Thesis Title : THE ACUTE TOXICITY OF B-ADRENOCEPTOR ANTAGONISTS

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ABSTRACT

The acute toxicity of propranolol was performed by giving various doses of propranolol intraperitoneally to rats. The LD_{50} value could be estimated to fall between 50-100 mg/kg. In experiment examining the acute toxicity of B-adrenoceptor antagonists, propranolol, bisoprolol or atenolol were administered intravenously to anaesthetized spontaneously breathing and artificially ventilated rats. In these experiments spontaneously breathing rats appeared to die from respiratory arrest. Artificial ventilation lengthened the survival time and increased the lethal dose significantly. Propranolol with its high degree of membrane stabilizing activity is by far the most toxic of the three B-blockers. Atenolol was the least toxic on a dose basis. The mean arterial blood pressure and heart rate for each of the three B-blockers in spontaneously breathing and artificially ventilated rats initially declined in

similar manners, which can be ascribed to beta adrenoceptor antagonist activity. In artificially ventilated rats arterial pH rose steadily during infusion while P_{CO_2} initially fell and then was maintained fairly constant indicating reduced metabolism and peripheral perfusion. On the other hand, in spontaneous breathing rats, arterial pH steadily fell during the infusion while arterial P_{CO_2} rose stedily during the infusion indicating CO_2 retention.

It was a consideration of this project to study the possibility that respiratory depression was enhanced in these experiments with the infusion of considerable volumes of fluid. Therefore a control group of spontaneously breathing rats receiving saline infusion alone at the rate of 0.5 ml/min was compared with another group receiving intravenous bolus of nadolol at the dose of 10 mg/kg. It is likely that the volume of intravenous fluid which can be acutely tolerated is increased by therapeutic dose of B-blocker. Lung wet weight to dry weight ratio of the rats was used as an index for the presence of pulmonary oedema. The ratios of bisoprolol and atenolol in the spontaneously breathing rats were significantly higher than those of control rats. This suggests that increased lung fluid in the B-blocker infused rats was due presumably to pulmonary oedema. The mean ratios for the artificially ventilated bisoprolol and atenolol infused rats were higher than those from the spontaneously breathing rats and it is not likely that the protective action of positive pressure ventilation was by preventing the development of pulmonary oedema.

In conclusion, ventilation was clearly demonstrated to increase the mean lethal dose of the B-adrenoceptor antagonists. The experiment definitely indicated that propranolol, bisoprolol and atenolol in the unventilated rats, caused death by respiratory depression. The actual mechanism of respiratory depression caused by B-blocker toxicity is as yet known. Further work is required to investigate this mechanism.