STEROID THERAPY IN SERIOUS INFECTIOUS DISEASES

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(Received for publication October 30, 1961)

INTRODUCTION

There have been numerous reports in recent years describing the marked beneficial effect of steroid hormones (S.H.) used in conjunction with antibiotics in the treatment of certain infectious diseases. There has been much discussion about the rationale of this combined steroid-antibiotic therapy. Antibiotics which act specifically against the offending organism is the ideal therapy. Antibiotics, though they may be bacteriostatic or bacteriocidal in action, have no direct effect on the inflammatory reaction. S.H. on the other hand do modify the inflammatory reactions of infectious disease. It is in those infectious disease with overwhelming systemic effects where S.H. may be of great value.

It is the purpose of this paper to report the experiences of the author in the use of combined steroid-antibiotic therapy in serious infectious disease treated subsequent to 1956.

MECHANISM OF ACTION

The effects of S.H. on infectious diseases are very complicated and there are still many indefinite points about them. The chief factor of them is an anti-inflammatory action of gluco-corticoid which is contained in S.H. themselves. On the other hand, we should never forget that this action weakens the defense mechanism for host vitality at the same time. This would make the use of S.H. difficult. Since it is not the purpose of the paper to report the mechanism of the action in detail, the author will only give a glimpse of this.

The action of S.H., especially glucocorticoid, in the process of inflammation, refrains the action of hyaluronidase, defends catabolic action of protein by fibrinolysin, streptolysin and so forth, promotes depolymerisation of cell-stroma, depresses exudation, makes cell-stroma compact and defends tissue from many

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kinds of toxin. That is to say, it exhibits so called antitoxic action, establishing a defensive wall between toxin and tissue. As it raises the tension of peripheral blood vessels and reduces the permeability of them, it defends a fall of blood pressure. That is the reason why it exhibits antishock effects for shock based on collapse of peripheral blood capillaries. In this case, some authors say that it strengthens the sensitivities of blood vessels for vasoconstrictive like adrenalin or noradrenalin. Moreover, it has an anti-allergic action in relation to the above mentioned actions. So it has positive effects on all kinds of allergic diseases and drug-allergy which contain allergy for antibiotics and besides, it has strong influences on great changes of allergic conditions. For instance, a strong infectious allergy such as pleurisy or allergic conditions or such as sepsis and miliary tuberculosis.

As above mentioned, it beneficially influences infected host, but, on the other hand, since it refrains leukocyte-moving, phagocytosis of granulocytes, and bacteriocidal-action of leukocytes, germs in host would freely proliferate and so asymptomatic bacteremia or sepsis would arise with a decrease of functions of reticulo-endothelial system (R.E.S.).

Moreover, the quantity of gamma-globulin would fall because of a disturbance of gathering of plasma cells and lymphocytes in foci, therefore, the tendency of inhibition for antibody-producing is generally recognized. Since disturbance of fibrocytogenesis of fibroblast causes the inhibition of fibrosis and granulation-tissue-formation, and this fact would be favorable for defending the cerebrospinal fluid block in meningitis and adhesion of pleurisy, it causes retardation of wound healing.

As there are many discussions about above mentioned actions, it is difficult that these are recognized as theories. However, the authors consider that they are certainly favorable for understanding anti-inflammatory actions of S.H.

The effects of S.H. on general infectious diseases are as above mentioned. In the cases of serious infectious diseases, we should attach importance to anti-inflammatory action which contains anti-shock, anti-toxic, and anti-allergic action. About unfavorable effects on host-vitalities, there is no need for considering carefully the inhibiting action of antibody-producing, and we should consider the depression of functions of R.E.S. and also decrease of phagocytosis and bacteriocidal ability of leukocytes as the most important factor. We cannot expect to minimize bad effects of S.H. on host-vitalities without the use of antibiotics. If we would use S.H. with antibiotics, we would be able to expect very highly the anti-inflammatory action of S.H. without depression of host resistance against infections agents.
In serious cases, we are really interested in those results which 17-OHCS of blood has often shown high level or the upper part of normal in the results of animal experiments and clinical cases. That is to say, it should be considered that the adrenal cortex has beneficial functions even in serious infectious diseases.

Inferences about this are as follows:

1. Insufficiency of adrenal cortex is rare.
2. It is disturbed that S.H. invades into cells.
3. The blood level of S.H. shows high, because it is difficult to come into tissue from blood. So it should be considered that there would be the disturbance of utilizing for S.H. in the peripheral tissue.
4. Although 17-OHCS has shown high level in blood, it has been very low in urine. What is the conclusion? Wouldn't it be excreted into urine because of indefinite analysis in spite of prosperous producing of it, or would S.H. remain in tissue?
5. The ability of decomposing S.H. falls in liver and so forth. However, the last conclusion has not been varified yet. The concentration of 17-OHCS is enough in blood. However, administration of S.H. strongly influences hosts.

The reasons are as follows:

(a) If the blood concentration of S.H. should happen to be over a certain limit after administering it, it would be permitted to come into tissue or cells.

(b) Exogenous S.H. is a little different from endogenous S.H. which hosts hold. In the conditions which the utilizing of the latter is disturbed and the former could be used, as soon as the former begins to be utilized the latter then becomes to be able to be utilized.

(c) It is known that blood concentration of S.H. is generally rather high in serious infectious diseases. However, it is considered that it is not so sufficiently high in conditions like that. Therefore exogenous administration is effective. These, however, are only inferences. The authors understand that although they don't ignor the replacement in the meaning of (c), above mentioned, a large amount of S.H. should be administered in the pharmacological meaning in spite of the conditions of S.H. from internal cause. It should be rather considered that a great amount of pharmacological administrations hold as incidental a meaning of replacement in addition to it under the circumstances of (c).
CASE REPORTS, INDICATION AND CONTRAINDICATION

1) Case Reports

The authors have treated 192 cases with combined therapy. These are tabulated in the table. It was effective in 89 cases.

Steroid Therapy in General Infectious Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Case</th>
<th>Effective Case</th>
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</thead>
<tbody>
<tr>
<td>Scarlet Fever</td>
<td>70</td>
<td>0</td>
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<tr>
<td>Typhoid Fever</td>
<td>7</td>
<td>6</td>
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<tr>
<td>Meningitis</td>
<td>18</td>
<td>13</td>
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<tr>
<td>Pneumonia</td>
<td>14</td>
<td>12</td>
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<tr>
<td>Subacute Bacterial Endocarditis</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Sepsis</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Cholangitis &amp; Cholecystitis</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td>Well's Disease</td>
<td>3</td>
<td>1</td>
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<tr>
<td>Hepatitis</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Empyema</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Liver Abscess</td>
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<tr>
<td>Bronchiectasis</td>
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<td>1</td>
</tr>
<tr>
<td>Bronchial Fistula</td>
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<tr>
<td>Bronchitis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
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</tr>
<tr>
<td>Surgical cases</td>
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<td>4</td>
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<tr>
<td>Others</td>
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<td>13</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>192</strong></td>
<td><strong>89 (46.4%)</strong></td>
</tr>
</tbody>
</table>

Case 1. Streptococcal meningitis:—This 35 years old male had meningitis due to a hemolytic streptococcus with the primary lesion in the sinus. Combined therapy with penicillin and streptomycin was ineffective. The addition of 30 mg of prednisolone daily brought about a prompt and dramatic drop in the temperature and relieving of many symptoms. A total of 380 mg of prednisolone was used during a period of 19 days. The patient recovered fully without any residue.

Case 2. Meningococcal meningitis:—Penicillin, streptomycin, tetracyclin, and chlortetracyclin were ineffective in this 15 years old male. Combined therapy with streptomycin and 100 mg of cortisone was effective. A total of 300 mg of cortisone was used during a period of 11 days. The patient recovered fully without sequel.

Case 3. Staphylococcal meningitis:—Streptomycin, penicillin and tetracyclin were ineffective in this 48 years old female, but the addition of 30 mg of prednisolone resulted in a prompt defervescence. A total of 210 mg of prednisolone was used during a period of 12 days. The patient remains well without side-effects.

Case 4. Septicemia:—This 47 years old male was admitted with acute septicemia with chills and fever. Causative organism was not isolated inspite of frequent blood cultures. Penicillin, streptomycin were ineffective. However the addition of predni-
solone brought about a prompt symptomatic response. 160 mg of prednisolone were used during a period of 16 days.

Case 5. Pneumococcal pneumonia:—This 45 years old male was admitted with right lobar pneumonia with high fever, severe back pain and prostration. Combined therapy with penicillin and 30 mg of prednisolone brought about a prompt defervescence and marked symptomatic improvement. 230 mg of prednisolone was given over a period of 11 days.

Case 6. Pneumococcal pneumonia:—This 50 years old male was treated with penicillin and streptomycin with no effects. The addition of 30 mg of prednisolone resulted in prompt symptomatic improvement. The total amount of prednisolone given was 340 mg over a period of 23 days.

Case 7. Tuberculous caseous pneumonia:—This 23 years old male with caseous pneumonia was treated with streptomycin and isoniazid (INH). The fever did not subside until prednisolone was added to the regimen. Total 530 mg of prednisolone was given over a 26 days period.

Case 8. Far advanced pulmonary tuberculosis:—This 31 years old male with far advanced pulmonary tuberculosis with a large cavity was treated with streptomycin, INH, and prednisolone. When the latter was discontinued, the fever recurred. Readministration of prednisolone had no effect on the fever which was subsequently discovered to be due to a staphylococccic septicemia. The latter responded to therapy with penicillin and oleandomycin. This case is illustrative of the masking of symptoms of severe infection by steroids.

Case 9. Miliary Tuberculosis:—This 20 years old female with continuous high fever was thought to have typhoid fever. Chloramphenicol was begun but had no effect on the fever. Addition of cortisone in the dose of 100 mg daily brought about defervescence. When the dose was reduced to 50 mg, the fever recurred. Chest X-ray at this time revealed miliary tuberculosis. This patient clinical course was aggravated by steroid therapy because anti-tuberculous chemotherapy was not instituted at the same time.

Case 10. Fever of Unknown Origin:—This 15 years old female with sore throat and fever was treated with penicillin and streptomycin. The fever did not subside. Steroid was added to the therapeutic regimen with temporary defervescence. The patient took a downhill course and at autopsy was found to have a necrotizing rhinitis.

Case 11. Subphrenic abscess:—This 41 years old male with subphrenic abscess was so febrile and toxic that it was felt that he could not withstand surgery. Combined therapy with streptomycin and erythromycin had no effect. The addition of prednisolone resulted in prompt defervescence and decrease in toxicity that surgical drainage could be performed. A total of 175 mg of prednisolone was given over a 10 days period.

Case 12. Acute pancreatitis:—This 56 years old male had a stormy post operative course after laparotomy with hypotension, ileus, and abdominal distension. There was dramatic improvement following the administration of cortisone in a dosage of 100 mg daily for 7 days.

Case 13. Peritonitis secondary to perforated peptic ulcer:—This 57 years old male was operated on for a perforated gastric ulcer. His post-operative course was
characterized by ileus, distension and debility. Prednisolone was given in addition to streptomycin and penicillin and resulted in dramatic improvement of all symptoms. The patient developed subcutaneous abscesses due to staphylococcus resistant to penicillin and streptomycin.

Case 14. Acute pancreatitis:—This 30 years old male had a stormy post-operative course following laparotomy. He was treated with combination of antibiotics and 200 mg cortisone daily with temporary amelioration of symptoms. He died after reoperation.

Case 15. Empyema:—This 54 years old male had empyema with chest pain, high fever and other toxic symptoms. There was no response to antibiotics. After prednisolone in the dose of 30 mg daily was added, there was prompt reduction in the toxic symptoms. On intercostal tube was placed for drainage and following this the patient developed acute adrenal insufficiency and the patient died. Since prednisolone had been given in dosage of 170 mg for 22 days, it was natural that S.H. had to be used before operation as well as in case 14. In the case that considerable amount of S.H. has been already used, S.H. should be given in addition to antibiotics before the operation.

2) By looking over the cases above mentioned, we can understand easily that S.H. has wide non-specific effects on serious infectious diseases.

S.H. would be effective on the poor conditions in which patients are inoperable despite the necessity of urgent operation in serious infectious diseases and it seems to be effective also for improving the postoperative poor conditions.

However, we should not forget that it has not the indication of being effective against all kinds of serious infectious diseases, but rather indicates effectiveness under certain important conditions.

It should be primarily indicated to infectious diseases to which antibiotics are effective. That is to say, it must be infectious diseases which respond very much to antibiotics. So it is not suitable for infectious diseases which would be caused by organisms that have no response to antibiotics or by organisms which have acquired resistance to antibiotics.

It should not be abused for serious infectious diseases with high fever of unknown origin. However, when the patient has become weaker and is critically ill with the lasting high fever, and shows no response to all kinds of antibiotics, S.H. would be permissible for a brief time. In this case, it is just the same as case 10 that we should take care of general condition of patients even if the fever would disappear.

It should be considered that combination therapy is contraindicated to definite mental disease, active stage of peptic ulcer, moderate or severer diabetes and severe cardiac and renal insufficiency.

Cases which are caused by organism acquired resistance to antibiotics, in
the infectious disease are accompanied by contraindications, above mentioned.

3) The combination therapy

Ideal methods of administration: The authors will mention the methods of administration and some cautions, referring to clinical experiences and results of animal experiments of them, and furthermore to domestic and foreign literatures.

(a) S.H. should always be used with those antibiotics which are favourable to the infectious diseases and, in that case, antibiotics should be used much more than in the single use of them. If S.H. would be singly used in infectious diseases, it would bring up the possibility of exacerbation of the diseases or sepsis even though the remission would appear transient. When the selection of the antibiotics would be inadequate to the infectious diseases, (for example in case 9), there could be such risks as in the single administration of S.H. Administrative doses of antibiotics, following the results of experimental infectious diseases by the authors should be increased a little more in the case of combination of S.H. and antibiotics than in the case of single use of them.

(b) At the institution of the therapy, antibiotics should be used with S.H., and at the termination, it would be used 5 to 7 days longer after discontinuing the administration of S.H.

Since the anti-inflammatory action of S.H. remains for some days after discontinuing it, there could be risks of relapse of remained foci when S.H. and antibiotics are discontinued concomitantly. Following the experimental results of the authors, it has been clearly recognized that there have been much more bacteria in the foci in the groups which antibiotics and S.H. were discontinued simultaneously than in groups which antibiotics were used for a long time.

Kinsell, Montgomery and Weissbecker recommend that antibiotics should be used for three days after discontinuing to administer S.H. Whenever S.H. is used for more than 3 weeks, 40 units of ACTH-Z is intramuscularly administered about three times for the purpose to prevent the atrophy of adrenal cortex. But some insist that such doses and times as this are ineffective.

(c) The daily dosage of S.H., especially Prednisolone, is initially 30 mg (Triamcinolone, Methyl-Prednisolone 24 mg, Dexamethasone 4.5 mg, Paramethasone 6 mg) and is reduced by 5 mg (Triamcinolone, Methyl prednisolone 4 mg, Dexamethasone 0.75 mg, Paramethasone 1.0 mg) every 2 or 3 days, and it is administered for about 2 weeks.

The authors usually administer 30 mg of Prednisolone for three days, and if there were no effect, would discontinue Prednisolone immediately and double
the dosage of antibiotics, change the drugs or add others. If, by the change of antibiotics and so forth, there would be effective, it is considered to reuse S.H. There is a remission of subjective and objective symptoms by the administration of 30 mg of Prednisolone, but if it would be incomplete, it is an idea to increase a daily dosage of Prednisolone to 40–50 mg. The reduction of S.H. is, as a rule, about 5 mg every 2 or 3 days. However, since there would be a relapse of the disease which contains pyrexia and so forth when it is too quick to reduce S.H., it is better to reincrease S.H. immediately and reduce it after a remission of symptoms.

It is difficult to decide a period of combination-therapy, but the nature of hormonal therapy is to get a “earning time” through which antibiotics will become effective. So although a long period of combined therapy is not necessary, the experiences of the authors show that about—14 days—combination-therapy is more effective than a short-time therapy of several days.

(d) “Decision for effectiveness, ineffectiveness and time when the combination-therapy should be discontinued by examinations.” It is not so difficult to decide if the combination therapy is effective or not, following a rapid and considerable remission of subjective and objective symptoms.

Views of leukocytes are valuable to a certain degree for a decision about effectiveness or not. Effective cases show that the count of lymphocyte was below 2,000 and the count of eosinophile cells was below 150 before the treatment, but after a week’s treatment lymphocytes intend to increase. Furthermore, effective cases show a rapid elevation of serum iron (SFe) and fall of serum copper (SCu), and ineffective cases don’t give any change to values of SFe and SCu. Therefore, it seems that effectiveness is not expected whenever SFe and SCu wouldn’t quickly return to normal value after the combined therapy. And when the normalized value of SFe and SCu would show a pathological change after the treatment, the period of treatment is not sufficient. On the other hand, if the value remained normal, the period is enough. That is to say, it is considered that a measurement of SFe and SCu could be a standard for decision about effects and times when the therapy would be discontinued. Particularly, even though fever would break and other signs improve by the administration of S.H., a measurement of SFe and SCu is naturally valuable for the decision of the effectiveness. Furthermore, they add that there were the rapid increases of erythrocytes and haemoglobin in the considerable effective cases.

(e) Catabolic action of steroid hormones has been noted both in animal experiments and clinical cases. In this face, it has been assumed that the
combined therapy of anabolic hormone is effective for the prevention of side effects due to catabolic action of S.H. Few authors believe that anabolic hormone also prevent the atrophy of adrenal cortex.

SIDE EFFECTS

In regard to side effects of combined therapy, not much differences were noted between case with infection and with other diseases. So, side effects were analysed among diseases including infections and others. Side effects of some kind were noted in 60 cases (22.2%). Those are, peptic ulcer (2.1%), inducement and/or aggravation of diabetes (3.1%), inducement of infection (3.1%) and adrenocortical insufficiency (5.2%). Frequency of these five items were not necessarily high but they are serious. They should be regarded as “MAJOR SIDE EFFECTS.”

Under “MINOR SIDE EFFECTS,” there are moon face (12.8%) profuse perspiration (9.5%), dermal disorder such as acne, hirstism, pigmentation and striae etc. (6.3%), insomnia (7.3%), abnormaly increased appetite (4.2%), edema (8.4%), weakness (6.3%) petechiae (3.1%), elevated blood pressure (2.1%) and others (6.3%). But most of these are not serious enough to discontinue medication. As to daily dosage and duration of corticosteroid to develop side effects, minor ones will be noted sooner among the group of patients with larger dose especially with more than 25 mg (prednisolone equivalent) than with smaller dose.

Some of major side effects appeared about a week but markedly increased in its frequency after 4 weeks. That is to say, major side effects have a tendency to occure among the group or patients with longer administration of corticosteroid. Among major side effects, inducement of infection and adrenocortical insufficiency are not only most dangerous but also life-threatened.

CONCLUSION

The serious infectious disease is at the present the best indication for the combined therapy of antibiotics and S.H., but the authors would like to emphasize that the most important fact is an infectious disease to which antibiotics are reasonable. And enough attention should be paid so that S.H. would not be used in vain for a long time. The main in indication for the addition of steroid therapy have been prolonged high fever, marked marasmus, severe anorexia, dyspnea or pain, overwhelming toxic symptoms and schock.

Furthermore, sufficient attention should be given for the appearance of
side-effect, especially "iatrogenic" adrenocortical insufficiency and "steroid induced" infections, therefore patients should be accurately observed. Particularly, it is important to prevent or to find early infections which are ineffective to antibiotics or caused by resistant organisms, and it should be considered that symptoms at the time are so called symptom-masking.

Any patients who have been treated with moderate amount of S.H. for more than 2 weeks or who are within 1 year especially 2 weeks after discontinuation of S.H. should get large amount of S.H. with antibiotics for fear of unexpected adrenal insufficiency when they suffer from serious infection or face to surgical operation.

(We are greatly indebted to Prof. I. Mikata for his advice in writing this paper.)

REFERENCES