Rapid Conversion From One Monoamine Oxidase Inhibitor to Another

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Background: Numerous sources state that switching from one monoamine oxidase (MAO) inhibitor to another can be done only after a 14-day washout period. In hospitalized patients and severely depressed outpatients, such a wait may be impracticable.

Method: We reviewed the case histories of eight consecutive and random patients whom we converted from one MAO inhibitor to another within less than the recommended waiting period.

Results: Only one patient experienced troubling adverse effects, and these effects were brief and time-limited. The patient's symptoms were indicative of either withdrawal from tranylcypromine or a mild serotonin syndrome. All other patients tolerated the conversion well with minimal or no adverse effects. Four of the eight patients eventually responded to the new MAO inhibitor.

Conclusion: These results suggest that some patients can be cautiously but rapidly switched from one MAO inhibitor to another without prolonged drug-free periods. Unquestionably, this strategy should be used *only* when the clinical picture mandates a rapid conversion. Further, it should be reserved for those patients with established high compliance and should include close monitoring and the use of a low-tyramine diet. Extreme caution must still be undertaken in utilizing this approach until larger studies more accurately determine the frequency of serious adverse effects.

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With the advent of tricyclic antidepressants (TCAs) in 1957 and the serotonin selective reuptake inhibitors (SSRIs) in 1988, the use of monoamine oxidase (MAO) inhibitors as a first-line treatment of depression dramatically diminished due to safety concerns. However, there has been a recent resurgence of interest in these compounds as they have become a primary treatment for some types of major depression. Several studies have suggested that they may be of particular benefit in patients with atypical depressive symptoms.[1–3] Moreover, there is mounting evidence that MAO inhibitors, compared with TCAs, may be of particular benefit in patients with bipolar depression[4] and substantially less likely to induce mania or rapid cycling.[5] Other reports have indicated that MAO inhibitors may be effective in up to 50% of patients who are treatment resistant.[6] Thus, MAO inhibitors have become the treatment of choice for some types of major depression. Despite the advent of the SSRIs and other newer antidepressant agents, MAO inhibitors continue to hold a major place in the treatment of depressive disorders, panic disorder, and other anxiety disorders.

Although MAO inhibitors do help many patients with resistant depression, not all patients respond to the first trial of one of these compounds. Scant attention has been paid to treatment algorithms for failed MAO inhibitor trials, and it is reasonable to ask: What does the clinician do when treatment with an MAO inhibitor fails? The uses of various MAO inhibitor augmentation strategies have been described, yet the potential for drug-drug interactions must always be considered.[7–12]

Switching from one ineffective MAO inhibitor to another that may be potentially effective may represent a more parsimonious approach to MAO inhibitor treatment failure. Unfortunately, information regarding direct switching among MAO inhibitor drugs remains rare. Many suggest that a 2-week drug-free elimination period is required when switching between different MAO inhibitors.[10,13–16] However, data to support such precautions are strikingly sparse. Further, the suggestion that a 2-week drug-free period be given before prescribing a subsequent antidepressant can be especially problematic in severely ill outpatients. In today's medicoeconomic climate, clinicians may be hard-pressed to keep medication-free patients in the hospital for this length of time.

Table 1. Characteristics of Eight Patients With Refractory Depression Switched Rapidly From One Monoamine Oxidase Inhibitor to Another

Case	Age (y)	Gender	Diagnosis	Original MAO Inhibitor/ Next MAO Inhibitor	Days Between MAO Inhibitors	Concomitant Medication	Vital Signs After Switch	Symptoms After Switch
1	24	F	Bipolar depression	Tranylcypromine/ phenelzine	0	Lithium, trazodone	Unchanged, but unable to assess until symptoms resolved	Anxiety, nausea, hyperventilation, flushing, sense of doom, increased insomnia
2	67	M	Bipolar depression, cerebrovascular disease, hypertension, non-insulin-dependent diabetes mellitus	Phenelzine/ tranylcypromine	0	Valproic acid, oxazepam, ranitidine, hydrochlorothiazide, acetysalicylic acid	Unchanged	Increased anxiety, restlessness, palpitations
3	22	M	Unipolar depression, HIV+	Tranylcypromine/ phenelzine	0	Clonazepam	Postural drop in systolic blood pressure of 15 mm Hg after 3 d on phenelzine	None
4	48	F	Bipolar depression	Phenelzine/ tranylcypromine	0	Trifluoperazine, carbamazepine, methylphenidate, lithium, lorazepam	Unchanged	None
5	33	M	Unipolar depression	Phenelzine/ tranylcypromine	1	Chloral hydrate	Postural tachycardia to 120 bpm	Postural light-headedness
6	24	F	Bipolar depression	Tranylcypromine/ phenelzine	5	Lithium, risperidone	Unchanged	None
7	42	F	Bipolar depression, posttraumatic stress disorder, dysmenorrhea	Phenelzine/ tranylcypromine	5	Valproic acid, haloperidol, lorazepam	Unchanged	None
8	37	F	Unipolar depression	Phenelzine/ tranylcypromine	8	Oxazepam	Unchanged	None

Because we realized we were facing this issue with greater frequency, we decided to examine our own experiences with switching between MAO inhibitors. We collected a series of consecutive and random cases in which patients resistant to antidepressant therapy were directly switched from one MAO inhibitor to an alternative MAO inhibitor without a 2-week washout period.

METHOD

We reviewed the charts of eight consecutive inpatients and outpatients whom we directly switched from one MAO inhibitor to another, without a 2-week washout period. Three men and five women ranging in age from 22 to 67 years were studied. Three had unipolar and five had bipolar depression. All were refractory to or intolerant of at least two adequate antidepressant trials, one of which included an MAO inhibitor. Four cases were switched directly with no MAO inhibitor–free elimination period, while four others had from 1 to 8 days between MAO inhibitors. Five patients were switched from phenelzine to tranylcypromine and three from tranylcypromine to phenelzine. All patients were receiving at least one additional medication during the switch period. Five were taking a benzodiazepine, five were receiving a concomitant mood stabilizer (lithium, valproic acid, or carbamazepine), three were taking a neuroleptic, and one was taking a sedative only at bedtime (see Table 1).

RESULTS

The results of the group's outcome are highlighted in Table 1. Overall, 50% (N = 4) of the patients experienced no adverse physical symptoms after rapidly switching from one MAO inhibitor to another. A fifth patient had a transient systolic blood pressure drop upon standing, but was asymptomatic. Of these five patients, three were switched from phenelzine to tranylcypromine and two from tranylcypromine to phenelzine. Two of the patients were directly switched, while the others had drug-free periods of 5 or 8 days.

Of the three patients experiencing some physical complaints after the switch period, two were directly switched and one had an MAO inhibitor–free period of 1 day. Two

of these three were switched from phenelzine to tranylcypromine. One experienced what may have been a mild serotonin syndrome involving symptoms of anxiety, nausea, flushing, hyperventilation, a sense of impending doom, and an increase in preexisting insomnia. Subject 2, from Table 1, had mild symptoms of anxiety, restlessness, and palpitations that had been experienced intermittently before the switch occurred.

The postural-dependent cardiovascular manifestations experienced by two patients were clinically trivial and transient. There is little reason to believe they were due to an interaction between the drugs because these cardiovascular changes are relatively common side effects of both drugs. No patients experienced myoclonus. Four of the eight patients eventually responded to the new MAO inhibitor.

DISCUSSION

MAO inhibitors appear to exert their antidepressant effects indirectly through inhibition of the interneuronal and extraneuronal enzyme that catabolizes serotonin and norepinephrine.[17,18] The acute increase and subsequent chronic reduction in brain concentration of these neurotransmitters set in motion downstream effects that ultimately appear to produce antidepressant effects.[3] Phenelzine and tranylcypromine represent nonselective brain and peripheral MAO enzyme inhibitors. Beyond the fact that both compounds inhibit the enzyme, these drugs are pharmacologically quite distinct from one another. Phenelzine is a hydrazine derivative that irreversibly binds MAO, thereby blocking all enzyme activity after a few doses.[13] This "lethal" effect on the enzymatic system necessitates a complete enzyme resynthesis to replenish interneuronal and extraneuronal stores.[13] This process may take up to 2 weeks. In contrast, tranylcypromine is a nonhydrazine, amphetamine derivative that appears to reversibly bind MAO enzymes.[13] While tranylcypromine rapidly blocks virtually all peripheral MAO enzymes, theoretically this effect is limited to the period in which the drug is present in the body. MAO enzyme activity could thus be reestablished within 3 to 5 days of discontinuing the drug.[13] However, the high concentrations of substrate needed for displacement from the enzyme may mean that 3 to 5 days is not long enough.

Although MAO inhibitors are highly effective as antidepressants, several factors have contributed to the limited use of these agents. First is the well-known hypertensive crisis ("cheese" reaction) that occurs when patients ingest products containing large amounts of tyramine while taking MAO inhibitors. In rare instances, this effect can be life-threatening. Though not entirely elucidated, this phenomenon is probably due to inhibition of MAO-A within the intestinal wall. Such inhibition permits large amounts of tyramine to pass the gut lumen into the blood stream after the ingestion of products containing it.[13] Tyramine is an indirect-acting sympathomimetic and extremely potent vasopressor. These properties appear responsible for the hypertensive reactions.

Second and somewhat less well appreciated is the serotonin syndrome that can occur in varying degrees when MAO inhibitors are combined with potent serotonin-enhancing drugs.[9–12,14] This set of signs and symptoms includes diaphoresis, flushing, myoclonus, hyperreflexia, and autonomic instability.[14] The combination of MAO inhibitor with tricyclic antidepressants has also been reported to produce a serotonin syndrome, although this has more often been associated with the use of clomipramine.[10,19]

While the manufacturers of phenelzine and tranylcypromine recommend a 7- to 10-day[16,20] drug-free period before switching to another MAO inhibitor, there have been no studies to substantiate the need to wait this long. Given the short half-life of tranylcypromine and reversible nature of its enzyme inhibition, this length of time would appear to be excessive when switching from tranylcypromine to phenelzine.

We are aware of only two other reports utilizing such a rapid switch from one MAO inhibitor to another. The first report described complications in two patients switched from phenelzine to tranylcypromine.[21] A 42-year-old woman was changed to tranylcypromine after a taper of phenelzine. Four days after the switch, she sustained a cerebral hemorrhage. In the second case from the same report, a 34-year-old woman was switched from phenelzine to tranylcypromine after a 2-day drug-free period. Two days after the switch, her blood pressure rose to 240/130 mm Hg. She had no sequelae, and the tranylcypromine was stopped.

The authors suggested that in their two cases, the conversion may have been causally related to the hypertensive crisis and cerebral hemorrhage. However, other possible causes for hypertension include dietary indiscretions, such as the ingestion of a large quantity of tyramine, or autoinduction of a pressor effect by tranylcypromine itself.[22,23] In another report, a patient was switched with no drug-free period from phenelzine to tranylcypromine and had no adverse effects.[15] Interestingly, for purposes of the patient's depression treatment, she was then rapidly switched back to phenelzine. She tolerated both switches with no problems.

Our report involves the largest series of patients switched rapidly from one MAO inhibitor to another. Most patients were able to rapidly switch between MAO inhibitors with few adverse effects. None of the patients suffered serious adverse events, and none demonstrated a clinical picture consistent with a hypertensive event. Only one patient experienced clinically significant side effects when switching medications, and the majority of her symptoms were consistent with a mild serotonin

syndrome or anticholinergic withdrawal. Trazodone and, to a lesser extent, lithium have serotonergic effects. Thus either or both drugs may have contributed to a serotonin syndrome. Her picture was not consistent with a hypertensive crisis. However, in theory, producing complete MAO inhibition with phenelzine and then switching to tranylcypromine, an amphetamine-like agent, might be more likely to produce a crisis than the opposite sequence. Such would be consistent with the adverse experiences described by Gelenberg[21] when two patients underwent conversion from phenelzine to tranylcypromine.

Unfortunately, the present report suffers from all of the inherent limitations of an uncontrolled case series. The small sample in this report leaves open the possibility of not finding an interaction. How a newer reversible MAO inhibitor, such as moclobemide, would be tolerated in rapid switches between MAO inhibitors is unknown. Unfortunately, this drug may never be available in the United States. Nonetheless, while the inferences that can be drawn from this report are limited, they are not without clinical significance.

The observations from the present study suggest that a cautious exchange between MAO inhibitors can be safely made, without untoward events, in well-selected patients who require a rapid drug change. Before directly switching between MAO inhibitors, we recommend that a cautious and detailed assessment of the risk/benefit ratio for each patient be undertaken. First, only when the clinical picture mandates a rapid switch between MAO inhibitors should such a transition be undertaken. Moreover, a full explanation of these factors should be given to the patient as part of the informed consent process. Only carefully selected and highly compliant patients who would benefit from a rapid switch between MAO inhibitors should be considered for this approach. They should be carefully monitored with frequent office visits (for outpatients), vital signs determinations, and the use of a restrictive low-tyramine diet. Patients must be given special instructions regarding the prodromal signs of the serotonin syndrome so that they can alert the physician before the full onset of any adverse events. Limited data suggest that going from phenelzine to tranylcypromine may be more hazardous than the opposite sequence. Clearly, a controlled experiment, with a substantially larger sample, designed to compare the tolerability of switching one MAO inhibitor for another after a brief or extended drug-free period would be ideal. Future controlled clinical trials can more carefully define the risks and benefits of serious adverse events.

Drug names: carbamazepine (Tegretol and others), chloral hydrate (Noctec), clomipramine (Anafranil), clonazepam (Klonopin), haloperidol (Haldol and others), hydrochlorothiazide (Esidrix and others), lorazepam (Ativan and others), methylphenidate (Ritalin), oxazepam (Serax and others), phenelzine (Nardil), ranitidine (Zantac), risperidone (Risperdal), tranylcypromine (Parnate), trazodone (Desyrel and others), trifluoperazine (Stelazine), valproic acid (Depakene and others).

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