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A Perspective on Pharmaceutical Industrial Research on Antihypertensive drugs

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Cardiovascular disease is at present the leading cause of death in the United States[1] and other industrialized countries[2,3]. A major contributing factor of cardiovascular disease is essential hypertension[4,5]. Untreated, essential hypertension is considered a risk factor for sudden death due to myocardial infarctions, as well as a risk factor for cerebral vascular disease, renal failure and congestive heart failure[6-8]. During the last decade, significant progress has been made in the basic knowledge of the pathogenesis of hypertension[9] as well as in the development of new antihypertensive drugs[10]. The currently available antihypertensive drugs are effective in reducing high blood pressure, but most of these agents have many liabilities. Diuretics such as hydrochlorothiazide cause hypokalemia and muscle cramping, and have been questioned from a risk point of view because of the possibility of cardiac complications due to hypokalemia[11]. The centrally acting agents, such as methyldopa and clonidine[12,13], cause sedation and sympatholytic side effects[14], whereas the peripherally acting alpha adrenergic blocker, prazosin, produces postural hypotension[15,16]. Vasodilators, such as hydralazine and minoxidil, cause reflex tachycardia[17] and activate the renin angiotensin system[18], whereas beta blockers produce a limited reduction in blood pressure and are effective in only a small segment of the hypertensive population[19-21].

Hypertension is usually asymptomatic and needs chronic treatment. Therefore, antihypertensive agents must be free of side effects in order to assure patient compliance[7,22]. The current emphasis in the development of new antihypertensive agents is being directed more towards selective agents with novel mechanisms of action designed to gain more insight into the etiology of hypertension. In this way, it may be feasible to substantially reduce side effects while retaining or enhancing efficacy. For example, the mechanism of action of the angiotensin converting enzyme (ACE) inhibitor captopril is interference with the renin-angiotensin system[23]. This type of agent effectively lowers the high blood pressure in renin-dependent hypertensive patients but produces few side effects (i.e., rash and loss of taste)[24-27]. The efficacy of such ACE inhibitors was expected in light of the suggestion that abnormalities in the renin-angiotensin system have long been implicated to be the cause of certain forms of hypertension[28]. Another example is the on-going efforts toward the development of calcium antagonists as antihypertensive agents[29-32]. In hypertension, defects in the cellular handling of calcium ions[33,34] result in increased intracellular calcium which would activate the vascular contractile elements. This in turn would produce vasoconstriction and hence high blood pressure. Calcium antagonists can reverse this phenomenon by blocking calcium uptake, thus normalizing elevated vascular resistance in hypertension[35]. Recent clinical studies using calcium antagonists[36] (*i.e.*, verapamil, diltiazem and nifedipine) indicate that these agents are effective antihypertensive drugs[30] but have a relatively short duration of action, and cause cardiac conduction disturbances, as well as tachycardia[37-40]. Ideally, a new agent for the treatment of hypertension should have the following characteristics in order to represent a significant advancement over the present therapy: 1) a long duration of action, *i.e.*, a single daily dose, 2) absence of tachycardia and orthostatic hypotension, 3) the ability to promote sodium excretion, 4) absence of increased plasma renin activity, 5) a mechanism of action related to the cause of the hypertensive disease, and 6) fewer side effects and less toxicity than seen with presently available agents.

Various approaches within the pharmaceutical industry can be taken in search of new antihypertensive agents. One basic approach is to establish the primary *in vivo* screening model that most closely relates to the clinical situation of hypertension therapy. There are several hypertensive animal

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models that are routinely used for screening of antihypertensive drugs: These include the 1) spontaneously hypertensive rat (SHR)[41], 2) renal hypertensive rat[42-44], and dog[45,46], 3) deoxycorticosterone acetate (DOCA)/salt hypertensive rat[47] and 4) neurogenic hypertensive dogs[48]. These animal models resemble human hypertension of various pathogenic origins and therefore can be excellent tools in evaluating new agents during the drug development phase of research. The use of the Okamoto-Aoki strain[41] of SHR is of considerable importance during the screening evaluations of new potential antihypertensives. This strain is commercially available and the responsiveness to antihypertensive drugs in this model is similar to that found in essential hypertension in man[49,50].

Various *in vitro* methods such as the radioligand receptor-binding technique[51] or biochemical assays[52,53] can be utilized as drug-screening systems for novel antihypertensive compounds. These *in vitro* assays are suitable for the determination of structure-activity relationships without the complications (*i.e.* absorption, metabolism etc.) of *in vivo* experiments. *In vitro* assays are of considerable use in aiding towards understanding the basic biochemical mechanisms associated with new agents as they relate to therapeutic effectiveness[51]. Furthermore, the pharmacologically active portions of compound molecules (pharmacophores) are often identified using these simple and inexpensive *in vitro* assays. This can provide considerable chemical information leading towards the design of more effective (potent, long acting, selective, *etc.*) therapeutic agents. Other isolated organ and tissue preparations[54] may be additionally needed to generate the *in vitro* functional data to assure selectivity of action, desirable mode of action and to perhaps point out possible side effects. In general, when an agent or group of agents are identified as having some of the desired action (*i.e.*, mechanism, potency, *etc.*) and oral antihypertensive efficacy with a favorable duration of action compared to the existing standards, then secondary and tertiary tests are necessary. These include; 1) efficacy in other types of hypertensive rat models, *i.e.*, one kidney and two kidney hypertension[55,56] and DOCA/salt hypertension[57]; 2) efficacy in a second species, for example, the renal hypertensive dog[58-60]; 3) systemic and regional hemodynamic mechansims of action in both the hypertensive[61,62] and normotensive animal[63,64], either in the acute anesthetized state or semichronically using the conscious model; 4) determination of the acute and chronic effects of the antihypertensive dose on the cardiac function in the hypertensive animal[65,66]; 5) therapeutic or safety index determination based on acute, subchronic and chronic toxicity evaluations; 6) a renal function test[67] in the anesthetized or conscious dog or determination of the presence or absence of diuretic activity in conscious rats; 7) miscellaneous CNS and GI pharmacological profiling, and 8) preliminary genetic safety evaluations such as the Ames test (carcinogenic) and mouse lymphoma test (mutagenic)[68] to rule out these toxic potentials.

The above descriptive list of various cardiovascular research techniques is typical of approaches used in drug research programs by many pharmaceutical companies in the United States, in the search for novel antihypertensives. However, each of the primary screening methods as well as the secondary follow-up tests should be tailored for the specific objectives and directions of a given research program.

Industrial cardiovascular pharmacologists have made significant contributions to the therapy of hypertension which has resulted in decreasing the morbidity and mortality of hypertensive subjects[69-71], thus substantially improving the quality of life for these patients. Nevertheless, there is still an increased demand for newer antihypertensive drugs with improved safety profiles for prolonged use over a lifetime[5]. Future progress will be facilitated by collaborative efforts between investigators in academia, as well as industrial pharmacologists and government health regulatory agencies.

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