcemia) a más de hidratación del acido isonicotínico (INH) 100 mgm. tres veces al día (para prevenir las reactivaciones tuberculosas). Eran además sometidos a examenes clínicos a intervalos regulares, incluyendo pruebas de laboratorio. La administracion concurrente de esteroides anabolicos (androgeno y estrogeno) es de reconocido efecto para la prevencion o control de la osteoporosis. Es de lamentar que la "cara de luna" aparece con frecuencia en el curso del tratamiento y persiste en muchos casos.

Los corticoestroides son agentes potentes y efectivos en el tratamiento de la tuberculosis aguda o crónica. Su empleo sin embargo requiere discreción, indicaciones precisas y supervisión clínica estrecha.

ZUSAMMENFASSUNG

Die Dauerbehandlung auf lange Zeit oder Behandlung auf supportiver Basis (2 - 12 mg. pro Tag) mit Corticoestroiden ist oft erforderlich, um eine symptomatische Besserung aufrecht zu erhalten. Bei unserer Untersuchung fanden wir den gleichen klinischen Effekt unabhängig davon, ob das Corticoid einmal am Tag oder in gleichen Dosen mehrmals über den Tag gegeben wurde. Diese Beobachtung spricht im Sinne einer Bestätigung eines kürzlichen Berichtes von Demos und anderen über eine Therapie einmal am Tag.

Der nützliche Effekt kann aber durch unerwünschte Nebenwirkungen kompliziert werden. Bei einer supportiven und prophylaktischen Behandlung wurden alle Patienten auf eine proteinenreiche Diet gesetzt (bezügl. Osteoporose); zwischen den Mahlzeiten wurde Milch usw. gegeben (bezügl. Geschwürsbildung); entsprechende wasserzufuhr (zur Vermeidung eines allzu konzentrierten Urins mit Hypercalcurie); INH 100 mg täglich (gegen eine Reaktivierung der Tuberkulose); mit regelmäßigen kompletten Untersuchungen einschliesslich Laboratoriumsstest.

Die gleichzeitige Verabfolgung von anabolenen Steroiden (androgen und estrogen) hat gezeigt, daß sich eine Osteoporose verhüten läßt, wenn sich eine solche entwickelt und daß sie von definitiven Wert ist zur Verhütung derselben. Leider trat oft ein Mondgesicht schon frühzeitig im Behandlungsverlauf auf und blieb auch bei einer großen Zahl von Patienten bestehen.

Die Corticoestroiden sind wirksame effective Medikamente bei akuten und chronischen Lungenerkrankungen. Man muß sie mit sorgfältiger Auswahl geben, wenn sie indiziert sind, und unter engster klinischer Überwachung.

REFERENCES


8 Reifenstein, E. C., Jr.: Symposium on Adrenal Corticoid Therapy, Metabolism, "Control of Corticoid-Induced Protein Depletion and Osteoporosis By Anabolic Steroid Therapy," Metabolism, 7:78, 1958.