Fixed-Dose Combination Therapies for Hypertension

D. Gareth Beevers, MD FRCP,
University Department of Medicine, City Hospital, Birmingham

Cardiovascular disease (CVD) is the commonest cause of death worldwide and with the aging population and the emergence of developing countries the problem will become even commoner. A major risk factor for CVD is hypertension which is also becoming commoner. This, therefore represents a public health issue for all nations. Since the first open label study in 1964, there had been a large number of randomised controlled trials of the treatment of all grades of hypertension. The latest study in patients aged over 80 years was published in April 2008. All show that anti-hypertensive drug treatment brings about a 40% reduction in stroke and a 20% reduction of coronary heart disease. The treatment of hypertension is clearly successful.

Targets

From an epidemiological point of view the target should be to lower the blood pressure as low as is possible. However from a clinical point of view, we only have evidence that we should lower blood pressure to around 140/85 mmHg. The opinion that blood pressure should be lower still is not evidence-based but rather is based on extrapolations from population surveys. Future clinical trials may address this issue. In the mean time it is clear that in order to achieve blood pressure of 140/85 mmHg, monotherapy will be the exception rather than the rule. Most of the trials found that in the majority of patients, two, three or even four drugs are necessary to achieve targets. Around 10% of patients need five or more drugs in order to control their blood pressure.

Compliance and the Tablet Load

Given that hypertension is, until its late stages, a symptomless condition, it is difficult to motivate patients to take tablets for years on end. If they need to take multiple drugs they may be even less motivated. There is good evidence that poor compliance leads to poor blood pressure control, and that poor blood pressure control leads to a greater frequency of cardiovascular complications. Consideration also must be given to the number of patients who are taking other drugs in addition to their antihypertensive regime. Many may be taking lipid lowering agents, many are on aspirin or other antithrombotic agents and some may require anti-diabetic treatment.

Patients may also be taking treatment for unrelated conditions. Table 1 shows a survey of 218 consecutive patients attending the blood pressure clinic at City Hospital, Birmingham. Patients were taking an average of 3.9 drugs per day to control blood pressure (range 1-8). However the patients are also taking other medications so the average number of drugs being taken was 6 per day with a range of 1-13. One can only speculate how many of these tablets were actually swallowed.

Fixed-dose Combinations

A good case can be made therefore to reduce the number of tablets patients needs to take whilst not reducing the strength of the treatment. We know that simplified drug regimes are more likely it is to be taken. There is evidence that compliance is better when patients are prescribed a single tablet containing two drugs than when they take the two drugs separately.

Arguments Against

The sales of fixed-dose combination (FDC) therapies for hypertension in the United Kingdom are lower than any other comparable economy. The reasons for this are complex. In general healthcare, economists, clinical pharmacologists and pharmacists tend to frown on use of FDC and this may explain their low take up rates. The arguments against them are that they may sometimes be more expensive than two components prescribed separately.
There is also the suspicion and that sometimes they are merely “gimmicks” by drugs companies to get round competition laws once the two components have come out of patent. By marketing a combined preparation, using a trade name, the pharmaceutical company can continue to make profits. This conspiracy theory is not baseless, as some FDC must be regarded as somewhat suspect. Some products do contain inappropriate contents and some have the correct drugs but in inappropriate doses. Some beta blockers/thiazide preparations contain too much of both agents.

Opponents of FDC may also disapprove of them because it is easier to use the trade name for such products rather than to name the two components simultaneously. Thus zestoretic 20 is easier to say than lisinopril/hydrochlorothiazide 20/12.5. In many hospitals in the UK, the use of drug trade names is regarded as unacceptable. Another objection is that they abolish the flexibility to increase the dose of one agent whilst not increasing the dose of the other. A clinician might want to increase a dose of an ACE inhibitor but if this were given in the form of FDC, he would also be increasing the dose of the diuretic, which he might not wish to do.

**Arguments in Favour**

The arguments in favour of FDC therapies and that they reduce the tablet load so the patients are more likely to take their pills. It is possible to achieve good blood pressure control with a fewer pills. Better control will lead to fewer clinical visits and a better longer term outcome with prevention of heart attacks and strokes. Whilst there is evidence that FDC do improve compliance and blood pressure control, evidence that they affect long-term outcome is not available. Another argument in favour of the FDC available for the treatment of hypertension is that they are logical in that they use an angiotensin-blocking drug with a diuretic or calcium channel blocker.

The use of these agents in combination produces genuine synergy, and may also show mutual offsetting of side effects. A FDC of a calcium channel blocker with a diuretic would be expected to be less effective and not “logical” and no such products are available.

Some of the newer FDC do have built in flexibility as they are available in several strengths. For example is the combination of an angiotensin receptor blocker with two possible doses of a diuretic or calcium channel blocker. Another factor is that there may be real financial savings to health services and to patients who pay prescription charges. Some, but not all FDC available do cost less than the two components prescribed separately. More complicated FDC therapies for hypertension, which might also contain a statin or a third antihypertensive drug, are not yet available. There use would be an example of the move to the “polypill” where a single tablet might contain up to five drugs targeting blood pressure, cholesterol and antithrombotic therapy.

The currently available FDC for hypertension with two drugs in one tablet will not however make a major impact on the number of tablets the patient has to take. In the clinic at City Hospital the average number of drugs required to control the blood pressure was 3.9. With the full use of the currently used FDC this figure would come down to 2.9. The average number of pills the patients needed was 6 and this would be reduced to five. Only with the introduction of polypills containing more agents could these numbers be reduced further. If the problem of the patients “tablet load” is to be addressed, FDC of three different agents might be helpful. It could be anticipated that these would be greeted with disapproval by clinical pharmacologists, pharmacists and those who are generally suspicious of the pharmaceutical industry and its motives.

**Table 1.** The number of tablets prescribed for daily consumption in 218 consecutive patients attending a hospital-based blood pressure clinic.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Numbers of patients</th>
<th>Average number of tablets/day</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment for hypertension</td>
<td>218</td>
<td>3.9</td>
<td>1-8</td>
</tr>
<tr>
<td>Statins</td>
<td>102</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Antithrombotic agents</td>
<td>94</td>
<td>1.1</td>
<td>1-2</td>
</tr>
<tr>
<td>Anti-diabetic agents</td>
<td>24</td>
<td>2.6</td>
<td>1-4</td>
</tr>
<tr>
<td>Unrelated conditions</td>
<td>84</td>
<td>2.3</td>
<td>1-5</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>218</strong></td>
<td><strong>6.0</strong></td>
<td><strong>1-13</strong></td>
</tr>
</tbody>
</table>

**FURTHER READING**

Stanton T, Reid JL.