Graylands Hospital
Drug Bulletin

Medications and Electroconvulsive Therapy

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Introduction

Electroconvulsive therapy (ECT) has been shown to be highly effective and safe for many psychiatric disorders such as major depressive disorder, catatonia, psychosis and mania.[1] It is well documented that certain medications interact with ECT and can impact on the quality of the treatment or cause adverse effects. This bulletin attempts to summarise the effect of medications on ECT and vice versa.

Medication Optimisation Pre-ECT

Anticonvulsants

Anticonvulsants, in theory, will reduce the quality of seizures obtained with ECT as they are designed to prevent seizures. However, evidence of anticonvulsants interfering with the efficacy of ECT is lacking.[2] Most guidelines still advise cessation of anticonvulsants prior to ECT. The Chief Psychiatrist's Guidelines for the use of Electroconvulsive Therapy in Western Australia 2006 recommends cessation of anticonvulsants if possible prior commencement of ECT.[3]

A search of the literature produces mixed results on this question. A large retrospective study demonstrated that patients on anticonvulsants are associated with poorer response to ECT, with 3.7% of responders receiving anticonvulsants compared to 17.9% of non-responders.[4] On the other hand, Rakesh *et al* found a statistically significant improvement in patients on full dose anticonvulsants.[5] This study randomised patients to three groups, anticonvulsants at full dose, half dose or no anticonvulsant and used bitemporal (BT) ECT.

A review by Sienaert *et al* concluded that ECT can be administered safely with anticonvulsants with no reduction in efficacy.[6] A trial comparing the efficacy of ECT with or without concurrent sodium valproate therapy concluded that continuation of valproate during ECT does not impair or enhance the efficacy of ECT.[7] Similarly, a small clinical trial of 19 patients concluded that therapeutic doses of lamotrigine does not significantly influence the stimulus dose required or length of ECT-induced seizures.[8]

Benzodiazepines

Benzodiazepines are gamma-aminobutyric acid (GABA) receptor modulators which increase seizure threshold, shorten seizure duration and reduce seizure intensity.[2]

Multiple studies have shown that benzodiazepines affect the efficacy of right unilateral (RUL) ECT but not BT ECT. [2, 4, 9, 10] It has also been shown that withholding benzodiazepines from the night before ECT night is sufficient to mitigate the anticonvulsant properties of low dose benzodiazepines (<6mg lorazepam equivalent).[4] No studies looking at the impact of z-drugs in ECT could be found, but the half-life of zopiclone and zolpidem are quite short (5 hours and 3 hours respectively) and they are likely to have little impact on ECT when they are given the night before. Promethazine is used as the first-line hypnotic at Sir Charles Gairdner Hospital Mental Health Unit (SCGH MHU) for clients requiring an hypnotic the night before ECT but zopiclone is routinely administered as a hypnotic if there is inadequate response to promethazine.

Lithium

There are older case reports associating concomitant lithium and ECT with excessive cognitive disturbance, prolonged apnoea and spontaneous seizure.[11] Furthermore, there is a potential that lithium can enhance and prolong the action of suxamethonium.[12] More recent evidence show that concomitant lithium is safe to administer with ECT but all reviews still suggest maintaining lithium therapy at the lower range of the therapeutic serum level as there is potential for rare complications such as prolonged seizures or, confusion.[11, 13, 14]

Antipsychotics

There are multiple trials of concurrent administration of antipsychotics with ECT. A meta-analysis of 23 studies assessing the efficacy of antipsychotics and ECT found no significant adverse effects with concurrent treatment.[15] A large retrospective study concluded that adverse effects were not influenced significantly by concomitant antipsychotic medication.[16] Several studies evaluated the safety of ziprasidone or aripipazole with ECT and showed minimal adverse effects. [17, 18] Clozapine and phenothiazines are more likely to prolong seizure duration[16] and a recent systematic review found 14% of cases reported adverse events with concurrent clozapine administration and ECT,[19] most likely due to clozapine lowering the seizure threshold.[19]

Chi *et al* investigated the relationship between seizure threshold and psychotropic drugs on ECT and found an association between initial seizure threshold and the total chlorpromazine equivalent dose of antipsychotic.[20] The authors concluded that the higher the dose of most groups of antipsychotics, the higher the initial seizure threshold which is contrary to the popular belief that all antipsychotics lower the seizure threshold. The exact mechanism on how antipsychotic increase seizure threshold is unclear but the authors hypothesised that dopamine is a proconvulsant and the use of antipsychotics reducing dopamine may result in a raised seizure threshold.[20]

Antidepressants

An indirect comparison meta-analysis shows no adverse complications with combined antidepressant use and ECT except for a high rate of memory deterioration four weeks after ECT treatment.[21] There are case series demonstrating the safety of SSRIs in ECT.[22, 23]

Nevertheless, risk of complications with concurrent administration of antidepressants and ECT remain. A retrospective review found SSRIs prolonged seizure duration compared to an SNRI or TCA,[24] while another study found paroxetine increased the length of seizure during ECT.[25] There is one case report of bupropion causing status epilepticus,[26] but a recent retrospective case-control study found bupropion is associated with a shorter seizure duration. [27]
Another clinical trial found that concomitant administration of nortriptyline with ECT is associated with less cognitive adverse effects compared to placebo while venlafaxine has the potential of worsening cognitive adverse effects compared to nortriptyline and placebo with lower mini-mental state exam (MMSE) and worse recall. [28] There seems to be a higher risk of asystole when the dose of venlafaxine exceeds 300mg/day[29] while doses under 225mg appear to be safe when administered concurrently with ECT.[30] Monoamine oxidase inhibitors appear to be safe with ECT.[31]

Other Medications

Cardiovascular medications

Catecholamine surge during the clonic phase of ECT can lead to tachycardia and hypertension. [32] At SCGH MHU, it is routine practice to give patient's regular antihypertensive and antianginal medication with a small sip of water before ECT. The only exceptions to the practice are diuretics which should be withheld, if possible, to reduce risk of urinary incontinence as a result of the seizure.

Asthma Medications

If a patient uses routine preventers, they should be administered prior to ECT as there

is a small risk of asthma exacerbation post ECT.[33] Theophylline has been associated with prolonged seizures and status epilepticus and should be ceased if possible or maintained at the lowest effective dose during a course of ECT.[34]

Gastrointestinal Medications

There is a risk of reflux and possible aspiration during ECT, hence routine medications for dyspepsia and reflux should be administered prior to ECT with a small sip of water.[34]

Medication	Effect on ECT treatment	Recommended Action
Anticonvulsants	Potentially reduce efficacy of ECT	If used as mood stabiliser – cease medication if possible. Withhold dose the night before ECT if it cannot be discontinued. If used for epilepsy – continue medication and withhold dose the night before ECT.
Benzodiazepines	Potentially reduce efficacy of ECT	Aim to cease if possible, if benzodiazepine cannot be discontinued, suggest converting to benzodiazepines with shorter half-life such as lorazepam. Consider flumazenil pre-treatment prior to ECT if benzodiazepine cannot be discontinued or converted to alternative benzodiazepines with shorter half-life [36].
Antipsychotics	Potential increase in seizure threshold, clozapine and phenothiazines may decrease seizure threshold[20, 34]	Continue treatment unless issues are encountered. Generally safe.
Lithium	Risk of cognitive disturbances, prolonged apnoea and spontaneous seizures based on old case reports[11] but more recent evidence demonstrated safety with concurrent administration Theoretical interaction with suxamethonium prolonging its action	Reduce dose to lower end of therapeutic range prior to ECT At SCGH MHU, it is routine practice to halve the regular lithium dose prior to ECT
Antidepressants	Small risk increasing seizure duration but minimal clinical impact[21] Potential cognitive impairment and asystole t with venlafaxine[28]	Continue treatment for all antidepressants except for : Venlafaxine/desvenlafaxine – dose reduction to <225mg is recommended
Antihypertensives	Risk of hypertension during clonic phase of ECT if routine dose not given	Administer with small sip of water before ECT
Diuretics	Risk of incontinence during seizure	Administer post-ECT
Asthma preventers	Risk of asthma exacerbation post-ECT	Administer before ECT with the exception of Theophylline
Theophylline	Risk of prolonged seizure or status epilepticus	Cease before ECT if possible, or maintain at lowest therapeutic dose
Gastrointestinal medications	Risk of reflux and potential aspiration during ECT	Administer with small sip of water before ECT
Antidiabetic medications	Hypoglycaemia as patient fasting from night before ECT	Administer post-ECT when patient can start eating
Gingko biloba, ginseng, St John's Wort, Valerian, Kava kava	May Interfere with efficacy of ECT	Cease before ECT

Diabetic Medications

As the patient is fasting overnight prior to ECT, antidiabetic medications should be withheld until post ECT to prevent hypoglycaemia. When the patient starts eating, these medications can be given.[34]

Complementary Medications

There are reports of certain complementary medications such as ginkgo biloba, ginseng, St John's wort, valerian and kava kava interfering with ECT.[35] Given the lack of evidence of efficacy of these medications, it is advisable to cease these supplements prior to commencement of ECT as the risks outweigh the benefits.

Anaesthetic Agents in ECT

The ideal induction agent for ECT is an agent with low anticonvulsant properties, rapid onset of action, short duration of action with a good safety and tolerability profile. The most commonly used agents for induction are propofol, thiopental, methohexital, etomidate, ketamine, alfentanil and remifentanil.

Propofol

Propofol is a short acting anaesthetic agent with rapid onset of action. It has an advantage of better haemodynamic control with lower postictal blood pressure and heart rate control compared to etomidate, ketamine, sevoflurane, thiopental and methohexital.[37] Propofol also has better recovery times compared to most agents, [37, 38] with less risk of nausea and vomiting compared to methohexital[39] and is superior to thiopental in terms of cognitive adverse effects.[40] The main disadvantage of propofol is that it has anticonvulsant properties. Compared to other anaesthetic agents, seizure durations have been shown to be shorter,[40-42] and required higher stimulus charge[41, 43] with more failed seizures[43] compared to other anaesthetic agents. However, a more recent network meta-analysis has cast doubt on the significance of the difference between propofol and other agents. This paper concluded that ECT given with propofol only has a shorter seizure duration compared to methohexital but not the other agents.[44]

Thiopental

Thiopental is a barbiturate that is commonly used in ECT. In terms of seizure duration, three published articles were found looking at thiopental anaesthesia in ECT. In two articles, ECT with thiopental was found to have longer seizure duration compared to propofol.[38, 41] However, a recent network meta-analysis found no significant difference in seizure duration with the different anaesthetics present.[44]

Cardiovascular adverse effects are comparable to etomidate but propofol exhibits better haemodynamic control compared to thiopental.[45] There is also a higher reported incidence of cardiac arrhythmias with thiopental compared to methohexital.[38]. Emergence time (the time from drug administration until eye opening) of thiopental is longer compared to propofol.[38, 42]

Methohexital

Methohexital is a barbiturate regarded as the "gold standard" anaesthesia for ECT due to its rapid onset and recovery with minimal effect on seizure. However, use of methohexital in Australia is restricted by its availability as it is not a Therapeutic Goods Administration (TGA) registered product and can only be procured through the Special Access Scheme (SAS).

It has a small, dose dependent anticonvulsant property. Studies have shown superior seizure duration compared to propofol, thiopental, but shorter seizure duration compared to etomidate and ketamine.[38, 42, 43, 46] Methohexital has longer recovery time compared to propofol but shorter than etomidate, sevoflurane[38]. Cardiac arrhythmias tend to occur more frequently with methohexital compared to propofol and etomidate but at a similar incidence to thiopental.[38]

Etomidate

Etomidate is another agent only available in Australia, through the SAS scheme. ECT with etomidate has good seizure duration

compared to methohexital, thiopental and propofol, [38, 41, 43, 44, 47] although a meta-analysis comparing differences in seizure durations of ECT while anaesthetised with etomidate, methohexital, thiopental and propofol failed to achieve significance.[47] There are non-significant differences in seizure quality (as measured by better seizure duration, better central inhibition, higher amplitude, high ictal coherence and adequate autonomic activation) when ECT under etomidate and ketamine are compared. ECT with etomidate also produces better seizure quality compared to propofol and thiopental. [41] In terms of adverse effects, a retrospective study found etomidate has a better cardiovascular profile compared to methohexital.[48] Studies comparing propofol, etomidate and thiopental found no significant differences in terms of risk of cardiovascular and cognitive side effects.[49, 50] A meta-analysis found insignificant recovery time differences between etomidate and propofol or thiopental.[42]

One known side effect of etomidate is transient adrenal suppression which can last for up to 24 hours post administration.[51] Adrenal suppression can result in hypotension which would be beneficial during the clonus phase of ECT but may impact on the patient post ECT with effects such as increased falls risk. The clinical significance of this issue is not well documented in the literature with only a single, small study of 40 subjects reporting no significant difference changes in adrenocortical function post ECT.[52]

Ketamine

Ketamine is an N-methyl-D-aspartate (NMDA) receptor modulator which can lower seizure threshold to improve the efficacy of the treatment.[46] Ketamine has also well documented anti-depressant effects by itself although there appears to be no additive antidepressant effect when administered concurrently with ECT [44, 53-55] Hoyer *et al* found that ketamine is superior compared to propofol and thiopental in terms of seizure quality but several meta-analyses found the efficacy of ECT while using ketamine as the anaesthetic agent to inconsistent.[44, 56] Moreover, ketamine is associated with higher risk of cardiovascular adverse effects and poorer tolerability compared to other anaesthetic agents.[44, 46] Emergence reactions are a commonly cited concern with ketamine, but clinical trials have found the incidence of emergence reactions is not significant greater than either placebo or other anaesthetic agents. [57, 58]

Remifentanil/Alfentanil

Remifentanil and alfentanil are short acting μ-opioids receptor agonist similar to fentanyl. These agents are administered as adjunct to other anaesthetic agents during induction and/or maintenance of general anaesthesia. They reduce the amount of anaesthetic required and they do not increase seizure threshold, allowing better seizure quality.[59-61] They also have the extra benefit of attenuating the sympathetic response associated with ECT,[59, 60] resulting in better haemodynamic stability. One concern with remifentanil and alfentanil is the risk of serotonin syndrome as they are pharmacologically similar to fentanyl. Potential serotonin syndrome like reactions have been reported with the use of remifentanil in the literature[62] but no cases were reported during the clinical trials of adjunct remifentanil administration during ECT.[60, 61] Remifentanil has more rapid clearance and a rapid decline in blood level on cessation of the infusion.[63] Most studies for ECT use remifentanil instead of alfentanil because of this.

A meta-analysis investigating the effect of added remifentanil or alfentanil reported significantly prolonged seizure duration as a result of reduction in the dose requirement of co-administered anaesthetic agents.[38, 59-61] Concurrent administration of remifentanil is also associated with lower systolic blood pressure during ECT.[59, 60] There are mixed reports as to whether adjunctive remifentanil improves or worsens recovery time post-ECT.[38, 59-61]

Agent	Advantage	Disadvantage	Cost
Propofol	• Best recovery time • Lower Incidence of post ECT nausea • Better haemodynamic control	• Poorer seizure quality	$3.80/ 200mg vial
Thiopental	• Better seizure duration compared to propofol	• Higher incidence of cardiac arrhythmias compared to methohexital • Longer recovery time compared to propofol	$3.95/ 500mg vial
Methohexital	• Superior seizure quality compared to propofol and thiopental • Shorter recovery time compared to other agents except for propofol	• Limited availability – only via SAS in Australia • Cost	$60/ 500mg vial
Etomidate	• Superior seizure quality • Better cardiovascular side effects compared to methohexital	• Limited availability – only via SAS in Australia • Risk of adrenal suppression (unclear significance)	$4.90/ 2mg vial
Ketamine	• Potential superior seizure quality	• Haemodynamic instability • Risk of emergence phenomena	$6.00/ 200mg vial
Remifentanil/ Alfentanil	• Improved seizure quality when used as adjunct • Improved haemodynamic control	• Risk of respiratory depression, hypotension and bradycardia • Cost of remifentanil	*Remifentanil* $50/ 200mg vial *Alfentanil* $3.60/ 1mg vial

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