Mirtazapine metabolism in rat’s perfused liver


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Abstract: Background: Mirtazapine is a tetracyclic antidepressant which belongs to noradrenergic and specific serotonergic antidepressant. Its pharmacological activity results in an increase in both serotonine and norepinephrine levels. Previous clinical studies have shown mirtazapine effectiveness in depression treatment, moreover, mirtazapine is superior to SSRIs and TCAs from the aspect of having less undesirable effects such as nausea induction or anticholinergic side effects.

The aim: Since mirtazapine could be a valuable drug in clinic and no study have been published on its metabolism via liver perfusion, isolated perfused rat liver served as a sophisticated model to investigate the pharmacokinetic of mirtazapine.

Method: 6 male Sprague-Dawly rats were applied and undergone the surgery. The drug-containing medium was delivered into the portal vein. The perfusate samples were collected every 10 minutes from the inferior venacava. After injecting them to the HPLC system, mirtazapine and its two major metabolites called N-desmethylmirtazapine and 8-hydroxymirtazapine were detectable.

Result: Their concentrations were determined separately using validated calibration curves:

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\text{8-hydroxymirtazapine: } y = 93874x - 196158, R=.997 \\
\text{N-desmethylmirtazapine: } y = 55757x - 87292, R=.996 \\
\text{Mirtazapine: } y = 77819x - 81605, R=.996
\]

And mirtazapine reached to the concentration of 140ng/ml during perfusion, then the pharmacokinetic parameters such as AUC were calculated.

Conclusion: Mentioned method has the advantages of controlling physiological factors that may influence the hepatic metabolism such as protein binding.

In conclusion this study is the first investigation of mirtazapine metabolism in isolated perfused rat liver. To our knowledge there are few studies in intact animals or perfused organs. Further studies are suggested to complete the result of the present study.

Keyword: mirtazapine, metabolism, liver perfusion, pharmacokinetic