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-hallucinogenic 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-administered the hallucinogen 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. Patients maintained a headache diary prior to and post treatments for at least 6 months. 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 75% 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 hallucinogenic 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 anecdotaly 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. 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.

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 episodic attacks. Patient S4 reported a profound reduction in attack frequency, though without full 1 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 episodic form with remission extending for many months or longer. Except for very mild and transient 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 the biological clock of the organism. BOL's mechanism of action for cluster headache is unrelated to those receptor systems thought involved with hallucinogenicity. Therefore, 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, dihydroergotamine, and methysergide) likely have positive treatment effects for cluster headache through serotonin-receptor-mediated vasconstrictor. 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 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 stringent 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 may 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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