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The Effect of Phenothiazines on the Electrocardiogram

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ABSTRACT

Thioridazine, chlorpromazine and trifluoperazine were administered to six psychiatric patients. Each was used in four dosage levels (thioridazine and chlorpromazine: 200, 400, 800 and 1200 mg. daily; trifluoperazine: 8, 16, 32, 64 mg. daily); and each increase in dosage was effected after four days of drug administration.

Before the trial, twice during each drug period and before commencement of the next dose regimen, an electrocardiogram (ECG) was recorded. The findings indicated that thioridazine modifies the terminal portion (S-T segment, T and U waves) of the human ECG. A similar change occurred in three of six subjects while taking chlorpromazine and in one of six while taking trifluoperazine. Thioridazine induced changes in all six subjects studied, viz., blunting and notching of T waves with or without prolongation of QT interval. In some the notching produced a double-hump appearance in which a T wave of reduced voltage formed the proximal hump and a positive U wave of increased voltage formed the distal hump.

Thioridazine-induced alterations in the ECG have been described as resembling those caused by quinidine; they also resemble changes associated with hypokalemia.

SOMMAIRE

On a administré la thioridazine, la chlorpromazine et la trifluopérazine à six malades mentaux. Chacun de ces médicaments a été donné à quatre posologies (thioridazine et chlorpromazine: 200, 400, 800 et 1200 mg. par jour; trifluopérazine: 8, 16, 32 et 64 mg. par jour) les augmentations de la posologie se faisaient après quatre jours d'administration du médicament.

Avant l'essai, deux fois durant chaque période de médication et avant le début de la posologie suivante, on procédait à un électrocardiogramme (ECG). On a constaté que la thioridazine modifie la portion terminale du tracé de l'ECG chez l'homme (segment ST, ondes T et U). Une modification semblable s'est produite chez trois des six malades traités à la chlorpromazine et chez un des six traités à la trifluopérazine. La thioridazine a entraîné des changements chez les six sujets étudiés, notamment aplatissement et crochetage des ondes T, avec ou sans prolongation de l'intervalle QT. En certains cas, le crochetage avait l'apparence d'une double bosse dans laquelle une onde T de voltage réduit constituait la bosse proximale et une onde U positive de voltage augmenté formait la bosse distale.

On a dépeint les altérations provoquées par la thioridazine dans l'ECG comme ayant une ressemblance avec celles qu'on observe avec la quinidine; elles ressemblent aussi aux changements observés dans l'hypokaliémie.

A RECENT report in *The Canadian Medical Association Journal* by Kelly, Fay and Laverty[1] presented 28 electrocardiograms which depicted a quinidine-like effect of thioridazine on ventricular repolarization in doses as low as 200 mg. a day. Since two fatal cases were reported, it seemed to be important to re-test the effect on the electrocardiogram of the very widely used, therapeutically active, psychotropic drugs of the phenothiazine group, of which thioridazine is one of the prominent members.

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PROCEDURE

Thioridazine, chlorpromazine and trifluoperazine were administered to six psychiatric patients. The study followed a Latin-square design in which each drug was administered in increasing dosages for a 16-day period, with a two-week free interval before the commencement of the next medication. Each drug was used in four dosage levels and each increase in dosage took place after four days of drug administration. Dosages used in this study were in each case as follows: thioridazine and chlorpromazine, 200, 400, 800 and 1200 mg. daily; and trifluoperazine, 8, 16, 32 and 64 mg. daily, each quantity being administered in four equally divided dosages.

The criteria of selection in this study were a diagnosis of schizophrenia (chronic) and age ranging between 20 and 50 years. Patients selected were free from heart, kidney or liver disease, had not received medication for a minimal period of four weeks before the trial, and had not been at any time on drugs with a known effect on the electrocardiogram. An additional criterion for selection was a normal electrocardiogram (ECG) prior to the trial.

Prior to the trial, twice during each drug period (8th and 16th day) and before the commencement of the forthcoming medication an ECG was done, potassium and sodium levels of the blood were determined, blood pressure and pulse rate were checked and at the same time patients were interviewed and examined to detect possible adverse reactions to the drug.

RESULTS

The results of this study are tabulated in Tables I and II.

TABLE I.—QUALITATIVE ECG FINDINGS BEFORE, AND 8 DAYS AND 16 DAYS AFTER ADMINISTRATION OF THE THREE EXPERIMENTAL COMPOUNDS TO THE SAMPLE

Patient No.	*Thioridazine*			*Chlorpromazine*			*Trifluoperazine*		
	Days			*Days*			*Days*		
	Before	*8th*	*16th*	*Before*	*8th*	*16th*	*Before*	*8th*	*16th*
1	N	A	A	N	N	N	N	N	N
2	B	A	A	N	N	A	N	N	N
3	N	A	A	N	A	A	N	N	N
4	N	A	A	N	N	N	N	A	N
5	N	A	A	N	N	A	N	N	N
6	N	A	A	A	N	N	N	N	N

N — Normal A — Abnormal B — Borderline

TABLE II.—FREQUENCY OF ABNORMAL ECG FINDINGS IN THE POPULATION STUDIED BEFORE, AND 8 AND 16 DAYS AFTER ADMINISTRATION OF THE EXPERIMENTAL COMPOUNDS

	Before	*8 days*	*16 days*
Thioridazine	0	6*	6*
Chlorpromazine	0	1	3
Trifluoperazine	0	1	0

*$p \geq .016$ (one-tailed binomial test).

CASE 1.—This patient was a 47-year-old man with a diagnosis of schizoaffective psychosis. Sodium and potassium values remained within normal limits and no changes in blood pressure and pulse rate were detected at any time during the period of the drug trial. However, the patient was somewhat drowsy during thioridazine and chlorpromazine administration. The first medication this patient received was thioridazine. A prolonged QT ratio (1.52) with slight blunting of apices of T waves was manifested after eight days, and an increasingly prolonged QT ratio (1.67), blunted and notched T waves, especially in the left chest leads, were seen on the 16th day of thioridazine administration (Fig. 1). The tracing became normal at the end of the interval when no medication was given and re-

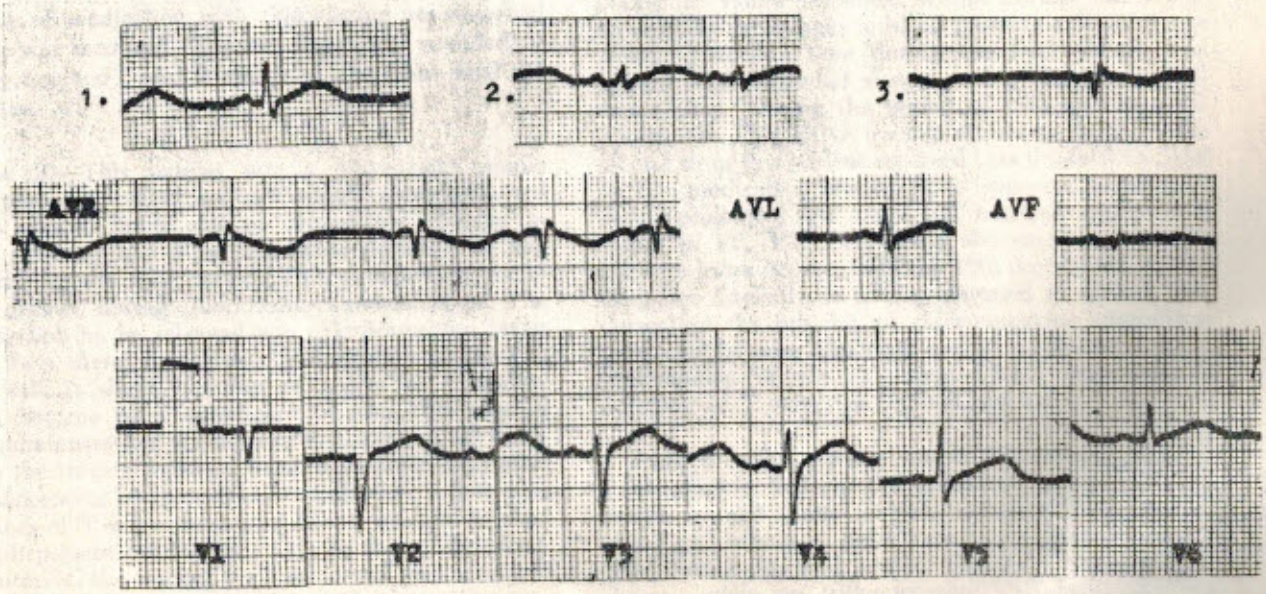

Fig. 1.—ECG tracing taken while patient No. 1 was receiving thioridazine, 1200 mg. daily.

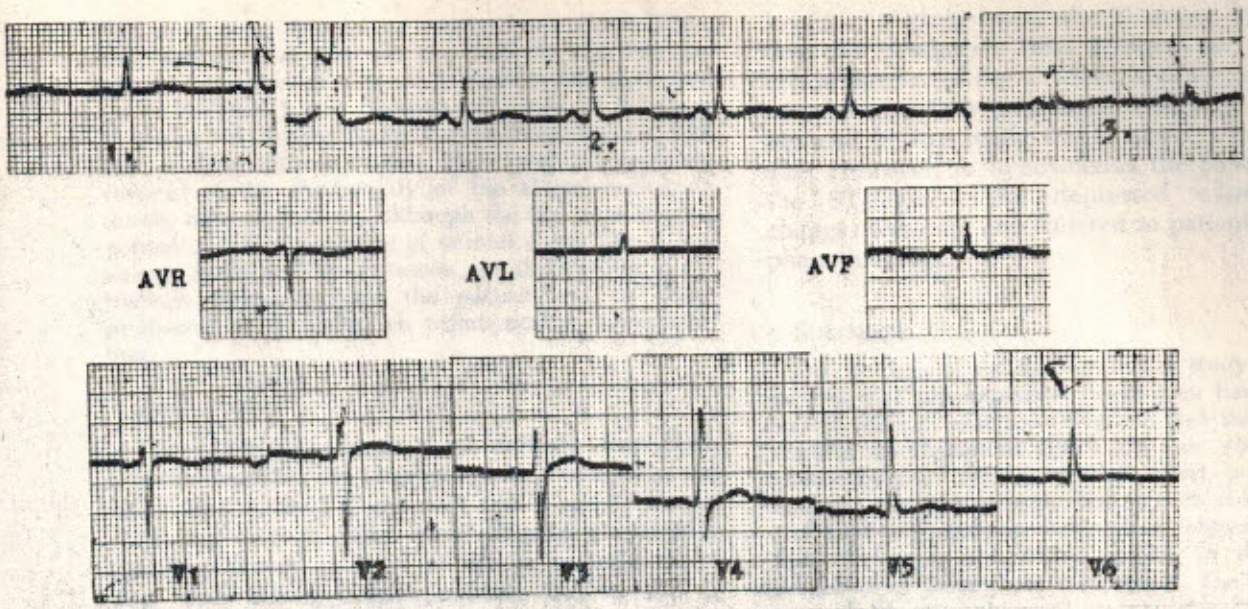

Fig. 2.—ECG tracing while patient No. 4 was receiving thioridazine.

mained normal during trifluoperazine and later chlorpromazine medication.

CASE 2.—This patient was a 37-year-old man with a diagnosis of simple schizophrenia. Sodium and potassium values remained within normal limits and no changes in blood pressure and pulse rate were detected at any time during the drug trial. He was somnolent while on thioridazine administration. The first medication this patient received was chlorpromazine. The electrocardiogram was normal after eight days on this drug, but a slightly prolonged QT ratio (1.09) with blunted apices of T waves appeared on the 16th day of drug administration. During the interval when no medication was given the tracing returned to normal, and remained normal during trifluoperazine administration but did show borderline features (T flat in AVF and a low voltage in V6) before thioridazine administration was begun. On the 8th day of medication with thioridazine an abnormal tracing was recorded (T-waves broad and rounded or slightly notched), and it remained abnormal until the 16th day.

CASE 3.—This patient was a 49-year-old simple schizophrenic. Sodium and potassium values remained within normal limits and no remarkable changes in blood pressure and pulse rate were detected at any time during the trial period. This patient was somewhat drowsy during thioridazine administration. The first medication he received was chlorpromazine. After eight days there appeared a prolongation of the QT ratio with a slight blunting of apices of T waves, which became more prominent on the 16th day of drug administration; during the first interval off medication the tracing returned to normal. Eight days after commencement of thioridazine medication a flattening of apices of T waves appeared which was less marked but still present on the 16th day. In the second drug-free interval, the tracing became normal and remained normal while the patient was on trifluoperazine.

CASE 4.—This patient was a 42-year-old man with catatonic schizophrenia. Sodium and potassium values remained within normal limits and no remarkable changes in blood pressure and pulse rate were detected at any time during the trial period. The patient was somewhat somnolent while on thioridazine administration. After eight days of trifluoperazine administration a slightly prolonged QT ratio (1.12) was revealed; however, the tracing returned to normal after 16 days and remained normal during the period when the second drug, chlorpromazine, was administered. On the 8th day and also on the 16th day of thioridazine medication the QT ratio became prolonged (1.15 and 1.20, respectively), owing to widened T waves, mostly of low voltage (Fig. 2). The widened T waves were considered to be due to a fusion of T and U waves.

CASE 5.—This patient was a 36-year-old man with schizophrenia of undifferentiated type. Sodium and potassium values remained within normal limits and no remarkable changes in blood pressure and pulse rate appeared at any time during the trial period. The patient was somewhat sleepy during thioridazine administration. During the period of trifluoperazine administration, his ECG tracing remained normal. The second drug this patient received was thioridazine, and on this medication abnormalities appeared after eight days (prolonged QT ratio and notched apices of T waves in V2, V3, V4). Some abnormality remained, but to a lesser degree, until the 16th day. In the second drug-free interval the tracing returned to normal, was normal on the 8th day of chlorpromazine administration, and became abnormal on the 16th day, with a prolongation of the QT ratio (1.12) and minimal notching of T waves in V2, V3 and V4.

CASE 6.—This patient was a 35-year-old paranoid schizophrenic. Sodium and potassium values remained within normal limits and no remarkable changes in blood pressure and pulse rate were detected at any time during the trial period. The patient was slightly drowsy while on trifluoperazine administration. The

first medication this patient received was thioridazine. The electrocardiogram was abnormal on the 8th day of administration of this drug, manifesting prolonged QT ratio (1.17) and blunting of apices of T waves in V2 to V6. Similar findings were found on the 16th day of drug administration. There was no complete reversal of the abnormality of the electrocardiogram during the free interval, although the QT ratio became normal and T waves were of normal shape but of low voltage in V4 and V6. However, no abnormality in the tracings appeared while the patient was on chlorpromazine or thereafter on trifluoperazine administration.

DISCUSSION

The foregoing observations indicate that thioridazine modifies the terminal portion of the human ECG, that is, the S-T segment and T and U waves.

In the case of other phenothiazines a similar change occurred in three of the six subjects while they were taking chlorpromazine, and in one of the six subjects while taking trifluoperazine. On the other hand, thioridazine induced changes in all six subjects. These consisted of blunting and notching of the T waves with or without prolongation of the QT interval. In some cases the notching produced a double-hump appearance in which a T wave of reduced voltage formed the proximal hump and a positive U wave of increased voltage formed the distal hump.

The recognition of the etiology of the ECG changes described requires a knowledge of the character of the response of the terminal portion of the ECG to different clinical situations.

The ECG alterations induced by thioridazine have been described as being similar to those due to quinidine.[1] Quinidine does prolong the QT interval by widening the T waves. It may also lower or slightly invert the T waves. However, it does not produce a bifid T wave nor does it increase the size of the U wave. A closer resemblance may be seen in hypokalemia where the T wave is reduced in size while the U wave is increased in size. However, in hypokalemia the ST-takeoff and the ST-segment are depressed whereas these changes were not encountered in patients receiving phenothiazines.

SUMMARY

On the basis of the findings in this study we have to assume that phenothiazine drugs may have an effect on the human electrocardiogram and this effect resembles manifestations which are seen with quinidine administration. This particular effect is most pronounced with thioridazine, less so with chlorpromazine and least with trifluoperazine. It is interesting to note that the same rank order applies to the hypnotic properties of these three compounds. The ECG alterations which were observed are non-specific and at the present stage would hardly suffice to justify the exclusion of any of these valuable compounds from therapeutic usage. On the other hand, they point the way to further investigations which may cast light on the basic characteristics and the mode of metabolic action of these drugs. From the purely clinical view, caution is indicated in prescribing these drugs in high dosage, particularly for patients with a history suggestive of heart disease or those presenting symptoms of electrolyte imbalance.

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REFERENCE

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