**Drug induced hypertension – a QUM opportunity for pharmacists?**

**By Angus Thompson**

**Learning objectives**

After reading this article, pharmacists should be able to:

- Identify patients who may be at risk of drug induced hypertension.
- Recommend appropriate action to patients who may have drug induced hypertension.
- Liaise with other members of the healthcare team to minimise the risks of drug induced hypertension.

**Competencies addressed:** 3.1.2, 3.1.3, 3.2.2

This article relates closely to PSA Professional Practice Standard 14 – Monitoring and Case Detection.

**Introduction**

Antihypertensives may be one of the most commonly prescribed classes of drugs, but a significant proportion of other medications passing through the hands of pharmacists may be contributing to the burden hypertension places on Australians.

With an ageing population and the associated management of multiple age-related pathologies, there will inevitably be an increasing number of patients whose existing risk of cardiovascular disease may potentially be exacerbated by drug induced hypertension. The Heart Foundation 2008 Guide to management of hypertension consequently draws attention to the need to include consideration of those medications that may increase blood pressure when taking a patient’s history.

Among those drugs known to cause or exacerbate hypertension are:

- Clozapine
- Corticosteroids (systemic)
- Haemopoietic agents (darbepoetin, epoetin)
- Immunomodifiers (cyclosporin, tacrolimus)
- Leflunomide
- Monoamine oxidase inhibitors (reversible and irreversible)
- NSAIDs (conventional and COX-2 selective)
- Oral contraceptives
- Sibutramine
- Stimulants (dexamphetamine, methylphenidate)
- Sympathomimetic agents (e.g. oral decongestants such as pseudoephedrine)
- Venlafaxine.

**Monitoring recommendations for specific medication**

For many of the medications recognised as potentially causing or exacerbating hypertension, the literature contains specific recommendations for monitoring blood pressure. This article will focus on some of the most commonly encountered drugs that and others where the potential for effects to increase blood pressure may not be recognised.

Angus Thompson is a Research Fellow at the School of Pharmacy, University of Tasmania, a part-time practising community pharmacist and a former UK Prescribing Advisor.
Non-steroidal anti-inflammatory drugs (including COX-2 inhibitors)

The frequency with which non-steroidal anti-inflammatory drugs (NSAIDs) are prescribed means they are among the most likely causes of drug induced hypertension.

The mechanism by which NSAIDs increase blood pressure, like so many of their adverse effects, is inextricably linked to the delivery of their desired therapeutic effects, namely inhibition of prostaglandin synthesis. Prostaglandins play an important role in maintaining renal perfusion, and the use of NSAIDs can lead to reductions in glomerular filtration rate, with the consequent retention of sodium and water. These effects are seen with both traditional NSAIDs and selective COX-2 inhibitors.

Standard sources of prescribing information contain widespread references to the potential hypertensive effect of these drugs and advise that blood pressure should be monitored closely at both initiation and throughout the course of NSAID therapy.

In some patients, for example, those with rheumatoid arthritis, a significant reduction in the use of NSAIDs is unlikely to be achievable. However for those patients taking NSAIDs for osteoarthritis and other musculoskeletal disorders, optimising use of analgesia may be a realistic possibility and enable use of lower doses or less frequent dosing of NSAIDs. Many patients take NSAIDs as monotherapy for pain where there is only a modest inflammatory component, unaware that paracetamol (with or without codeine) can often be taken safely and fulfil a useful NSAID-sparing function. Although over the counter NSAIDs are less problematic than the generally higher doses used on prescription, there remains a potential for effects to elevate blood pressure, especially amongst those who disregard the recommended doses or who have other pre-disposing factors.

It is increasingly recognised that NSAIDs, through the same mechanism, can precipitate or exacerbate heart failure. A recent Danish study added weight to the argument that NSAIDs should be avoided in this group of patients where possible. It would therefore seem appropriate for pharmacists to extend their concern about NSAID related hypertension to heart failure and similarly consider discussion of analgesic regimes that may minimise the potential harms of NSAIDs in this patient group.

Venlafaxine

Hypertension is recognised as a potential adverse effect of this serotonin and noradrenaline reuptake inhibitor (SNRI), with the incidence rated as common, occurring in between 1% and 10% of patients, in the product literature. This also states that measurement of blood pressure is recommended for patients receiving venlafaxine and that hypertension is particularly seen in patients receiving doses greater than 200mg daily.

Some prescribers, most commonly psychiatry specialists, are willing to push the dose of venlafaxine way beyond the 300mg daily that is the generally recommended maximum and these patients are therefore of particular concern.

Vasoconstriction as a result of the potentiation of noradrenergic pathways has been proposed as a mechanism by which venlafaxine induces rises in blood pressure. Desvenlafaxine, a metabolite of venlafaxine, has recently been launched in Australia. Hypertension is similarly listed as an adverse effect, consequently regular monitoring of blood pressure is also recommended for patients on this drug.

Sibutramine

Hypertension has been recognised as a potential adverse effect of this anti-obesity agent for some time. Concerns over the cardiovascular safety of sibutramine led to the suspension of its marketing authorisation by the Italian authorities in 2002. However it was reinstated following a comprehensive review by the European Commission's Committee for Proprietary Medicinal Products (CPMP) which concluded that the risk benefit profile of the drug was favourable, whilst recognising the potential for effects on blood pressure and heart rate.

The pharmacologic activity of sibutramine is similar to venlafaxine, a serotonin and noradrenaline reuptake inhibitor (SNRI), and its potential to induce hypertension is also considered to be due to activation of the noradrenergic pathways. The current product information suggests that hypertension occurs 'commonly', i.e. affecting between 1% and 10% of patients.

Monitoring recommendations include that blood pressure (and pulse) should be checked every two weeks in the first three months of treatment; and once-monthly and regularly thereafter from months four to six, at a maximum interval of three monthly. For those whose systolic / diastolic blood pressure increases by >10 mmHg (or heart rate by >10 bpm) at two consecutive visits, sibutramine therapy should be discontinued.

Patients who are experiencing useful weight loss may be particularly disheartened in such circumstances, but it should be recognised that reductions in cardiovascular risk from weight loss would be offset by these significant increases in blood pressure and alternative approaches to weight management may need to be considered.

Leflunomide

Leflunomide has become a popular alternative to methotrexate or sulphasalazine, when an oral disease...
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modifying anti-rheumatic drug (DMARD) is indicated. Whilst it shares many of the potential adverse effects of these more established drugs, such as hepatic and haematological toxicity, it may also cause hypertension.

Data collected in trials of the drug suggest that increased blood pressure is a common effect, occurring in around 10% of patients. As a consequence, the product literature recommends that blood pressure is measured when therapy is initiated and periodically thereafter.

It is also worth considering that the long half-life (two to four weeks) of one of the metabolites of leflunomide means that adverse effects may persist for some time after cessation of therapy.

**Products with high sodium content**

Although relatively infrequently used, some soluble analgesics may be of concern due to the significant amounts of sodium that they contain, typically around 400mg per tablet.

Consequently those taking the full dose are consuming the equivalent of around eight grams of salt per day, exceeding the recommended daily maximum salt intake of six grams for the general population and four grams for patients with hypertension. With the link between excess sodium and hypertension now well recognised, considering alternatives to soluble analgesics would be a prudent step for those who are regular users of these products.

Although other preparations such as Mylanta Heartburn Relief and Zantac Effervescent tablets contain potentially significant amounts of sodium per dose, the frequency of dosing means they are less likely to have a major impact on blood pressure levels.

**Immunomodifiers**

Hypertension is widely recognised as a significant risk with the calcineurin inhibitors cyclosporin and tacrolimus.

In the case of cyclosporin, hypertension is reported to occur in up to 50% of patients receiving the drug post-transplantation, and approaching 10% of those with other indications. Standard references advise that regular monitoring of blood pressure is required during cyclosporin therapy, with specific recommendations that this should be undertaken every two to three months once the patient is clinically and biochemically stable.

For those cyclosporin patients who have undergone renal transplant, routine follow-up will include close monitoring of both renal function and blood pressure. However, when the drug is used for other indications, e.g. in dermatology and rheumatology, the lower incidence of hypertension associated with the drug may mean that less attention is sometimes paid to blood pressure monitoring, which is of concern.

With tacrolimus, hypertension is reported to be very common (>10% of patients) therefore monitoring blood pressures is again advised.

In view of the relatively limited options available to prescribers, there is a recognition that acceptance of some adverse effects from these immunomodifiers may be necessary to preserve transplants.

**Clozapine**

The literature contains inconsistent information regarding the incidence of blood pressure elevation with this atypical antipsychotic. Some sources suggest it is a common adverse effect, but others report it as being rare and to complicate issues, postural hypotension is also a known adverse effect. Monitoring blood pressure in patients on clozapine is therefore particularly prudent.

The haematological toxicity of clozapine means that it is usually considered only in those patients who fail to respond to other antipsychotics or where they have caused intolerable adverse effects. It may therefore be the case that even if elevated blood pressure is found, the options are limited and treatment of clozapine induced hypertension may be the only option.

Any such treatment should be supported with lifestyle modification and with additional good reason in the case of clozapine, given the tendency of the drug to increase weight and the risk of diabetes. Improving diet, exercise and moderating excess alcohol intake would therefore provide a useful double-whammy of effects.