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THE EFFECTS OF PHENOTHIAZINES ON THE HUMAN ELECTROCARDIOGRAM*

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During the course of therapy with psychoactive drugs, numerous secondary effects have been observed. Some of these reactions are related to known mechanisms of the drug (side effects), while others are unrelated to any known mechanism (adverse

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effects). One of these hitherto little studied adverse reactions is the effect of the phenothiazines on the electrocardiogram.

Modifications of the human ECG with the use of psychotropic drugs were described in animals. MOYER[7] found occasional widening of the QRS when chlorpromazine was given to dogs in a dosage of 10 mg/kg and in larger doses, ventricular tachycardia. COURVOISIER[2] confirmed these findings in rabbits and also depicted auricular fibrillation when chlorpromazine was given in toxic dosage. HALEY[5] found that thioridazine (10 mg/kg) induced bradycardia in cats, increased the height of P-waves and produced inversion of the T-waves.

In human experiments, ELIAKIM[4] administered 25 mg of chlorpromazine to 15 humans and observed transient flattening or inversion of the T-wave in four cases and ST depression in one case.

More recently, reports have appeared in the literature suggesting that thioridazine hydrochloride has an adverse effect upon the heart. KELLY[6] and his associates, in an uncontrolled study, have reported on 28 electrocardiograms which depicted the quinidine-like effect of thioridazine on ventricular repolarization. In the same study, two fatal cases of arythmia occurred. We have reported[1] on a double-blind controlled study in which thioridazine, chlorpromazine and trifluoperazine were found to cause non-specific ECG alterations which resembled the effects of quinidine or of hypopotassemia. These effects were most pronounced in the case of thioridazine, less so with chlorpromazine and least with trifluoperazine. In all cases the effects were reversible and disappeared with the discontinuation of medication. Despite the hypopotassemic effect on the ECG, sodium and potassium values were found to be within normal limits. DESAUTELS *et al.*[3] reported on a case of ventricular tachycardia observed in a patient who had been on high dosages of thioridazine. In this case, successful therapeutic action was taken. This consisted of discontinuing thioridazine immediately, administering oxygen with external cardiac massage and giving methoxamine in dextrose solution and 40 mg of procaine amide first by the intracardiac route followed by 60 mg intravenously. An ECG was taken five days later and showed signs of posterior ischemia which later disappeared completely. An ECG taken two weeks after the episode was normal in all respects.

In the light of these findings it seemed desirable to test the effect on the electrocardiogram of a variety of psychoactive drugs in the high dosage range employed in psychiatric hospitals.

METHODS

One-hundred-fourteen chronic psychotic patients were chosen from the population of Hôpital des Laurentides in l'Annonciation, Quebec. They represented a variety of diagnostic categories, receiving various drugs. The diagnostic categories represented were: schizophrenia 72, manic–depressive psychosis, depressed 3, chronic brain syndrome 28, miscellaneous 11. The age range was from 21 to 87 years with a mean of 47.9 years and a median of 48.0 years. Other pertinent information regarding the experimental population is presented in Table I. The top row shows the drugs used, the dosage range employed and the number of patients receiving each drug. It will be noted that 10 active drugs and a placebo were employed in the following daily dosage ranges: placebo, 12 capsules; imipramine, 50–200 mg; amitriptyline, 30–150 mg;

dextroamphetamine, 10–40 mg; levomepromazine, 6–150 mg; thioproperazine, 3–30 mg; phenelzine, 30–60 mg; nicotinic acid, 300–1500 mg; chlorpromazine, 75–1500 mg; thioridazine, 75–1500 mg. All patients had been receiving the same medication for at least four months prior to the ECG recording.

TABLE I

Drug / *Reaction*	*Placebo* *12 ca/die* *2 pts.*	*Imipramine* *50–200 mg/die* *3 pts.*	*Amitriptyline* *20–150 mg/die* *12 pts.*	*Dextro-amphetamine* *10–40 mg/die* *3 pts.*	*Levome-promazine* *6–150 mg/die* *11 pts.*	*Thioproper-azine* *3–30 mg/die* *3 pts.*
Normal	2	3		3	8	2
Abnormal					3	1
Per cent Abnormal	0	0	0	0	27.3	33.3

Drug / *Reaction*	*Phenelzine* *30–60 mg/die* *3 pts.*	*Nicotinic acid* *300–1500 mg/die* *11 pts.*	*Trifluoperazine* *1–60 mg/die* *21 pts.*	*Chlorpromazine* *75–1500 mg/die* *23 pts.*	*Thioridazine* *75–1500 mg/die* *22 pts*	*Total* *114 pts.*
Normal	3	9	19	19	5	85
Abnormal		2	2	4	17	29
Per cent Abnormal	0	18.2	9.5	17.4	77.3	25.4

RESULTS

The results also are presented in Table I. It will be noted that abnormal ECG's, as determined by the participating cardiologist, occurred under only six of the eleven experimental conditions. These were: levomepromazine, 3 cases; thioproperazine, 1 case; nicotinic acid, 2 cases; trifluoperazine, 2 cases; chlorpromazine, 4 cases; thioridazine, 17 cases. Of the 92 patients receiving drugs other than thioridazine, 12 patients or 13%, yielded an abnormal ECG. 17 patients, or 77.3% of all patients receiving thioridazine manifested abnormal ECG's. This compares unfavorably to a similar reaction in 17.4% of the patients under chlorpromazine and 9.5% of the patients under trifluoperazine. The differences between trifluoperazine and thioridazine and between chlorpromazine and thioridazine were found to be significant beyond the .001 level of probability when analyzed by the non-parametric Chi-square technique.

Thioridazine was discontinued immediately on these 17 patients manifesting abnormal ECG's. Examination of the ECG one month later showed that the thioridazine effect was reversible as 15 of the 17 patients registered normal profiles.

The mean age of the entire population was 47.9 years and the mean age of those 29 patients having abnormal ECG's was 50.2 years. Therefore, it does not seem that age was a factor. However, when these 29 patients were dichotomized into the 17 receiving thioridazine and the 12 receiving other medication, it was found that the mean age of the thioridazine group was 47.9 years or the same as that of the total population, whereas the mean age of the non-thioridazine group was 54.3 years. When the total abnormal group was subdivided into those 55 years of age and under, and those 56 years and over, it was found that there were significantly more patients 55 years of age or under receiving thioridazine as compared to those receiving other medications ($p \geqslant .04$, Chi-square test).

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The abnormal ECG reactions did not appear to have any relation to diagnostic categories.

CONCLUSION

ECG's were recorded in 114 chronic psychiatric patients of various diagnostic categories who had been receiving high dosages of 10 psychoactive drugs and a placebo for at least four months prior to ECG recording. Abnormal ECG's were recorded in 29 of the 114 patients. 17 patients, or 77.3% of the patients, receiving thioridazine had abnormal ECG's which was a significantly greater number than in those patients receiving either trifluoperazine or chlorpromazine. This effect was reversible, however, as 15 of the 17 thioridazine patients exhibited normal ECG profiles one month after the drug was discontinued.

Age was apparently not a factor in the patients receiving thioridazine but advancing age may have been a contributing factor to the abnormal ECG's found under other psychoactive drugs.

These results should not be interpreted to mean that thioridazine, a medication of proven therapeutic value, should be removed from the therapeutic armentarium. Rather, it is suggested that in cases where high dosages are employed, caution should be used and a periodic ECG should become a routine procedure. Further research is indicated in order to investigate the mechanisms involved in this potentially serious adverse reaction.

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