

## Feedback Studies from/to Clinical Aspect in Point of Pharmacological View.

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The role of the Department of Pharmacology is broad and may depend on the faculties of university. In the Department of Pharmacology of Medical School we must always direct our attention toward clinical aspect and medical contribution to the patients. In point of pharmacological view, to keep good correlation between basic medical science and clinical field is very important for us especially in the Medical School.

From the above point, we always pay attention to keep good correlation with clinical field and try to do our best for performing the feedback studies from/to clinical aspect. Consequently, in the meeting, I would like to present our experiences concerning the feedback studies from/to the clinical field in my Department: 1. Analysis of drug-induced adverse effects in the clinical application and 2. Development of experimental animal models.

### **1. Analysis of drug-induced adverse effects in clinical application**

a. Glucagon-induced emesis and preclinical assessment of antiemetics or emetogenic compounds in pigeons: In clinic, glucagon has been reported to induce nausea and vomiting. First, we studied the emetic effect of glucagon, using dogs and cats which have been widely used for the emetic and antiemetic experiments. But, in non-restrained dogs and cats, nausea and emesis were not observed at any doses of glucagon (10 ~ 300  $\mu\text{g/kg}$  i.v.). In non-restrained pigeons, the incidences of glucagon-induced emesis were 40% in 100  $\mu\text{g/kg}$ , 43% in 300  $\mu\text{g/kg}$  and 67% in 1 mg/kg i.v.. No deaths occurred at glucagon 300  $\mu\text{g/kg}$ , but the fatality was 33% at 1 mg/kg i.v.. The emetic mechanism of glucagon was analyzed mainly at 300  $\mu\text{g/kg}$ . The onset and recovery times of glucagon-induced emesis were prolonged by increasing the dose, and were  $55.6 \pm 11.2$  and  $93.5 \pm 16.1$  minutes at 300  $\mu\text{g/kg}$ , respectively. In restrained pigeons, changes of the intra-glandular stomach pressure were not corresponding to the emetic behaviors.

The dose-dependent glucagon-induced emesis observed only in pigeons was suppressed almost completely by chlorpromazine and reserpine, but not by haloperidol and bilateral vagotomy. Glucagon induced no behavioral changes in cats and dogs, but licking, gnawing, sniffing and mastication behaviors in mice and rats. These results suggest that glucagon-induced emesis may be mainly induced by dopamine release in chemoreceptor trigger zone, and may partially derive from its participation of the noradrenergic system.

The glucagon-induced emesis was completely suppressed by alpha-methyl-dopa and not blocked by phenoxybenzamine and propranolol at all. Apomorphine-induced pecking was not suppressed by alpha-methyl-dopa and reserpine, but completely by haloperidol and chlorpromazine. Glucagon-induced elevation of serum cAMP was partially suppressed by propranolol, but not by chlorpromazine and haloperidol. On the other hand, dopamine-induced emesis was also completely suppressed by chlorpromazine, but not by haloperidol. Dopamine-induced elevation of serum cAMP was completely suppressed by chlorpromazine, but not by haloperidol.

The above data suggest that the glucagon-induced emesis is mediated mainly via dopamine receptor unrelated doubtfully with  $D_2$  and partially through the releases of catecholamines. We are now examining some antiemetics, and emetics including drugs for cancer and pain. To increase the preclinical assessment of emetic adverse effect and the patient compliance for anticancerous and analgesic therapies is very useful in the therapeutic concept.

b. Evaluation of the role of the beta and extra-beta blocking actions of beta-adrenergic blockers: On the suggestion of clinical study of Moriya (1969) that propranolol evoked transient hypotension, we explored the interrelation of extra-beta-blocking action and beta-blocking action comparing to those in the whole animal preparations which are thought to have no adrenergic beta-receptors.

In cat nictitating membrane, occasional potentiation or inhibition appeared in ganglionic and neuroeffector junctions, more evidently by practolol than by propranolol and sotalol. Guanethidine-induced ptosis of mice was potentiated by sotalol and practolol, but not by propranolol. Reserpine- and hexamethonium-induced ptosis were suppressed by sotalol and practolol, but not by propranolol. Thirty minutes prior-treatment with any beta-blockers suppressed the noradrenaline-induced mydriasis, and 3 hours prior-treatment of sotalol potentiated slightly noradrenaline-induced mydriasis and those of propranolol and practolol potentiated and suppressed the mydriasis at low and high doses, respectively. In the reserpinized mice, noradrenaline-induced mydriasis was suppressed by the beta-blockers. In Vagus-amine test, all the beta-blockers induced arrhythmia due to the noradrenaline release. Practolol shortened thiopental anesthetic time and propranolol shortened it at low doses and prolonged it at high doses. Strychnine and pentetrazol convulsions were not suppressed but the mortality was slightly reduced by all the beta-blockers. Carageenin-induced edema was suppressed by sotalol and propranolol, but not by practolol. Propranolol and practolol suppressed acetic acid-induced writhing in mice. Propranolol possessed local anesthetic effect on the rabbit conjunctiva. Sotalol and propranolol lowered normal body temperature.

Furthermore, propranolol prevented partially the morphine-induced emesis in pigeons and long-term pretreatment with propranolol (30 and 100 mg/kg/day, p.o.) partially suppressed the isoproterenol (80 mg/kg, s.c.)-induced cardiac injury which may result from autooxidation of isoproterenol in rats.



From the above results, it can be suggested that the beta-blockers have releasing and antireleasing actions on adrenergic nerve endings, ganglion stimulating effects and anticonvulsive effects other than their proper beta-blocking action, and interactions probably based on their parent drugs and their active metabolites in vivo. And, it is also suggested that propranolol has cardio-protective effects as an antioxidant and antiemetic effects as a result of its 5-HT antagonism.

## 2. Development of experimental animal models

### a. *Wilson's disease*

Wilson's disease (hepatolenticular degeneration) is an inherited metabolic copper disease which results in cirrhosis of the liver and degeneration of the basal ganglia due to excessive copper deposition. The goal of therapy for Wilson's disease is to reduce the excessive copper deposition and increase copper excretion. D-penicillamine promotes the urinary copper excretion. During the treatment with D-penicillamine, about 20-25% of patients complain of adverse reactions: early acute hypersensitivity reactions such as fever, eruption and proteinuria, and serious intolerable state for D-penicillamine such as nephrotic syndrome, systemic lupus, pemphigus, myasthenia or pancytopenia. Other less toxic chelating agents have been sought and investigated. Animal models for Wilson's disease are very important in the screening test for the chelating agents.

We measured serum ceruloplasmin concentrations by the enzymatic method, and the copper contents in serum, urine and liver by the ICP atomic absorption spectrometry in Long-Evans cinammon (LEC) rats and control (Long-Evans Agouti: LEA) rats. Serum ceruloplasmin and copper levels of the LEC rats were very low. Urinary copper excretion was much increased in the LEC rats; LEC rats had extremely increased copper contents in the liver by more than 40-45 times of the LEA rats. The LEC rats most often have acute or chronic hepatitis, and have genetically autosomal recessive inheritance. It is suggested that LEC rats are useful as an animal model of Wilson's disease. We have evaluated trientine-2HCl in Wistar rats and LEC rats in point of cupr uretic effect. Our results suggest trientine-2HCl has one-fourth cupr uretic effect of D-penicillamine.

### b. *Evaluation model of drugs for antipollakisuria and incontinence.*

In the world, especially in Japan, year by year, the population of aged people is increasing and the patients suffering from pollakisuria and/or incontinence are also much increasing. In point of silver aged people, the methodological development of evaluating the drugs is necessary and urgent. We are now developing a method by which voiding volume and intravesical pressure are measured simultaneously. In the meeting I would like to report some results of alpha-1 and muscarinic antagonists in this preparation of rats.