Impact of a Theophylline Loading Dose on Seizure Quality Indices During Electroconvulsive Therapy: A Retrospective Study

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Background
• Patients on occasion receive ECT treatments which do not elicit a seizure, or the seizure is deemed to be not effective.
• A seizure duration of < 15 sec. is considered abortive (APA, 2001). Minimal adequate duration ~ 20 to 25 sec.
• Methylxanthine derivatives have been shown to prolong seizures in patients receiving ECT.
  – IV caffeine sodium benzoate is a suggested option for the management of missed seizures (APA, 2001).
  • Not commercially available in Canada.
  – Theophylline
  • Only 1 published study (N=8) (Swartz 1991) and 3 case reports (Stewart 1996, Fink 1998).
  • SR 200-400 mg administered the night before ECT.
  – Aminophylline
  • One naturalistic study (N=14) (Stern 1999) and 1 case series (N=7) (Leentjens 1997).
• No data available on theophylline’s impact on seizure quality indices.

Objective
• To determine the safety and impact of a calculated oral theophylline loading dose (resulting in a 10-15 mg/L plasma concentration) on seizure duration, maximum sustained coherence (MSC), and post-ictal suppression index (PSI) when administered 1.5 hours prior to the ECT.

Methods
• Design
  – Retrospective study using inpatient hospital records between January 2007 and June 2012 at the Dr. George L. Dumont University Hospital Center, Moncton, NB, Canada.
• Data Collection:
  – Age, sex, height, weight
  – ECT parameters for each ECT during the series
    • electrode placement, charge delivered, static and dynamic impedance, average seizure energy index, maximum sustained power. EEG endpoint, MSC, PSI, time to peak power, time to peak coherence.
  – Medications (name, dose, start date, modifications)
  – Treatment related side effects

• Inclusion Criteria:
  – Therapeutic indication for using oral theophylline (5.3 mg/mL) was a missed or inadequate seizure.
    – The 1st ECT was performed without and the 2nd ECT with theophylline adjuvant.
  • For dose-response: the 1st ECT was performed with theophylline and the 2nd with theophylline adjuvant at an estimated plasma concentration.
• Exclusion Criteria:
  – Modifications to treatment parameters other than the addition of oral theophylline between the 2 ECTs (e.g. stimulus intensity, electrode placement, anesthetic regimen, and medication change).
  – Dose of theophylline not calculated.
  – Pertinent information missing for one or both ECTs.
  – The 2 ECTs to be compared are separated by more than 1 ECT excluded by the above criteria (i.e. not “near successive”).
Methods

• Outcomes:
  – Primary: The change in seizure duration measured by the EEG endpoint.
  – Secondary: The change in the MSC and PSI.

• Statistics:
  – The normality assumption: graphically and with the Shapiro-Wilk test.
  – For MSC: logit transform of the values.
  – The drug level effect: a mixed linear model was fitted with the patient as a random effect.

ECT and theophylline administration:
  – All ECTs where administered using a Thymatron® System IV with a 0.5 ms brief-pulse waveform.
  – Initial target plasma concentration for theophylline was between 10-12.5 mg/L.
    • Option ↑ the dose to achieve a 15 mg/L if not effective.
    • Use IBW or DW if ABW >20% of IBW.
    - \[ DW = IBW + 0.4 \times (ABW - IBW) \]
    - \[ LD = VD_p \times CP \]
  – If ECT on consecutive days:
    • Gave 60% of the calculated dose on 2nd day (50% if significant interaction ↓ elimination).

Results

• Patient Selection and Characteristics:
  – 46 different admissions involving 35 patients were identified.
  – 30 of the admissions were deemed ineligible for inclusion.
  – 16 admissions eligible for inclusion in the primary analysis.
    • Length of the failed seizure immediately preceding the addition of theophylline was 14.3 sec (SD: 12.0 sec).
    • Series consisted of 10.0 (SD: 3.5) ECT sessions.
    • Theophylline was first administered at ECT session number 6.1 (SD: 2.4) and then continued for the remaining ECTs in the series.
    • Predicted theophylline plasma concentration was 12.83 mg/L (SD: 1.11 mg/L).

Results: Primary Endpoint

• Seizure Duration:
  – N=16
  – ↑23.5 sec (95% CI, 3.64 to 43.3); \( p = 0.023 \)
  – Represents an increase of 164.9%

Results: Secondary Endpoint

• Maximum Sustained Coherence
  – N=11
  – +8.3% (95% CI, -1.03 to 17.61), \( p = 0.076 \)
    • If <92% (N=5), all achieved ≥ 94.8%.
    • If ≥ 92% (N=6), all remained ≥ 89%

• Post-Ictal Suppression
  – An insufficient number of cases (N=2) precluded any meaningful analysis.

Results: Other

• Change in other measured variables
  – Time to peak power (N=11)
    • +13 sec (95% CI, 5.72 to 20.28), \( p = 0.003 \)
  – Time to peak coherence (N=10)
    • +20.4 sec (95% CI, -1.69 to 42.49), \( p = 0.066 \)
  – Average seizure energy index (N=9)
    • -4669.3 μV² (95% CI, -12666.9 to 3331) \( p = 0.21 \)
    • Maximum sustained power (N=12)
      • -18.16 μV² (95% CI, -9065.4 to 9029), \( p = 0.997 \)
  – Dose-Response Relationship (N=7)
    • Seizure duration 18.24 sec/mg/L (theophylline); (95% CI, -10.47 to 22.95), \( p = 0.596 \)
  – Safety
    • 22 admissions were analyzed representing 344 ECT’s, and 142 of those were administered under the influence of theophylline.
    • No seizure duration > 120 sec.
    • During the ECTs (both with and without theophylline), 36 adverse events were documented, none directly attributable to theophylline.
Limitations

- Data not available for all parameters of interest.
- Patients not systematically questioned for AEs.
- Theophylline plasma concentration were predicted only.
- Unable to examine EEG morphology.
- Theophylline’s effect on seizure threshold was not measured.

Discussion/Conclusion

- A calculated oral loading dose of theophylline is well tolerated and effective in prolonging seizure duration.
- Theophylline (5.3 mg/mL) is a viable alternative to using intravenous caffeine sodium benzoate as an adjuvant for ECT.
- This retrospective study could not adequately estimate effect of theophylline on the other measured efficacy variables, possibly due to the small sample size. These effects should be further explored in a prospective study.
- Establishing the dose-response relationship between seizure duration and theophylline plasma concentration will require a study designed specifically for that purpose.

References


Question #1

- M.S. is a 54 y/o male (weight: 100 kg, height: 5 feet) currently receiving ECT (M,W,F) for the treatment of his major depressive disorder. During his last treatment, he was unable to achieve an adequate seizure. The attending psychiatrist would like to know which seizure quality indices are significantly modified with theophylline.

A) Seizure Duration
B) Maximum Sustained Coherence
C) Post-Ictal Suppression Index
D) A and B

Question 2

- The attending psychiatrist decides that he would like to prescribe theophylline for M.S. He now inquires about how it can be safely prescribed. Which of the following is true concerning the suggested administration of theophylline?

A) Theophylline (5.3 mg/mL) should be administered 2 hours pre-ECT.
B) The initial loading dose should be calculated to achieve a 15 mg/mL plasma concentration.
C) The initial loading dose is calculated based on Mr. Shock’s actual body weight.
D) Dose adjustments will be required if M.S. receives ECT on two consecutive days.