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THE EFFECT OF STEROID THERAPY ON NORMAL AND ABNORMAL ATRIO-VENTRICULAR CONDUCTION

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Since a report by Prinzmetal and Kennamer (1954) illustrating the return of sinus rhythm in a case of heart block after an injection of corticotrophin, a number of reports on the use of corticosteroids in this context has been published. Some of these have continued to show recovery of sinus rhythm as the principal effect (Phelps and Lindsay, 1957; Aber and Jones, 1960; Dall and Buchanan, 1961, 1962), while others have found this to be not a constant feature but regard the abolition of Stokes-Adams seizures as the chief benefit (Friedberg *et al.*, 1960; Pay and Waverley, 1961; Caramelli and Tellini, 1960). This discrepancy has resulted in three theories as to the effect of steroids in these cases. The original authors suggested an "anti-inflammatory" effect; Friedberg *et al.* (1960), influenced by the abolition of Stokes-Adams attacks even when heart block persisted, suggested an "arousal of the ventricular pacemaker"; and Lown *et al.* (1955) studying the electrocardiogram in cases of Cushing's syndrome and Addison's disease noted significant shortening of the P–R interval in the presence of excessive adrenocortical activity, and conversely significant lengthening when there was a reduction in corticosteroid secretion. They suggested that corticosteroids had a "facilitating" effect on atrio-ventricular conduction. To evaluate these theories, the effect of corticosteroids on the P–R interval in patients in whom it was "normal" at the outset has been compared with control subjects. A further group of patients with heart block has been given a course of steroid therapy, and the effect on rhythm, A-V conduction, and Stokes-Adams attacks has been observed during and after the treatment.

Subjects and Methods

Group 1: Normal Conduction. Twenty-five patients with acute myocardial infarction were given a 14-day course of oral prednisolone decreasing from 30 mg. daily to nil over that period. The P–R interval was recorded on an *initial* electrocardiogram, on the *eighth day* (in the middle of the steroid course), and a *final* record at *four weeks* (i.e. two weeks after stopping steroids), and these readings were analysed (Table I). A further 25 patients with infarct were studied in the same way but had no steroids, and these formed a control series. The two groups were obtained by random sampling of 50 consecutive cases of established myocardial infarct. All records were taken on a direct-writing electrocardiogram: all measurements of P–R were made from lead II of the tracing. In both treated and control groups patients were lost by death. Complete sets of readings were obtained in 17 patients treated with steroids, and in 18 controls. In 3 others from each group, "initial" and "one week" records are available; where only a single "initial" record was obtained, this was not included in the calculations for the mean initial P–R interval.

Group 2: Patients with Heart Block. This group can be conveniently divided into two subsections according to whether the heart block is "acute", complicating a recent myocardial infarct, or chronic.

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TABLE I

EFFECT OF STEROIDS ON THE P–R INTERVAL IN PATIENTS WITH CARDIAC INFARCT WITH NORMAL RHYTHM

Cardio-gram	Treated group						Control group					
	Cases	Mean P–R	Standard deviation	Change in P–R	Standard error	Significance	Cases	Mean P–R	Standard deviation	Change in P–R	Standard error	Significance
Before treatment (initial)	20	0·159	±0·021	—	—	—	21	0·159	±0·186	—	—	—
8th day of treatment	20	0·148	±0·022	−0·011	±0·004	$p<0·05$	21	0·159	±0·248	+0·001	±0·004	N.S.
Treatment stopped (final)	17	0·158	±0·016	+0·010	±0·005	$p<0·05$	18	0·154	±0·022	−0·005	±0·006	N.S.
Pre- and post-treatment compared	17	—	—	0·000	±0·004	N.S.	18	—	—	−0·005	±0·005	N.S.

N.S.=not significant.
Final record=two weeks after stopping therapy.

TABLE IIA

ORAL THERAPY: PATIENTS WITH ACUTE INFARCTION

Case No., sex, and age	Conduction defect	Infarct	Drug used	Effect	Outcome
1 M 65 ..	Complete block	Posterior	Prednisolone (after 4 days)	Sinus rhythm in 36 hours	Remains well, no therapy in 39 mth.
2 F 59 ..	Complete block	Anterior and posterior	Prednisolone (after 3 days)	Sinus rhythm on 8th day	Well; on anti-coagulant therapy
3 M 65 ..	Complete with atrial fibrillation	Posterior	Dexamethasone 2 mg. q.i.d.	Wenckebach in 24 hr.; first degree 5 days; sinus rhythm 1 week	Well
4 M 73 ..	Complete block	Posterior	Prednisolone 20 mg. daily	First degree 72 hr.—sinus rhythm in 7 days	Well 33 mth; no therapy
5 M 61 ..	Complete block	Anterior	Dexamethasone 2 mg. q.i.d.	Sinus rhythm in 4 days	Developed Wenckebach when steroid reduced; died suddenly
6 M 63 ..	Complete block	Antero-lateral	I.V. hydrocortisone (100 mg); dexamethasone 2 mg. q.i.d.	Died on second day	Necropsy—septum completely infarcted
7 M 63 ..	Complete block	Posterior	Prednisolone 5 mg. q.i.d.	First degree 3 days; sinus rhythm in 7 days	Died of gastro-intestinal hæmorrhage ? ulcer

TABLE IIB

PARENTERAL HYDROCORTISONE THERAPY—PATIENTS WITH ACUTE INFARCTION

Case No., sex, and age	Conduction defect	Infarct	Hydrocortisone (1st day)	Effect	Outcome
1 M 60 ..	Complete block and Stokes-Adams attacks	Antero-septal	I.V. 650 mg.	Sinus rhythm in 53 min.	Well 24 mth.
2 M 58 ..	Complete block	Posterior	I.V. 450 mg.	Sinus rhythm in 78 min.	Well 15 mth.
3 M 42 ..	Complete+ right bundle-branch block	Anterior	I.V. 600 mg.	Sinus rhythm in 12 hr.	Well 18 mth.
4 M 58 ..	Complete block	Posterior	I.V. 700 mg.	Sinus rhythm in 24 hr.	Died 10th day
5 M 72 ..	Complete block	Posterior	I.V. 400 mg.	Sinus rhythm in 40 min.	Well 18 mth.
6 M 54 ..	Complete block	Posterior	I.V. 300 mg.	Sinus rhythm in 24 hr.	Well 8 mth.
7 M 70 ..	Complete block +Stokes-Adams attacks	Posterior	I.V. 500 mg.	Sinus rhythm in 2 hr.	Well 8 mth.
8 M 39 ..	Complete+ right bundle-branch block with Stokes-Adams attacks	Posterior	I.V. 300 mg.	Sinus rhythm in 16 hr.	Died 5 wk.
9 M 44 ..	Complete block	Septal	I.V. 450 mg.	Sinus rhythm in 4 hr.	Well 6 mth.
10 M 42 ..	Complete block	Antero-septal	I.V. 600 mg.	Sinus rhythm in 1 hr.	Well for 4 mth. then fresh infarct
11 M 77 ..	Complete block	Posterior	I.V. 600 mg.	Sinus rhythm in 26 hr.	Died 9 mth.
12 M 76 ..	Complete block	Posterior	I.V. 400 mg.	Sinus rhythm in 12 hr.	Well 6 mth.
13 F 52 ..	Complete block	Posterior	I.V. 200 mg.	No change	Died 2 hr.
14 M 71 ..	Complete block	Posterior	I.V. 300 mg.	Sinus rhythm in 24 hr.	Well 5 mth.
15 F 70 ..	Complete block	Posterior	I.V. 400 mg.	Sinus rhythm in 6 hr.	Subsequent C.C.F. 3 mth. and died
16 M 44 ..	Complete block	Posterior	I.V. 500 mg.	Sinus rhythm in 2 hr.	Well 5 mth.
17 F 57 ..	Complete block	Posterior	I.V. 200 mg.	No change	Died 3 hr.

Recent onset (acute)—Complete Block

(a) Oral therapy—7 patients (Table IIA).
(b) Parenteral therapy—17 patients (Table IIB).

Chronic Block

(a) Partial: first 3 patients in Table III.
(b) Complete: remaining 11 patients in Table III.

Oral therapy was given as prednisolone in maximum dosage of 40 mg. daily, reducing progressively over 14 days after a high initial dose. Parenteral therapy was based on a dose of 10 mg./kg. body weight in the first 24 hours of treatment, reducing progressively over 12 days thereafter. Amongst the chronic group is one patient with congenital heart block (Table III, Case 9) and one with congenital aortic stenosis (Table III, Case 5); otherwise all had coronary artery disease, whether acute or chronic.

TABLE III

PATIENTS WITH HEART BLOCK OF LONG DURATION

Case No., sex, and age	Disease	Degree of block	Therapy	Effect
1 F 49 ..	Postero-lateral ischæmia	Grade 1. P–R=0·28 sec.; Stokes-Adams attacks	Prednisolone 30 mg. daily for 2 mth.	P–R=0·24 sec.; no Stokes-Adams attacks
2 M 64 ..	Old myocardial infarct	Grade 1	Prednisolone 30 mg. daily	No change
3 M 63 ..	Old myocardial infarct	Grade 1	Prednisolone 30 mg. daily 2 wk. only	No change
4 F 83 ..	Coronary artery disease	Complete heart block	Prednisolone (48 hr.)	No change
5 M 47 ..	Aortic stenosis (congenital)	Intermittent complete and left bundle-branch block	I.V. hydrocortisone, 100 mg. (12 hr.)	No change
6 M 71 ..	Coronary artery disease	Complete block; atrial fibrillation; Stokes-Adams attacks	Prednisolone 30 mg. daily reducing to maintenance of 5 mg. daily	Atrial fibrillation 100 per min.; no Stokes-Adams attacks
7 F 92 ..	Coronary artery disease	Complete/partial (variable)	I.V. 400 mg. hydrocortisone in 12 hr.	Sinus rhythm after I.V.—twice with recurrence despite oral therapy
8 F 63 ..	Coronary artery disease	Complete block with Stokes-Adams attacks	I.V. 500 mg. hydrocortisone in 12 hr.	No change in rhythm; no Stokes-Adams attacks
9 F 23 ..	Congenital heart block	Complete block	I.V. 300 mg. hydrocortisone in 12 hr.	No change
10 M 63 ..	Coronary artery disease	Complete block	I.V. 600 mg. hydrocortisone 12 hr.	No change
11 M 71 ..	Old septal infarct	Complete block	I.V. 300 mg.	No effect
12 M 68 ..	Coronary artery disease	Complete block	Hydrocortisone 400 mg. I.M.	No change
13 F 56 ..	Coronary artery disease	Complete and left bundle-branch block with Stokes-Adams attacks	Hydrocortisone 400 mg. I.M.	No change but Stokes-Adams stopped
14 M 53 ..	Coronary artery disease	Complete block and Stokes-Adams attacks frequent	Hydrocortisone 500 mg. I.M.	No change but Stokes-Adams attacks abolished during therapy

RESULTS

Normal Conduction. In both treated and control groups the "initial" P–R interval was compared with the "one week" value (eighth day) and with the "final" record. The final and eighth day values were also compared. For each group, a mean value was calculated from each set of figures and the significance of the mean difference was calculated (Table I).

In the prednisolone-treated group, the mean P–R interval on the eighth day of treatment was significantly shortened as compared with the "initial" and "final" records, which were almost identical. In the control group of patients, no such shortening occurred (Table I). It has been shown that the shortening observed in the steroid group at the "one week" stage is statistically significant ($p<0·05$). It is noteworthy that this shortening did not persist after withdrawal of therapy.

Patients with Heart Block. Of 24 patients with heart block of recent onset, 7 were treated with oral therapy (Table IIA). Sinus rhythm was restored in 6, and one died after only a few hours

TABLE IV

STEROID THERAPY IN HEART BLOCK
Collected Cases from Published Work

Author(s)	No. of patients	No. of recent infarcts	Effect on block	Time taken	Preparation used
Prinzmetal and Kennamer (1954)	1	1	Sinus rhythm with recurrence treated successfully	Several hours	I.M. corticotrophin
Phelps and Lindsay (1957)	1	1	Sinus rhythm	9 hours	I.M. cortisone, 100 mg.
Rosenfeld and Segall (1955)	3	1	One only given steroids —sinus rhythm	—	I.M. cortisone
Friedberg *et al.* (1960)	6	3	Four achieved sinus rhythm; recurrence in 3; not restored again	36 hours	Prednisolone, oral, 40 mg. daily
Aber and Jones (1960)	5	2	Three achieved sinus rhythm	6 hours—7 days	A.C.T.H., I.M.
Pay and Waverley (1961)	8	2	Two achieved sinus rhythm	—	Oral prednisolone 80 mg. per day
Caramelli and Tellini (1960)	19	7	Sinus rhythm in 5	4–5 days	I.M.
Present report	38	24	Sinus rhythm in 22	1 hour–6 days	Oral prednisolone, 30 mg. per day and I.V. steroids
Totals	81	41	39 (37+2)		

Note:—Of 41 patients with recent onset of block, 37 (90%) were restored to sinus rhythm; of those not of recent onset only 2 (5%) reverted to sinus rhythm.

treatment with persisting heart block. In this group the average duration of treatment before recovery of sinus rhythm was six days.

Seventeen patients have been treated with parenteral hydrocortisone régime (Table IIB): 2 died with persisting complete heart block within two hours of admission, after a single injection of hydrocortisone (Table IIB, Cases 13 and 17), and the remaining 15 regained sinus rhythm within the first 24 hours of treatment, the delay varying from 58 minutes to 24 hours, and the dose of hydrocortisone varying from 300 to 800 mg. (in the first 24 hours). Recurrence of block did not occur after withdrawal of steroids, and 13 left hospital well. One patient died after a mesenteric embolism on the tenth day (Table IIB, Case 4).

In this group of 24 patients with complete heart block of recent onset, only 3 did not recover sinus rhythm, and they died at an early stage in treatment before success could be anticipated. The only difference between those treated with oral therapy and those given parenteral steroids is the delay before the achievement of sinus rhythm.

Among those patients in whom some degree of block had been present for months, if not years, there were three with Grade 1 or latent heart block (Table III, Cases 1–3).

In one of these, some shortening of the P–R interval occurred during oral prednisolone therapy but this remained outwith normal limits (Table III, Case 1). The remainder in this group had complete heart block (Table III, Cases 4–14): 9 of these were uninfluenced by a trial of intravenous or oral steroids. One was twice restored to sinus rhythm during an intravenous infusion, only to revert to complete block each time, despite oral therapy (Table III, Case 7). In one patient the rate was increased to 100 a minute in atrial fibrillation by 30 mg. prednisolone daily (Table III, Case 6). A maintenance dose of 10 mg. daily was necessary for some time in this patient since repeated attempts to withdraw steroids were not successful until ten months later.

In both groups, recent and chronic, Stokes-Adams attacks ceased when treatment was established. In 5 in the chronic group (Table III, Cases 1, 6, 8, 13, and 14), a small maintenance dose of prednisolone (5 or 10 mg.) was given to prevent recurrence of these attacks. Of the patients with recent block, the successful restoration of sinus rhythm put an end to Stokes-Adams seizures in the three patients in whom these had been present (Table IIB, Cases 1, 7, and 8).

Discussion

From these results several features emerge to suggest that there is a dual effect of steroid therapy. In the first place, there is significant shortening of a "normal" atrio-ventricular conduction time during steroid therapy, but this effect is dependent on the therapy and is lost when steroids are withdrawn, the P–R interval returning to its former value. Only one patient with chronic heart block showed similar acceleration of conduction (Table III, Case 1); this may possibly be the mechanism that eliminates Stokes-Adams attacks in chronic heart block when the conduction defect persists (Friedberg *et al.*, 1960). In circumstances where the conduction defect is of long standing, it seems unlikely that therapy produces any structural alteration of the conducting tissues; what is more likely is an alteration of the intracellular/extracellular electrolyte balance, in particular a shift of potassium out of the cells during steroid therapy. That a similar therapeutic effect in chronic heart block with Stokes-Adams attacks can be achieved by the use of a chlorothiazide and salt régime (Tobian, 1961) is further evidence in favour of an electrolyte change as the principal effect, and this is in keeping with the "facilitating" effect on atrio-ventricular conduction observed by Lown *et al.* (1955) in cases of Cushing's syndrome.

In contrast, when complete heart block is associated with a recent myocardial infarct, the effect of steroid therapy has been a return of sinus rhythm, within 24 hours, in response to parenteral hydrocortisone, and within six days when treated with an oral régime. Normal rhythm persists after therapy is withdrawn and the effect is therefore not dependent on a continuing steroid influence.

This outcome differs from the "natural" recovery only in the time elapsing before the block disappears. It is well established that if such patients survive the acute infarct, the heart block resolves in 10–14 days (Penton, Miller, and Levine, 1956; Gilchrist, 1958), and this interval is roughly synchronous with the natural clearing of the inflammatory reactions at the site of the infarct (Lodge-Patch, 1951; Mallory, White, and Salecedo-Salgar, 1939). That this is not a chance finding is illustrated by a review of other published series (Table IV), which shows very clearly a difference in the response of "acute" and "chronic" cases of heart block to steroid therapy.

The consistency of recovery of sinus rhythm in the "acute" cases of block and the speed with which this is achieved and the lack of this effect in the chronic cases points to a relation between the effect of the therapy and the presence of a recent injury in the conducting tissue. That this "injury" is frequently an inflammatory infiltrate and not actual infarct has been illustrated by Rossi (1962) and is in keeping with the natural history of recovery of normal conduction. It seems likely that an anti-inflammatory effect of steroid therapy, as suggested in the first instance by Prinzmetal and Kennamer, is the principal effect in these circumstances. This possibility is being investigated (Frew and Dall, 1963) and will form the subject of a separate publication.

Summary

The effect of oral and parenteral corticosteroid régimes on atrio-ventricular conduction has been studied in patients with heart block, both of recent onset and of long standing. A group of patients with normal atrio-ventricular conduction has been observed during a similar oral steroid course, and the effect on the P–R interval noted.

It is suggested that the shortening effect of corticosteroids on atrio-ventricular conduction in normal subjects or in patients with chronic heart block is due to an alteration in the extracellular/intracellular potassium balance, but in the case of a recent infarct with block, corticosteroids may have

an anti-inflammatory effect on the disturbance in the conducting tissues, promoting earlier recovery of normal function as shown by the return of sinus rhythm.

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