CHAPTER IV

DISCUSSION AND CONCLUSION

The actions of this ALKALOID on systemic blood pressure were clearly indicated that it could lower both systolic and diastolic blood pressures significantly. An intravenous infusion in low doses of ALKALOID (0.4, 0.8 and 1.6 mg/kg), both systolic and diastolic blood pressures were relatively reduced, whereas the highest dose (3.2 mg/kg) showed more initial reduction in diastolic than systolic blood pressure (Fig. 3, 4, Table 1-3). It is generally known that there are many factors controlling systemic blood pressure. Thus, the hypotensive effect of ALKALOID could be due to either the action on heart function or vascular musculature. ALKALOID caused bi-phasic responses on the heart rate (Table 4). It produced a transient significant decrease in heart rate as well as the initial fall in blood pressure. These revealed the primary depression of ALKALOID on the heart. The effect of ALKALOID on isolated right atrial contraction rate of the rats showed depression effect which relatively on the doses (Fig. 20). Then, it could be suggested that ALKALOID caused an initial direct depression on the heart. However, a sustained hypotensive effect may induce reflex mechanisms and cause secondary increase in heart rate (Guyton, 1981).

In order to investigate the possible mechanisms of action mediating the hypotensive effect of ALKALOID, it should be studied with pharmacological tools in intact, as well as on the isolated heart. The sites or modes of hypotensive action of ALKALOID may be due to

1. action like beta-adrenergic agonist
2. action like vasodilating substance or mediating release of vasodilating substance
3. action mediated via cholinergic receptors
4. action somehow on central nervous system
5. action on sympathetic nerve terminal
6. action direct on cardiac musculature

Beta-adrenergic agonist such as isoproterenol has powerful effect on beta-adrenergic receptors which finally caused reduction of arterial blood pressure. This hypotensive effect is completely blocked by propranolol (Allwood et al., 1963; Blinks, 1967; Daly et al., 1975; Andersson, 1982; Clark, 1982). According to experiment 2, propranolol which completely abolished the hypotensive effect of isoproterenol could not inhibit the hypotensive effect of ALKALOID, as shown in Fig. 6-8, Table 6-8. It could be suggested that mode of hypotensive action of ALKALOID does not be mediated via beta-adrenergic receptors. By the observation, it could be suggested that propranolol may potentiate the hypotensive effect of ALKALOID.

Hypotensive effect of histamine resulting from vascular dilator is mediated by receptor of both H_1-and H_2-blockers (Black et al., 1972; Flynn et al., 1975; Black et al., 1975; Powel and Brody, 1976). In experiment 3, mepyramine (H_1-receptor antagonist) in combination with cimetidine (H_2-receptor antagonist) completely blocked hypotensive effect of histamine (Fig. 9, Table 9). Combination of mepyramine and cimetidine which effective in blocking hypotensive of histamine could not block the hypotensive effect of ALKALOID (Fig. 10, 11, Table 10-11). It could be suggested that mode of action of ALKALOID may not mediate via histaminic receptors and may not act like histaminic liberator.

Cholinergic agonist or some other substances which act on muscarinic cholinergic receptors cause vasodilation and decrease in cardiac rate and force of contraction (Taylor, 1980a). The action of atropine is a competitive antagonism of action of acetylcholine at muscarinic cholinergic receptors (Shutt and Bowes, 1979; Weiner, 1980a). It was found in experiment 3 that the preadministration of atropine (0.3 mg/kg) resulted in partial reduction of hypotensive effect of ALKALOID significantly (Fig. 13-15, Table 14-16). According to this experiment, hypotensive effect of ALKALOID may partly mediate via muscarinic cholinergic receptors.

It is well known that several antihypertensive drugs have been shown to have their action mediating

through the hypothalamic or brain stem centers. It is postulated that the reduction of activity of peripheral sympathetic nervous system of clonidine is primarily due to the central adrenergic mechanism (Klupp et al., 1970; Van Zwieten, 1973). In order to determine the hypotensive effect of ALKALOID which may act like those antihypertensive drugs, ganglionic blocking drug was used to prevent the impulse from the central nervous system. Hexamethonium which block the transmission of impulse from the preganglionic axon by occupying receptor sites at the postganglionic axon (Moe and Freyburger, 1950; Paton and Zaimis, 1952; Taylor, 1982b) was performed in experiment 5. Hexamethonium 3.5 mg/kg was partially reduced the hypotensive effect of ALKALOID (Fig. 16, 17, Table 17-19). It is suggested that ALKALOID may act somehow on central nervous system which resulting in hypotension.

Several hypotensive drugs having the sites of action at the sympathetic nerve terminal such as rauwolfia alkaloid and guanethidine (Frolich, 1974; Weiner, 1980b), both of which interfere the release and synthesis of the neurotransmitters at postganglionic adrenergic nerve ending, which finally result in a decrease in vascular resistance. ALKALOID may produce hypotensive effect by acting like the two agents as mentioned above. In order to investigate this possible action, tyramine was performed in experiment 6. Tyramine exerts effect by releasing norepinephrine from storage sites in sympathetic

nerves of the effector organ. The response are therefore similar to those of norepinephrine (Trendelenbrug et al., 1962; Smith, 1973). Pretreatment with ALKALOID was not abolished the increase in blood pressure of tyramine (Fig. 18, 19, Table 20). This result indicated that the hypotensive effect of ALKALOID may not due to deplete norepinephrine from storage sites in sympathetic nerve terminal.

In order to investigate the effects of ALKALOID on cardiac contractility, experiments were performed on isolated rat atrias. Chronotropic effect was determined on the spontaneously beating right atrial strips and inotropic effect on strips of left atrium driven electrically at constant frequency. It was found that ALKALOID exhibited dose-dependent negative chronotropic response (Fig. 20) and limited negative inotropic response (Fig. 21). In order to determine whether the negative chronotropic effect of ALKALOID involved cholinomimetic actions, experiments were performed in the presence of atropine. Preincubation of atrial tissues in the presence of a muscarinic cholinergic antagonist did not mitigate ALKALOID effects on atrial rate (Fig. 22). Since the same concentration, atropine effectively nullified the action of acetylcholine which considered more potent than effects of ALKALOID in decreasing heart rate (Fig. 23). Therefore, the negative chronotropic effect of ALKALOID was independent the involvement of cholinergic mechanism.

Another potential site which could be involved by ALKALOID is vascular musculature. It is well known that drugs causing the relaxation of vascular smooth muscle by direct action are reported to be effective in reducing blood pressure (Koch-Weser, 1974). From preliminary study of the author, experiment which performed on isolated rabbit aortic strips was found that ALKALOID did not significantly alter tension of the aortic strips. However, more studies are required to elucidate the detail mechanism of ALKALOID on blood vessel.

In conclusion, it could be postulated that there are more than one mechanisms of ALKALOID which mediate a sustained reduction of blood pressure. The first is ALKALOID mediating via cholinergic receptors, second is ALKALOID acting somehow on central nervous system which finally result in reduction of blood pressure. The other, a direct action on vascular resistance may be suggested. The results obtained from this present study may indicate the possible mechanisms of hypotensive action of ALKALOID. However, more studies are required to illuminate the detail mechanism of this alkaloid on cardiovascular and other systems should be recommended.