

## THE EFFECTS OF ADRENOCORTICAL STEROIDS ON THE REDNESS AND HEMORRHAGE AT THE OPERATION WOUND AFTER PACEMAKER IMPLANTATION\*

By

Hideki YAMASHINA, Yuichiro MATSUURA, Mutsuo TAMURA,  
Masanori HIGO and Takanori FUJII

*Department of Thoracic & Cardiovascular Surgery, Hiroshima Prefectural Hospital,  
Hiroshima 734, Japan*

(Received November 28, 1980)

### ABSTRACT

This study was performed to investigate the effects of adrenocorticoid steroids, Prednisolone sodium hemisuccinate, Dexamethasone, and Betamethasone disodium phosphate, on the wound healing of permanent pacemaker implantation, especially on the findings of redness and local hemorrhage.

It was found that prednisolone sodium hemisuccinate and betamethasone disodium phosphate had a remarkable prophylactic effect on the redness along the operation wound and, moreover, on the hemorrhage from the wound, but dexamethasone had not any prophylactic effect on the redness and hemorrhage along the wound. It might be, therefore, said that the mode of action of adrenocortical steroids on the redness and inflammatory reaction along the wound or the pharmacological efficiency differed by those chemical compounds.

### INTRODUCTION

Surgical procedure for intravenous implantation of pacemaker is relatively simple and the operation time is usually within one hour. Although pacemaker implantation is easily carried out in any institute, provided the X ray fluoroscopy is available, early and/or late complications and accidents in association with the implantation of pacemaker are not ignored. The mechanical troubles of the pacemaker itself are beyond our management, while an adequate managements during and after the surgery might reduce the severity and the incidence of troubles such as wound infection,

skin necrosis due to compression by generator, displacement or malposition on the electrode and twitching of the diaphragm.

Among these troubles wound infection is most embarrassing since pulse generator should be removed at the occasion of wound infection. In our hospital adrenocortical steroids have been used with prophylactic chemotherapy and the anti-edematous and anti-inflammatory effects on the operation wound were obtained. However, it was found that these actions of adrenocortical steroids were somewhat varied by the kind of steroids applied and their doses.

This study was made to investigate the ef-

\*山科秀機, 松浦雄一郎, 田村陸奥夫, 肥後正徳, 藤井隆典: Pacemaker 植え込み創部の発赤, 腫脹に対する副腎皮質ホルモンの効果

**Table 1.** Number of subjects studied by group

| Group   | Corticosteroids used                     | initial intravenous dosis | Number of subjects |
|---------|--|---------------------------|--------------------|
| Control | not administered                         | —                         | 29                 |
| A       | prednisolone sodium hemisuccinate (PS-h) | 1 mg/kg/day               | 42                 |
| B       | prednisolone sodium hemisuccinate (PS-h) | 3 mg/kg/day               | 20                 |
| C       | dexamethasone (DM-sf)                    | 0.2 mg/kg/day             | 7                  |
| D       | dexamethasone (DM-sf)                    | 1.0 mg/kg/day             | 6                  |
| E       | dexamethasone (DM-sf)                    | 2.0 mg/kg/day             | 5                  |
| F       | betamethasone disodium phosphate (BM-dp) | 0.2 mg/kg/day             | 8                  |
| G       | betamethasone disodium phosphate (BM-dp) | 0.4 mg/kg/day             | 11                 |
| H       | betamethasone disodium phosphate (BM-dp) | 0.8 mg/kg/day             | 3                  |

abbreviations were shown in paracethesis

fects of adrenocortical steroids on the operation wound, especially on hemorrhage and redness due to inflammatory reaction.

### SUBJECTS AND METHODS

During November, 1972 through December, 1977, pacemaker implantation have been performed for 131 patients, 74 males and 57 females, to whom 167 pacemakers were implanted at the Department of Thoracic & Cardiovascular Surgery, Hiroshima Prefectural Hospital. Age distributions of the patients were from 15 to 86 years with a mean of 68 years.

As the details of the technique of implantation have been reported elsewhere, the catheter electrode was inserted through either the left or right cephalic vein into the right ventricle under fluoroscopy. The electrode tip was then fixed into the trabecle in the right ventricle and connected to a generator. The generator was then buried under the fascia of the major pectoral muscle. Kanamycin of 1 gm was usually spread inside the subcutaneous space where the generator was implanted, unless there was found any hypersensitivity. The patients wore postoperatively the thoracic compression belt which had been specially designed by the authors.

The cases examined in this study were divided into 9 groups, as shown in table 1, by the kind of the adrenocortical steroids administered and the doses thereof. The doses equivalent to a half of the initial doses in each of these groups were succeedingly administered to the patients every three days, and

the administrations were discontinued after 7 days.

The effects of adrenocortical steroids upon the redness and hemorrhage were investigated with each group. The redness appeared on the skin of the operation wound within 48 hours after the surgery were graded in the following manner; a mild redness remained in the stitched part for less than several days was marked (-), a redness spread over the area surrounding the stitched wound and continued for less than several days (+), and a redness spread all over the skin above the pacemaker pocket (++) . The hemorrhage from the operation wound within 48 hours after the surgery were also graded as follows; a grade wetting less than 3 guazes with the blood per day marked (+), a grade of 3-7 guazes (++) , and a grade of more than 8 guazes (+++).

In addition to the above mentioned study, 5 cases treated with 1 mg/Kg/day of PS-h (group A), 5 cases treated with 1 mg/Kg/day of DM-sf (group D) and 15 cases treated with 0.2-0.8 mg/Kg/day of BM-dp (group F, G, H) were also investigated for urinary excretions of 17-KS and 17-OHCS.

### RESULTS

The extents of the redness observed in those who have received the prophylactic chemotherapy in association with administration of various steroids after the implantation of a pacemaker are shown in table 2. The combination of ABPC and CET was most commonly used, and the use of the combination of ABPC and

CEZ was second in its frequency. Each grade of the redness in cases treated with ABPC and CET shared; 74.8% of (-), 24.1% of (+), and 1.1% of (++) , while those in the cases

**Table 2.** Relationship between prophylactic chemotherapy and the redness along the wound in the patient with pacemaker implantation.

| Antibiotic | Redness   |           |         |
|------------|-----------|-----------|---------|
|            | -         | +         | ++      |
| ABPC-CET   | 65(74.8%) | 21(24.1%) | 1(1.1%) |
| ABPC-CER   | 5         | 2         | 3       |
| ABPC-VSM   | 2         | 0         | 0       |
| ABPC-CEZ   | 12(70.6%) | 4(23.5%)  | 1(5.9%) |
| ABPC       | 6         | 0         | 0       |
| CEZ-EM     | 0         | 1         | 0       |
| CEZ-KDM    | 6         | 0         | 0       |
| CET-LCM    | 1         | 0         | 0       |
| DKB        | 0         | 1         | 0       |
|            | 97(74.3%) | 29(22.4%) | 5(3.2%) |

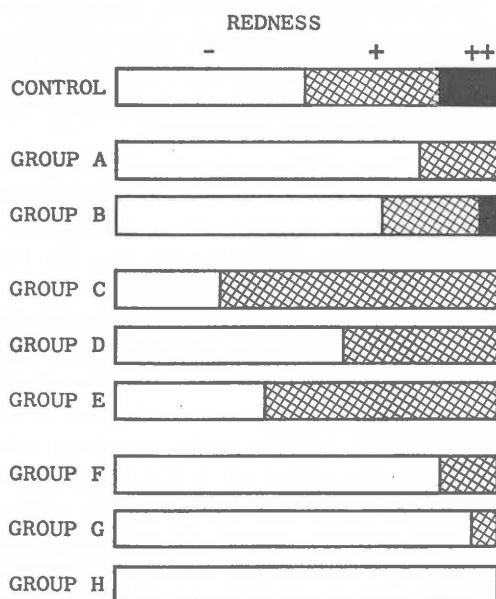
ABPC : Aminobenzyl penicillin, CET : Cephalotin, CER : Cephaloridine, VSM : Vistamycin, CEZ : Cephalozolin, EM : Erythromycin, KDM : Kanendomycin, LCM : Lincomycin, DKB : Dibekacin sulfate

treated with ABPC and CEZ did; 70.6% of (-), 23.5% of (+), and 5.9% of (++) . These results might indicate that the differences in antibiotics used did not provide any significant differences in the grade of the redness.

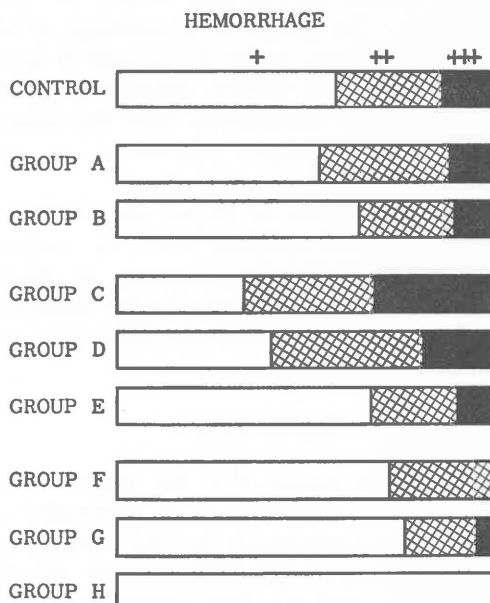
Figure 1 shows the relationship between the kind of adrenocortical steroids and the grade of the redness. The grades of the redness in the control to which only the chemotherapy was made were 50.0% of (-), 34.6% of (+), and 15.4% of (++) , whereas the group A and B showed 80.5% and 75.8% to be graded (-), respectively. Similarly, in the group F, G, and H the redness to be marked (-) were 85.7%, 93.7%, and 100.0%, respectively, which indicates a remarkable prophylactic effect of the adrenocortical steroids on the redness of the operation wound after implantation of pacemaker.

On the other hand, the group C, D, and E showed the redness to be marked (-) of 28.6%, 60.0%, and 40.0%, respectively. Thus, it may not be expected to obtain a suppressive effect on the redness of the wound with DM-sf.

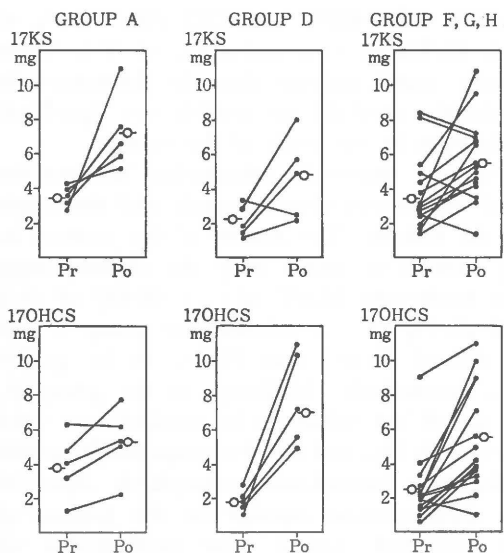
Examinations on the relationship between the dose and kind of adrenocortical steroids and



**Fig. 1** The effect of adrenocortical hormone on redness of the operation wound in the patients with pacemaker implantation by group.



**Fig. 2** The effect of adrenocortical hormone on hemorrhage from the operation wound in the patients with pacemaker implantation by group.



**Fig. 3** Urinary excretion of 17-OHCS and 17-KS in the patients with pacemaker implantation. Pr : prior to implantation, Po : postoperative. Number of cases : A (5), D (5), G (15)

the hemorrhage from the operation wound resulted in the following as shown in figure 2; the control showed 57.7% of (+), 26.9% of (++) , and 15.6% of (+++), while the group A and B showed 54.1% and 67.5% of (+), respectively. The grades of hemorrhage to be marked (+) in the group F, G, and H were 71.4%, 75.0%, and 100.0%, respectively. Thus the grade of the hemorrhage from the wound seems not to be largely affected by the administration of PS-h or DM-sf.

Urinary excretions of 17-KS and 17-OHCS were found to be increased after the surgery in all groups examined as shown in figure 3, while there were statistically not observed significant differences between those prior to implantation and after operation.

## DISCUSSION

It has been known that the surgical procedure for the implantation of pacemaker is occasionally accompanied by the malposition or displacement of the electrode, the redness of the skin and the hemorrhage eventually extended to infection as an early complication.

In order to prevent these troubles, the use of special thoracic wall compression belt de-

signed by the authors was applied to the patients after the implantation at the author's clinic. In addition to this procedure, the patient was kept in the bed rest for approximately 5 days to keep quiet on the wound and to reduce the hemorrhage from the operation wound. The prophylactic chemotherapy with two kinds of antibiotics and steroid therapy were also made.

Ogawa<sup>1)</sup> studied the effect of adrenocortical steroids on the survival rate of Wistar rats to which endotoxin at the dose equivalent to the LD<sub>50</sub> was given, and demonstrated that the survival rate become higher with increasing doses of the steroids and that, when the activity of hydrocortisone (Sodium-1, 7-hydrocorticosterone-21-succinate) was expressed as 1.0, the relative activities of methylprednisolone (methylprednisolone sodium succinate), DM-sf, and BM-dp were 4.3, 13.3, and 15.3, respectively.

Yonemasu and his coworkers<sup>2)</sup> reported that prednisolone at the dose of 1 mg/Kg/day showed a complete suppression of the edema, and that dexamethasone sodium phosphate (DM-p), DM-sf and BM-dp at the doses from 1/6 to 1/7 mg/Kg/day were expected to exhibit a similar anti-edematous action to that of 1 mg/Kg/day prednisolone. According to Brown and his coworkers<sup>3)</sup> the anti-inflammatory activities of DM-p, DM-sf, and BM-dp could be 6, 6, and 7 times stronger than that of prednisolone, respectively.

On the basis of the above mentioned evidence and practical efficiency preventing redness and/or inflammatory reaction along the operation wound, the doses of 1-3 mg/Kg/day for PS-h, 0.2-2.0 mg/Kg/day for DM-sf and 0.2-0.8 mg/Kg/day for BM-dp were selected in this study. The administration of DM-sf at a high dose up to 2 mg/Kg/day was found to exhibit little prophylactic action on the redness along the operation wound, while treatment with BM-dp at the doses of 0.2-0.4 mg/Kg/day produced a nearly suppression of the redness along the operation wound. These findings may suggest that the mode of action of adrenocortical steroids on redness and inflammation along the operation wound or the pharmacological efficiency differed by the compounds.

Imai and his associates<sup>4)</sup> compared the action

of DM-sf with that of DM-p on the endotoxin shock and pointed out that DM-p significantly increases the survival rate of the animal, while that with DM-sf resulted in little effect on the survival rate of the animals. Kitagawa and his associates<sup>5,6)</sup> studied on the anti-inflammatory activity among DM-p, DM-sf, prednisolone-21-phosphate (P-p), and prednisolone sodium sulfate (P-sf) which were all water soluble, and found that both DM-p and P-p had a marked anti-inflammatory action, while DM-sf and P-sf did not at all. Moreover, they examined the changes of plasma contents of DM-p and P-p after intravenous administration by measuring free 17-OHCS as the major metabolite in the rabbit and observed that the plasma content of 17-OHCS was rapidly increased and was still high even after 5 hours, while that after the administration of DM-sf or P-sf was not increased at all.

Miyabo and his associates<sup>7)</sup>, in their study on the blood and urinary contents of free glucocorticoid and conjugated metabolites after intravenous administration of hydrocortisone sodium phosphate (H-p), P-p, DM-p and DM-sf, demonstrated that the concentration of the free steroid was higher than that of glucuronate when P-p or DM-p was administered, while those were gradually excreted for the period of 48 hours after the administration, led largely to the formation of glucuronate and to considerable amounts of sulfate and unknown conjugate (probably unhydrolyzed ester) when DM-sf was administered.

It is commonly believed that the glucocorticoid action of the corticosteroid is brought by the following processes; the corticosteroid taken up by the cell through the cell membrane combined with intracellular receptor, then the complex migrated into the nucleus where it combined with chromatin molecule to alter the amount or the activity of mRNAs<sup>8)</sup>.

It is also considered that differences in anti-shock, anti-inflammatory and anti-edematous activities among the various steroids may be attributed to the difference in the initial cellular uptake process<sup>9)</sup>. Thus, those which release a large amount of the free steroid into the blood such as DM-p or P-p exhibit a high activity and may be taken up more efficiently

than the sulfate such as DM-sf or P-sf.

Adrenocortical steroids were used in this study for the purpose of the suppression of the redness, edema and infection at the operation wound. It was confirmed that the effects of such steroids on the above mentioned postoperative troubles were considerably greater in the nonsulfuric ester such as PS-h or BM-dp than the sulfuric ester such as DM-sf.

The results of this study and those previously reported by other investigators agree with the generally accepted concept that the selection of the corticosteroids for the therapeutic purposes and the administration methods thereof should be based on thorough considerations on not only the efficiency of the steroid but also on its metabolic fate in the body<sup>9)</sup>.

## REFERENCES

- 1) Ogawa, R.: Anti-shock effect of corticosteroid, Comparative study of four agents. *Jap. J. Anesthesiol.*, 24, 1358-1362, 1975.
- 2) Yonemasu, Y. and Kitamura, K.: Treatment of brain edema with steroid hormone. *Jap. J. Clin. & Exper. Med.*, 52, 2186-2190, 1975.
- 3) BROWN, J. and PERSON, C.M.: Clinical uses of Adrenal Steroids. p. 344. McGraw-Hill Co., New York, 1962.
- 4) Imai, T., Tamao, H., Sakuraya, N. and Fujita, T.: The effect of estrogen on endotoxin response, II. Difference in anti-endotoxic potency among some water-soluble analogues of dexamethasone. *Jap. J. Anesthesiol.*, 25, 1364-1369, 1976.
- 5) Kitagawa, H., Mohri, T. and Kitagawa, M.: Comparative studies on dexamethasone and prednisolone esters; Carrageenin edema-depressive effect of phosphates and sulfates and plasma concentrations of the corticosteroids. *J. Pharma. Soc. Jap.*, 91, 909-910, 1971.
- 6) Kitagawa, H., Mohri, T. and Kitagawa, M.: Comparative studies on anti-inflammatory effect and biological fates of 21-phosphates and sulfates of dexamethasone and prednisolone. *Arzneim Forsch.*, 22, 402-410, 1972.
- 7) Miyabo, S., Kishida, S. S. and Hisada, T.: Metabolism of synthetic corticoid esters in man. *Folia Endocrinol Jap.*, 52, 997-1007, 1976.
- 8) Baxter, J.D. and Forshman, P.H.: Tissue effects of glucocorticoid. *Amer. J. Med.*, 53, 573-589, 1972.
- 9) Kishida, S., Miyabo, S. and Hisada, T.: Studies on metabolism of synthetic corticoids. *Jap. J. Clin. Pharmacol.*, 5, 377-379, 1974.