

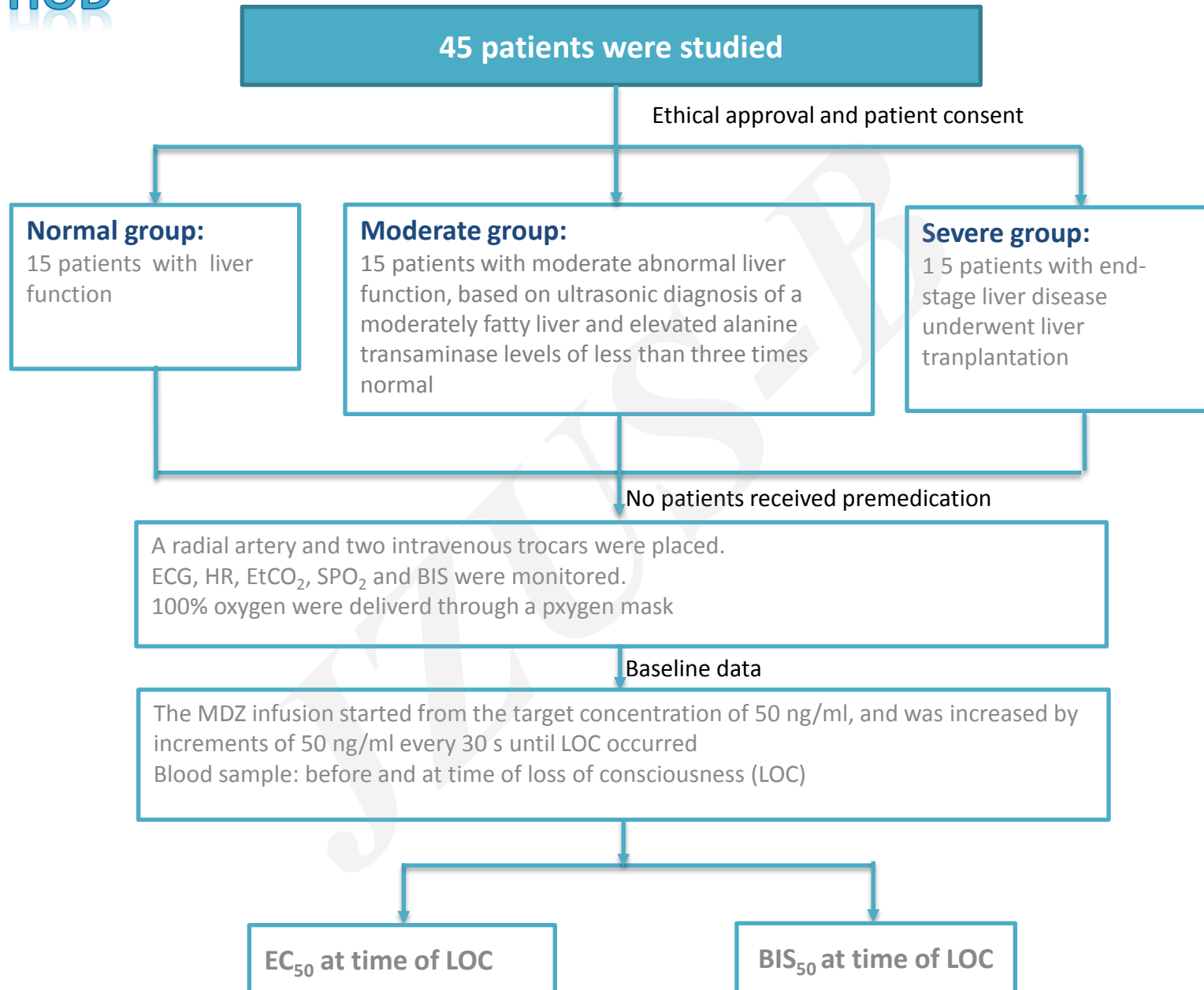
Cite this as: Yu-hong LI, Rui HE, Jin-guang RUAN, 2014. Effect of hepatic function on the EC_{50} of midazolam and the BIS_{50} at the time of loss of consciousness. *Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)*, 15(8):743-749. [doi:10.1631/jzus.B1300242]

Effect of hepatic function on the EC_{50} of midazolam and the BIS_{50} at the time of loss of consciousness

Key words: Midazolam, Hepatic function, EC_{50} , BIS_{50} , Loss of consciousness

- Midazolam (MDZ) is widely used to sedate patients in intensive care units and to induce anesthesia because of the rapid onset and short onset and short duration of its effects.
- MDZ is rapidly and extensively metabolized by the liver and intestinal microsomal enzymes. Many factors, such as age, sex, concomitant medication, and hepatic function may influence the activity of CYP3A isoforms
- The bispectral index (BIS), a processed electroencephalographic parameter is widely used to quantify the hypnotic effects of anesthetics and can serve as a tool to monitor and titrate the pharmacodynamic effects of anesthetic drugs.
- Both the pharmacokinetics and pharmacodynamics of MDZ were significantly impaired in patients with hepatic cirrhosis. The effects of liver function on sensitivity to MDZ and prediction of the BIS for loss of consciousness (LOC) remains unclear.
- The main focus of this research was to examine the influence of liver function on the MDZ concentration and the BIS value at the time of loss of consciousness in patients. The results may provide guidance for clinicians using MDZ and the BIS when treating patients with liver malfunction.

METHOD





RESULTS AND CONCLUSIONS

- The results for the EC50 of MDZ and the BIS50 for LOC (95% CI) for each group are listed in Table 2. Logistic regression analysis showed that the EC50 of MDZ for LOC in the severe group was significantly lower ($P<0.05$), while the BIS50 was significantly higher compared with the corresponding values in the normal and moderate groups ($P<0.05$).
- Regression analysis showed a coefficient of correlation between the concentration of MDZ at LOC and ALT of $r=-0.542$, and a correlation with ALB of $r=0.590$. The coefficient of correlation between the BIS at LOC and ALT was $r=0.630$, and the correlation with ALB was $r=0.681$. All correlation coefficients from the regression analysis were much lower than 0.5, indicating that ALT and ALB explained less than 50% of the concentration of MDZ and of the BIS at LOC.
- The linear range of MDZ detected was 20-500 ng/mL and the limit of detection of MDZ in plasma was about 15 ng/mL. The coefficient of variation of this HPLC method was less than 10% within the range of concentrations measured in this study
- Relationship between the probability of unconsciousness and the concentration of MDZ and the BIS showed that compared to the normal and moderate groups, in the severe group the concentration curve shifted to the left, whereas the BIS curve shifted to the right.
- In summary, we have investigated the effect of hepatic function on the LOC and the BIS in patients. We demonstrated that patients with end-stage liver disease were more sensitive to MDZ and the prediction of the timing of LOC following MDZ treatment was affected, while there were no changes in patients with moderately abnormal hepatic function. Clinicians should be aware of the possible need to reduce anesthesia or the sedation dose of MDZ for patients with hepatic dysfunction.