Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: https://www.tandfonline.com/loi/iafd20

ALSUntangled No. 22: Propofol

The ALSUntangled Group

To cite this article: *The ALSUntangled Group* (2013) ALSUntangled No. 22: Propofol, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 14:7-8, 640-642, DOI: 10.3109/21678421.2013.826469

To link to this article: https://doi.org/10.3109/21678421.2013.826469

Published online: 23 Aug 2013.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2013; 14: 640–642

informa
healthcare

REVIEW ARTICLE

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On 27 April 2013 a post appeared in the online forum ALS.net describing 'near miraculous' improvements in a patient with ALS exposed to propofol on three separate occasions (1). Since then, ALSUntangled has received more than 700 requests to review the use of propofol for ALS (2). Here we respond to these requests.

What is propofol?

Propofol is an intravenous, short acting amnestic/hypnotic agent that is primarily used for procedural sedation, or to induce or maintain general anesthesia (3). At higher dosages, it has also been used to execute prisoners (4). Recreationally, propofol has been used to promote sleep, and because it is associated with euphoria upon awakening (5). Recreational use is rare due to its risks; deaths (6) including that of pop star Michael Jackson (7) have been reported among those using propofol without appropriate cardiac and respiratory monitoring.

Why might it work in ALS?

Theoretically, propofol has multiple mechanisms of action that might be relevant for ALS (8). It blocks sodium channels (9) and potentiates the activity of inhibitory (GABA-ergic) neurons (10). In doing so, it might be able to ameliorate the motor neuron hyperexcitability that occurs in ALS (11); administration of propofol with fentanyl suppressed electromyographic fibrillation potentials in a single case report on a patient with ALS (12). Reduction in hyperexcitability may be one of the ways that riluzole works to prolong survival in patients with ALS (13), and is the rationale for an upcoming trial of mexiletine in ALS (14). Propofol also acts on the endocannabinoid system (15). We have previously discussed the involvement of the endocannabinoid system in ALS and the potential role of endocannabinoid receptor agonists in ALS treatment (16). Finally, propofol has antioxidant and immunomodulatory activities (8). Oxidative stress (17) and neuroinflammation (18,19) occur in ALS, although attempts to manipulate these events have not yet shown clear benefits in human ALS trials.

Propofol has a short half-life; once infusion is stopped, its clinical effects last only minutes (3). For this reason, it is difficult to understand how a single dose of propofol could influence the above-described events for long enough to produce meaningful improvements in a degenerative disease such as ALS.

What relevant animal data exist?

ALSUntangled has been unable to find any relevant studies of propofol in animal models of ALS.

What is known about the efficacy of propofol in human ALS?

On ALS.net, six users reported that they or their spouse have ALS and have improved with propofol, which was typically given for procedural sedation (1). Doses range from 150 mg to 1400 mg. Other drugs were also used and in some cases surgery was performed. Improvements described include limb strength, dexterity, walking, breathing, speech, and swallowing. These improvements were said to start within a few days of propofol exposure, and to last between nine days and one month. Medical records were requested but have been received for only one of these ALS.net users. The records confirm that the user had ALS and was exposed to propofol for septoplasty on 14 May 2013. No clear objective change in speech, or rate of decline of the ALSFRS-R or the FVC was seen coincident with propofol exposure (Figure 1), with the last measurements having been made 10 days after propofol exposure.

In a survey of ALSUntangled investigators, 213 patients from three ALS centers received propofol at a mean dose of 190 mg (range 90–360 mg) for sedation during PEG placement. No improvements were noted in any of these patients by either the surgery teams or their neurologists (20).

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.3109/21678421.2013.826469

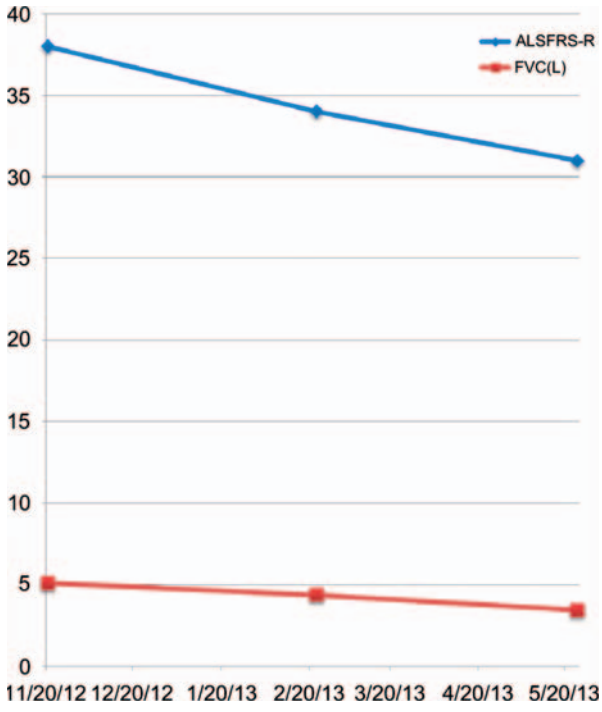

Figure 1. Objective ALS measurements before and after receiving 1100 mg propofol on 14 May 2013.

Within the PRO-ACT database (21) 14 patients with confirmed ALS were exposed to propofol at various dosages (Table I). ALSFRS-R scores before and after propofol exposure are available for 10 of these, although it is not possible to determine how long before or after exposure these were obtained. None of these patients showed a significant improvement in their ALSFRS-R scores with propofol.

Within a recent study of intraspinal embryonic stem cells (22), 12 patients with confirmed ALS received propofol at unknown doses for procedural sedation, along with other medications, immunosuppression and stem cell transplants. Patients were evaluated at two and four weeks post surgery, and then monthly after that. One of these 12 patients improved by objective measurements (22). Unlike the ALS.net cohort, this patient's improvements started slowly and continued to improve for several months after propofol.

Table I. Fourteen patients with ALS exposed to propofol in the Pro-Act Database, with dosages and ALSFRS-R scores before and after (– means data unavailable).

Propofol dose	ALSFRS-R Before	After
120 mg QD	21	18
150 mcg once	29	25
–	33	–
10 cc	1	0
–	32	29
–	17	–
1U/day	21	–
100 mg IV once daily	26	22
–	35	35
200 mg	21	22
250 cc	15	10
2250 mcg	26	–
175 mg	23	20
80 mg	30	27

At this time, no members of the PatientsLikeMe online ALS community report using propofol.

What is known about the safety and cost of propofol?

Propofol has many serious risks including respiratory depression, cardiac arrhythmias such as bradycardia and asystole, hypotension, metabolic acidosis, rhabdomyolysis, renal failure and death (6,23–25). There are no specific drugs available to reverse the undesirable effects of propofol (25). Due to its significant risks, many different national societies of anesthesiology have stated that propofol should be given only by those trained in administering general anesthesia and with appropriate cardiopulmonary monitoring (25). While the cost of the drug itself is not high, the cost of administration with appropriate monitoring is likely to be more than a thousand dollars per treatment (26).

Conclusions

Propofol has mechanisms of action that may be relevant in treating ALS, although the short action of the drug makes it unlikely that a single infusion could influence ALS pathophysiology in a meaningful way. On ALS.net, six patients with ALS reported wide-ranging subjective benefits coincident with propofol use. Unfortunately, none of these benefits has been verified on validated ALS outcome measures. Only one of 235 patients with confirmed ALS who received propofol for PEG at an ALS center, or in the PRO-ACT database, or in a stem cell trial, improved objectively. The improvements in this patient were much slower to begin, and longer in duration, compared to those reported by the cohort on ALS.net, suggesting that they were more likely due to other longer acting medications the patient received (such as immunosuppression), the stem cell treatment, or an unusual reversible form of ALS (27–30). While we cannot conclusively rule out a very brief benefit from propofol in rare patients with ALS, the risks and costs involved do not appear to justify its use. We strongly discourage the off label use of propofol in ALS patients at this time. Patients with ALS who are going to have propofol on label for a procedure or surgery may wish to have their ALS neurologist measure an ALSFRS-R and FVC before and in the first few days after propofol exposure and to send these results to ALSUntangled for a possible follow-up review.

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Note: this paper represents a consensus of those weighing in. The opinions expressed in this paper are not necessarily shared by every investigator in this group.

Acknowledgement

We thank Ervin Sinani and Alex Sherman for providing the PRO-ACT data.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

ALSUntangled is funded by the Motor Neurone Disease Association.

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