CHAPTER 1

INTRODUCTION

Glaucoma is a chronic ophthalmic condition affecting approximately 15 million people. Several therapies are currently available (e.g. beta-blockers, sympathomimetics, carbonic anhydrase inhibitors), but the use has been limited by many side effects (Marchetti et al., 2001). Brimonidine (5-bromo-N-(2-imidazolidinylideneneamino) quinoxaline L-tartrate), a new ophthalmic solution with improved efficacy and lowering the side effect has been used to decrease intraocular pressure in human patient with chronic open-angle glaucoma or ocular hypertension as adjunctive therapy when intraocular pressure is not adequately controlled by a topical beta-blocking agent. It acts by reducing aqueous humor production and increasing uveoscleral outflow (Greenfield et al., 1997). The recommended dose is 1 drop of 0.2% solution every 8 hours to cause an effect.

Brimonidine is a selective and potent alpha 2-adrenoreceptor agonist and also binds to nonadrenergic imidazoline receptors. It is 1000 times more selective for the alpha 2 than for the alpha 1- adrenoreceptor (Welch and Richardson, 2002). Since Theuse of brimonidine tartrate 0.2% ophthalmic solution (Alphagan®)* has become increasingly popular for the initial and long-term management of ocular hypertension and glaucoma (Cantor, 2000). In addition, neuroprotective effects of brimonidine were also reported by various investigators (Ahmed et al., 2001; Cantor, 2001; Mussie et al., 2001). In rats, brimonidine has a neuroprotective activity unrelated to its effect on ocular hypotension. This drug is able to reduce the progressive loss of ganglion cells following the laser-induced chronic ocular hypertension in rats (Mussie et al., 2001).

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*Alphagan® is a product of Allergan Pharmaceutical, it contained 0.2% brimonidine tartrate in benzakonium chloride solution.

Although brimonidine is used as topical ophthalmic drops, it can also cause systemic side effects. The most common adverse effects reported in human patients are oral dryness, headache, blurring and fatigue or drowsiness (Walters, 1996; Welch and Richardson, 2002). Other adverse effects include gastrointestinal symptoms, muscular pain, depression, hypertension, anxiety, palpitation/ arrhythmia, nasal dryness and syncope (Welch and Richardson, 2002). Carlsen et al. (1999) reported two cases in which topical brimonidine resulted in apparent central nervous system depression in infants. One was 11-day-old infant became lethargic and apneic after a single drop of brimonidine, while the other was 5-month-old infant with lethargic and poorly responsive after receiving 1 drop of brimonidine in each eye. Therefore the use of brimonidine was not recommended in the infants.

Brimonidine suppresses cardiovascular function in conscious cynomolgus monkeys (Burke et al., 1995). The reduction of mean arterial blood pressure with dose- dependent manner and decrease in heart rate was also reported. (Gabelt et al., 1994)

After brimonidine ophthalmic solution ingestion in dogs. The report summarized typical clinical signs and characterized the anticipated course of brimonidine toxicoses (Welch and Richardson, 2002) Clinical signs were developed within 2-4 hours. Incidence of clinical signs reported including bradycardia (67%), depression (46%), ataxia (27%), hypotension (25%), pallor (23%), weakness (17%), change in mucous membrane color (17%), hypothermia (13%) and vomiting or retching (13%). Other signs were shock, weak pulse and poor capillary refill time.

The mechanism of action in reducing intraocular pressure is direct effect on production and outflow of aqueous humor (Enyedi and Freednan, 2001) whereas systemic effects are more likely to cause by central nervous system activities than peripheral vascular postjunctional alpha 2-adrenoceptor activities (Burke et al., 1995). Because brimonidine can pass blood brain barrier. Imidazoline or alpha 2 adrenoceptor in the brain may play an important role in systemic alterations (Burke et al., 1995). Baroreflex activity may not involve in this mechanism since clinical signs

of bradycardia was associated with hypotension in dog (Welch and Richardson, 2002) human (Enyedi and Freedman, 2001) and monkey (Burke et al., 1995).

A few data are available in the mechanism of brimonidine acts via central pathway or peripheral receptors. The experimental research of brimonidine toxicosis in dog does not exist. Therefore in the present study, an investigation for the effects of brimonidine ophthalmic drops ingestion on blood pressure, electrocardiogram, acid-base balance and renal function were carried out.