The Use of Single Pill Combination Treatments in Patients with Hypertension

Statement from the British Hypertension Society
September 2012

In 2004, the British Hypertension Society (BHS) guidelines stated that “when no disadvantages of cost exist, fixed-drug combinations are recommended” (1). More recently, the 2006 & 2011 NICE guidelines (2,3) produced in collaboration with the BHS did not discuss the use of fixed-drug combinations (FDCs) because it did not fall within the pre-specified NICE remit. In anticipation of a further set of BHS guidelines this statement is to update the BHS position with regard to the use of FDCs.

Tablets capsules or pills containing two or more active ingredients have traditionally been known as fixed-dose or fixed-drug combination (FDC) treatments. However in the field of hypertension these single-pill combinations of drugs are usually not fixed in terms of the doses included but rather are “flexible” in that different formulations are usually available including more than one dose of at least one (and often both) components. Hence the terms single-pill combination or flexible-dose combinations are preferred to the traditional meaning of FDCs.

The use of FDC’s for the management of hypertension is limited in the UK, and much less commonly used than in the rest of Europe. This is in part because the use of FDCs to manage hypertension has been considered by some as “poor” medicine. It is difficult to explain this apparent prejudice when the use of FDCs is “the norm” in several fields of medicine including asthma, oncology, diabetes, anaesthesia and gynaecology. The largely outmoded arguments used against FDCs for hypertension management, which are based on concerns over cost and dose-flexibility are discussed below. One genuine difficulty associated with using FDCs for hypertension is the situation which arises when the recipient complains of a side effect (e.g. feeling “generally unwell,”) which is not clearly attributable to one or other of the components of the FDC. In that situation the patient is often, not unreasonably, loathe to continue with either of the component drugs! This shortcoming however is relatively rare (most side-effects are usually attributable to a specific drug class) and is generally greatly outweighed by the benefits of FDC use.

More Effective BP-Lowering

One of the reasons for promoting the use of two antihypertensive agents at low-dose as first-line therapy is that by doing so, more than one of the possible putative mechanisms for the raised blood pressure (BP) being treated may be addressed and hence the chance of providing more effective BP-lowering is increased. Unfortunately in most situations it is not possible to identify the aetiology or mechanisms behind any given patients raised BP, and
hence the optimal drug to provide best BP-lowering is not obvious. To date only crude surrogates – age and ethnic group are used in some guidelines\(^{1,2,3}\) to provide markers of renin status and hence to guide drug choice.

Otherwise we have no means of targeting specific drugs to specific patients and hence the potential value of trying to address 2 potential aetiological mechanisms by using two drugs as initial therapy. As mentioned previously this 2-drug approach is now enshrined in the latest European\(^{4}\) and American\(^{5}\) guidelines for a large proportion of newly diagnosed hypertensive patients.

The initial use of two antihypertensive drugs may also have the theoretical advantage of over-riding compensatory physiological mechanisms which are induced by initiating a single-drug class and which may reduce the BP-lowering efficacy of any single-agent. An example of these compensatory actions is the potential adverse effects of stimulation of the renin angiotensin and sympathetic nervous systems caused by administering a CCB which are blocked by concomitant use of a RAS blocker.

In addition to these theoretical mechanistic reasons for using two agents for the initial treatment of hypertension is the reality that most patients will need ≥2 drugs to control their BP levels to currently recommended targets. There is a reasonable hope therefore that by starting with two drugs, more rapid and effective BP reduction will be achieved with reduced need for drug titration. Such benefits were suggested by the excellent BP achieved in the ACCOMPLISH trial\(^6\).

**Mahmud Study**

Some of the best clinical data to support the idea of addressing >1 mechanism for the treatment of hypertension arise from a trial carried out by Mahmud and colleagues\(^7\). This trial compared the BP-lowering efficacy of four drug classes at full dose with a single-pill mixture of all four classes of drugs each at one quarter dose. The single-pill mixture of four drugs at one quarter dose provided a significantly superior BP-lowering effect to that of any of the individual drugs used at full dose. The other benefit of such an approach is that, because only low doses of the agents used were incorporated into the single pill mixture, the side effects of the 4 low-dose components are less likely to occur than when using the full dose of any of the single agents.

**Improved Side Effect Profile**

It might reasonably be expected that 2 drug classes would generate more side effects than 1 drug class. However side effects of all the drug classes except RAS-blockers are dose responsive\(^8\). Consequently the recommendation to use low doses of 2 agents in combination\(^{4,5}\) may reasonably be expected to produce reasonable BP lowering – perhaps equivalent to at least that of either drug at full dose – but without producing the side effects associated with the individual drugs. Furthermore, in certain situations the effects of a second agent may reduce the side effects induced by the first agent used. One such example relates to the combined use of CCB’s with a RAS-blocker.

The major side effect which limits the use of dihydropyridine CCBs is ankle oedema, as witnessed in several RCT’s including ASCOT\(^9\) and VALUE\(^10\). However several studies have now shown that the concomitant use of a RAS-blocker reduces this side effect significantly\(^{11,12,13}\). In addition a recent meta-analysis of trials comparing the effects of the
of FDCs of 2 drugs versus the same 2 drugs included in FDCs but given separately has shown that side effects tended to be reduced by using the FDCs (14).

Cost Savings

One frequently quoted reason for avoiding the use of FDCs has been the belief that they are more expensive than the sum of the costs of the constituent drugs given separately. Whilst this is sometimes true, in many situations it is not. For example in UK those FDCs including a RAS-blocker and a diuretic, provide the diuretic “free”. Hence direct drug costs may be reduced. This reduction in direct costs may be further enhanced by generating fewer prescription charges and reducing the costs due to several titration steps associated with introducing drugs separately. Indirect costs may also be reduced by the use of FDCs because of improved compliance. Several studies confirm a clear relationship between increased compliance and lower healthcare costs not least because good compliance even with placebo is associated with positive health outcomes (15). Whilst this undoubtedly reflects confounding in relation to some characteristics of the type of person who takes their tablets more carefully, the fact remains that compliance is, in itself, important. Meanwhile some small studies have shown that levels of compliance are linked with levels of BP- control achieved (16).

Compliance and FDCs

A recent meta-analysis of trials which compared the effects of FDCs of 2 antihypertensive agents with the use of the components of the same FDCs given as separate pills showed that compliance was significantly improved and compliance or persistence was also significantly improved among patients receiving the FDC’s (14). Whilst these findings appear logical and therefore unsurprising, high quality data to “prove” the apparently obvious are sorely lacking. Nevertheless the study which gave rise to these results is a collection of the best available data to date. An obvious extrapolation of these findings is that, on the assumption that it is true, the use of fewer tablets to deliver the same drugs produces better compliance it is a reasonable expectation that FDC’s would generate better BP-reduction and BP-control than when the components are given separately. The same meta-analysis did indeed show this tendency to improve BP parameters in association with FDC use. Unfortunately these finding are not statistically significant although this most likely reflects the limited data (both in terms of quality and quantity) available to make these comparisons and hence the power which the meta-analysis had to achieve statistical significance. More robust data are required to confirm these findings.

Impact of Compliance on CV events

No data are available to confirm that the increase use of FDCs compared with separate pill administration in the management of hypertension would translate into reduced CV events. However pending further evidence – which is badly needed – it seems a reasonable conclusion that given that the use of FDCs seems to improve compliance and thereby that improved BP levels are associated with FDC use, then it is logical expectation based on a wealth of RCT data that these benefits would translate into reduced CV events.

Summary

The table summarises the relative benefits of monotherapy and combination therapy provided as 2 pills or a single pill for the management of hypertension. In view of the apparent benefits of FDCs over free-drug combinations, the BHS believe that if there are no
significant cost disadvantages “fixed-drug” or single-pill combinations of drugs should be used preferentially for the routine management of hypertension when \( \geq 2 \) drugs are required.

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