The role of clinical pharmacology and pharmacogenetics in electroconvulsive therapy : from safety to efficacy

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General introduction

Electroconvulsive therapy (ECT) is an effective treatment in patients with acute and chronic psychiatric disorders resistant to psychotropic medications or need urgent control of their symptoms. Worldwide, it has been estimated that about one million patients receive ECT annually.[1,2] The aim of ECT is to induce a therapeutic tonic seizure with the minimum required energy, tailored to the condition of each patient. ECT has evolved into a widely recognized treatment modality in the practice of psychiatry.

While the efficacy ECT is mainly inherent to the biological alterations in brain through the induced therapeutic seizure, ECT procedural safety is pivotal to the outcome of treatment such that optimizing the procedural safety will improve the efficacy of the therapy outcome. An effective ECT procedure requires a good knowledge of anesthetic principles, understanding of the interaction between anesthetic drugs and seizure activity, the effect of anesthetic drugs on the ECT response and the clinical pharmacologic effects of the drugs used to attenuate the side effects related to ECT, and an awareness of the physiologic responses to the electrical stimulus. Additionally, it has been shown that some anesthetic drugs could augment the response to treatment or affect the quality of seizure that might be associated with short or long term efficacy of ECT.

Pharmacogenetics is the science to investigate an individual's sensitivity and response to a variety of drugs or the outcome after therapeutic intervention via studying genetic variations and gene-gene interactions.[3] Clinical insights into pharmacogenetics of ECT and understanding the biological mechanism of ECT not only improves its safety and efficacy in the patients, but also helps to develop alternative and more effective therapeutic agents in psychiatric disorders. This required knowledge also includes the adjunctive medications that might augment the response to treatment and can help to improve the efficacy of treatment in patients who do not respond to antidepressants or other psychotropic medication.

Therefore, the aim of this dissertation is to investigate the "safety and efficacy" of ECT, the two integrated aspects of this therapy procedure and how conducting investigations on these two indispensable precepts might lead to improving the quality of ECT outcome for treatment of indicated disease. To achieve this objective, we firstly explore the literature on the history of ECT application as a therapeutic procedure for psychiatric disorders and how the anesthetics, particularly invention of neuromuscular blocking agents (NMBAs) for ECT, improved the safety of this procedure (*chapter two*). Anesthesia for ECT includes the use of an induction agent and short acting muscle relaxant such as succinylcholine to minimize the amount of muscle contraction that occurs with the seizure. Accordingly, in *chapter two*, we also provide a comprehensive review on the neuromuscular blocking agent usage in ECT, their applied doses and potential side effects. Furthermore, we attempt to find supportive evidences on the suggestive NMBA 'rocuronium' as an alternative NMBA for choline that has

mainly been used for ECT due to its rapid onset time and short duration of action. [4]

In *chapter three*, a crossover randomized trial is designed to compare the commonly used muscle relaxant i.e. succinylcholine with rocuronium during the ECT and define the optimal doses that could predict the acceptable seizure induced muscle activity. The optimal doses for rocuronium and succinylcholine are defined and recovery time indices are explored. This research is distinguished as the first study, which identifies the optimal (minimal effective) doses of mostly used neuromuscular blockers in ECT using objective assessment by neuromuscular monitoring. The main objective of this investigation is providing a clinical guidance for clinicians in applying the minimal dose of succinylcholine or rcocuronium that could result in an optimized seizure activity during ECT.

Increasing our knowledge on pharmacology of succinylcholine and other nondepolarizing NMBAs in different conditions, i.e. simultaneous measurement of their plasma concentrations or a surrogate measure (pharmacokinetics) and neuromuscular blockade (pharmacodynamics) during ECT could help in increasing the safety of NMBA application or even the search for a new alternative NMBA. Pharmacokinetic–pharmacodynamic models help in measuring the drug effect and the relation between blood concentration and the target organ under the effect of drug. In *chapter four* and as a follow-up study on *the chapter three,* we conduct a PK-PD study to provide a quantitative model to describe the kinetics and the dynamics of succinylcholine chloride and rocuronium after the different bolus doses applied for inducing muscle relaxation in patients underwent ECT.

As earlier mentioned, inherent genetic differences and neurobiological alterations could be of high importance in response to ECT. In *chapter five,* we explore the past and current knowledge of pharmacogenetics in electroconvulsive therapy and adjunctive medications whose applications might augment the response to ECT and present the evidence of pharmacogenetics role in patients with psychiatric disorders undergone ECT. The safety of the procedure has two aspects: (i) safety of medications used during ECT (ii) side effects of ECT procedures e.g. cognitive disorders. In addition to reviewing these two aspects from pharmacogenetics perspective, we will also explore the functional genomics, gene polymorphisms and biological brain transmitters might play role in the effectiveness of ECT.

In spite of the availability of multiple pharmacologic classes of antidepressants (ADs) and their sequenced trials using available guidelines for depression treatment, majority of patients with unipolar or bipolar depressive disorders fail to achieve complete remission. [5] The enzyme cytochrome P450 2D6 (CYP2D6) plays an important role in the pharmacokinetics of many ADs (i.e. SSRIs and TCAs). Consequently, The *CYP2D6* gene could be a prominent contributor to interindividual drug response variability and predicted phenotype of enzymes

i.e. poor metabolizer (PM), intermediate metabolizer (IM), extensive metabolizer (EM) and ultrarapid metabolizer (UM).[6] In *chapter six***,** we investigate the accumulation of aberrant *CYP2D6* genotypes and predicted metabolizer phenotypes (UM, IM, and PM) potentially affecting the antidepressant treatment response in depressive patients indicated for ECT compared to patients with single episode of depression.

Anesthesiological care during ECT differs from the usual anesthesiological management for surgical patients [7,8] and a short acting hypnotic is used along with muscle relaxant. The ideal hypnotic agent for ECT has a short half-life, does not influence seizure duration and quality, and guarantees the patient's hemodynamic stability. Propofol has the shortest half-life of all the available hypnotic agents that makes it as the first choice hypnotic agent for induction of anesthesia for ECT. [9] Compared with methohexital, another hypnotic agent for ECT, propofol is associated with improved hemodynamic stability and an earlier return of cognitive function after ECT, though it might decrease the duration of seizure. [10] Although few side effects have reported after infusion of this hypnotic, it has increasingly been administered for general anesthesia and short procedures such as ECT in recent years. Therefore, clinicians should be attentive to any probable new side effect of propofol. The potential adverse effect of any drug could be due to either chemical structure of the drug (medication side effect) or an interaction with another drug (interaction side effect). In *chapter seven*, we investigate a new potential interaction side effect of propofol based on a series of reported occurrences of severe hypotension after induction with propofol in patients who had received rifampin for prophylaxis of infection for spinal surgery. We would like to focus on this not previously reported severe hypotension after induction with propofol in comparison to induction with other anesthetics and explore the literature for evidences that could support this observation.

In recent years, there has been substantial increase in the number of noninvasive and short procedural interventions that shorten patients' duration of stay at health care facilities. Consequently, healthcare practitioners are faced with a larger number of patients requiring procedural sedation. Effective sedation and analgesia during procedures not only provides relief of suffering, but also frequently facilitates the successful and timely completion of the procedure. However, any of the agents used for sedation and/or analgesia may result in adverse effects. [11] It has been reported that postoperative hemodynamic severe adverse events (PHASE), i.e. severe bradycardia and hypotension, can occur during recovery from spinal anesthesia. Incidence, contributing factors, and consequences of PHASE are unclear. In *chapter eight*, we aim to evaluate the incidence of PHASE, contributing factors and the impact on post anesthesia care unit (PACU) length of stay. Finally, in *chapter nine,* we will discuss the importance of the findings presented in this dissertation and the proposed future direction.

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