Amyotrophic Lateral Sclerosis

ISSN: 1748-2968 (Print) 1471-180X (Online) Journal homepage: informahealthcare.com/journals/iafd19

ALSUntangled 13: Bee Venom

The ALSUntangled Group

To cite this article: The ALSUntangled Group (2011) ALSUntangled 13: Bee Venom, Amyotrophic Lateral Sclerosis, 12:6, 471-472, DOI: 10.3109/17482968.2011.625168

To link to this article: https://doi.org/10.3109/17482968.2011.625168

Published online: 24 Oct 2011.

Amyotrophic Lateral Sclerosis, 2011; 12: 471–472

informa
healthcare

REPORT

ALSUntangled 13: Bee Venom

The ALSUntangled Group

Bee venom (BV), also known as apitoxin, is extracted from honeybees and contains several bioactive compounds including phospholipase A2, histamine, epinephrine, free amino acids and the peptides melittin and apamin (1–3). Melittin, the major component of dried bee venom, has anti-tumor, anti-microbial, anti-nociceptive and anti-inflammatory activities (1–5), and can protect cultured neuronal cells and glial cells from glutamate toxicity (6). BV is being advertised on a number of websites (see, for example, 7) as a potential treatment for a wide variety of human diseases including ALS.

Why might BV work in ALS?

Neuroinflammation (8,9) and glutamate toxicity (10) are believed to be important in the pathogenesis of amyotrophic lateral sclerosis. If BV can modulate these in just the right ways in vivo it could conceivably slow ALS progression.

Is there any evidence of BV efficacy in ALS?

There are two published animal studies of BV in ALS, both by the same group. In the first, BV (n = 11) or saline (n = 11) were injected into the "Zusanli acupoint" (an anatomic location reported to influence inflammation) of 14-week old (pre-symptomatic) hSOD1^{G93A} mice at a dose 0.1ug/g twice a week. Disease onset, rotorod analysis, lifespan and post-mortem immunohistochemistry were pre-specified outcome measures. BV-treated animals had delayed disease onset, performed significantly better than controls on the rotorod at days 7–15, and had a median survival increase of 22d (18%). Immunohistochemistry showed suppressed caspase-3 activity, decreased iba-1 (a microglial marker), decreased TNF-alpha, decreased phosphorylated p38 MAP kinase and preserved mitochondrial morphology and neuronal survival compared to controls (11). In the second animal study melittin (n = 11) or saline (n = 11) were injected into the "Zusanli acupoint" of 14-week old (pre-symptomatic) hSOD1^{G93A} mice at a dose 0.1ug/g twice a week. Rotorod analysis, lifespan and post-mortem immunohistochemistry were pre-specified outcome measures. Melittin-treated animals again had delayed onset of weakness, and performed better on the rotorod at days 7-15 compared to controls. Survival was not affected in this animal study. Melittin-treated animals again had decreased iba-1, decreased TNF-alpha, decreased phosphorylated p38 MAP kinase and preserved neuronal survival compared to controls. Additionally, melittin-treated animals had increased HSP70, reduced ubiquitin expression, and improved proteasome function compared to controls (12).

To date, ALSUntangled has been unable to find any human trials or well-designed case series in which BV was given to patients with ALS. One of our investigators (JG) is aware of four patients with ALS using this therapy. One receives multiple bee stings in the arms and legs every week, and in the lumbar region every 5 weeks; the protocol the other three are receiving is not clear. The caregivers of two of these feel that the BV is helping; one says it is helping the patient's muscle spasms and the other believes it is slowing disease progression. No objective outcome data are available on any of these patients. Within the PatientsLikeMe community there are no detailed reports of BV treatment in patients with ALS.

What are the costs and side effects associated with BV?

One of the patients described above reports paying 100 euros per session (sessions given every week), plus travel (100 euros/trip) and additional supplements recommended by the apitherapist such as honey, pollen, propolis, royal jelly and vitamin C (approximately 50 euros/month). This patient reports swelling and pain around the bite areas lasting 4–5 days. Rare, but more serious side effects from BV are possible including abdominal cramps, nausea, vomiting, incontinence of stool or urine, fainting, loss of vision, hematologic abnormalities, anaphylaxis, seizures, respiratory or cardiac arrest and death (13).

Conclusions

In our opinion, BV has biological effects that could potentially be useful in ALS. Two ALS-animal studies

ISSN 1748-2968 print/ISSN 14\71-180X online © 2011 Informa Healthcare
DOI: 10.3109/17482968.2011.625168

in which BV was injected into an unusual anatomic location showed positive effects on motor preservation and inflammatory markers; one showed improved survival. However, there are some significant problems with these animal studies. They do not meet methodological standards for preclinical animal research (14, 15) for the following reasons: treatment allocation was not randomized, power arguments are not presented, sample sizes are too small, potential confounders such as gender and copy number variation are not adequately addressed, criteria for determining symptomatic disease onset are not defined, blinding is not described, outcome measures in control animals are not compared to those in other studies to demonstrate external validity, and replication of results is via the same, rather than an independent group of authors. Furthermore, it is not currently possible to replicate pre-symptomatic drug delivery in humans with sporadic ALS. Many other compounds given pre-symptomatically to ALS-animals have failed to yield any positive benefit in human patients (16); indeed one immune-modulator that worked in ALS-animals actually appeared to accelerate disease progression in patients with sporadic ALS (17). It may not be possible to replicate the dosage of BV that was used in future human studies; by one estimate, for a 70g human this would require 70,000 bee stings twice a week (18). Finally and most importantly, we found very little data of any kind on BV exposure in humans with ALS; the two anecdotal reports describe unverified, non-overlapping benefits. Given all this, and the costs and risks of BV (which include death), ALSUntangled does not support the use of BV by patients with ALS outside of a study at this time. Replication of the animal studies via an independent group following published methodological guidelines and using a dosing regimen that could eventually be translated to human studies would be a reasonable next step.

The ALSUntangled Group currently consists of the following members: Richard Bedlack, Orla Hardiman, Tulio Bertorini, Tahseen Mozaffar, Peter Andersen, Jeff Dietz, Josep Gamez, Mazen Dimachkie, Yunxia Wang, Paul Wicks, James Heywood, Steven Novella, LP Rowland, Eric Pioro, Lisa Kinsley, Kathy Mitchell, Jonathan Glass, Sith Sathornsumetee, Hubert Kwiecinski, Jon Baker, Nazem Atassi, Dallas Forshew, John Ravits, Robin Conwit, Carlayne Jackson, Alex Sherman, Kate Dalton, Katherine Tindall, Ginna Gonzalez, Janice Robertson, Larry Phillips, Michael Benatar, Eric Sorenson, Christen Shoesmith, Steven Nash, Nicholas Marigakis, Dan Moore, James Caress, Kevin Boylan, Carmel Armon, Megan Grosso, Bonnie Gerecke, Jim Wymer, Bjorn Oskarsson, Robert Bowser, Vivian Drory, Jeremy Shefner, Terry Heiman-Patterson, Noah Lechtzin, Melanie Leitner, Robert Miller, Hiroshi Mitsumoto, Todd Levine, James Russell, Khema Sharma, David Saperstein, Leo McClusky, Daniel MacGowan, Jonathan Licht, Ashok Verma, Michael Strong, Catherine Lomen-Hoerth, Rup Tandan, Michael Rivner, Steve Kolb, Meraida Polak, Stacy Rudnicki, Pamela Kittrell, Muddasir Quereshi, George Sachs, Gary Pattee, Michael Weiss, John Kissel, Jonathan Goldstein, Jeffrey Rothstein, Dan Pastula.

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.

Disclosures: ALSUntangled is sponsored by the Packard Center, the Virginia Gentlemen Foundation and the Motor Neurone Disease Association.

References

1. Habermann E. Bee and wasp venoms. Science 1972;177: 314–322.
2. Gauldie J, Hanson JM, Rumjanek FD, Shipolini RA, Vernon CA. The peptide components of bee venom. Eur J Biochem 1976;61:369–376.
3. Son DJ, Lee JW, Song HS, Lee CK, Hong JT. Therapeutic application of anti-arthritis, pain-releasing, and anti-cancer effects of bee venom and its constituent compounds. Pharmacol Ther 2007;115:246–270.
4. Lariviere WR, Melzack R. The bee venom test: a new tonic pain test. Pain 1996;66:271–277.
5. Orsolic N, Sver L, Verstovsek S, Terzic S, Basic I. Inhibition of mammary carcinoma cell proliferation in vitro and tumor growth in vivo by bee venom. Toxicon 2003;41:861–870.
6. Lee SM, Yang EJ, Choi SM, Kim SH, Baek MG, Jiang JH. Effects of bee venom on glutamate-induced toxcitity in neurons and glial cells. Evid Based Complement Alternat Med 2012. Epub 2011 Aug 28.
7. http://www.beewelltherapy.com/
8. Papadimitriou D, Le Verche V, Jacqier A, Ikiz B, Przedborski S, Re DB. Inflammation in ALS and SMA: sorting out the good from the evil. Neurobiol Dise 2010:37:493–502.
9. Appel SH, Zhao W, Beers DR, Henkel JS. The microglial-motoneuron dialogue in ALS. Acta Myol 2011;30:4–8.
10. Foran E, Trotti D. Glutamate transporters and the excitotoxic pathy to motor neuron degeneration in amyotrophic lateral sclerosis. Antioxid Redox Signal 2009;11:1587–1602.
11. Yang EJ, Jiang JH, Lee SM, Yang SC, Hwang HS, Lee MS, Choi SM. Bee venom attenuates neuroinflammatory events and extends survival in amyotrophic lateral sclerosis models. Journal of Neuroinflammation 2010;7:69.
12. Yang EJ, Kim SH, Yang SC, Lee SM, Choi SM. Melittin restores proteasome function in an animal model of ALS. Journal of Neuroinflammation 2011;8:69.
13. http://www.drugs.com/pro/wasp-and-bee-venom.html#AdverseReactions
14. Ludolph A, Bendotti C, Blaugrund E, Chio A, Greensmith L, Loeffler J, et. al. Guidelines for preclinical animal research in ALS/MND: a consensus meeting. Amyotrophic Lateral Sclerosis 2010;11:38–45.
15. Scott S, Kranz J, Cole J, Lincecum J, Thompson K, Kelly N, et. al. Design, power and interpretation of studies in the standard murine model of ALS. Amyotrophic Lateral Sclerosis 2008;9:4–15.
16. Benatar M. Lost in translation: treatment trials in the SOD1 mouse and in human ALS. Neurobiol Dis 2007;26:1–13.
17. Gordon PH, Moore DH, Miller RG, Florence JM, Verheijde JL, Doorish C, et. al. Efficacy of minocycline in patients with amyotrophic lateral sclerosis. Lancent Neurol 2007;121054–1053.
18. http://www.ibiblio.org/pub/academic/agriculture/entomology/beekeeping/general/venom_therapy/bevenfaq.html