CHAPTER 1

BACKGROUND AND RATIONALE

Hepatic encephalopathy (HE) is a complex neuro-psychiatric syndrome which appears to be characterized by augmented neural inhibition[1,2,3]. The syndrome is associated with acute, subacute and chronic hepatic failure diseases. The characteristic neuropsychiatric abnormalities vary widely[1,2] from subclinical impairment of neurological and psychometric performance to overt episodic or persistent changes in a global depression of central nervous system (CNS) function. Though HE is generally considered to be a potentially reversible metabolic encephalopathy[4,5,6], it is the consensus that intervention must be done for the HE patients before the possibly undesirable and irreversible neurological deficits might ultimately happen -- seriously impaired consciousness, coma, brain death and death itself because of the underlying liver functional failure, its other complications and other concomitant diseases. The primary objective of HE treatment is, other than correcting and improving the fundamental impairment, to

normalize the patient's mental status[2,4]. The mental status includes 3 components -- the state of consciousness, intellectual function and personality behavior (Appendix 1)[2], which is relevant not only in the field of medicine, but also in the field of society.

The mechanisms by which the liver affects normal brain function remain poorly understood, though such phenomena and relationship have already been found since the time of Hypocrites[2]. Most authors now agree that it is a multifactorial disorder[3,7] and it is likely that several substances contribute to the altered mental status[3,8]. The basic pathophysiological changes associated with HE involve the accumulation of neuroactive and potentially comagenic substances in the systemic circulation. These compounds are normally absorbed from the gut and metabolized by the liver, but in hepatocellular failure they can bypass the diseased liver and enter the systemic circulation. These putatively toxic substances then cross the blood-brain barrier and accumulate in the brain to alter or ultimately damage the CNS function through a variety of mechanisms[3].

The successful treatment of HE, like virtually all other disorders, is based on an understanding of the

pathophysiology that underlies the condition. Several hypotheses of the pathogenesis of HE have been proposed[4,8]. The validity of none has been definitely proved experimentally. Since there is no unanimity of opinion concerning the important aspect of HE, it is no surprise to learn that there is no single form of therapy that is clearly the best and preferred to the exclusion of all others[4,5]. Although the ideal goal of treatment for HE is to improve hepatocellular function and if possible, to block the porto-systemic shunts, conventional efficacious and effective therapies[3,4,5,9], besides removal or correction of precipitating factors, are directed at reducing the systemic accumulation of gut-derived comagenic toxins by decreasing their intestinal synthesis or absorption and increasing the cleansing based on the basic pathophysiological changes in HE. Thus these therapies act on the organ that is considered to be the origin of the substances causing the problem. An alternative approach is to give such a treatment that can act on the brain which is the target organ by reversing neuropathophysiological events directly related to the encephalopathy[4,10,11]. This approach is based on the novel hypothesis that the altered neuronal transmission involves in mediating manifestations of HE.

Since 1982[12], evidence has been accumulating which indicates that benzodiazepine (Bz) ligands with agonist properties may contribute to the pathogenesis of HE by potentiating the neuroinhibitory action of gamma-aminobutyric acid (GABA)[4,7]. Moreover, the improvement of HE, clinically and electrophysiologically, has also been noted by using the Bz receiver (BzR) antagonist, such as flumazenil (Ro 15-1788), for the animal models as well as for man[13,14,15]. These data supporting that hypothesis seem to constitute a rational basis for developing a new therapeutic modality for the management of HE[4]. It has been found that BzR antagonists mediate their effects rapidly, their toxicity is minimal and can be repeatedly administrated[4].

However, like the other pathogenic hypotheses of HE, this GABA/BzR hypothesis has not obtained the fully positive support from all the researches in the related field[7,8]. Moreover, the results of not-a-large-amount-of previous experimental therapies by BzR antagonists on HE remain controversial to be resolved.

This clinical study is designed to evaluate the effectiveness of flumazenil in the treatment of HE.