Chiral Molecules in Hypertension: Focus on S-Amlodipine

Lekha Adik-Pathak

Stereochemistry is now influencing most areas of pharmacotherapy. The chirality that is inherent in the enzyme systems of living organisms’ results in an abundance of enantiopure organic molecules in the living world. In addition to the optical properties first noticed by Pasteur, stereospecific interactions at recognition sites result in differences in both biological and toxicological effects. With chirality becoming so important in pharmacotherapy, the need to develop chirally pure molecules has greatly increased. The pharmaceutical industry has recognised and accepted the need for developing chirally pure molecules. Research into new chemical entities that can interact specifically with enzyme families may potentially lead to new therapies for complex disease processes.

The basis for the development of chirally pure drugs lies behind the fact that the human body is chiroselective i.e. the body interacts with different isomers differently. Besides, two-third of the molecules are chiral, so nature itself uses chiral molecules, hence the best way to interact with nature for a positive outcome would be to use chiral molecules. Often only one stereoisomer of a racemate drug is able to affect the desired process so, when given as a racemate; patients end up absorbing and metabolizing useless quantities of the other stereoisomer of the drug. This unnecessary fraction is usually the one, which causes adverse effects. Thus, purifying the active part of the drug gives a better efficacy with reduction in side effects.

Calcium antagonists are a biochemically heterogeneous group of drugs that share the property of blocking the entry of calcium into cells by voltage-operated channels in cardiac and smooth muscle. They are useful in the management of angina pectoris and hypertension. The drugs included in this class are amlodipine, nifedipine, verapamil, diltiazem etc. Of all these drugs, amlodipine has been shown to have a completely different pharmacokinetic profile. Amlodipine has a long half-life and hence provides with an advantage of a once daily dosing. It has a slow onset and a slow offset of antihypertensive action, which avoids any sudden changes in blood pressure. Amlodipine, because of its novel pharmacokinetics, offers practical advantages over the other calcium antagonists in the long-term treatment of cardiovascular disease. But the use of amlodipine has been associated with side effects such as headache, dizziness, peripheral edema etc., with peripheral edema being the commonest reason for the withdrawal of the drug in most of the patients.

Interestingly, amlodipine exhibits chirality, i.e., it exists as two isomers. Moreover, the receptor binding studies have shown that it the S (-) isomer of amlodipine that has L-type calcium channel blocking activity. The R (-) isomer exhibits a 1000-fold weaker calcium channel blocking activity. Thus, the antihypertensive and antianginal activity of amlodipine can be attributed only to S (-) amlodipine, whereas the R (-) isomer can be regarded as inactive. Since racemic amlodipine contains R (+) and S (+) isomer in 1:1 ratio, purifying the pharmacologically active S (-) isomer can reduce the dose of racemic amlodipine to half.

Clinical studies conducted at four centres in India have shown that S (-) amlodipine at half the dose i.e. 2.5 mg produces a similar blood pressure lowering efficacy as that of racemic amlodipine 5 mg. Thus, S (-) amlodipine reduces the dose of amlodipine to half. Studies have even shown that S (-) amlodipine produces a significant reduction in the total serum cholesterol and triglyceride levels in hyperlipidemic patients.

It is seen that the S (-) component is found to produce vasodilation by blocking the calcium channels in the arterial circulation. This property contributes to its antihypertensive effect. The R (+) isomer on the other hand produces venodilation and is responsible for the side effects associated with racemic amlodipine.

In atherosclerosis it is seen that the smooth muscle cell membrane becomes enriched with unesterified cholesterol. The membrane becomes thicker and develops distinct cholesterol domains. These alterations increase the permeability of smooth muscle cells to Ca++ ions, which further consolidates the atherosclerotic plaque. Only the S (-) component of amlodipine has calcium channel blocking activity, hence, it is S (-) amlodipine that has anti-atherosclerotic activity. Since R (-) amlodipine has no calcium channel blocking activity, it has no anti-atherosclerotic effect.

Another clinically relevant observation with S (-) amlodipine was that there were no reported cases of any adverse event with the drug. No cases of peripheral edema have been reported by any of the patients included in the trial. Our own multicenter trial showed that S-amlodipine in...
equivalent inefficacy and tolerability compared to amlodipine. Recent studies have shown that nitric oxide (NO) produced in the peripheral blood vessels by different nitric oxide synthetase (NOS) isoforms contributes to edema and development of hyperalgesia. The R (+) isomer of amlodipine has been shown to release nitric oxide in a concentration-dependent manner by kinin-mediated mechanisms. Since amlodipine has a peripheral action, the release of nitric oxide by the R (+) isomer in the peripheral blood vessels may lead to edema. On the other hand, the S (-) isomer has been shown to have no effect on the nitric oxide release at any concentration. Thus, it is R (+) amlodipine that is responsible for the development of peripheral edema, commonly associated with racemic amlodipine. Hence, purifying S (-) amlodipine can reduce the incidences of peripheral edema and other side effects.

Thus development of S (-) amlodipine and new S-atenolol can be regarded as a milestone in the management of hypertension. In fact S-isomers of common compounds like amlodipine and atenolol by Indian manufacturers in collaboration with Indian Scientist is a worthy contribution to science.

### REFERENCES

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