CLINICALLY IMPORTANT QT INTERVAL PROLONGATION WITH THREE ANTIPSYCHOTICS:

THIORIDAZINE

PIMOZIDE

SERTINDOLE

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Thioridazine Hydrochloride (Mellaril): Its Effect on the Electrocardiogram and a Report of Two Fatalities with Electrocardiographic Abnormalities

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THIORIDAZINE is a member of the family of phenothiazine compounds. It was introduced into clinical practice in 1959 for the treatment of neuropsychiatric disorders, and has since gained wide acceptance because of its substantial margin of therapeutic safety. It provokes little extrapyramidal reaction and so far has produced no jaundice or agranulocytosis, two complications which have limited the use of certain other phenothiazines. As a consequence, it has been possible to administer thioridazine in large doses to severely psychotic patients in the hope of inducing transient or even lasting remission of disease. But larger doses have been found to cause pigmentary retinopathy[1, 2] and also, as will be shown in this report, regularly affect the electrocardiogram (ECG) and may produce cardiovascular collapse.

This report describes the effect of thioridazine on the ECG of 28 patients confined to the Ontario Hospital in Kingston with major psychoses, two of whom died while receiving large doses of the drug. It also summarizes the pertinent clinical data in the two fatal cases, in one of which autopsy data are available.

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ABSTRACT

Twenty-eight electrocardiograms are presented which depict a quinidine-like effect of thioridazine on ventricular repolarization, in doses as low as 200 mg. a day. T waves have been found to flatten out and sometimes invert. Occasionally S-T segments have become convex and U waves have appeared.

Case reports are presented of two patients who died while receiving large doses of thioridazine, 1500 and 3600 mg. daily, respectively. Terminal ECG patterns in each instance were those of heart block, alternating with episodes of ventricular tachycardia.

The myocardium of one of the fatal cases revealed edema, increased vascularity, and some increase in connective tissue elements, along with fragmentation of muscle fibres. These changes were most pronounced in the interventricular septum.

It is concluded that, because of the quinidine-like action of thioridazine on ventricular repolarization, caution is indicated when it is administered in large doses.

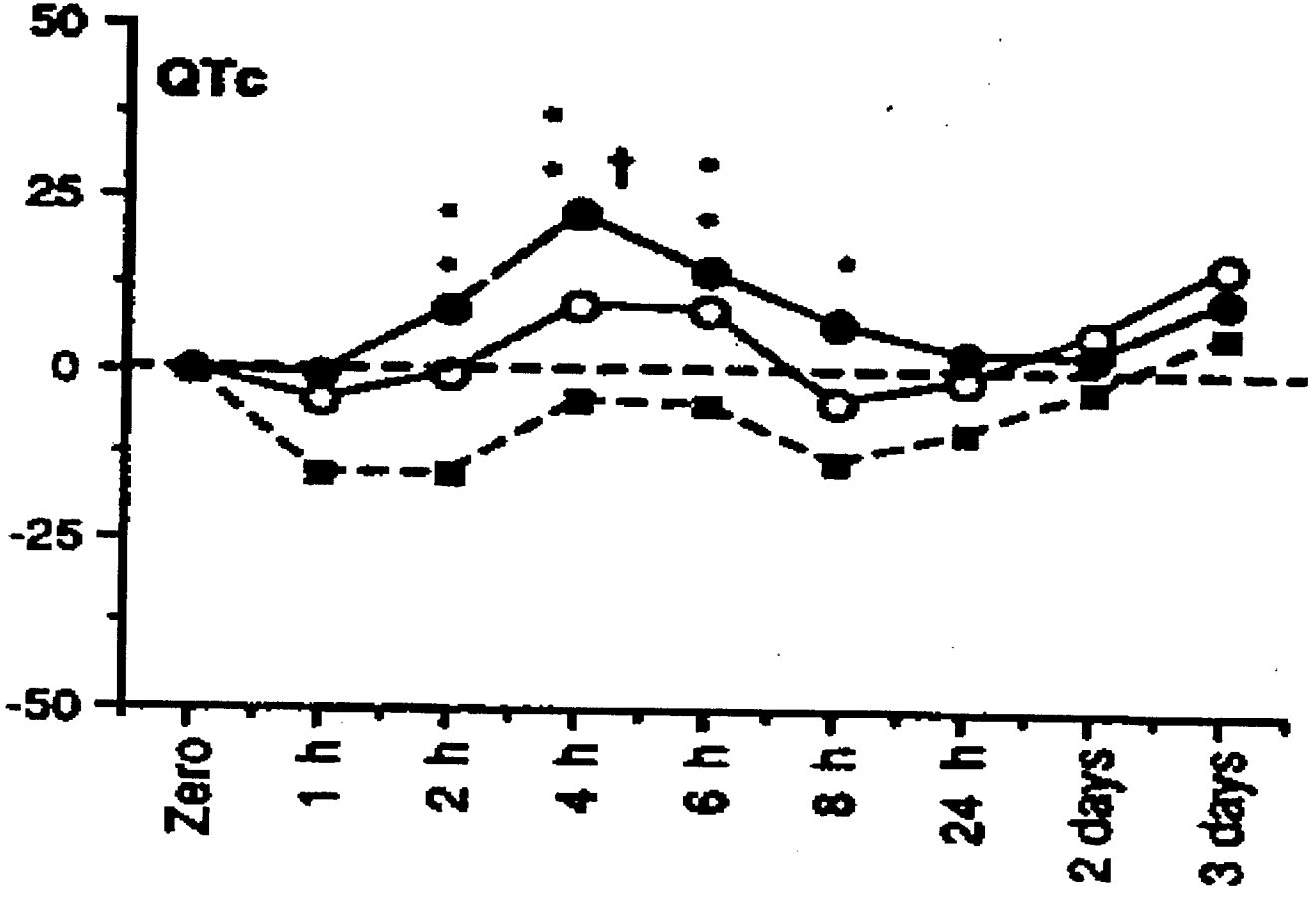
Kelly HG, et al. Can Med Assn J. 1963;89:546-554.

Hartigan-Go, et al.
(Clin Pharmacol Ther 1996;60:543-553)

- Randomized, DB, 3 period crossover
- Single dose
- Placebo, thioridazine 10mg or 50mg
- One week inter-period washout
- 9 healthy, male volunteers (ages 18-33)
- All subjects completed the study
- All debrisoquin rapid hydroxylators

Mean Changes from Baseline in QTc

(Bazett's correction)



Placebo O 10mg • 50mg

No cardiac adverse events and QTc generally < 440 msec.

HOWEVER, findings may underestimate experience in clinical practice:

- single doses
- low doses
- healthy volunteers
- no concomitant medication

Pfizer Study 054

- Open-label, parallel group study
- After taper & washout, titrated to:

  ziprasidone 80mg bid
  thioridazine 150 mg bid
  haloperidol 15 mg/day

- ECG's at ~Tmax at steady state

Results

(without inhibitor) (Bazett's correction)

QTc Mean Change from Baseline (95% CI)

- Ziprasidone +20.3 msec (14, 26) (N=31)
- Thioridazine +35.6 msec (31, 41) (N=30)
- Haloperidol +4.7 msec (-2, 11) (N=27)

QTc Categorical Change from Baseline
(without inhibitor) (Bazett's correction)

	Ziprasidone N=31	Thioridazine N=30	Haloperidol N=27
≥30 msec	65%	97%	41%
≥60 msec	23%	30%	4%
≥75 msec	3%	10%	0%

No subject had a QTc ≥500 msec.

Study 054 Clinical Events

- No deaths or other serious events
- No torsade de pointes
- No syncope

Several Case Reports from MedWatch and Medical Literature with Thioridazine:

- Torsade de Pointes
- Ventricular Tachycardia
- Sudden Unexplained Death

Mellaril Labeling Changes (July 2000):

- Black box warning: cardiac risks
- Second-line use
- Indication restricted to schizophrenia
- Added contraindications
  - Drug-drug interactions
    - CYP 2D6 inhibitors
      - Fluvoxamine, propranolol, pindolol
    - Drugs that prolong QT interval
  - Congenital long QT syndrome
  - CYP 2D6 poor metabolizers
- Baseline, periodic ECG's, Serum K^+

Pimozide

Electrocardiography Report from Clinical Studies in Acute Schizophrenia (NDA Protocols OAI, OAO-1, OAO-2)

- DB TX with pimozide or thioridazine
- Pimozide dose 20-80 mg/day
- Thioridazine dose 200-800 mg/day
- ECG's pre-TX, after 5-12 days of TX

Studies interrupted due to 3 serious adverse events in pimozide patients:

- Two sudden deaths
  - -Doses of 70 and 80 mg/day
  - -QTc increases
    - 400 → 500 msec
    - 420 → 530 msec
- One patient with gran mal seizures and episodic ventricular tachycardia
  - -Dose 80 mg/day
  - -↑ QTc at BL (560 msec) and F/U

Uneventful QTc ↑ ≥100 msec (6 patients)

QTc findings after 5-12 days on pimozide (N=27):

- Mean change from BL ~ 50 msec
- 15% on-drug QTc ≥ 500 msec
- Categorical change from BL:
  - 85% with increase ≥20 msec
  - 55% with increase ≥50 msec
  - 11% with increase ≥100 msec

Pimozide Labeling:

- Not indicated for schizophrenia
- Second-line use for Tourette's D/O
- Contraindications
  - Prolonged QTc
  - Cardiovascular disease
  - Drugs that prolong the QT interval
- Baseline and periodic ECG's
- Limited maximum dose

Recent change: contraindicated with CYP 3A inhibitors (e.g., ketoconazole)

Sertindole

NDA 20-644

3 adequate and well-controlled Phase 2/3 studies contributing ECG data:

- M92-762
- M93-098
- M93-113

ECG findings consistent among studies

Study 113

- 8 week, randomized, double-blind study
- 7 fixed dose parallel treatment arms
  Sertindole (12, 20, 24 mg/day)
  Haloperidol (4, 8, 16 mg/day)
  Placebo
- 497 inpatients with schizophrenia
- Incl. patients w/cardiac abnormalities
- ECG's every 2 weeks

Study 113 Results

	Plac	Sertindole			Haloperidol		
		12mg	20mg	24mg	4mg	8mg	16mg
N	68	69	60	64	66	61	64
QTc Mean Δ BL→Final (msec)	-4	+13*	+20*	+22*	0	-3	+4
% QTc≥500	0%	0%	7%*	8%*	0%	0%	0%

* p≤0.05 versus placebo
(QTc by Bazett's correction)

Sertindole NDA
Phase 2/3 Safety Database

1,446 patients (476 person-years)

Relevant findings:

- 12 sudden unexplained deaths (SUD's)

- No symptomatic torsade documented BUT
  -only 30-40 hours monitored time on drug
  -23 cases of syncope, 22 with no ECG data

Meaning of these data vis-a-vis cardiac risk discussed at PDAC meeting in July 1996:

"Has the sponsor provided evidence that sertindole is safe when used for the treatment of psychotic disorders?"

Yes - 4 No - 2

Outcome:

- Sertindole not approved in U.S. at present

Subsequently:

- December 1998: voluntarily withdrawn from U.K. due to cardiac arrhythmias and sudden deaths (12/2/98 MCA message)

- January 2000: European marketing authorization suspended by EMEA for one year based on spontaneous ADR data from U.K. ADROIT database:

  -reports of SUD's and fatal arrhythmias as % of all reports several-fold higher for sertindole vs. olanzapine and risperidone (www.eudra.org).