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Ask the Doctor

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The Recent Alert on Cardiac Effects of Psychotropic Medications

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Q. Dr. Silka, since the FDA alert on the possibility of increased risk of sudden death in patients treated with Mellaril (thioridazine), there has been much confusion among patients and caregivers of patients with mental retardation and developmental disabilities (MR/DD). Can you give your perspective on this alert and how it has affected your practice?

A. I found it interesting that the alert came out recently because it has been known for a long time that Mellaril can potentially cause this problem. Also, there are many other medications that can cause this problem. The FDA alert, or "Black Box Warning," was mailed to all physicians. The Black Box is the part of the PDR that notifies prescribers of serious adverse reactions. The alert advised clinicians that Mellaril is known to prolong the QT interval. (1,2,3,)

Q. Dr. Levitas, can you explain the QT interval?

A. That is a measure of the electrophysiological changes in heart tissue. It is a measure of the time from when the heart depolarizes, the Q wave, until it repolarizes, which is the R, S, and finally T wave. The time between the onset of the Q and onset of the T is called the QT interval. This is the interval during which the large lower chambers of the heart contract, sending blood around the body. By the time the lowest parts are contracting, the upper parts are repolarizing in preparation for the next contraction. which will begin with the contraction of the heart's upper chambers signaled on the EKG by the P wave. If this wave of contraction, the P wave, reaches the lower chambers before their repolarization, i.e. before the next QRS, disorganization of heart contraction, or arrhythmia, can occur, with consequences including sudden death. Any medication that prolongs the QT interval risks such an occurrence. Any medication that increases heart rate increases the risk. The QTc is the measure of QT interval corrected for heart rate; the QT interval varies inversely with the heart rate.

Q. Dr. Silka, is Mellaril the only drug therapy of concern?

A. Mellaril and many other medicines (see Table 1) are known to potentially prolong this interval. Any drug that does this can increase the risk of certain types of ventricular arrhythmias, and thus abnormal and unstable heart beat. The most worrisome arrhythmia is called "torsade de pointes" and this has been associated with sudden death– in fact sudden deaths have occurred with this rhythm. Most importantly, this event and sudden death cannot be predicted. The patient can be absolutely normal and then can die suddenly from this condition without warning.

Clinicians are advised to obtain a baseline EKG (an electrocardiogram, which will include a measurement of the QT interval, from which QTc is calculated) and to check serum potassium levels, which, if elevated can increase the risk of the prolonged interval

Table 1: Examples of drugs that can cause prolongation of Q-T Interval

Trade Name	Generic Name
Pamelor	nortriptyline
Tofranil	imipramine
Anafranil	clomipramine
Sinequan	doxepin
Mellaril	thioridazine
Haldol	haloperidol
Thorazine	chlorpromazine
Serentil	mesoridazine
Risperdal	risperidone
Zyprexa	olanzapine
Seroquel	quetiapine
Geodon	ziprasidone

Also, people with certain types of heart conditions are at increased risk, such as people with a history of existing cardiac arrhythmias. Other potential risk factors include obesity, hypothyroidism, alcohol use, hypoglycemia and concurrent use of other medications that can prolong the QT interval.

If a patient falls in one of the risk groups, it is recommended to consider tapering off the medication, and possibly switching to another antipsychotic agent. Continuation of Mellaril should be based on a careful assessment of the risks and benefits to the patient.

Q. Dr. Silka, if many drugs can cause this, why was Mellaril highlighted?

A. It is really not clear to practicing clinicians, although there are many rumors circulating. Many other drugs can cause this same effect. Serentil (mesoridazine), for example, another antipsychotic, is the major active metabolite of Mellaril. Other antipsychotics known to prolong the QT interval include Thorazine (chlorpromazine), Haldol (haloperidol), Risperdal (risperidone), Seroquel (quetiapine) and Geodon (ziprasidone). In addition, a number of antidepressants cause this, including Norpramin (despiramine) and Sinequan (doxepin). There are also other antipsychotics, antidepressants and other classes of medications that can have the same effect; the list is too numerous for this discussion. By the way, although Mellaril can cause arrhythmias such as torsades de pointes, which can lead to sudden death, there are no known cases of Mellaril as a cause of sudden death from an arrhythmia. On the other hand, this would be impossible to verify at autopsy. There is only one study so far comparing effects of antipsychotics on the QTc, and this only covers four drugs, two of which are not available in the US.

Q. Dr. Levitas, a number of years ago, there was great concern about prescribing desipramine for children after reports of several sudden deaths.(4) Is this related to the problem of drugs therapies and the QT interval?

A. This story goes back 20 years, to the first rational use of antidepressants in children, when the only drug studied was Tofranil (imipramine). Early in its use as a childhood antidepressant, careful dosing by body weight and EKG monitoring was recommended by the pioneers of antidepressant treatment in childhood, and was (to an unknown extent) practiced. Few psychiatrists or child psychiatrists at that time were familiar or comfortable with regular EKG monitoring. The culprit in the concern was supposed to be the anticholinergic effects of imipramine (Tofranil), and it was thought that desiprmaine (Norpramin), imipramine's less anticholinergic metabolite, could be substituted. This satisfied everyone—until desipramine was associated with sudden cardiac death. All of this was carefully documented and reviewed in the child psychiatry literature. Meanwhile, throughout this controversy, pediatricians were regularly prescribing imipramine for nocturnal enuresis without any such concern. Most child practitioners today do not obtain an EKG prior to commencing treatment with Tofranil; many if not all do so with desipramine. There is little if any scientific or clinical logic to this. It does demonstrate the art of "defensive medicine:" taking measures against possible legal liability for literature-documented consequences, and avoiding use of drugs that require monitoring . No "Black Box Warning" was involved; there is a warning against using desipramine in children, and no such warning with imipramine or the closely-related drug

clomipramine (Anafranil). The point of the story is that legal liability, not clinical, issues, determined the use of these drugs.

Q. Dr. Silka, was the QT interval problem known about Mellaril before the recent alert?

A. It has always been listed among potential effects, and I was aware of this as well as for the other medications during my psychiatric training, The likelihood is not very high this will happen, and you cannot really predict to whom this would happen or when.

It is one of the potential risks, but for people that are not in a high-risk group, it was not a major consideration compared to any other side effects which may be rare. For each medication there are possible serious adverse effects; for example, a small number of patients treated with Depakote (valproic acid) develop life threatening acute pancreatitis. The issue is one of being prepared to monitor patients for changes in EKG just as we monitor them for changes in platelets, liver functions and pancreatic enzymes in patients on Depakote.

Q. Dr. Levitas, in the advertising information about the new medicine Geodon (ziprasidone), the QT interval adverse effect is prominently mentioned. Are the potential risks here more worrisome?

A. I am not aware of any comparison data telling us definitively whether Geodon is more or less worrisome than the other medications listed—and that is the heart of the problem. It may be more prominently listed because it has just recently received FDA approval, during the time at which concerns about the QTc were coming to the fore. There were rumors and reports of a substantial incidence of cardiac problems in the course of testing. It is impossible for clinicians to separate legal from clinical issues, since the warning has the effect of transferring the liability for cardiac effects from the manufacturer to the clinician.

The central problem for the clinician is that there are no definitive studies addressing the comparative risks to cardiac conduction of the antipsychotic drugs. In the absence of such data, manufacturers are free to make, and clinicians to believe, any argument for or against the relative risk of any drug. No such argument, however, applies to any single patient—each patient must be evaluated individually for the appropriateness, risks and benefits of any drug regimen, and monitored appropriately.

Q. Dr. Silka, have you seen patients doing poorly as a result of reduction or discontinuation of Mellaril since the FDA warning?

A. One of the results of the recent FDA Black Box Warning is that many physicians have been frightened about prescribing Mellaril and have rapidly discontinued it or rapidly switched to another antipsychotic agent. This can put the individual at risk for psychiatric decompensation even when the patient has a normal EKG and serum potassium level.

Q. Can you predict which patients will suffer this adverse effect?

A. I am not aware of any evidence that you can predict who will be affected—in other words, abnormal EKG, serum potassium etc. does not appear to be linked to the cases of sudden death, just to risk.

Clinicians should not indiscriminately switch drug therapies, rather than thinking about the possibility, especially if the patient has been very stable. There are many people with MR/DD in the community who has been treated with Mellaril for many years, and who are very stable. Although this may not be the drug of choice today, it is often difficult to titrate the dose down because of a neuroleptic withdrawal syndrome. Switching to another antipsychotic does not necessarily eliminate a neuroleptic withdrawal syndrome, especially a switch to a drug which does not have as much anticholinergic activity as Mellaril. So, there is a risk that a person who was stable and functioning can become unstable and end up being hospitalized. We have had several cases on our inpatient unit of people who are hospitalized within a few months of having Mellaril rapidly tapered and discontinued. There can be similar problems with replacement. This certainly does not happen to everyone; there are many people who tolerate the taper fairly well. However, there are a significant number of people who do not, especially those who have been on the medication for years or decades.

Q. Dr. Silka, what would you recommend to clinicians?

A. First, evaluate the individual for any of these risk factors and obtain an EKG and a serum potassium level. If the patient has these risk factors, a taper and discontinuation or replacement with a novel antipsychotic should be considered.

However, the taper should be slow, cutting no more than 10% dose every 3 months. It should be noted that one could have made this recommendation before the recent "Black Box Warning."

Past history of response to Mellaril is extremely important in any consideration. Clinicians must consider whether Mellaril was ever indicated in the first place. If there is not clear evidence of a psychotic disorder or a bipolar disorder, this would be a major factor in deciding to taper and eventually discontinue. If there is no clear indication, I prefer to attempt to discontinue the antipsychotic agent altogether, rather than assume a switch to an atypical antipsychotic agent is necessary.

When diagnosis or emergent withdrawal effects make replacement of Mellaril necessary, one should preferentially consider the novel (atypical) antipsychotics. Many atypical antipsychotic agents also cause prolongation of the QT interval, leaving only Zyprexa (olanzapine) and Clozaril (clozapine), which have the least effect on the QT interval, as possible alternate agents. Then, one must weigh the risks and benefits of those drugs; e.g. Zyprexa can cause obesity and diabetes, and Clozaril can cause agranulocytosis. A switch is not necessarily a benign move, merely an exchange of one set of risks and necessary monitoring for another.

Q. Dr. Levitas, what are some of the pitfalls of replacement of Mellaril or other neuroleptic with one of the novel antipsychotics?

A. Mellaril has a wide spectrum of neurotransmitter action, including the desired effect of dopamine blockade shared by all antipsychotics, and acetylcholine, norepinephrine, and histamine blockade, as well as some blockade of numerous other neurotransmitters. The novel antipsychotics have much less of this other neurotransmitter blockade activity. The most troublesome resulting withdrawal effect is in the cholinergic system, so-called "cholinergic rebound." There can be sialorrhea (drooling) and diarrhea, i.e. the opposite effects of the cholinergic blockade caused by the Mellaril, and withdrawal akathisia, or motor restlessness. The latter can be sufficiently torturous as to result in assault and self-injury. Use of Cogentin can reverse the symptoms, but may again prolong the QT interval.
When this happens, Benadryl can be effective, but can be sedating.

Q. Dr. Silka, if the discontinuation or replacement of Mellaril is merely the exchange of one set of risks for another, what should a clinician do?

A. The clinician should approach this issue as one would any other clinical issue: thoughtfully. First, realize that the days of unmonitored antipsychotic use are over. These drugs all have health consequences that must be monitored medically and planned for. Learn the side effects of the neuroleptics and novel antipsychotics, and do not trust that nonpsychiatric physicians will monitor these. All patients to be started on an antipsychotic should have baseline cardiac history, chem scan, CBC and an EKG. All patients currently on Mellaril—and for that matter any neuroleptic or other medication that can prolong the QT interval—should have an EKG. If the QT interval is normal, plans should be made to monitor EKG at least yearly. If prolonged QT interval (QTc>450-500msec) or low serum potassium is found, re-evaluation of the need for Mellaril or other offending drug should be undertaken.

If deemed unnecessary, Mellaril should be tapered by 10% of the starting dose every three months as tolerated. If a clear history of psychosis or nonpsychotic mood disorder is found and an alternative antipsychotic is deemed to be absolutely necessary, Zyprexa could be started and brought to an appropriate dose (there is no known bioequivalency of Mellaril and Zyprexa; maximum recommended doses, a rough guide at best, are 600-800 mg/day and 20 mg/day respectively), followed by tapering of Mellaril by 10% of the starting dose per month. Emergent "cholinergic rebound" symptoms can be treated with Cogentin, starting with

0.5 mg BID and titrating upward with EKG monitoring for QT prolongation. Benadryl 25-100 mg/day in divided doses can be used if Cogentin is contraindicated. Clearly, the less Mellaril on board, the greater the tolerance for Cogentin. Emergent mood or psychotic symptomatology can be dealt with by increases in the Zyprexa.

In patients with obesity, seizure disorder or diabetes, Risperdal may have to be substituted for Zyprexa; this requires cross-tapering Mellaril and Risperdal with careful EKG monitoring since Risperdal can also prolong the QT interval.

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