New Centrally Acting Antihypertensive Drugs Related to Methyldopa and Clonidine

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SUMMARY It has been well established that the antihypertensive drugs clonidine and methyldopa lower blood pressure by acting on postsynaptic α2-adrenergic receptors within cardiovascular control centers of the brain. A number of novel agents designed as lipophilic and highly selective α2-adrenergic stimulants have been synthesized and in general the pharmacological features of these agents resemble clonidine or α-methylnorepinephrine, the principal metabolite of methyldopa. The clonidine analogs, ICI-106,270, UK-14,304, piclonidine (LR-99,853), and the bridge analogs (ST-1913, ST-1966, ST-1967) exhibit varying activity on the central cardiovascular control centers. ICI-106,270 is of interest because relative to clonidine it appears to exert fewer CNS side effects. Azepexole (BHT-933) is also of interest because, although structurally unrelated to clonidine, it appears to interact with central α-adrenergic receptors in a manner similar to that of clonidine. In contrast, central administration of ST-1966, a monoatomic bridge analog of clonidine, lowers blood pressure in animals treated with an α2-antagonist, which suggests other mechanisms may be involved in its action. Novel antihypertensive agents structurally similar to methyldopa have not been described, although viable prodrugs of methyldopa such as 2-oxo-1,3-dioxol-4-yl-methyl and pivaloyloxyethyl esters have been shown to have greater oral activity than methyldopa, presumably because they are more lipophilic than the parent moiety. α-Monofluoromethyldopa, a highly potent and irreversible inhibitor of aromatic amino acid decarboxylase, has interesting central properties related to catecholamine depletion and inhibition of dopa-decarboxylase, but because this agent is not metabolized to the corresponding fluorinated catecholamine, a central antihypertensive response similar to methyldopa could not be demonstrated in spontaneously hypertensive rats. Tyrosine prodrugs may offer another approach to reducing blood pressure centrally, although their precise mechanism is not understood. In summary, newer and more selective α2-adrenergic receptor agonists have been described, but none of these agents appears to be totally free from the sedative liability of clonidine and methyldopa.

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KEY WORDS • clonidine • methyldopa • CNS • α2-agonists • antihypertensive drugs
mans et al. demonstrated that ST-1913 administered by vertebral artery infusion was less active than clonidine in cats and that, unlike ST-1966 and ST-1967, the centrally induced hypotension with ST-1913 was antagonized by the \( \alpha_2 \)-blocker piperoxan. Ruffolo et al. observed that clonidine was about 25-fold more potent than ST-1913 after intravenous injection in spontaneously hypertensive rats (SHR), but both compounds were similar in their ability to lower blood pressure when administered beyond the blood-brain barrier (intracisternal administration). Because of pKa considerations (clonidine = 7.7; ST-1913 = 9.7), a greater percentage of clonidine exists in the un-ionized form relative to ST-1913; therefore, it is more likely to penetrate the blood-brain barrier. Definitive sedation studies have not been reported for members of this series.

**Clonidine Analogs with Chemical Modification on Bridge Nitrogen**

Piclonidine (LR-99,853), \((\pm)-2-[2,6-dichloro-N-(tetrahydro-2H-pyran-2-yl)anilino]-2\text{-imidazoline}\), has been demonstrated to be as potent as clonidine in lowering blood pressure in rats by the oral route. Unlike clonidine, however, its hypotensive action was not preceded by a pressor phase, and the hypotensive phase occurred more gradually and was generally longer lasting than in clonidine. By the intravenous and intracerebroventricular (i.c.v.) routes, piclonidine was significantly less active than clonidine and caused no sedation at 1 mg/kg p.o. Because full dose-response curves were not reported, the separation between the hypotensive and sedative effects of the compound could not be accurately ascertained. The dose of piclonidine that reduced blood pressure by 10% (0.2 mg/kg p.o.) was considerably lower than that required to inhibit GI motility and induce mydriasis and hyperglycemia. These findings suggest that piclonidine may be somewhat more selective than clonidine.

Hepatic metabolism was involved in generating an active moiety that apparently is not clonidine nor a clonidine metabolite. Consistent with a prodrug profile of action are studies that demonstrated a delay in the onset of action, the lack of the early phase of hypertension, and lower CNS depressive activity.

Another agent that has a chemical substitution on the bridge nitrogen is the N-allyl derivative of clonidine ST-567, or alinidine 2-[N-allyl-N-(2,6-dichlorophenyl)amino]-2-imidazoline]. In anesthetized cats and dogs the most prominent action of this agent was a pronounced hypotensive effect. Alinidine, 80 mg p.o., produced tiredness and dry mouth in humans. Another chemical substitution on the bridge nitrogen is the N-allyl derivative of cionidine metabolite. Consistent with a prodrug profile of action are studies that demonstrated a delay in the onset of action, the lack of the early phase of hypertension, and lower CNS depressive activity.

**Piclonidine**

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**UK-14,304**

5-bromo-6-[2-imidazoline-2-ylamino]-quinoloxaline has been termed a potent and highly selective \( \alpha_2 \)-adrenergic agonist. Unlike clonidine, it is a full agonist and its \( \alpha_2 \)-adrenergic agonist properties have been demonstrated in the guinea pig ileum and rabbit pulmonary artery. The high selectivity of UK-14,304 for \( \alpha_2 \)-adrenergic receptors has been confirmed in pithed rats and in ligand binding studies. In rat brain membranes, 1 nmol UK-14,304 displaced bound \([H] \)-clonidine (\( \alpha_2 \)-adrenergic agonist) by 50%, whereas a concentration of 1 \( \mu \)mol was needed to displace bound \([H] \)-prazosin (\( \alpha_1 \)-adrenergic agonist) by an equivalent amount. In a double-blind clinical study comparing oral clonidine (0.3 mg) and UK-14,304 (0.75 mg), Ashton and Rawlins found that both clonidine and UK-14,304 caused a progressive increase in the subjective ratings of sleepiness, which was maximal 2 to 4 hours after treatment. According to these researchers, UK-14,304 was less depressant than clonidine, but it also had a less marked hypotensive effect.

Most of the compounds previously described in this review show structural similarities to clonidine. Azepxole \(2\text{-amino-6-ethyl-4,5,7,8-tetrahydro-6H-oxazo-lo-[5,4-d]-azepin-dihydrochloride}\) or BHT-933 was developed from a chemical group of substances with antitussive properties that coincidentally lowered blood pressure. In cats and rats azepxole caused pronounced hypotensive effects accompanied by bra-
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Ester Progenitors of Antihypertensive Amino Acids

Methyldopa is variably and incompletely absorbed in humans. One strategy that has been successful in enhancing the absorption of biologically active chemical species has been to increase lipid solubility by incorporating different esters into molecules. Lipophilic progenitors of methyldopa, the α-pivaloyloxyethyl (POE) and the 1,3-dioxolonomethyl ester, have been described. It was predicted that the prodrug form (compared with the polar amino acid) would be better absorbed than methyldopa because of better gut transport. In SHR single doses of the pivaloyloxyethyl (POE) ester of methyldopa were somewhat more active than the parent compound in lowering blood pressure. As shown on Figure 1, the onset of action of this agent occurs somewhat sooner than for methyldopa, but the duration of action does not appear to be different for these agents. Previous work from our laboratories has indicated that this ester is approximately 2 times more potent than methyldopa in lowering blood pressure in unanesthetized SHR. The 1,3-dioxolonomethyl ester has been synthesized recently; it was also highly active in reducing blood pressure in SHR (Figure 2) but compared with the POE ester its onset of action was comparable to the parent drug.

Administered to healthy volunteers, the POE ester of methyldopa was hydrolyzed on the first pass. The delivery of methyldopa POE in plasma in one study was more uniform compared with that of orally admin-

Dyadocardia. An involvement of central α-adrenergic receptors in its action seems justified from studies with piperoxan. In normotensive people, 10 mg of azepoxide and 0.15 mg of clonidine produced similar hypotensive effects. A dose-dependent sedation and dryness of mouth were observed with both agents. Thus, azepoxide, although a structurally unique compound, was not free of troublesome CNS side effects.

FIGURE 1. Acute antihypertensive effect of methyldopa (top panel) and the pivaloyloxyethyl (POE) ester of methyldopa (bottom panel) in unanesthetized SHR. Shown are the mean arterial pressure (MAP) values before treatment at time 0 and at regular intervals thereafter. A vehicle-treated group was given hydroxymethylcellulose (HMC). Values are the averages of at least six rats per group. For proper comparison a 60.5 mg/kg p.o. dose of methyldopa POE is equivalent to 25 mg/kg p.o. of methyldopa. All MAP values in the methyldopa group from the 2nd- to the 8th-hour interval were significantly different from the pretreatment control. Blood pressure changes in the group of SHR given methyldopa POE (121 and 242 mg/kg p.o.) were also significantly different during this same time interval. Top panel: • Methyldopa, 50 mg/kg p.o.; ○ Vehicle (HMC). Bottom panel: • 60.5 mg/kg p.o.; ○ 121.0 mg/kg p.o.; □ 242 mg/kg p.o.
Figure 2. Acute antihypertensive effect of methyldopa (Aldomet) and the 1,3 dioxolonyl-methyl ester of methyldopa in unanesthetized SHR. A 58 mg/kg p.o. dose of this ester is equivalent to 25 mg/kg p.o. of methyldopa. All mean arterial pressure values in the three groups were significantly different from the control value at time 0, \( p < 0.05 \). Top panel: ○ Methyldopa, 50 mg/kg p.o.; ● Vehicle (HMC); Bottom panel: ● 58 mg/kg p.o.; ○ 116 mg/kg p.o.; □ 232 mg/kg p.o.

Tyrosine is another amino acid that has received attention because of its possible central antihypertensive properties. We have evaluated the acute antihypertensive effects of L-tyrosine given intraperitoneally and orally to SHR. Although tyrosine was active by the intraperitoneal route (100 and 200 mg/kg) it was inactive orally up to 400 mg/kg. One prodrug, the 2,2-dimethyl-1-oxopropoxyethyl ester, lowered mean arterial pressure (MAP) in SHR both acutely on Day 1 (22 ± 5 mm Hg decrement) and consistently over 3 days (21 to 25 mm Hg decrement). The rate of hydrolysis and thus the stability of the ester linkage was assessed for four different esters to determine if there was a correlation between oral activity and the rate of generation of tyrosine. Two of these esters had approximately the same hydrolysis rate yet differed substantially in oral activity, which suggests that other factors may be influencing absorption, distribution, or penetration in the CNS. There have been no systematic studies to determine whether tyrosine produces undesirable CNS side effects. From our experience, SHR treated with tyrosine esters did not appear sedated as they often do after equivalent antihypertensive doses of methyldopa.

\( \alpha \)-Monofluoromethyldopa

The decarboxylation of L-dopa to dopamine by dopa-decarboxylase is a critical step in the biosynthesis of norepinephrine, but because intraneuronal activity of this enzyme is in excess of that for tyrosine hydroxylase, inhibition of this step by inhibitors such as carbidopa or benserazide does not result in either a reduction of neurotransmitter stores or significant lowering of blood pressure. DL-\( \alpha \)-Monofluoromethyldopa and S-\( \alpha \)-fluoromethyldopa have been synthesized recently and these compounds, through the principle of enzyme-activated irreversible inhibition, produced complete inhibition of the enzyme and substantially depleted tissue catecholamines. Fozard et al. and Johansson and Henning have described some of the biological characteristics of this agent.
These include penetration into the CNS, depression of peripheral sympathetic nervous function, depletion of peripheral stores of norepinephrine, sedation, and blood pressure interactions with L-dopa. Unlike methyldopa the α-fluorinated amino acid is not metabolized to the corresponding fluorinated catecholamines. Figure 3 shows data in unanesthetized SHR from our laboratories that are consistent with this conclusion. Methyldopa produced a dose-related fall in blood pressure after intracerebroventricular injections in SHR. In contrast, α-fluoromethyldopa did not act as a depressor over 24 hours in SHR and, in fact, actually elevated blood pressure; this elevation persisted for approximately 6 hours. The advantage of α-fluoromethyldopa seems to be that it causes selective inhibition of dopa-decarboxylase, but as expected both endogenous catecholamine and serotonin stores were reduced. Its antihypertensive mechanism of action is best explained by a depletion of peripheral and central catecholamine stores, which results in a diminution of sympathetic function (Ulm, E.H. and Smith, P. et al., unpublished observations).

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