ISA—vasodilatation: improvement of organ perfusion

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1 In almost all forms of established hypertension the increase in blood pressure can be attributed to increased total peripheral vascular resistance.

2 β -adrenoceptor blocking compounds, which are frequently used as first-line therapy in hypertension, may compromise blood flow to vital organs in view of the fact that they reduce cardiac output both acutely and during long-term treatment.

3 β -adrenoceptor blocking agents with a marked intrinsic sympathomimetic activity (ISA) such as pindolol differ in this respect by lowering arterial pressure without lowering cardiac output while causing a reduction in total peripheral resistance.

4 Direct vascular effects of β -adrenoceptor blockers with marked ISA could contribute to the normalisation of hypertension-induced structural arteriolar changes. The effect appears to be dissociated from the effect caused by the lowering of blood pressure *per se*.

Keywords intrinsic sympathomimetic activity β -adrenoceptor blockers

Introduction

In almost all forms of established arterial hypertension the underlying haemodynamic change is an increase in vascular total peripheral resistance (TPR) (Freis, 1960). Several factors contribute to the increased vascular resistance in established hypertension, one of the important ones being structural changes in the pre-capillary arterioles (Folkow *et al.*, 1983). Structural arteriolar changes can also be demonstrated in individuals with mild blood pressure elevation or borderline hypertension (Sannerstedt *et al.*, 1976).

There are many haemodynamic consequences of such structural vascular changes, in addition to their contributing to the raised TPR. Thus, the blood pressure response to any stressful stimulus will be amplified for purely mechanical/geometrical reasons (Folkow *et al.*, 1983). This means that the transient increments in blood pressure, which occur normally during daily life, will be more pronounced. This could in itself lead to accelerated atherosclerosis (Hansson & Lundin, 1984). Moreover, repeated peaks of abnormally high blood pressure could initiate a vicious circle resulting in aggravation of the structural arteriolar changes.

Another potentially important effect of structural changes in the resistance vessels is that they could contribute to a compromised blood flow to vital organs, e.g. by reducing the coronary reserve (Strauer, 1980).

In the treatment of patients with arterial hypertension relatively little concern has been devoted to the problem of whether a specific antihypertensive agent may cause reversal of structural cardiovascular changes or not (Hansson, 1985). This is perhaps surprising in view of the fact that not all blood pressure lowering compounds are equally effective in preventing the development of structural cardiovascular changes (Freslon & Giudicelli, 1983) or in reversing already established changes in the heart or blood vessels (Hansson & Sivertsson, 1984).

In more general terms, it can be argued that the influence of antihypertensive agents on haemodynamics at rest is another factor that could be considered in the choice of treatment for arterial hypertension. Quite frequently, β -adrenoceptor blocking drugs are used in the treatment of hypertension, and this choice of first-line treatment (together with thiazide

diuretics) has been advocated repeatedly by joint WHO/ISH Expert Committees (1983, 1986).

Treatment of hypertension with β -adrenoceptor blockers

The first clinical report that propranolol had a useful antihypertensive effect was published more than 20 years ago (Prichard & Gillam, 1964). The mechanism by which β -adrenoceptor blockers reduce elevated arterial pressure is still not fully understood but the haemodynamic events that take place after acute as well as long-term administration of propranolol were elucidated already some 15 years ago (Tarazi & Dustan, 1972; Hansson, 1973). In these studies it was shown that acute administration of propranolol caused a marked drop in cardiac output and an equally drastic increase in TPR; the resultant effect of these changes being that blood pressure remained unchanged. However, during prolonged administration of propranolol cardiac output remained significantly reduced whereas TPR was readjusted down towards the initial level, which resulted in a significant fall in arterial pressure. These initial studies with the nonselective β -adrenoceptor blocker propranolol, which is devoid of ISA, have since been confirmed in several haemodynamic studies (Man in 't Veld & Schalekamp, 1983).

In view of the fact that the main haemodynamic abnormality in hypertension, aside from the elevated arterial pressure, is the raised TPR, the changes induced by β -adrenoceptor blockers devoid of ISA appear to be less than ideal.

Effects of β -adrenoceptor blockers with ISA

Acute haemodynamic studies in which β -adrenoceptor blockers with different pharmacological profiles have been used, clearly show that compounds with pronounced ISA affect cardiac output and heart rate to a much lesser degree than drugs devoid of ISA (Lysbo-Svendsen *et al.*, 1979). Of particular interest was the report in 1976 that pindolol, a β -adrenoceptor blocker with marked ISA, caused a reduction both in blood pressure and vascular resistance during long-term treatment of hypertensive patients (Atterhög *et al.*, 1976). These findings have later been confirmed by other investigators and in an extensive review of the literature covering the haemodynamic effects of β -adrenoceptor blockers in hypertension, it was clearly demonstrated that pindolol reduces blood pressure by causing a fall in vascular resistance to levels

below the initial untreated value (Man in 't Veld & Schalekamp, 1983, Figure 1).

Studies of haemodynamics in isolated vascular beds such as the forearm or the calf also confirm that the fall in systemic blood pressure caused by pindolol after 6 weeks of treatment was associated with a reduction in vascular resistance whereas no fall in resistance was seen during treatment with metoprolol (Svensson *et al.*, 1981). These findings were confirmed in an extended double-blind comparison of pindolol and metoprolol given to 36 hypertensive patients (Svensson *et al.*, 1982). This study not only suggested that pindolol lowered blood pressure mainly through a vasodilating action, which was attributable to its marked ISA, and that metoprolol lowered blood pressure mainly via cardiac mechanisms (Figure 2). It also showed that pindolol, but not metoprolol, reduced vascular resistance at maximal dilatation following 6 months of treatment (Figure 3). This indicates that during long-term treatment with pindolol the hypertension-induced arteriolar changes to some extent had been reversed. Since the antihypertensive effect was similar during treatment with pindolol and metoprolol, it is obvious that the reversibility of structural vascular changes seen during treatment with pindolol must be attributed to a factor other than the antihypertensive effect. The most

Figure 1 Relationship between the cardiac output and the total peripheral resistance in supine resting hypertensive patients during treatment with 10 different β -adrenoceptor blockers. ● = after acute i.v. administration, ▼ = after chronic oral administration. * = values before treatment. (From Man in 't Veld & Schalekamp, 1983, with kind permission by the Editor of the Journal of Cardiovascular Pharmacology).

Figure 2 Change in percentage of vascular resistance at rest in the calf after 6 weeks and 6 months of treatment with pindolol (▨) or metoprolol (□) as compared with placebo. Mean values $\pm$ s.d. * $P < 0.05$, ** $P < 0.005$. (From Svensson *et al.*, 1982).

Figure 3 Change in percentage of vascular resistance at maximal vasodilatation in the forearm after 6 months of treatment with pindolol (▨) or metoprolol (□). Mean value $\pm$ s.d. (From Svensson *et al.*, 1982).

likely explanation is that pindolol, due to its marked ISA, had affected vascular β_2 -adrenoceptors during periods of low endogenous sympathetic tone and thereby caused an active relaxation of the resistance vessels, which in turn had reduced the tone of the smooth vascular muscle cells. Other studies have indicated a similar dissociation between the antihypertensive effect and the beneficial effect on structural cardiovascular changes (Freslon & Giudicelli, 1983).

Conclusions

β -adrenoceptor blocking drugs play an important role in the treatment of hypertension today. Based on strictly haemodynamic considerations this would appear to be less than ideal since the reduction in arterial pressure is caused mainly by a fall in cardiac output. Obviously treatment with β -adrenoceptor blockers causes a 'delayed vasodilating effect' (Hansson, 1982), but this reduction in resistance is not from the initial untreated level but from the level which is acutely raised during initial treatment. In this respect β -adrenoceptor blockers with ISA have a marked advantage since they do not raise resistance initially. Therefore, the 'delayed vasodilating effect' will take place from the initial untreated level and the net result will be a drop in TPR. This is undoubtedly a physiologically sound change since it is in the direction of achieving a 'normalisation' of the elevated TPR seen in hypertensive patients. In addition, by maintaining a virtually unchanged cardiac output during chronic treatment with β -adrenoceptor blockers possessing marked ISA, one would expect a general improvement of organ perfusion as compared with the effects caused by β -adrenoceptor blockers devoid of ISA.

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