SUMMARY

Electroconvulsive therapy (ECT) is the transcutaneous application of small electrical stimuli to the brain to produce generalized seizure for the treatment of selected psychiatric disorders, mostly treatment resistant depression, acute mania, and schizophrenic syndromes. ECT has evolved into a widely recognized treatment modality in the practice of psychiatry such that today, ECT is worldwidely administered to an estimated one million patients a year. Safety of ECT increases the efficacy of therapy and provides fulfillment of a series of required treatments resulting in longer treatment effect of ECT. During the last few decades, researchers have been attempting to identify and improve the effectiveness of ECT, to learn how and why it works, to understand its risks and adverse side effects, and to determine the best treatment technique. As a result, the safety and efficacy of ECT has been improved and its indications have been relatively defined to increase the efficiency of outcome of therapy. While there has been considerable improvement in safety features, further investigation have been done to promote both the safety and efficacy of the treatment. Such efforts could also increase our knowledge on the biological mechanisms involved in effectiveness of ECT that might result in discovery of new treatments. In this dissertation, we investigate how preprocedural medications could improve the safety and efficacy of ECT and further investigated the potential role of pharmacogenetics in the efficacy of ECT and procedural side effects such as cognitive disorders.

Chapter one contains a general introduction and describes the current concept of electroconvulsive therapy (ECT) and its aim to induce a therapeutic tonic seizure with the minimum required energy, tailored to the condition of each patient. This chapter provides an overview of the safety and efficacy of ECT depicts the general schema of this dissertation in investigation of the role of clincial pharmacology and pharmacogenetics in improvement of the safety and efficacy of ECT.

Chapter two reviewes the current concepts of neuromuscular blocking agents (NMBA) application for ECT. Anaesthesia and neuromuscular blocking agents (NMBAs) are required to ensure patients' safety during ECT. The optimal dose of muscle relaxant for ECT reduces muscle contractions without inducing complete paralysis. Slight residual motor convulsive activity is helpful in ascertaining that a seizure has occurred, while total paralysis prolongs the procedure unnecessarily. This chapter reviews the current NMBAs and their applied doses for ECT and the potential gap in knowledge for an ideal NMBA during ECT.

Chapter three describes a conducted crossover, assessor-blinded, prospective randomized study to study the optimal effective dose of succinylcholine and rocuronium for ECT.

Succinylcholine or rocuronium were randomly administered in 227 ECT sessions to 45 patients. The initial dose was incrementally increased or decreased by 10% based on two psychiatrists' (blinded to treatment) assessment of 'acceptable' or 'not acceptable' control of evoked muscle contractions (sufficient vs. insufficient or excessive paralysis). The optimal effective doses of succinylcholine and rocuronium in 50% of patients (OED_{50}) were 0.85 $mg.kg^{-1}$ (95% CI: 0.77-0.94) and 0.41 $mg.kg^{-1}$ (95% CI: 0.36-0.46), and the 90^{th} percentile of the applied optimal doses (OED_{90}) 1.06 $mg.kg^{-1}$ (95% CI: 1.0-1.27) and 0.57 $mg.kg^{-1}$ (95% CI: 0.51-0.62), respectively. The inter-individual variability of the OED_{50} (coefficient variation) was 1.24-fold greater for succinylcholine than rocuronium.

Chapter four presents a follow-up study on chapter three to analyze the pharmacokinetics-pharmacodynamics (PK-PD) relationship of succinylcholine and rocuronium during ECT. In this study the data on the first twitch height (T1) of 31 patients who underwent ECT as well as the corresponding intravenously applied doses of succinylcholine and rocuronium were used for the analyses in the study using NONMEM. The PD model parameter estimates for succinlcholine and rocuronium during ECT were k_{e0}= 0.04 min^{-1} (SEE=0.004) and k_{e0}= 0.17 min^{-1} (SEE=0.19), respectively. The Ce50 estimations for these two NMBAs were amounted to 0.7 µg/ml (SEE=0.06) and 1.6 (SEE=0.1), respectively. The Ce50 of neostigmine was measured to be 0.412 (SEE=0.06). The results showed that the estimated PK-PD parameters for succinylcholine and rocuronium during ECT are almost comparable to previous PK-PD estimates for these two NMBA. According to the observed higher Ce50 for rocuronium in this analysis, we suggested this observation might explain faster recovery after ECT from NMB and proposed further investigation.

Chapter five discusses the clinical insights into pharmacogenetics of ECT and adjunctive medications and how the acquired knowledge could improve safety and efficacy of ECT in the indicated patients. This chapter also describes the role of pharmacogenetics in leading to the identification of novel treatments in psychiatric disorders through understanding of potential molecular and biological mechanisms involved. Our review demonstrates that the knowledge for safe application of ECT has been improved, at least partly due to the role of pharmacogenetics in application of anesthetic agents. Some genes such as *CACNA2D1* and C*ACNA1S*, *BCHE* and *RYR1* are associated with safe practice of anesthesia in ECT. We identified several genes (i.e. BDNF, COMT, DDR2, DDR3, CREB, VEGF, COX-2, TRKB and NMDA receptor) that might interactively play important roles in treatment response to ECT. These genes are co-expressed as part of transcriptionally regulatory sub-networks in the brain. In these sub-regulatory networks,

AP-1 transcription including CREB demonstrated the most regulatory effects on the network

objects.

Chapter six reports an investigation on the accumulation of aberrant *CYP2D6* genotypes and predicted metabolizer phenotypes (UM, IM, and PM) in depressive patients indicated for ECT compared to patients with single episode of depression. 76 Dutch Caucasian subjects with unipolar or bipolar treatment resistant depression who underwent ECT were genotyped using Amplichip® CYP450 Test for *CYP2D6* and 208 patients with single episode of unipolar or bipolar depression were used as controls. The result showed that there was no difference in prevalence of CYP2D6 phenotypes (PM, IM, EM and UM) between the ECT and control patients (5.3%, 38.7%, 56.0% and 0.0% vs. 6.4%, 51.0%, 42.6% and 0.0%, respectively). The types of depression (OR=0.33, p=0.018) and age (OR=1.55 for a-10-year increase, p<0.001), but not CYP2D6 phenotype or activity score were associated with the response to antidepressant treatment. In conclusion, preemptive genotyping for *CYP2D6* currently appears to have no clinical implications in treatment resistant depressive patients indicated for ECT.

Chapter seven describes a case report on occurrence of profound hypertension during the induction of general anesthesia with propofol, potentially due to interaction with rifampin. The conducted retrospective data analysis on series of similar cases demonstrated that the risk of a prolonged hypotensive episode increased almost three-fold when propofol rather than thiopental was used for induction in patients who had received rifampin. Almost 40% of cases showed exaggerated hemodynamic responses that required vigorous treatment with vasopressors and fluids. The applied dose of phenylephrine was significantly greater in the propofol-rifampin group vs. control groups, i.e. propofol alone and thiopental and rifampin (p=0.039). The mechanism for this interaction was not investigated and is unknown. Intravenous administration of rifampin alone can induce hypotension by a direct, dose-dependent reduction of vascular tone and systemtic vascular resistance (SVR). Propofol-induced hypotension is largely due to venodilation and rifampin might augment this effect as a result of increased NO production by upregulating iNOS mRNA transcription. While this study reemphasizes that clinicians should be vigilant for the reported drug-drug interaction during procedural treatment, it suggests a prospective study to investigate the mechanism of this drug-drug interaction.

Chapter eight describes a prospective observational investigation on hemodynamic clinical factors that cause delays in post anesthesia care unit (PACU) discharge. 232 consecutive patients were evaluated for postoperative hemodynamic adverse severe events (PHASE, simultaneous severe bradycardia and hypotension). Fifteen patients showed severe hypotension and twelve patients with severe bradycardia, resulting in PHASE in ten patients

(5%). PHASE occurred on average 307 ± 82 min after spinal anesthesia with a mean spinal anesthesia level of L1 at the time of PHASE. Insertion of spinal anesthesia in the lateral position (PHASE: 80%, no PHASE: 34%, p=0.030) and morphine dose (20±12mg versus 9±8 mg, respectively p=0.011) were found to be associated with PHASE. In conclusion, PHASE during recovery from spinal anesthesia is associated with significantly increased PACU length of stay, a 60-minute increase in median PACU length of stay.

Chapter nine provides a discussion on several important aspects of safety and efficacy of ECT that were investigated in this dissertation and how the study contents contributes to the existing literature and clinical principals in application of ECT as well as understanding of the role of clinical pharmacology and pharmacogenetics in ECT. Finally, future research directions to improve safety and efficacy of ECT based on acquired knowledge are explored.