PARNATE: ADJUSTING THE DOSE

Summary

This commentary offers practical advice for starting treatment, and adjusting the dose to get a timely response, with irreversible MAOIs (Tranylcypromine/Parnate™, Phenelzine/Nardil™, Isocarbxazid/Marplan™). It brings together information from my published scientific papers [1-12] and from other previous commentaries on this website (see MAOI menu). I am an internationally recognised expert on MAOIs and their interactions.

Whilst preparing to start tranylcypromine (TCP) it is helpful to be confident about what other drugs can be used to help while waiting (although a washout period is often not necessary), and what can be given in combination. Contrary to what many doctors have been led to think, it is actually pretty simple — anything, except a drug with potent serotonin reuptake inhibitor (SRI) properties. But the details are discussed here.

Foods now have lower tyramine levels than in the past, so the diet is quite easy to follow; for many patients it involves few, if any, changes. Exhaustive details and discussion about that are in the MAOI sub-menu. Alongside the peer-reviewed and freely accessible 'Prescriber's Guide to the MAOI diet', aimed primarily at physicians, there is my downloadable monograph, which caters to patients in its writing and explanation — indeed, it may rightly be regarded as the seminal, up-to-date source of data published on the topic (as most of the information in medical texts and on the jnternet is either incorrect, or decades out-of-date, or both).

Not only do foods have less tyramine in them now, but the risk generated by an episode of hypertension due to ingesting tyramine has almost certainly been overestimated and misunderstood: see here for a discussion about that [link].

Introduction

It is preferable to use proper drugs names, not 'trade' names — one should know what one is using/taking, and navigating the scientific literature requires using the proper chemical name in order to find information.

So, **Parnate™ is tranylcypromine (TCP)[1]; Nardil is phenelzine (PLZ); Marplan is isocarboxazid (ISO).[2]**

The general principles of clinical pharmacology, in relation to the initiation and adjustment of drug treatment, are not well observed. I have commented previously on how important it is for doctors to clearly document at every visit the exact current treatment and dose duration. Unless that information is readily to hand, along with the degree of improvement at each stage, it is not possible to make logical decisions about future treatment adjustments (there is further discussion on this, and similar issues, in my AD algorithm).

Also, it is useful to remind oneself of the 'Ten principles of good prescribing' [13]; see a separate upcoming commentary on this subject here. The old epithet '**start low, go slow**' is particularly apposite. This is because pharmaco-

1 In the text I will just use 'TCP' but, unless specifically stated, comments apply to all irreversible MAOIs. Which of these drugs are, or are not, available in which countries is variable, and without any sound logic whatsoever.
2 The alternative spelling 'iscocarboxazide' is also common; there are about equal numbers of references retrieved with each spelling variant.

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kinetic interactions usually come on slowly, but pharmaco-dynamic interactions, which are the main problem with MAOIs, can reach a severe degree in a matter of a few hours. That reflects the basic mechanistic difference between the two processes.

These comments apply particularly to TCP, but many of them can be generalised to non-MAOI drugs. However, the important difference of TCP lies in its unique mechanism of action — as an irreversible inhibitor of MAO — which is different to almost all other drugs used in medicine, most of which act reversibly at various different sites, receptors and enzymes, etc. Once a molecule of an irreversible MAOI drug has interacted with the MAO enzyme, that molecule of MAO is permanently disabled. Enzyme function is then restored only by the production of new enzyme from the genetic code, via synthesis of new proteins that make up the structure of the enzyme.

PET studies indicate that human MAO is replaced at the rate of approximately 3% of the total per day (more slowly with advancing age), so it takes a while for *full* function to be regained (like 30-40 days [14]), and if 80-85% blockade is a threshold level for full therapeutic effectiveness, as is generally posited, then full effectiveness would be expected to last 3-7 days after the last dose, if full 100% blockade of MAO had previously been achieved (which also indicates that twice weekly dosing should be sufficient — see below). It has also been shown that ~40% MAO inhibition is required to reduce MTTP toxicity [15] which indicates some significant changes are probably taking place at a dose of ~10-20 mg daily (of TCP), even if 85% blockade is required for the maximal effect. That data coincides closely with my extensive clinical experience.

Starting dose: monitor blood pressure (BP)

TCP has been shown to inhibit >50% of human brain MAO-A after a three-day treatment with 10 mg/day [16]. Clinical experience indicates that a small proportion of patients will get effects from that dose (I do not mean optimal or maximal effects, just noticeable ones), even sometimes significant postural hypotension of the degree depicted in the bar graph in the MAOI_BP pdf, which illustrates BP changes at days 4 and 11.

It is generally supposed that approximately 85% inhibition (of blood platelet MAO-B, which is the only peripheral marker measurable — we do not know how that corresponds to blockade of MAO in different types of cells in the CNS) is required for full clinical effect to occur.

Using the sound pharmacological principle of 'start low, go slow', it is clearly prudent to start with no more than 20 mg TCP per day, to assess the effect for 5 days by monitoring **sitting and standing BP**[3] to ensure there is not an excessive postural drop at that dose — but note, maximal BP drop, on a constant dose, will take about 10 days to develop. This is explained in the downloadable MAOI_BP pdf document here.

In my considered opinion, BP monitoring is an important procedure to follow because there is a small risk that sudden unexpected postural hypotension might lead to injury — I once had a patient who got out of a hot bath and stood at the top of the staircase listening, because they thought the telephone was ringing (in a world long before mobile phones, oh young ones, when the only phone in the house was in the downstairs hallway!). Fortunately, they did

[3] I say sitting and standing BP, rather than lying and standing BP, because most of these assessments will be taking place in the 'office', not the hospital. It is therefore easiest to standardise all measurements to sitting and standing.

not tumble down the stairs when they fell to the floor. Hot days, hot baths (or here in tropical Queensland, warm swimming pools — *eat your heart out if you are in the Northern hemisphere!*), dehydration, etc., are what doctors need to remind people to be careful about.

Educating patients (and doctors) about the practical aspects of postural hypotension is wise and one particular paper is especially useful.

Sadly, many practitioners do not understand the above, and as soon as a patient feels faint, or falls, they react by ceasing treatment — a completely unnecessary mistake. In this day and age it seems almost mandatory for patients to have their own (upper-arm or wrist) BP monitor, and to be schooled in is proper use to monitor their own BP at home and to keep a written record of BP results [we are planning to develop an app for devices to display these results graphically, as in my pdf (any accomplished app-developer who can help with this should contact me)].

It is important to appreciate that this hypotensive effect is near-maximal during the 10-14 days after reaching the 'BP-effective' dose — that is often around 30 mg TCP per day, and then, if the dose is kept the same, diminishes progressively after that, as the receptors adjust their sensitivity (see pdf file mentioned above re BP). At that point, the dose may be safely increased.

By 'BP-effective' dose, I mean the dose that will induce a consistent postural BP drop of ~10-15 mmHg systolic, as illustrated in the bar graph (days 11 and 14).

Most people on long-term MAOI treatment experience a useful drop in BP, and anyone previously on treatment for hypertension will need to have that medication monitored and reduced; sometimes it will need to be ceased completely. If MAOI treatment is ceased, remember to monitor BP and re-assess need for further anti-hypertensive treatment.

Reliable monitoring of these BP changes requires that the measurements have been done in a consistent manner, after being seated at rest for 5 minutes, and that a few pre-treatment measures are done as a 'baseline'. The pattern shown in the bar graph shows why it is vital that two standing measurements are done. All the published papers on MAOIs and BP are of limited value because they do not provide data on the relevant dose-change-BP timing, nor two successive standing measurements: I have reviewed this subject here where I commented 'these are drugs which were used as anti-hypertensives over 50 years ago! and even now psychiatrists are congratulating themselves for discovering hypotension as a 'side-effect'! When used like that, the term 'side-effect' is devoid of meaning — it is not a 'side-effect', it is a predictable therapeutic effect. And people wonder why I make disparaging remarks about the knowledge exhibited by psychiatrist.

For patients who are not in hospital I would usually wait a minimum of 10 days for the dose to manifest its full effect before any further increase.

So, starting with 20 mg TCP and increasing to 30 mg after 10 days would be the most frequent pattern — however, if after 5 days on 30 mg, the BP drop on standing was less than 10 mmHg, then I would probably proceed to 40 mg, but then allow a full 14 days on 40 mg to judge the effect. If BP drop on 30 mg was more than 15 mmHg, then I would wait the full 10-14 days to assess the maximal degree of postural hypotension at that dose. If that level of postural hypotension was still present at 14 days, I would wait a full 4 weeks on that dose to assess the degree of illness improvement.

Experience in using these drugs will allow doctors to fine-tune these suggestions to their own practice-population and circumstances, and during this phase education and confidence building about BP and diet is timely.

A small proportion (~20%) of patients will get a good response to 30 mg TCP, so progressing hastily beyond that dose, without fully assessing response, means there is a chance of using an excessive dose for that patient: that is not good clinical pharmacology practice.

My AD algorithm stresses the importance of critical assessment of the degree of improvement at each 'stage', particularly improvement in 'core' symptoms of anergia and anhedonia as reflected in work, social and leisure activities. If there is a good BP drop, and these indices are showing significant improvement within 4 weeks, then I would wait as long as 3 months to assess the full benefit. If such a degree of improvement is not evident, or there is no drop in BP, I would press on, in similar stages, to a dose of 60 mg daily.

Side-effects and problems

A majority of patients who have had multiple different antidepressant drugs rate MAOIs as having less side effects than most, or all, of their previous treatments — not many doctors know that [17, 18].

It is relevant to mention that patients who experience even profound hypotension, sufficient to prevent them standing at all, will usually develop tolerance given time — and it may take 3-4 weeks or more, not just 10 days. I have seen quite a number of patients who were unable to stand for significant durations without fainting, who persisted with treatment, and went on to take and benefit from TCP for years without further trouble.

The first simple essential intervention re low BP is to ensure adequate salt intake — this may mean 5-10 grams per day (two tea-spoons of sea salt — which has a higher magnesium content), especially in those whose normal diet is low in salt.

In my experience fludrocortisone is not usually required, and if used can often be tapered-off within a couple of months. Midodrine is not usually helpful and may have an unpredictable and fluctuating effect.

So, the mantra 'slow and steady wins the race' has never been truer.

Insomnia and its treatment

Incidentally, the same long adaption period applies to severe insomnia: this sometimes resolves completely with time — sometimes 3 months, or even more.

The lady who had a letter published in CNS Spectrums, in response to my 2017 editorial in that journal [19], said she had severe insomnia for around 3 months (see 'patient stories'). Interestingly, she noted that when she was awake in the night her thoughts were of pleasant past achievements and events, not horrible depressive thoughts or dreams. Indeed, her doctor wondered if she was manic (she was not). Her hypotension also lasted at least 3 months.

My comment about the 'manic' idea is that those who are not familiar with the dramatic improvements one sees with TCP might well suspect mania, because they have so little experience of seeing 'proper cures'. We used to see such rapid and dramatic improvements sufficiently frequently that one of the senior nursing staff in the hospital (the best colleague I ever had the privilege of working with) came up with the flippant line 'the impossible we do today;

miracles take a little longer'. When one has seen severe psychotic depression resolve in 7 days, one appreciates that comment is not without substance.

In the interim, trazodone seems to work well for insomnia, and nortriptyline can be useful too (both are potent 5-HT2A antagonists). Likewise, the potent central antihistamine effects of doxepin (or mirtazapine or quetiapine) can be helpful, although both these drugs substantially promote weight gain in larger doses given for longer periods of time. The fact that most texts, and most psychiatrists, think the drugs above cannot be combined safely with TCP is simply a testimony to lack of knowledge and experience.

Melatonin helps some.

The benzodiazepine-type drugs seem less effective, but if used, the medium half-life drugs like lorazepam seem preferable. Long half-life drugs like clonazepam and diazepam are not ideal — the levels can build up over a couple of weeks or more; alprazolam and ultra-short half-life 'Z' drugs are less effective. Half-lives of Z drugs are approximately: zaleplon 1 hour, zolpidem 3 hours, zopiclone 5 hours.

Lastly, L-tryptophan (the amino-acid precursor of serotonin) should not be forgotten. Gradually escalating doses starting with 1-2 **grams** (not milligrams) at night can be effective (again, the old mantra of start low, go slow). We used to use as much as 4 grams, but at such higher doses one sometimes sees hyperreflexia and clonus. There are rare reports of toxicity and confusion [20-24]. Some of the cases of confusion reported in association with L-Tryptophan exemplify a wanton disregard of the principles of good clinical pharmacology mentioned above: e.g. in one of the cases described: dothiepin 300 mg daily was ceased abruptly and PLZ started the next day and increased the day after that — and with addition of tryptophan! One would really have to wonder if someone who does that has even a basic grasp of pharmacology and therapeutics… so, if you go looking for trouble you will find it.

Change only one drug at a time, and do not suddenly cease drugs known to produce withdrawal effects! Allow at least five half-lives to elapse before assessing the result: you just cannot help some people who are wilfully stupid and disobey the basic rules of sensible clinical pharmacology.

So to reiterate: as far as L-tryptophan is concerned, it is safe if used sensibly — even in large doses it will not cause serious ST [25]: it will induce predictable hyperreflexia and clonus with higher doses, so just back off a little if that happens – no need to panic, these serotonin-mediated effects are dose-responsive and wear off quickly (a few hours).

My observation is that the longer the duration of the depressive illness, and the more severe it is, the greater the degree of sleep disturbance & 'REM deficit', and the longer it takes for the sleep pattern to normalise as recovery proceeds. As far as REM sleep is concerned, the brain seems to be like a money-lender — you can accumulate a big debt, but you have to pay it back eventually. EEG monitoring is an area where further research would be useful.

Adjusting dose: ongoing BP monitoring

Once there is a useful, but not problematic, BP drop on standing (see day 14/18 on graph) it is ideal to stick with that dose for a full 4 weeks to critically assess the speed and degree of improvement, unless the severity of the illness, and/or the life situation, mandate a more aggressive approach.

In this manner, if no substantive response was manifest, I would proceed to 60 mg daily and if there was still no substantive response, would re-assess the case

or look for a second opinion, before proceeding with higher doses. In my experience, most patients who are going to respond to TCP do so in the dose range of 30-60 mg per day. If only a partial response is evident, at the maximum tolerated dose, one would then consider augmentation with nortriptyline, or L-tryptophan, or lithium, or even all three together (for an example of cases histories like this, see the article by my old boss in London, Paul Bridges [26]). This illustrates well the type of case I was 'brought up on' in our tertiary referral unit. We did psychosurgery too — actually a modified prefrontal tractotomy using radio-active Yttrium seeds — and it produced some spectacular results (but, as one wag said, 'I'd rather have a full-bottle-in-front-of-me than a full frontal lobotomy').

It is often satisfactory to time the TCP doses about 4 hours apart, starting with the largest portion of the dose first thing in the morning. If somebody was taking 50 mg, one might often give 30 mg as the first dose, and 20 mg between two and four hours later. Doses taken later in the day do seem to be associated with greater problems with insomnia. However, I have had patients who have taken the whole dose at night and claimed to sleep well, so one cannot be dogmatic. Sometimes taking four equal doses spaced at two-hourly intervals during the morning suits some patients better. Some people find that taking the whole dose first thing in the morning lessens insomnia. The bottom line is you have to be your own 'guinea-pig'.

Paradoxical hypertension

It is invaluable to have an ongoing record of blood pressure as described above. This is especially so when episodes of paradoxical hypertension occur, which is sometimes seen (in approximately 5% of cases, in my experience)[4]. This paradoxical hypertension (not related to tyramine ingestion) characteristically commences an hour or so after the second TCP dose of the day, especially when the dose is a little higher, and lasts for up to a couple of hours before subsiding spontaneously. Although such episodes do cause concern in some people, especially doctors, they are rarely, if ever, sufficiently high to be problematic. In my experience, they rarely go over 180 to 200 mmHg, and then only briefly (see my comment on this here [8]). Again, this phenomenon often dwindles away over time. If treatment is thought to be advisable, a beta-blocker like propranolol is appropriate, although it should be noted that propranolol is not suitable for severe hypertension secondary to tyramine ingestion.

And also

This is an appropriate point at which to note a couple of interesting things. I well recall that in many of the cases referred to us in the London unit, which usually came from other teaching hospitals, it would be said that a full course of various kinds of treatment had been given. It was of course my job to check all these things, and when I went through the notes of the referring hospital, I would quite often find that such statements were inaccurate and that the treatment had been prematurely truncated, or not given in the dose stated. Many referrers were convinced that if their favourite treatment did not work, there was no point in continuing their efforts. This was especially so when the patients had failed to respond to ECT. Many doctors would effectively give up on treatment after that. We sometimes used to proceed to psychosurgery —

[4] [More data from people who have measured the blood pressure as I recommend demonstrates this is in fact much more common than her to believed although it is usually quite mild.]

even though people had not had a course of an MAOI — simply because we knew full-well that if we sent them back to the referrer with instructions to institute such a regime, that it simply would not happen. This was the genesis of my habit of always recording the total duration of treatment, and duration of treatment on current dose, and the maximum tolerated dose. If this information is not readily available, it is inevitable that major mistakes in the treatment decisions will occur.

MAOIs frequently work when ECT has failed. It is most unfortunate that so few doctors appear to understand that.

Indeed, the enquiries I have had through the website so far this year (six months in at the time of writing) have included half a dozen such patients, a couple of them being medical practitioners. One of those doctors had had 38 ECTs (besides just about everything else in the book including TMS and ketamine), still has substantial islands of complete memory loss, yet got completely better after only a few weeks on TCP.

Other considerations

PLZ & ISO 'dose equivalence'

TCP 20 mg is approximately equivalent to PLZ 30 mg. The usual dose range for PLZ is 45 up to 90 mg daily.

Isocarboxazid seems a little more potent than PLZ (they are both hydrazines), with the dose range being 20-60 mg or thereabouts. ISO may have less of a sedative effect.

The only recent review of ISO I know of is Larsen's [27].

Pyridoxine

The hydrazine MAOIs (isoniazid, carbidopa, PLZ, and ISO, but **not TCP**) inevitably reduce pyridoxine [28], and it is probably wise to do a pre-treatment pyridoxine level and routine follow-up levels after 6 and 12 months. It seems logical to give pre-emptive B6 supplementation at 100-200 mg per day [29-32], particularly in vulnerable patients. Apart from Larsen's small series [29] most of the evidence about pyridoxine supplementation comes from the tuberculosis literature (isoniazid) where guidelines now suggest that supplementation should be routine in cases of general poor health, poor diet, pregnancy, children, the aged, etc.

Such hydrazine-related drugs can cause acute pyridoxine-responsive neurotoxicity [33-38] and that is *ipso facto* proof that they have a consequential effect on the pyridoxine levels.

Sub-lingual?

It has now been convincingly demonstrated using PET that **sublingual** absorption of selegiline (aka deprenyl) inhibits brain MAO-A [39], as well as MAO-B — selegiline is only slightly selective for B over A, so quite a small increase in 'normal' levels will produce MAO-A inhibition. It would be expected that TCP would likewise be absorbed sublingually, perhaps thereby reducing some side effects; but its higher acidity might cause irritation.

In a unique paper by my old friend (I lectured in Toulouse many years ago) Jean-Michel [40], it was neatly demonstrated that selegiline works well given twice weekly. TCP would be expected to do the same; sadly, no-one has tested

that very important hypothesis — a testimony to the paucity of perspicacity in research.

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