CHAPTER 5

DISCUSSION

This randomized double-blind controlled trial was conducted to investigate and demonstrate the clinical improvement of HE stages of selected cirrhotic patients by administration of flumazenil, a special BzR antagonist, a bolus injection of 1.0 mg. This dose was intermediate compared to the other controlled studies (0.4-1 mg, Cadranel et al[39], 1995; 2.0 mg, Pomier-L et al[45], 1994; 2.2 mg, Gyr et al[51], in press) or uncontrolled studies (0.2-9.6 mg, Bansky et al[18], 1989; 2-15 mg, Grimm et al[35], 1988). An assessment grading HE was based on Conn[2] (1977). The primary therapeutic objective for flumazenil in this indication was to alleviate the CNS impairment enabling them to be managed with less clinical intensity, evaluated by the improvement of the clinical stages of HE from 2, 3 or 4 up to 0 or 1.

In order to get stable and relatively "pure" controlled underlying clinical conditions of these patients, only those suffering from cirrhosis were

included, moreover they should have stable vital signs and without the other metabolic or pathological encephalopathies which could mimic the manifestation of HE.

5.1 Unprocessed Procedures

There are two measured procedures, according to the protocol, which haven't been processed during the trial, because of the technical unavailability. These might be the drawback of this research.

5.1.2 Screening for Bz in Serum and Urine

The first unprocessed one was screening serum or urine Bz compounds of the patients to exclude the positive ones. The method used for exclusion in this trial was to get a negative history of Bz intake, which, the investigators believe, is reliable, because most of these patients rarely ingest pharmaceutical sedatives and the intaken drugs are mostly supervised by their family members. Three recent controlled studies[39,45,51] presented that there was unlikely relationship between the beneficial effect of flumazenil and the presence of positive blood or urine Bzs in the chronic liver failure patients. Some explanation have proposed[4,8,26,27] that it might be from the different sensitivity of the detection

of Bzs; and the "endogenous" Bz of HE might combine to a subgroup of GABA/BzR, other than the classical receptors.

5.1.2 EEG Recording

EEG was not applied during the practical trial period. This electrophysiological test[2,5] has been utilized in the clinical field for a long time, and found that it has certain relationship with the progress of encephalopathy. Some previous studies[39,45,49] introduced EEG as the primary effect parameter for evaluating the reaction after flumazenil administration. However, the grading by EEG and grading by clinical condition of HE has also been found to be not linear-related or not correlated well even since EEG was first adopted. EEG is quite difficult to record appropriately and interpret objectively, unless analyzed by a computer program. The patients, except the comatose ones, dislike to be tested by the "wire-net-cap" machine[5]. In the daily clinical service, the improvement, worthy to be emphasized and accepted by the patients and their families, should be the clinical effect or benefit. That is why the clinical evaluation for the HE stages and for the corresponding changes was adopted as the primary measuring instrument in this research.

5.2 The Therapeutic Outcomes and Clinical Patterns

This study demonstrated the alleviative function of flumazenil for hepatic encephalopathy in a subgroup (8/13) of cirrhotic patients. This compound could induce a fast-onset reaction of improving the HE clinical stage, whatever the initial stage (2, 3 or 4) the patient was in. Such result is consistent with most of the previous uncontrolled and controlled trials of flumazenil on HE (refer to Chapter 2 "Literature Review").

If the favorable therapeutic definition is strictly confined to making the patient regain nearly normal mental status (improve to Stage 0 or 1) after the proposed administration, there was no statistically significant difference (p=0.124, Table 4.4) between the flumazenil and placebo (normal saline) (3/13 vs. 0/12). However, when recalculating the power of this trial result from the obtained data (2 proportions: 23.08% vs. 0%) and the final enrolled sample size (13 in the treatment and 12 in the control group, respectively), it was found that the power was unfortunately low -- 56%. If these 2 'effectively improved" proportions of the samples in this study represent that of the populations, to have 90% power to detect the actual difference needs 31 patients in each group. Even for the 80% power, 23

patients per group is the minimal needed. Therefore, quite possibly, a difference existed in this study but the sample size was too small to detect it.

If the definition was broadened to see whether there would be any degree of improvement (positive response) of the clinical stages of these patients during the short trial period, the significant difference could be found between these 2 group -- flumazenil group (8/13) and placebo group (1/12) -- with the p value of 0.008 (Table 4.5) and the high power of 91.5%. Since these 2 proportions (61.54% vs. 8.33%) were quite close to those estimated in the proposal (50% vs. 10%) for determining the sample size, this power is acceptable. Subgroup analysis by the grade of HE at baseline also supported this result of the difference of the positive responses (p=0.028). It is clear that in the clinical service, the "effective" definition is more relevant than the "positive" one in the point view of the health providers, while for the patients' family members, even a little positive improvement of mental condition is also urgently expected, this is the reason that the definition of positive responder was also introduced in this research.

Such improvement in several cases was neither stable nor able to last for a sufficient long period of

time. This clinical phenomena is consistent with the pharmacokinetic and pharmacodynamic studies of flumazenil and have also been found in the other previous clinical studies.

It is interesting to identify that one patient in placebo group showed positive change of his clinical stage of HE, though initiating quite lately (from the 60th to 75th minutes), while none (Table 2.9) of the previous controlled trials presented the similar change in the placebo or control group. This discrepancy might be from the different definition of the "effect" or "reaction" based on different degree and different onset time. In addition, in this study, the patients in the control group also received the routine therapies for HE, which might show some changes (late onset?) in certain degrees. The spontaneous remission of the symptoms of HE which has already been recognized by the physicians might play a role in his improvement. It is lack of evidence, here, to exclude or include definitely the reasons mentioned above. For a randomized trial, individual characteristics still exists, though the effects of those have been minimized and, hopefully, balanced.

These positive changes after administering flumazenil were not related to the HE stages at the

baseline, indicating that the BzR ligands do play a role in the pathogenesis of any severity of HE. So far, no variables (predictors) could be found to help in estimating the possibility of the therapeutic reaction for flumazenil in these patients. Those who showed the improvement after the administration exhibited different long-term outcomes -- discharge with regained normal mental function or death in the ward. Though all the patients who died in the treatment group were the responders to that special drug, it was not significantly different from those who didn't improved in the statistical sense of death rate (p= 0.231, Table 4.8). The positive response of such patients in this study could not give an index of prognosis, good or bad, in some sense, like that supposed by Bansky[18], though only a phenomena, which haven't been proven clinically and statistically. As said in "Literature Review", it is difficult to conduct a controlled trial to study the long-term outcome of flumazenil for its relatively pure effect, the therapeutic effects of other drugs could not be excluded, since flumazenil, which doesn't change any underlying liver diseased function, cannot be prescribed alone.

A single case report[36] showed successfully the effectiveness in long-term treatment of chronic HE (PSE)

on an outpatient basis. This may highlight the future management of HE by different ingestion route of flumazenil and other therapies.

Like in the other studies[3,5], the prognosis of this subgroup of patients (HE complicating with cirrhosis) was unfavorable. Six out of 23 of the eligible cases died in the respective episode of admission at last, if accounting the 2 who were discharged early but soon died later, the mortality increased to over 1/3. Among them, 6 died within one week after the onset of that episode of HE, reflecting the severity of HE and the underlying liver diseases.

Statistically, in this study, there was no difference found in the death rate between the 2 groups. Even if conducting subgroup analysis according to the HE Stage or Child-Pugh Grade at the baseline (Table 4.9), flumazenil did not change the final fate -- death or not death -- of these HE patients in the treatment and control group. However, since the sample numbers in these groups or subgroups were quite small, the power of these statistical tests was very low.

However, when conducting another co-variance analysis for all the HE patients regardless their initial allocation to the treatment or control group (Table

4.10), a reasonable trend seems to be found that generally the higher grade of the HE, the higher the mortality; the higher the Child-Pugh Score, the higher the mortality.

It is interesting to find that the predictive value of HE stages was different between the treatment and control groups, so it was with that of Child-Pugh grade (Table 4.10). However, there was no significant different of the mortality (Table 4.9) between these 2 groups (3/13 vs. 5/12, p=0.41), while the power was obviously low (16.5%), which made this "no difference" in the position of that "there might be actual difference in the populations". The p value of being predictors in the control group was less than 0.05 (0.045, HE stage) or a little higher than 0.05 but less than 0.10 (0.072, Child-Pugh grade), while the p values in the treatment group were far more than 0.1. Moreover, if merging these 2 groups together, the after-merging p-value were much closer to those in the control other than those in the treatment group. Whether this discrepancy of p values between 2 groups and the similarity of p values between the controlled cases and the whole cases implied that flumazenil changed the fate of these patients who had been administered flumazenil is in question. It is unlikely this way. All the cases were allocated randomly

and no significant difference of the variables between the two groups was found at baseline. There was no extra treatment, except flumazenil, for the patients in the treatment group during the trial. In addition, theoretically the pharmaceutical effect of flumazenil lasts quite short and this agent does not change the underlying liver diseases or improve the liver functions. At last, the first subgroup analysis (Table 4.9) didn't support the presumed effect of flumazenil on the mortality of these patients. This disagreement probably arose from the individual characteristics of these patients, and the possibly different management for them in the follow-up period according to their respective conditions. Moreover, some numbers of the subgroups in those statistical cells were not big enough to resist the alteration of the results after the by-chance changes, even little, of the numbers in cells.

Flumazenil induced few and non-severe adverse reactions or side effects after its bolus injection in this study. Because of the decreased liver function of these cirrhotic patients, the $t_{1/2}$ of flumazenil could be prolonged[26,31]. It should be cautious for the possible adverse effect of large dosage or continuous injection, even by oral route[50].

5.3 Assessing Instrument

Though the clinical grading method for HE by Conn[11] has been accepted in the medical practice and found easy to manage and relevant to the clinical state and this study also used this grading criteria, this 4-grade (or 5 grades if including the grade 0) scale has been found to be not discriminative enough and quantitative enough to measure the mild stage (0 or 1) and the slight changes within one grade or stage of HE. Sometimes it showed the conflict results by evaluating certain items. Psychometric tests (e.g., NCT) have been introduced into this field, however, they are suitable for the mild cases only and it takes time to accomplish the test in a mental diseased patient. Glasgow coma scale[1,3] is a quantitative scale but only for the stage 4 (coma) patients. Gyr and Meier et al[51] modified that 4-grade scale into a PSE score (0-16 points) mainly including the disorders of sleep pattern. Average improvement in PSE score of at least 2 points was considered clinically relevant. Though it was better than Conn's scale in the sense of quantification, this scoring has not been reported in the other relevant researches. PSE Index[11] has been tried to introduce into this study, however, during the intensive observation period, it was not practical. Like the most

investigators ever using PSE Index, this Index and its some components individually are suitable for the chronic and continuous changes of the HE stage. More practical and quantitative scale to measure the mild changes of mental status awaits further collaborative researches in various medical fields.

5.4 Clinical Implication

Though, in this study, only part of the HE patients showed the positive reaction of flumazenil, and the sustain effect time was not stable and long in that group of patients, for an individual patient and his family members, the possible, or even unpredictable, improvement of mental status which might make the fast reconstruction of the communication in different degrees between the patient and the surroundings after the administration of flumazenil is extremely significant. Facing the generally unfavorable long-term prognosis of these patients, the favorable response with little adverse effects of this drug may help the doctors and the patient's family members as well to select the decision of using this agent.

Obviously, flumazenil has no curable effect for HE. Moreover its long-term effect on the survival and the maintenance of normal mental activities has not been

established. However the rapidly-decreased inhibitory GABA-ergic tone by flumazenil, theoretically, might have some potential impact on the present and future brain function of those HE patients. In addition, flumazenil administration might induce rapidly-onset positive effects of improving the mental status even in the comatose HE patients. Comparing with the other conventional therapies for HE, this is its unique characteristic.

It is natural for people to keep communication with the patients who are close family members, friends or colleagues, even during their desperate (dying) period. It is also not unusual to find the expression that "I am willing to pay with all I have, if you save him". However, in the real situation, it is difficult to estimate how much they, the family members, would like to pay. Nevertheless, to weigh of the favorable short response with the social and economic influencing factors by the family members, and along with the medical factors by the health providers (doctors) seems to be the way to evaluate the therapeutic position of this drug.

The doctors should not overlook the facts that 1) there is a spontaneous remission trend for part of HE patients, especially for the slight or non-severe ones;

2) not a few HE patients could be treated to regained their normal or close-to-normal mental function one or several days after conventional therapies; and 3) the relapse of HE episodes is not uncommon. They should explain these phenomena to the patients' family members, along with the introduction of the characteristics of flumazenil's effects. It's better to mainly let the family members make the decision, which might be largely on the basis of "willingness to pay".

There are many alternatives: for a severe comatose HE patient without any response to routine therapies, is it worth offering flumazenil to, hopefully, make him show some response to the calling of his close relatives? For a moderate HE patient but with bizarre and uncooperative behavior, is it worth administering flumazenil to control his activity to the level of receiving treatment and not disturbing others, even for a while? For a slow-computing or disorientated patient, is it worth using flumazenil to improve his intellectual ability as soon as possible at that moment? For an often-relapse HE patient, is it worth injecting flumazenil at each relapse?

The average retail price of flumazenil in Shanghai is $45/0.5mg, it costs $90 per bolus injection,

which lasts several hours averagely. The other drugs for HE are comparatively much cheaper, e.g., lactulose (30g, tid, $12 per day), BCAA (500ml, qd, $8 per day) or glutamates (5g, qd, $4 per day). The other costs, such as the ward charge, lab test charge and the personnel charge are almost similar in the clinical service setting. However, focusing only on the direct medical costs is not enough in this kind of diseases or syndromes. The compensation for the patient's family members by the possibly rapid improvement of mental status after flumazenil administration should be taken into accounted for the total costs related to the management for HE patients.

It may well be that an increase in the treatment resources including flumazenil and other therapies available to evaluate and treat HE patients would yield benefits, which would outweigh the cost of this specific drug an other therapies, e.g., the fast reconstruction of communication of the patients and the relief of the anxiety of the family members might decrease the disability time and in-ward time of the patients, decrease the opportunity cost the family members leaving from their work, and potentially prolong the productivity of the patients and their families as well. It is worth conducting these studies, however, it is not easy to do.

In Shanghai where the research setting is, flumazenil is not a drug in the list of those which can be reimbursed. The price is not so cheap comparing to the salary of ordinary people. A short questionnaire had been planned to ask the maximal financial affordability of the families of those patients for this kind of drug. Finally, it automatically stopped, because how to ask this question in that situation? And who will present one's real thoughts after that critical period? This is not an economic dilemma that one can consider for a long time to make a decision.

So far, it has no evidence strong enough to demonstrate the first-line therapeutic position of flumazenil for HE patients. However, it seems rational to apply this drug on those critical patients to achieve the purpose that other therapies could not achieve. Non-intravenous route of flumazenil should be another practical way in the management of HE.