

Multiple drug-intolerant hypertension:

a case series utilising a novel-treatment algorithm

INTRODUCTION

Poor adherence to antihypertensive medication is a major cause of suboptimal blood pressure (BP) control¹ and frequently arises from intolerance to antihypertensive medications due to adverse drug reactions (ADRs). A meta-analysis of antihypertensive drug trials using monotherapies demonstrated that ADRs occur in up to 39% of patients, resulting in a frequency of discontinuations of medication from 6.8–17%.² These ADRs can be due to hypersensitivity reactions or dose-dependent, pharmacologically predictable adverse effects. In addition, patients also report bizarre, unpredictable reactions, without a clear pharmacological basis, which are sufficiently debilitating to warrant discontinuation of treatment.

We classify hypertensive patients who have documented intolerances to three or more unrelated classes of antihypertensive medication as having multiple drug-intolerant hypertension (MDI-HTN).³ Such patients are unable to take antihypertensive drugs recommended by standard guideline-based algorithms⁴ and are difficult to manage, as treatment options are limited. This results in uncontrolled hypertension with end-organ damage and poor quality of life.⁵

We developed a novel pharmacological stepwise treatment protocol (Figure 1) to improve BP control in patients with MDI-HTN.³ At step 1 patients are tried on fractional doses of antihypertensive medication by quartering or halving tablets. If not tolerated or if BP is uncontrolled, step 2 comprises antihypertensive medication in liquid formulations, often at one-tenth of standard doses. If not tolerated or if BP is not at target, step 3 utilises transdermal patches of glyceryl trinitrate (GTN) or clonidine. Step 4 is to try drugs unlicensed for hypertension but known to lower BP such as 5-phosphodiesterase inhibitors (5-PDEI)⁶ or long-acting mononitrates.⁷

We describe a case series using this novel stratified approach. These cases were secondary/tertiary referrals to the Barts BP Clinic, made by primary care physicians or specialists from other hospitals. We have selected a convenience sample of four cases to best illustrate how the different steps of this treatment protocol are deployed and how this can require significant input from the specialist team. All patients undertook home BP monitoring

that not only excludes contribution of the white-coat effect but also allowed us to quantify the response to therapy.

CASE 1

A 71-year-old white male was referred with an office BP (OBP) of 190/100 mmHg and an average home BP (HBP) of 190/85 mmHg. Conventional antihypertensive medications in standard doses had made him feel non-specifically unwell. His regimen at referral consisted of bendroflumethiazide 2.5 mg, bisoprolol 2.5 mg, irbesartan 300 mg, indoramin 20 mg, and moxonidine 400 mcg, all taken daily. He exhibited an excellent response to fractional doses of conventional medication. His current regimen is losartan 12.5 mg, lercanidipine 5 mg, spironolactone 6.25 mg, bendroflumethiazide 2.5 mg, and indoramin 20 mg, all taken daily. Current BP control is much improved: OBP 156/82 mmHg and HBP averaging <130/70 mmHg.

CASE 2

A 61-year-old South Asian male with hypertension and pustular psoriasis was referred with an OBP of 208/131 mmHg and a daytime ambulatory BP (ABP) of 197/111 mmHg. His BP management was complicated by ADRs such as dizziness, extreme tiredness, cold extremities, and skin reactions to all antihypertensives, necessitating discontinuation. He was re-challenged with fractional dosing of tablets but could not tolerate them due to ADRs. Thereafter, liquid nifedipine (2 mg twice daily) caused no adverse effects and he was able to tolerate up-titration to a dose of 20 mg twice daily with significant BP reduction. In order to achieve target BP, liquid spironolactone 5 mg twice daily was added. His current HBP record indicates an average of 142/88 mmHg over the past 6 months, taking this combination of liquid antihypertensives.

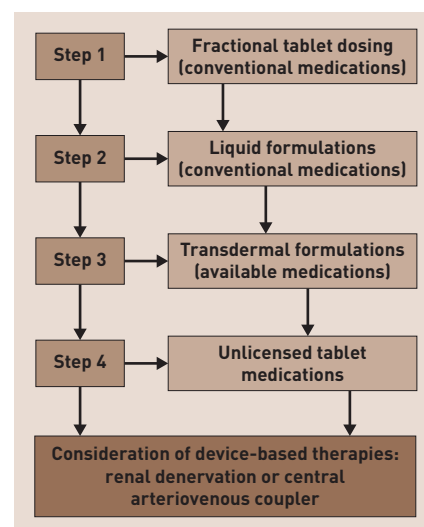


Figure 1. Multiple drug-intolerant hypertension (MDI-HTN) treatment algorithm.

CASE 3

An 80-year-old white female with MDI-HTN was referred with an OBP of 182/91 mmHg. She had suffered a previous stroke, and also had peripheral arterial disease, asthma, hypercholesterolaemia, gastro-oesophageal reflux disease, and atrial flutter. Numerous different antihypertensives in conventional doses were intolerable due to ADRs such as nausea, excessive tiredness, and lethargy. It was deemed unsafe to anticoagulate her for atrial flutter due to uncontrolled hypertension and she lived in fear of further strokes. Fractional doses of conventional tablet medication and liquid formulations of antihypertensives proved non-specifically intolerable. Subsequently, a clonidine transdermal patch (Catapres TTS-1; 0.1 mg/day) was well tolerated and resulted in an average HBP of 170/90 mmHg. The clonidine patch therapy was increased to 0.2 mg/day and a GTN patch (5 mg/24 hours) was added. Her HBP average has improved substantially to 155/85 mmHg and is closer to acceptable targets for her age (<150/90 mmHg). She has

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now started anticoagulation with rivaroxaban to reduce her risk of further stroke.

CASE 4

A 47-year-old white male presented with MDI-HTN and comorbidities including type 1 diabetes mellitus, asthma, hypercholesterolaemia, and gastro-oesophageal reflux disease. Initial OBP was 160/100 mmHg and ABP monitoring confirmed suboptimal control with a white-coat effect: daytime average 137/93 mmHg (target BP <130/80 mmHg). He could not tolerate the following antihypertensives in conventional doses: calcium channel blockers resulted in dyspnoea; angiotensin-converting enzyme inhibitors caused cough; rhinorrhoea was reported with angiotensin receptor blockers; and dysglycaemia was observed with diuretics. Fractional tablet dosing and liquid formulations of antihypertensives also caused debilitating ADRs: beta-blockers (asthma); liquid spironolactone/furosemide (intolerable diuresis). GTN patches caused severe headaches. However, tadalafil 2.5 mg daily was well tolerated; thereafter, an increase to 5 mg daily resulted in an improved OBP of 137/84 mmHg and HBPs that were at target.

DISCUSSION

Our stratified medicines approach to managing MDI-HTN appears successful and is predicated on a four-pronged rationale as follows. First, many ADRs are dose dependent⁸ and fractional tablet dosing reduces the incidence of dose-dependent ADRs. Second, combinations of drugs at lower doses can achieve greater BP reduction than high doses of monotherapy.⁸ Third, liquid formulations of antihypertensives exclude excipients such as lactose and silica that account for 90% of the weight of solid medication formulations and can cause ADRs.⁹ Transdermal patches avoid gastrointestinal irritability, have less frequent dosing intervals, avoid first-pass effects (fewer interactions), and limit rapid changes in plasma drug concentrations that may give rise to ADRs. Finally, 5-PDEI and long-acting nitrates have been shown to reduce BP in small clinical trials^{6,7} and can be helpful if other options fail.

Patients with MDI-HTN are at high cardiovascular risk due to uncontrolled hypertension and pose a serious challenge for clinicians. Many of our patients have reported tremendous difficulty in convincing their doctors of the pernicious side effects they experience, which are frequently disbelieved or disregarded, particularly where there is no clear pharmacological

basis to them. A common medical response to the issue of MDI-HTN is for clinicians to insist patients take their medication as failure to do so would inevitably result in cardiovascular events and therefore the ADRs have to be put up with. We however chose to take the approach that, in the instance of over-non-adherence due to intolerances, we would not expect patients to continue taking medications that caused unacceptable ADRs and poor quality of life.

Our novel-treatment algorithm has demonstrated substantial improvement in BP control with increased tolerability of medications and could be beneficial to other patients with MDI-HTN. There are some limitations to this approach, which clearly requires frequent clinic visits and multiple interactions with the prescriber, and is therefore labour intensive from a medications management perspective. Also, the halving or quartering of tablets can result in imprecision of dosing and is not easily managed by all patients, especially those with disabling arthropathy. Further, the costs of liquid and patch formulations of drug therapies are higher than conventional tablets, and the cost-effectiveness and efficacy of this algorithm therefore need to be tested in a rigorous clinical trial.

Despite our best efforts, a small number of patients are not able to tolerate any of these treatment strategies and are offered experimental device-based treatments for hypertension (for example, renal denervation) as a last resort. However, it remains indisputable that antihypertensive medication intolerance is a neglected cause of failed adherence, leaving patients at exaggerated cardiovascular risk and often desperate for a treatment strategy, and we strongly recommend increased focus by clinicians on ADRs for which the patient is not culpable. These patients can have a trial of fractional dosing of tablets with their primary care physicians before being referred on to specialist centres.

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Patient consent

The patients have consented to the publication of this article.

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