Attack Cessation and Remission Induction with 2-Bromo-LSD for Cluster Headache

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ABSTRACT

Objectives: An open-label trial of the ergot-based non-hallucinogen 2-bromo-LSD (BOL) for the Treatment of episodic and chronic cluster headache.

Background: Anecdotal patient reports as well as a clinical case series led by one of the authors (JHH) describe attack cessation, early termination of attack series, and remission induction/extension in cluster headache patients who self-administer the hallucinogens LSD and/or psilocybin. Evaluation of a non-hallucinogenic analog could clarify whether these reported effects are associated with hallucinogenicity or are due to other chemotherapeutic mechanisms.

Methods: 4 subjects with active cluster headache refractory to standard treatments were administered in an outpatient research setting in Hannover, Germany approximately 30 µg/kg of BOL on 3 separate occasions separated by 5 days. Subjects maintained a headache diary prior to and post treatments for at least two months. The Clinical Global Impressions Scale (CGI) was obtained at baseline and follow-up interviews.

Results: Subject 2 reported a 30% reduction in pain intensity for 2 months after final BOL treatment and a 73% reduction in attack frequency for 4 months; the other three subjects report complete or nearly complete remission of all headache symptoms for at least 2 months after final BOL treatment. No significant adverse effects were
observed/reported, including no evidence of hallucinogen intoxication.

Conclusions: If the hallucinogens psilocybin and LSD have important treatment effects for cluster headache, BOL – a non-hallucinogenic analog of LSD – may be safer for further research as indicated by these findings. Though open-label, BOL may be the first non-hallucinogenic agent identified to significantly modify the course of living with this severely debilitating disease.

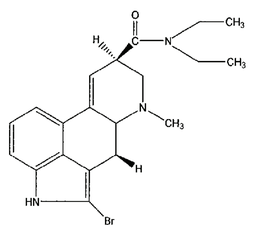
HYPOTHESIS

There are many cluster headache patients anecdotally reporting significant relief from LSD and psilocybin but these compounds are undesirable from both a regulatory and patient safety perspective. But could a non-hallucinogenic analog also provide similar dramatic effects? LSD's hallucinogenic effects are completely lost when the double bond in the D ring is saturated and with substitution at R2, e.g. by bromination in 2-bromo-LSD (BOL). BOL has been studied in volunteers and in patients suffering from vascular headaches but not previously in patients with cluster headache. These past studies concluded BOL is non-toxic and non-hallucinogenic. Only very mild side effects have been observed, if any, when given in the dose range used in our project (30 µg/kg BW) .

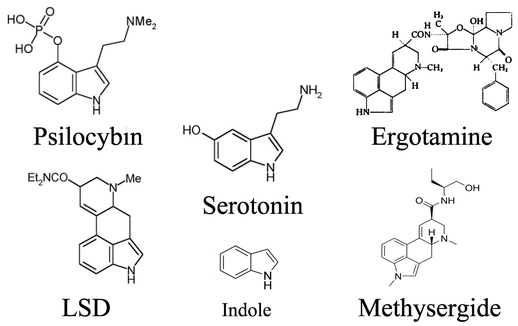
METHODS

Patients referred to Hannover Medical School's Pain Clinic were identified with cluster headache if they met the respective diagnostic criteria of the international classification of headache disorders. All patients were non-responders to verapamil (or could not tolerate its side-effects) and to some extent to other prophylactic medications, as well. However, all patients could abort an acute attack either with oxygen or sumatriptan. In accordance with German national and local ethics committee rules, all patients signed an informed consent that declared their agreement to participate in this project on the compassionate use of BOL for cluster headache. Patients kept a standardized daily diary of cluster headache symptoms (see www.clusterbusters.com for a copy) starting at least two weeks prior to BOL administration. BOL was manufactured by THCpharm GmbH (Frankfurt am Main, Germany). A purity of >99.2% was identified by HPLC and other analytical tests. BOL 30 µg per Kg body weight was dissolved into distilled water and then given once every 5 days for a total of 3 doses PO.). Alterations in consciousness, thought disturbances, and vital signs (blood pressure, heart rate) were measured during a three to four hour observational period since BOL is typically active for two to three hours. Patients were asked to continue completing daily headache diaries for the next months or until they experienced 3 days of attacks of a starting new cluster series.

2-Bromo-LSD



Structural homologs



Subject	S1	S2	S3	S4
Sex (m/f)	m	m	m	m
Age (years)	28	46	47	41
Body weight (kg)	68	83	106	105
Body height (cm)	168	180	188	195
Initial symptoms since (years)	10	3	10	33
Side	right	left	left (1999-2005) right (since 2005)	right
Cluster headache form	episodic	chronic	chronic since 2005	chronic since 2001
Attacks per week in the preassessment week	7	8	28	15
Mean intensity of attacks (VAS) in the preassessment week	8.3	8.4	4.0	6.4
Treatments (acute)	oxygen	sumatriptan nasally	frovatriptan (up to TID 2.5 mg) oxygen	oxygen sumatriptan s.c.
Treatments (prophylactic)	verapamil 240 mg/d	verapamil 240 mg/d	verapamil 240 mg/d	methysergide (1978) prednisone (only for 5 days) verapamil 320 mg/d for 3 months lithium for 3 months
BOL (30 µg/kg) three times within 10 days (day 1, 5 and 10)	2.0 mg	2.5 mg	3.1 mg	3.1 mg
Side effects	"funny feeling" for about 2 h	"flabby feeling" for about 2 h	rudimentally "tipsy" for about 2 h	rudimentally "tipsy" for about 2 h
Vital signs	unchanged	unchanged	unchanged	unchanged
Attacks per week after last BOL	0	2.3 (in the initial 4 months after	0.5	1

Table 1.

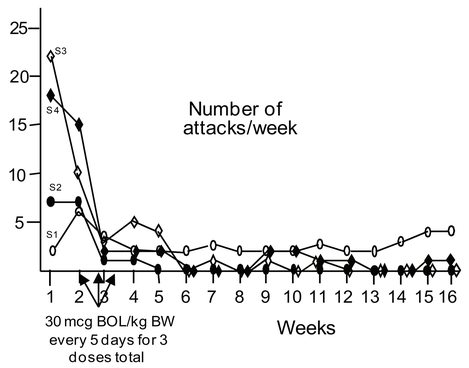


Figure 1.

RESULTS

Results are summarized in Table 1 and Figure 1. All but one patient (S1) had symptoms for more than 10 years. Patient S2's cluster period terminated after BOL with a long-lasting remission period of six months (at last follow-up) and continuing. Patient S3 reported pronounced reduction of attack frequency, including full remission for more than 1 month indicating transition from a chronic to an episodic form. In 9 months since BOL treatment, patient S3 describes ongoing remission of cluster period, reporting only a few solitary sporadic attacks. Patient S4 reported a profound reduction in attack frequency, though without 1 full month of remission. Attack frequency increased for patient S4 approximately 6 months after BOL treatment. In addition, patients S3 and S4 found the pain intensity of remaining occasional attacks so improved that they no longer administered an acute intervention as they had prior to BOL. Although patient S1 did not experience pronounced attack reduction similar to the other 3 patients, he indicated a decrease of attack intensity of about 30% within the first 4 months. It is likely relevant that patient S1 continued to drink alcohol (contrary to advice), a known and common trigger for attacks.

DISCUSSION

The results show that three single doses of BOL within 10 days can either break a cluster headache cycle or considerably improve the frequency and intensity of attacks, even resulting in changing from a chronic to an episodic form with remission extending for many months or longer. Except for very mild alterations of subjective state and mild to no sympathetic reactions for about 2 hours, no other side effects were observed.

Anecdotal reports of LSD and/or psilocybin for cluster headache include descriptions of a single dose or a few doses resulting in long-lasting effects, which we now also demonstrate from BOL. Such results indicate that BOL, psilocybin, and LSD may influence the expression of genes responsible for the biological clock of the organism. BOL's mechanism of action for cluster headache is unrelated to those receptor systems thought involved with hallucinogenicity: 5-HT-1A and 5-HT-2A. Similarly, psilocybin and LSD's treatment effects for cluster headache also, then, may have little to do with their capacity to induce hallucinogenic effects. The ergotamines (including BOL, LSD, dihyroergotamine, and methysergide) likely have positive treatment effects for cluster headache through serotonin-receptor-mediated vasoconstriction. BOL was specifically created as a completely non-hallucinogenic form of LSD but methysergide was developed to have even more potency at serotonin receptors (and less hallucinogenic effects than LSD). While methysergide taken daily is often an effective preventative compound, it does not generally induce remissions. Repetitive intravenous and subcutaneous application of 1 mg dihydroergotamine for up to 3 weeks has been shown in an open retrospective trial to sometimes break a cluster period. Yet chronic use of methysergide and dihydroergotamine increases risk for fibrotic complications (such as retroperitoneal fibrosis), but this risk is unknown for BOL and is also extremely unlikely from the limited, non-chronic dosing regimen of BOL we employ. None of the approved ergot-based medications for cluster headache realize the type of profound and lasting treatment response we report from just 3 doses of BOL.

The results of this case series must be regarded as preliminary, in that they are unblinded and uncontrolled. However, chronic cluster headache patients seem to have a relatively modest placebo response, especially when a very strict endpoint as cessation of headache is used, and the high reported effectiveness of BOL for this frequently treatment refractory condition makes it unlikely to be artifact. Where the current standard of care involves interventions that break single headache attacks and reduce pain duration, frequency, and intensity of attack cycles and without identified treatments that extend remission, the potential breakthrough treatment of BOL warrants wide dissemination of these early findings to encourage aggressive development to randomized controlled trials.

INFORMATION

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