SWAPPING FROM MAOI TO MAOI

The requirement or desire to swap from one MAOI to another MAOI is something that will be an uncommon occurrence. Furthermore, it will be an urgent need even less commonly. It may be indicated, for instance, because of the excessive weight gain, sexual dysfunction, or oedema, that occur with phenelzine.

Because opinion exists in the **literature**[1] suggesting co-administration, dovetailing, or a direct swap, is a potentially risky thing to do, some discussion about this is educative.

Insofar as I have been able to trace the original texts which postulate these sorts of dangers, I have one particular comment to make: case reports are notoriously unreliable. Also, they may be written by clinicians with little experience and who have an incomplete understanding of pharmacology, or toxicology, and they often contain errors of fact (they are poorly refereed). If such texts are books, they are not peer-reviewed at all (cf. my comments about the poor sections on TCAs and MAOIs In the American Psychiatric Association psychopharmacology textbook).

Analysis

First, there is no known, or even hypothesized, mechanism of interaction that would predict or cause a problem.

Second, neither is there a basis for postulating a pharmaco-kinetic interaction.

Third, nor is there a basis for a major pharmaco-dynamic interaction.

That leaves a mystery, or possibly a phantom? This is because, without any scientific basis for proposing an interaction, case reports are like ghost-hunting.

My extensive experience of analysing hundreds of case reports of ST indicates clearly that the overwhelming majority of case reports are misleading[2], and they often involve supposed interactions that have no known basis, either in fact or in theory [1]. To make decisions based on such reports has repeatedly proved to be inappropriate and the resultant actions have in some cases had serious negative consequences.

The literature is replete with inappropriate and groundless injunctions against a host of perfectly safe drug combinations (see my other papers for a detailed analysis of this topic in relation to ST) and various 'official' bodies like the WHO and the FDA have been repeatedly guilty of issuing such scientifically groundless injunctions: recent examples are warnings about 'serotonergic' drugs precipitating ST if combined with the anti-emetic 5-HT3 antagonists, and about ST with Triptans. Such 'cry-wolf' warnings are time-wasting and confuse and

[1] This myth originated in the somewhat hysterical (not my words, those in the JAMA editorial) discussions, at the time that TCP was removed from the American market in 1964 (see 'Tranycypromine a history' for more detail about this). The AMA 'Council on Drugs' summary of 1964 is an example of 'experts' asserting their 'authority': their monograph was poorly researched and did not even cite then current relevant research from world-famous pharmacologists. The incorrect information in it is still having an adverse influence on practice. The subsequent changes in recommended indications and precautions (DESI and FDA driven) included the 'mixing two MAOIs' prohibition or recommendation — without references or justification. It may be seen as a general overcautious response by doctors who had little knowledge or training in psychopharmacology (in the USA at that time most psychiatrists were psychologically orientated (even Freudian), not pharmacologically trained. People are understandably cautious about things they do not understand. These errors have been uncritically repeated in the literature ever since.

[2] This is why many reputable journals decline to publish case reports [1].

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misdirect practicing clinicians. Adopting the careful conservative approach is not the 'win-win' scenario that such cautious analysts suppose it to be.

I quote Professor Nick Buckley, a clinical pharmacologist and toxicologist and fellow expert on serotonin toxicity, who stated in a BMJ article:

> However, spurious associations and cautions have proliferated elsewhere in the medical literature, and product information is a major impediment to sensible decision support in this area [2].

In routine clinical practice the maxim 'start low and go slow and only change one drug or dose at a time' is wisely adhered to. When a changeover is being considered, or is indicated, in a patient who is *severely* ill, and in danger because of that, a degree of risk, imagined or real, is acceptable. In less urgent circumstances the patient and clinician may be well-advised to opt for a cautious approach.

Start low, go slow, change only one drug or dose at a time

The history, as of 2020, of accumulated references

In 60 years of MAOI use there are only a handful of uncertain and disparate reports of supposed difficulties: these are of a variety of different clinical presentations that are not indicative of a cause-effect relationship involving an MAOI-MAOI interaction.

Supposed adverse events

The following are the relevant contributions that I am aware of, in the **published literature**, relating to direct MAOI to MAOI change-overs: [3-14]. Concerning Torre et al., see 'case 2'; as with many case-reports, most of these contain insufficient information to draw reliable conclusions.

None of them are much help, nor do they provide a rational or substantive basis for prohibition of a rapid change-over from one MAOI to another MAOI.

It is notable that of these incomplete and unconvincing reports, one suggests subarachnoid haemorrhage, one a stroke, one a non-specific confusional state, and another serotonin toxicity.

One might also observe that these reports include all possible combinations of switch drug and switch sequence; hydrazine to hydrazine, hydrazine to TCP (non-hydrazine) and vice versa.

It is improbable that all of these could represent a cause-effect interaction, because the required explanatory mechanism would be different for each of them

The most parsimonious explanation is that none of them represent a cause-effect drug-interaction relationship — there may be a cause-effect relationship between the change in drug regime and the outcome reported, but that is not the same as a drug-drug interaction; cf. the withdrawal effect of rebound hypertension, after sudden cessation of antihypertensive drugs, viz. the MAOI.

An additional comment I would make from my extensive experience of analyzing case reports of serotonin toxicity (ST) is that surprising and anomalous case reports often have an alternative explanation that has not been considered; this is a point also discussed by Isbister [15]. ST has a categoric and predictable nature which provides examples of this: e.g., when people are supposed to have developed severe ST following a particular ingestion of drugs (which pharmacology predicts cannot cause serious ST). In several instances where I

have re-analysed cases, further inquiry (sometimes by correspondence with the authors) has revealed that a drug of type X (scil., an unrecognized MAOI, like MB or high dose linezolid) must also have also been ingested (a notorious example of this is the Libby Zion case, see my comment about this in this review [16]. Toxicology screening, or more penetrating questioning of the patient, has revealed that to be the case. Indeed, such a chain of reasoning was what led me to the discovery of the MAOI property of methylene blue. The original publication and the follow-up publication some years later in which I was involved with professor Stanford, are excellent examples of this [17, 18].

Lack of adverse events

One paper by Szuba et al. reported a series of 8 cases where MAOI>MAOI was accomplished without a problem [19], and another report has a couple of safe transitions [9].

In the paper Szuba et al. they cite five references to substantiate the comment that '*many people advise avoiding a direct switch*'. However, examination of those references shows that they are irrelevant, because they make this recommendation without any substantive scientific evidence or justification whatsoever, they are no more than casual asides — therefore, they do not advance or strengthen that argument.

A casual reading of Szuba's report may be misleading, because only three of the eight patients had what might be described as a more or less direct transition from one MAOI to the other; the others had between five and eight days off MAOI medication. Neither does the report state, either the dose prior to switching, nor whether any tapering of that dose occurred before that switch, nor even the starting dose of the second MAOI. Although this report came from a major university teaching center it demonstrates consequential deficiencies, as above, and a limited understanding of pharmacology and toxicology — for instance, the authors state that TCP exhibits reversible binding (a strange and incorrect statement), and also:

> One [patient] experienced what may have been a mild serotonin syndrome involving symptoms of anxiety, nausea, flushing, hyperventilatlon, a sense of impending doom, and an increase in preexisting insomnia.

Those symptoms do not justify that statement (mild SS) and evince a poor understanding of serotonin toxicity.

They concluded:

> 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.

This report exemplifies precisely what bedevils most of these case reports — the authors do not know what they should be looking for to report, and they misreport largely irrelevant observations — they reported 'no myoclonus' was observed; they should have been examining for hyper-reflexia and clonus. That is not state-of-the-art knowledge for a major academic teaching center.

Experience

I have personally made a direct switch only on a couple of occasions, but associates, and various people who have been in contact via my web site (both patients and doctors), have reported numerous (dozens) of other cases who have done so of their own accord and have reported uneventful transitions: one man

has reported changing abruptly from TCP>PLZ>TCP several times with high doses without any problems. It is also relevant to note that I know of a dozen or more patients who have taken both PLZ & TCP together without problems, but with added benefit.

A possible mechanism for hypertension

It is recognised that abrupt cessation of antihypertensive treatment can cause rebound hypertension; indeed, this is a not uncommon presentation in emergency departments. It is forgotten that MAOIs are anti-hypertensive drugs, and, as I have reviewed elsewhere, were indeed used for the treatment of hypertension in the 1960s and 1970s. I have seen patients who have developed high blood pressure when well-meaning primary-care physicians have stopped the 'dangerous-old-antidepressants-we-don't-use-anymore' that the (doddery old) specialist has been giving because he does not know about the wonderful new drugs we now have (that the young lady drug rep in the short skirt[3] who took me to lunch told me all about). I encountered some primary care physicians who exhibited extraordinary hubris and careless arrogance, usually for the purpose of 'big-noting' themselves to their private patients.

Here is an incidental tip for patients: beware of primary care physicians who repeatedly recommend the latest drug to come on the market, especially when they are changing the treatment previously instituted by a specialist. They may also have a clock, leather folder, blotting pad, box of pens etc. with the trade name of the drug in question emblazoned on it!

I have seen patients on long-term MAOI treatment who have developed idiopathic hypertension during the course of that treatment, which was 'disguised' by the MAOI. These patients then had substantial rises in blood pressure on cessation of the MAOI. Indeed, one of them had a small CVA whilst waiting for an appointment to see me, to decide on future treatment. The primary care doctor had already (unilaterally) instructed her to cease the tablets prior to the appointment with me. If that patient had already restarted the other MAOI, where then would the blame for her CVA have been laid? The case reported by Gelenberg fits this possibity (13).

Such observations add yet more weight to my recommendation that one should monitor sitting and standing BP regularly in everyone taking MAOIs, especially when changing treatment.

Opinion and conclusion

If there is ever good reason to swap rapidly, it is reasonable to do it, because:

1. There is no theoretical basis to suggest it might be contra-indicated
2. It has clearly been done many times without any problem
3. Existing reports do not constitute substantive evidence to the contrary

Also, monitor sitting and standing BP especially carefully and frequently when changing treatment (three times daily, more frequently for hospital patients).

There are some simple principles of clinical pharmacology relating to mixing medications which indicate that it is best to make changes slowly, and to only make one change at a time. Because the period for ongoing pharmacological effects from MAOIs is long, like weeks, not days, I would suggest that the following regime has a theoretical basis which recommends it. Add a small dose

[3] Reliable sources have reported that drug companies recruited female representatives from sports cheerleader squads.

of the new drug (TCP 5 mg, PLZ 7.5 mg), without changing the previous regime, and then build up the dose to the minimum therapeutic level (TCP 30 mg, PLZ 45 mg) slowly, i.e., over a couple of weeks or more, whilst tapering off the previous treatment[4]. If that can be achieved with adequate monitoring and supervision that would be my preferred approach.

Make dose increases and decreases slowly, make only one change at a time, start low and go slow

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[4] For example, if starting from TCP 50 mg, add 7.5 PLZ for 3-5 days, then <TCP to 40 mg, wait 3-5 days and >PLZ to 15 mg, and so on. One could call this stepwise dovetailing.

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