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SCIENTIFIC ARTICLE

Influence of propofol dose and blood components on duration of electrical seizures in electroconvulsive therapy

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Abstract

Background and objectives: Propofol is commonly employed as a hypnotic agent to perform electroconvulsive therapy, but it exhibits also anticonvulsant properties. The main objective was to study the effect of the weight-adjusted dose of propofol on duration of the electrical seizure. Secondary objectives were to study the effect of absolute dose of propofol on duration of electrical seizure, the effect of both absolute and weight-adjusted doses on values of bispectral index, and the influence of blood chemistry on anticonvulsant effect.

Methods: After approval of the Institutional Review Board, a retrospective chart review was performed of all patients who underwent at least one electroconvulsive therapy session. Multiple lineal regression analysis adjusted for potential confounders was employed to explore the effect of propofol dosage on values of bispectral index and on duration of seizure; bivariate correlation analyses were previously performed to identify variables fulfilling confounding criteria, specifically values of Spearman's rho >0.10. Results of regression analysis were expressed as B coefficient with its 95% confident interval.

Results: 76 patients received 631 acute phase sessions. Propofol showed a statistically significant negative effect on duration of seizure (specifically a reduction of 4.081 s for every mg.kg^{-1} of propofol; CI95%: −7906 to −0.255, $p = 0.037$) but not on bispectral index values. Slight anemia and hypoalbuminemia were very infrequent conditions, and the anticonvulsant effect was not influenced by these parameters.

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Conclusions: Propofol weight-adjusted dose is negatively related to duration of seizures. It should be carefully titrated when employed to perform electroconvulsive therapy.

Influência da dose de propofol e dos componentes sanguíneos na duração das convulsões elétricas em eletroconvulsoterapia

Resumo

Justificativa e objetivos: O propofol é comumente usado como agente hipnótico na terapia eletroconvulsiva, mas apresenta também propriedades anticonvulsivantes. O objetivo principal foi avaliar o efeito da dose de propofol ajustada ao peso na duração da convulsão elétrica. Os objetivos secundários foram avaliar o efeito da dose total de propofol na duração da convulsão elétrica, o efeito da dose tanto total quanto ajustada ao peso nos valores do índice bispectral e a influência da bioquímica do sangue no efeito anticonvulsivante.

Métodos: Após aprovação do Comitê de Ética em Pesquisa, foi feita uma revisão retrospectiva dos prontuários de todos os pacientes que fizeram pelo menos uma sessão de eletroconvulsoterapia. Análise de regressão linear múltipla ajustada para potenciais confundidores foi feita para explorar o efeito da dosagem de propofol sobre os valores do índice bispectral e a duração da convulsão; análises de correlação bivariada foram previamente feitas para identificar as variáveis que atendem aos critérios de confusão, especificamente valores de *r* de Spearman > 0,10. Os resultados da análise de regressão foram expressos como coeficiente B com intervalo de confiança de 95%.

Resultados: Setenta e seis pacientes receberam 631 sessões de fase aguda. Propofol mostrou um efeito negativo estatisticamente significativo sobre a duração da convulsão (especificamente uma redução de 4,081 segundos para cada mg.kg^{-1} de propofol; IC de 95%: -7906 para -0,255, *p* = 0,037), mas não para os valores do índice bispectral. Anemia leve e hipoalbuminemia foram condições muito raras, e o efeito anticonvulsivante não foi influenciado por esses parâmetros.

Conclusões: A dose de propofol ajustada ao peso está negativamente relacionada com a duração das crises convulsivas, deve ser cuidadosamente titulada quando usada na terapia eletroconvulsiva.

Introduction

Electroconvulsive therapy (ECT) is a well established non-pharmacologic therapeutic option to treat severe psychiatric disorders, mainly depressive ones.[1,2] The efficacy of ECT may be related to the length of elicited seizure and seizures of 20–25 s in duration are considered necessary for an antidepressant effect.[3,4] ECT sessions which result in shorter seizure duration are considered therapeutically inadequate and therefore represent an important economic burden to the Health system.[5]

Propofol is a hypnotic drug commonly used during ECT. It has a unique pharmacological profile: a hypnotic effect with rapid onset and offset.[6] Propofol also exhibits other favorable pharmacological effects such as antiemetic, anxiolytic, bronchodilator, muscle relaxant, and antipruriginous.[7,8] This drug could be considered the ideal hypnotic agent for brief procedures like ECT, except that it also exhibits strong anticonvulsant properties that can interfere with the length of convulsion elicited by ECT.[7,9] Therefore, the propofol

bolus dose must be carefully calculated to achieve a good balance between the desired effect (hypnosis) and the non-desired one (anticonvulsant). Weight-adjusted propofol doses employed for ECT are usually lower than those used for induction of anesthesia (1.5 and 2 mg.kg^{-1}),[10–13] but the precise dose to perform ECT is yet to be defined.[14]

Electroencephalographic (EEG) effects of propofol correlate better with blood concentration than with the administered dose.[6] Only free fraction present in plasma is able to diffuse from blood to its GABA receptors to produce its neurological effects. Free fraction is usually low (1–3%)[15–17] because propofol is a lipophilic drug which circulates almost completely bound to blood components, mainly albumin, red blood cells and lipoproteins.[15–19] Some clinical conditions, such as anemia or hypoalbuminemia,[19,20] should raise blood free fraction, which would enhance the amount of propofol reaching GABA receptors and, in turn, it would enhance the intensity of clinical effects, both desired (hypnosis for ECT) and non-desired (anticonvulsant). Apart from pharmacokinetic alterations, these two clinical effects of

propofol are subjected to pharmacodynamics interactions with psychoactive drugs acting on central nervous system.[21]

This retrospective analysis tested the hypothesis that there is a correlation between propofol dose and clinical effects (length of the electrical convulsion elicited by ECT and deepness of hypnosis), and such association will be influenced by blood chemistry factors which alter the free drug plasma concentration, or by psychoactive drugs causing pharmacodynamic interactions.

Materials and methods

This retrospective work was approved by the Ethic and Clinical Research Committee of our hospital on February 23th 2015.

Charts of all patients undergoing ECT while admitted to our hospital since this therapy was implemented in April 2008 until December 2014 were reviewed. Our ECT protocol includes propofol as the main hypnotic agent, plus atropine, remifentanil and succinylcholine for induction of anesthesia; all drug doses are decided by the attending anesthesiologist; there is no specific team of anesthesiologists for ECT. Deepness of hypnosis is monitored with BIS (BIS Quatro™ devices and BIS VISTA™ monitor; Aspect Medical Systems, Inc). ECT is applied using the ABBOT SPECTRUM (model 5000Q, EQ-ELMED class). The intensity of stimulus is calculated by the age method. Electrodes are placed in bifrontotemporal location for patients under 65, while unilateral location (right frontal) is usually selected for older patients.

All patients who had undergone at least one ECT session under propofol sedation were included for review; no exclusion criteria for patients were used. Demographic (age, sex, weight, height, Body Mass Index [BMI]) and analytical (hemoglobin, hematocrit, total proteins, albumin, cholesterol, triglycerides, urea) data measured prior to entering to the ECT program were collected.

Only data relating to the first acute phase cycle were used for the analysis. Data collected for each ECT session were absolute and weight-adjusted dose of propofol, BIS value after propofol was administered and just before the electric stimulus was applied, and the length of the elicited electrical convulsion. According to our protocol, each electrical convulsion was considered as adequate when it lasted 20 s or more, and inadequate when it lasted less than 20 s.

Psychoactive drugs can exhibit proconvulsivant (imipramine or clomipramine, bupropion, duloxetine)[22,23] or anticonvulsivant (benzodiacepines and several antiepileptics)[24] effect, which would interact with propofol and affect the length of convulsions. Each ECT session was classified into one of these four categories: 0 – Patients not taking any of these pro or anticonvulsivant drugs when the ECT session was performed. 1 – Taking anticonvulsivants; 2 – Taking proconvulsivantes; 3 – Taking both pro and anticonvulsivants.

Data analysis

Qualitative variables were described as absolute frequencies and percentages and quantitative variables were expressed as median and interquartile range. Kolmogorov–Smirnov and Shapiro–Wilks tests were used to test for normal distribution. In a post hoc analysis the semi-interquartile range was calculated as the quotient between the interquartile range (Q3−Q1) and the sum of the first and third quartile (Q1+Q3), in order to make the dispersion of different variables comparable.

Comparison between adequate and inadequate ECT sessions (defined as lasting $\geq$20 s or <20 s, respectively) were performed by employing Chi-squared test for categorical variables and U Mann–Whitney test for quantitative ones. Specifically Mann–Whitney U test was used to compare dose of propofol (mg, and mg.kg^{-1}) between adequate vs. inadequate sessions.

Simple lineal regression analysis was employed to explore the crude effect of propofol dosage on BIS value and length on convulsion. Multiple lineal regression analysis adjusted for potential confounders was employed to explore the same propofol dose effects but eliminating the eventual confounding effect of other variables; bivariate correlation analysis were previously performed to identify variables fulfilling confounding criteria, specifically values of r of Spearman >0.10. Being treated with psychoactive drugs was considered relevant from a clinical point of view and it was included for these analyses. Results of regression analysis were expressed as B coefficient with its 95% Confident Interval. Variance Inflation Factors (VIFs) were used to detect multicollinearity in multiple regression, and it was considered to be present when VIFs $\geq$ 10.

All statistical analyses were performed using SPSS 19.0. A value of $p \leq 0.05$ was considered as statistically significant.

Results

Between April 2008 and December 2014, 853 ECT sessions were administered to 76 patients; 60.5% were women. A total of 630 sessions (73.9%) were administered for first acute phase cycles, with a median of 8 ECT sessions per patient (interquartile range: 6–10). Basal demographic characteristics and analytical values collected from charts are shown in Table 1; anemia and hypoalbuminemia were very infrequent (5 and 1 patient, respectively).

Key results of the study are shown in Table 2.

Propofol and anticonvulsant effect (length of convulsion)

Comparative analysis of adequate and inadequate sessions showed significant differences for weight, triglycerides and propofol dose, both absolute and weight-adjusted (Table 3).

Bivariate correlation analysis found weight and height as variables to be taken into account in the multivariate analysis to explore the influence of propofol doses in length of convulsions.

Multiple linear regression crude analysis showed a significant decrease of 0.1 seconds in length of convulsion for every mg of propofol (Table 4). This significant effect persisted after adjusting for weight, height and drug therapy, although its magnitude decreased (−0.085 s for every mg of propofol).

Regarding weight-adjusted propofol dose, crude analysis showed a non-significant decrease of −1.662 s for every mg.kg^{-1} of propofol, but this effect turned into significant

Table 1 Demographic and analytical characteristics of patients before undergoing electroconvulsive therapy.

Variable	n	Median	Quartile 1	Quartile 3	Quartile coefficient of dispersion
Age (y)	76	50.5	39.7	66.2	0.25
Weight (kg)	73	71	62	80	0.13
Height (m)	41	1.66	1.57	1.72	0.05
Body mass index (kg.m^{-2})	41	26.5	22.4	30.4	0.15
Hemoglobin (mg.dL^{-1})	72	14.0	13.1	15.0	0.07
Hematocrit (%)	72	42.1	39.8	44.9	0.06
Total proteins (g.dL^{-1})	72	6.9	6.6	7.3	0.05
Albumin (g.dL^{-1})	73	4.4	4.1	4.6	0.06
Total cholesterol (mg.dL^{-1})	68	177	163	219	0.15
Triglycerides (mg.dL^{-1})	68	102	77	152	0.33
Urea (mg.dL^{-1})	73	35	26	45	0.27

Table 2 Propofol doses, BIS values, and length of electroencephalographic convulsion.

Variable	n	Median	Quartile 1	Quartile 3	Quartile coefficient of dispersion
Propofol (mg)	628	80	70	100	0.18
Propofol (mg.kg^{-1})	603	1.23	0.97	1.50	0.21
BIS	562	53	44	65	0.19
Length of convulsion (s)	620	24	17	34	0.33

BIS, bispectral index.

Table 3 Comparative analysis of variables according to adequate or inadequate length of electrical convulsion.

Variables		Electrical convulsion			Test value[a]	p
	n	Adequate (≥20 s)	n	Inadequate (<20 s)		
Sex					0.395	0.530
Men		193 (68.9)		87 (31.1)		
Women		233 (66.6)		117 (33.4)		
Age (y)	426	50.5 (40.5–65.5)	204	46.5 (40.5–61.25)	−0.811	0.417
Weight (kg)	407	69 (60–77)	197	72 (65–83)	−3.191	0.001
Height (m)	245	1.66 (1.60–1.72)	108	1.68 (1.56–1.72)	−0.538	0.590
Hemoglobin (mg.dL^{-1})	400	14.1 (13.1–14.9)	190	13.9 (13.2–14.9)	−0.149	0.882
Hematocrit (%)	400	42.2 (40.0–44.9)	190	42.1 (40.4–44.5)	−0.357	0.721
Total proteins (g.dL^{-1})	399	6.9 (6.6–7.4)	188	7 (6.7–7.3)	−1.124	0.261
Albumin (g.dL^{-1})	402	4.4 (4.2–4.6)	193	4.4 (4.2–4.6)	−0.532	0.595
Cholesterol (mg.dL^{-1})	368	179 (163–227)	181	179 (166–204)	−1.086	0.278
Triglycerides (mg.dL^{-1})	368	107 (70–155)	181	107 (78–191)	−2.062	0.039
Urea (mg.dL^{-1})	402	34 (27–45)	193	38 (26–49)	−1.532	0.126
Absolute propofol dose (mg)	424	80 (70–100)	204	100 (70–120)	−4.578	<0.001
Weight-related propofol dose (mg.kg^{-1})	406	1.17 (0.95–1.45)	197	1.35 (1.05–1.66)	−3.344	0.001
BIS just before ECT	371	54 (45–65)	191	50 (43–64)	−1.597	0.110
Drug therapy					1.473	0.688
No pro/anticonvulsivants		94 (65.7)		49 (34.3)		
Anticonvulsivants		263 (68.5)		121 (31.5)		
Proconvulsivants		21 (61.8)		13 (38.2)		
Both pro/anticonvulsivants		31 (62.0)		19 (38.0)		

Variables are expressed as n (%) or median (P25–P75), depending on the case.
 [a] Test value for comparison between variables (Chi-squared for qualitative and Mann–Whitney Z value for quantitative).
BIS, bispectral index.

Table 4 Effect of propofol dose on length of electrical convulsion.

Variables	Crude analysis				Adjusted analysis[a]			
	n	B coefficient	CI 95%	p	n	B coefficient	CI 95%	p
Propofol (mg)	618	−0.100	−0.141; −0.059	<0.001	336	−0.085	−0.146; −0.023	0.007
Propofol (mg.kg^{-1})	593	−1.662	−4.594; 1.269	0.266	336	−4.081	−7.906; −0.255	0.037

[a] Adjusted for weight, height and pro/anticonvulsivant therapy.
CI, confident interval.

after adjusting for confounding variables (−4.081 s for every mg.kg^{-1} of propofol) (Table 4).

There was no evidence of multicollinearity in any of the regression analysis since all VIFs were lower than 2.

Propofol and hypnotic effect (BIS values)

Comparative analysis between BIS values less or higher than 65[25] showed statistical significant differences for age, urea and drug therapy, but not for propofol dose (Table 5).

Bivariate correlation analysis found age and height as variables to be taken into account in the multivariate analysis to explore the influence of propofol doses in BIS values.

Multiple linear regression analysis showed no significant influence of absolute dose of propofol in BIS values (Table 6). Crude analysis showed a decrease of 0.012 points in BIS value with every mg of propofol, but an increase of 0.023 points was found after adjusting for age, height and drug therapy.

No significant results were found either when relative dose of propofol was analyzed (Table 6). Crude analysis showed a decrease of −0.796 points in BIS every mg.kg^{-1} of propofol, but an increase of 2.997 points was found after adjusting for the same confounding variables.

There was also no evidence of multicollinearity in any of the regression analysis since all VIFs were lower than 2.

Discussion

As expected, we have found a significant negative association between weight-adjusted dose of propofol and anticonvulsant effect (main objective), although such effect was not influenced by blood chemistry. No significant association was found between propofol dose and hypnotic effect, measured by BIS values.

Inverse relationship exists between propofol dose and its anticonvulsant effect

Studies comparing several discrete weight-adjusted doses of propofol (0.5 mg.kg^{-1}, 0.75 mg.kg^{-1}, 1 mg.kg^{-1}, or 2 mg.kg^{-1}, for instance)[9,10,26] have found that higher doses are related to shorter convulsions[9]; however, as far as we know, in no previous research doses of propofol were studied considering them as a continuum. Maybe the wide range of doses we found is reflecting that we lack a specific ECT team, therefore each anesthesiologist independently decided upon the dose of propofol to be administered for any given ECT session.

Influence of blood chemistry on anticonvulsant effect of propofol

We expected to find longer (or shorter) convulsions associated to lower (or higher) levels of propofol carriers, but this was the case only for triglycerides.

Lipoproteins exhibits a great affinity for propofol, but albumin and erythrocytes are present in much higher amount in plasma and whole blood, so they act as the main carriers for propofol.[16-19,27] Preclinical studies have shown this is true both for continuous infusions and for propofol boluses.[27] Considering this, anemia and hypoalbuminemia should influence the intensity of effect of propofol.[19]

However, we could not properly explore this influence. First, very few patients presented anemia or hypoalbuminemia, and it has been found that neither pharmacokinetic nor pharmacological effects of propofol were significantly affected when values of proteins and red blood cells are between normal range of reference.[28] Second, quartile coefficients of dispersion for albumin, proteins, erythrocytes and hematocrit were much lower than that for propofol dose (Tables 1 and 2), indicating they acted more as a constant than a variable; by definition, a correlation cannot be found between a variable (propofol dose) and a constant (any of these blood components). Maybe this same explanation is applicable to the different findings obtained for triglycerides, which exhibited a wide dispersion, and for cholesterol, with a narrow one.

Lack of relationship between propofol dose and its hypnotic effect

This lack of relationship is somewhat surprising considering the inverse relationship found with anticonvulsant effect. Maybe the explanation of these different results could lay on propofol kinetics. It has been observed a great variability in the blood concentrations of propofol in the first two minutes after the administration of a bolus of 2 mg.kg^{-1}, but afterwards concentrations tend to converge.[29] Two minutes fall into the lapse of time in which the patients are anesthetized for ECT, and such variability in propofol concentrations could explain the variability of BIS values. To support this argument, the administration of a fixed dose of propofol (1 mg.kg^{-1}) was associated with a wide range of BIS values just before the electrical discharge.[12,13]

Succinylcholine depolarizing effect appears quickly and it can usually increase BIS values due to fasciculations of frontal muscles. Electrical discharge is administered just after cessation of such fasciculations. BIS monitor works

Table 5 Comparative analysis of variables according to BIS values.[25]

Variables		BIS values			Test value[a]	p
	n	BIS < 65	n	BIS ≥ 65		
Sex					0.606	0.436
Men		189 (76.5)		58 (23.5)		
Women		232 (73.7)		83 (26.3)		
Age (y)	421	46.5 (37.5–60.5)	141	53.5 (42.0–71.0)	−3.068	0.002
Weight (kg)	400	70 (62–80)	140	69 (64–76)	−1.028	0.304
Height (m)	229	1.68 (1.60–1.72)	105	1.65 (1.55–1.70)	−1.799	0.072
Hemoglobin (mg.dL^{-1})	392	14.1 (13.2–15.0)	133	13.7 (13.1–15.1)	−0.501	0.616
Hematocrit (%)	392	42.3 (40.1–44.9)	133	42.0 (44.0–44.6)	−0.683	0.495
Total proteins (g.dL^{-1})	389	6.9 (6.6–7.3)	134	7.0 (6.6–7.4)	−0.380	0.704
Albumin (g.dL^{-1})	395	4.5 (4.2–4.6)	135	4.3(4.0–4.6)	−1.835	0.066
Cholesterol (mg.dL^{-1})	364	178 (164–220)	128	185 (164–226)	−1.053	0.292
Triglycerides (mg.dL^{-1})	364	107 (76–172)	128	107 (83–140)	−0.144	0.886
Urea (mg.dL^{-1})	395	34 (26–42)	135	41 (32–51)	−4.992	<0.001
Absolute propofol dose (mg)	420	85 (70–100)	141	90 (65–100)	−0.407	0.684
Weight-related propofol dose (mg.kg^{-1})	400	1.20 (1.00–1.47)	140	1.25 (0.90–1.51)	−0.254	0.799
Length of convulsion (s)	415	23 (16–32)	137	25 (18–36)	−1.653	0.098
Drug therapy					9.313	0.025
No pro/anticonvulsivants		103 (80.5)		25 (19.5)		
Anticonvulsivants		258 (76.1)		81 (23.9)		
Proconvulsivants		18 (56.3)		14 (43.8)		
Both pro/anticonvulsivants		33 (68.8)		15 (31.3)		

Variables are expressed as n (%) or median (P25–P75), depending on the case.
[a] Test value for comparison between variables (Chi-squared for qualitative and Mann–Whitney Z value for quantitative).
BIS, bispectral index.

Table 6 Effect of propofol dose on BIS values just before ECT.

Variables	Crude analysis					Adjusted analysis[a]			
	n	B coefficient	β coefficient	95%CI	p	n	B coefficient	β coefficient	95%CI	p
Propofol (mg)	561	−0.012	−0.023	−0.053; 0.030	0.587	328	0.023	0.043	−0.038; 0.085	0.458
Propofol (mg.kg^{-1})	540	−0.769	−0.023	−3.614; 2.076	0.596	328	2.997	0.095	−0.602; 6.596	0.102

[a] Adjusted for age, height and pro/anticonvulsivant therapy.
BIS, bispectral index; ECT, electroconvulsive therapy; CI, confident interval.

with several seconds of delay,[30] thus allowing for the muscular interference not to be fully disappeared at the time the electrical discharge was administered.

Limitations

From a pharmacokinetic point of view, there are several factors beyond our retrospective study which can interfere with propofol concentrations and clinical effects after a bolus dose. For instance, cardiac output is inversely related to drug concentrations.[31] The rate of infusion of the bolus of propofol could also affect the immediate clinical effect[6]; as binding of propofol to blood components is non-linear,[19] blood concentrations reached at the end of any infusion would be greater the faster the bolus infusion was.[11] In our opinion, the rate of infusion is as important and decisive for

getting successful convulsions as the total dose of propofol chosen, and it merits for further anesthetic research.

Total body weight was employed for calculations instead of lean body weight, which has been suggested as a more precise parameter to calculate induction dose of propofol.[32] Unfortunately, height was not available for a great number of clinical charts, which precluded us for calculating lean body weight. This limitation can be easily solved in a prospective work.

Conclusions

Propofol weight-adjusted dose is negatively related to duration of seizures. It should be carefully titrated when employed to perform electroconvulsive therapy. Further research is necessary to clarify the role of anemia and hypoalbuminemia on propofol requirements for ECT.

Conflicts of interest

The authors declare no conflicts of interest.

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