Simple solutions mitigate herpes simplex virus (HSV) infections: Further evidence for a Retardant Effect

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ABSTRACT

Background. Human herpesvirus infection is commonplace yet existing topical treatments for this vexing complaint have limited effectiveness. Scant progress has been made of late to alleviate or remedy this situation. *Objectives*. To investigate the efficacy of various formulations for topical administration in a comparison trial. This study sought to test claims made in old patents that certain mixtures or basic substances were capable of suppressing the symptoms of HSV disease. In particular, to investigate an intriguing claim of a 'Retardant Effect' by which subsequent viral symptoms become less severe or less frequent. *Methods*. A cohort of 97 voluntary participants tried three preparations, reporting their impressions via a website questionnaire. The solutions contained a mixture of acids or BHT, these being a subset of trials of more novel formulations. *Results*. Many of the participants found these basic formulations helpful and superior to existing products. Of the three preparations described, HA1 showed the most promise. Across the whole trial involving 223 participants, 30 (13%) volunteered reports of a residual, longer-term benefit. *Conclusions*. This provisional investigation appears to demonstrate the superior performance of certain simple solutions in suppressing the symptoms of HSV infection. Multiple suggestions were made that topical administration is capable of moderating future episodes. If confirmed, the Retardant Effect would have profound implications for the future treatment of HSV disease.

Keywords: cold sores, herpes simplex virus, HSV, infection, retardant effect, topical administration

INTRODUCTION

HSV infection is a distressing, troublesome and sometimes serious concern worldwide. A constant demand exists for OTC preparations intended to alleviate "cold sores." However existing topical preparations are often only marginally effective and an attempt was made to improve on this.[1] An internet-based trial of potential treatments for herpes simplex virus infections was undertaken.

This paper highlights a general problem in medicine, whereby generic treatments can be neglected even when known to be effective. One of many such instances is moroxydine, a putative broad-spectrum antiviral which has shown promise in the treatment of hepatitis.[2, 3]

None of the preparations tested contained analgesics and were designed purely as antivirals using relatively commonplace ingredients. Three primitive solutions were investigated for

particular comparison and it is these which will be detailed here. The preparations can be produced with the minimum of equipment and expertise. Reports were also received of other, considerably more complex formulations.

MATERIALS AND METHODS

A website at target.org.uk carried a reporting system programmed in Perl. Shortly registration was also done via the website. Participants were supposed to have "frequent outbreaks," defined (but not disclosed) as six or more per year, though a few exceptions were made and some evidently exaggerated the frequency of their outbreaks to gain entry to the trials. Most were referred by the Herpes Viruses Association in London. Applicants and participants with ambiguous symptoms were excluded, though this occurred very infrequently. More frequently encountered were drop-outs, when applicants enlisted and were sent a preparation but never reported. This proportion was entirely expected, since it was impossible to establish beforehand whether applicants would be compliant and return to the website to report.

HA1 was to be used once per day for suppression (i.e. prophylaxis) or "as required." The HB2 preparations were to be used 2–3x/week for suppression or 1–3x/day for an active outbreak. Around 1.5g of the liquid in a 3ml or 5ml brush bottle (with air) was sent by post. An accompanying Directions leaflet contained instructions to paint a thin layer over and around the affected area and fresh supplies were provided as requested. Some participants tested two or more preparations.

HA1 was formulated after a 1981 US patent.[4] It was a solution of 40.5/40.5/7.6/7.6/3.8 w/w PG (monopropylene glycol), DMI (dimethyl isosorbide), tannic acid, boric acid and salicylic acid respectively. Mixing takes about one and a half hours.

HB2 was an elementary solution of 60/40 w/w DMI/BHT (butylated hydroxytoluene) respectively. This trial began as a test to determine whether BHT was worth using as an ingredient in later formulations.[5, 6] Scant information exists of its effect when used topically. BHT is the food additive E321 and DMI is a common ingredient in sunless tanning products.

HB2 was superseded by HB2A, which was 62/28.5/9.5 w/w DMI, BHT and PG. It forms a clear solution with about three hours' stirring. The solutions were prepared by the author using a balance with 1mg readability or better and standard laboratory equipment. Typically, batches of about 20ml were prepared.

These basic formulations were not without problems however. DMI degrades, albeit slowly, in contact with air. HB2 and HB2A to a lesser extent had a tendency to sometimes form crystals, which may have been associated with a drop in temperature. Refinements in the HB2A ratio attempted to minimise this.

There were three key questions in the report questionnaire, detailed with their attributed scores as follows. The Summary question asked "Is the Target preparation any good? Compared to previous treatments you have tried, is this Target preparation more or less effective?" The selections were: Better than anything (4); Better than most (3); About the same (2); Less effective (1) and Not effective at all (0).

The Pain Relief question asked "When you use the Target preparation during an outbreak, does it reduce pain or other viral sensations (e.g. burning, itching) at the skin?" Selections were made of: Completely (4); A lot (3); Moderately (2); A little (1) and Not at all (0).

The Side-effects question asked "Did the Target preparation have side-effects? Please rate the irritation the Target preparation caused. 'Inflammation' is when the skin goes red. Note: This concerns side-effects of the Target preparation, not any symptoms you have." Responses were: Painful, prolonged inflammation or irritation (–5); Mild but prolonged inflammation or irritation (–4); Discomfort for over ten minutes (–3); Significant brief irritation (–2); Mild, brief irritation (–1) and No irritation (0).

Interspersed with these three key questions, participants were also asked about usage, symptom severity and miscellaneous problems (e.g. discolouration of the liquid). For each question there was a "Can't say/Don't know" (or equivalent) option which did not count toward the score. A Comments field was available at the end but was often left empty.

Programs were written to process the results according to the above scoring scheme. To obtain the overall scores, the individual participant's ratings were averaged, then these averages were themselves averaged across all participants in a particular trial. Finally the Summary and Pain Relief averages were multiplied by 25 to give percentage scores. The Tolerance ratings were

averaged similarly with a perfect score being zero.

The website was 'write-only' to ease security concerns. Local processing of the gross website output was accomplished using several programs written in Bbcbasic, including routines to identify duplicate lines and other anomalies which could distort the results. The double-averaging scoring scheme was designed thus to account for the widely varied reporting activity of the participants. Some participants made only one report while others made dozens. A participant might find the test preparation irritating or inflammatory, make a single report to that effect, then drop out of the trial. A simple average of all the tolerance ratings would result in that rating being subsumed by those participants for whom the preparation was well-tolerated and who continued to make reports. Accordingly, each participant's ratings were summed, then divided by the number of corresponding ratings. In this manner each participant was given equal weight when their averaged rating was used to calculate an overall average for the trial.

Quantifying the Retardant Effect was more problematic, being perforce subjective since each potential instance required appraisal. Generally, to be counted as a manifestation of RE the participant had to comment that an established pattern of herpetic recurrences had been interrupted, this being credibly attributable to the test preparation. Similar comments while the test preparation was being used concurrently for prophylaxis were excluded, as was one participant's claim of having been cured since her use of the test preparation was inconsistent and the event could be attributed to remission. At issue at this early stage is not the degree to which RE exists, but whether it exists at all.

Participants in this cohort of 97 were UK residents, had white skin and birth-years 1950–1998. Reports were encouraged by an emailed newsletter, with news of the trials, humour (a favourite theme being the decisions of a mythical "funding committee"), some virology and a reminder to report. The routine developed of sending reminders to new participants who had not reported after three months, and removing those who had not reported for six months. Otherwise a participant would be changed to another preparation when their particular trial ended. The newsletter and incidental communications were non-committal so as not to influence the reports.

However, this protocol was broken in the case of HA1, because its Directions leaflet borrowed from the patent, stating "If the preparation is working there will be alleviation of pain within a couple of hours and a significant reduction of visible symptoms within four days. If the preparation has no effect, discontinue treatment and report that the treatment has failed." In retrospect this was a mistake, though only 4 selections of "Not effective at all" were made in 281 reports.

Eight other, considerably more complex formulations were tested which are not detailed here. The HF series, which used *Melissa officinalis* with its distinctive odour, were the only preparations for which the participants were informed of an ingredient.

RESULTS

The costs of an extensive and extended investigation such as this which conformed to conventional protocols would have been enormous. Thus achieving full scientific rigour was not feasible in the circumstances of this unorthodox study. Notwithstanding, looking past its shortcomings, the volume of positive reports has weight. All three preparations have Summary scores over 50%, which implies greater efficacy than existing topical treatments. Overall statistics of the trials are given in Table 1. Most of the participants were women with oro-labial infections, as shown in Table 2. The results obtained are shown in Table 3.

Table 1. Trials data

Preparation	Never reported	Reporters	Total reports	Date span
HA1	14	36	281	9/2/18–12/8/20
HB2	14	22	152	5/7/17–4/11/19
HB2A	21	39	300	21/5/18–8/2/21

Table 2. HA1, HB2 and HB2A participant composition by infection site

	Upper body	Lower body	Both upper and lower
Male	14	3	4
Female	37	29	10

Table 3. Double-averaged scores

Preparation	Summary	Pain relief	Tolerance	RE suggested
HA1	76.4% (*n* = 33)	49.4% (*n* = 33)	–0.63 (*n* = 36)	5
HB2	79.7% (*n* = 19)	39.6% (*n* = 12)	–0.50 (*n* = 22)	0
HB2A	72.6% (*n* = 32)	44.0% (*n* = 35)	–0.85 (*n* = 39)	4

A few participants expressed difficulty with the Summary (comparison) rating because they had never used anything to treat their symptoms before. With the Summary ratings, extra comparison processing could be performed to determine improvement or diminution when a participant moved from one test preparation to another. These issues do not apply to the Tolerance and Pain Relief scores. The Pain Relief question was not added until May 2018, 16 months after the first report, accounting for the lower *n* for some results. Some participants had painless outbreaks.

Undoubtedly there were spurious and inconsistent entries in the reports. For example, a few participants reported symptomatic pain as a side-effect and some reports had contradictory ratings. Despite this, reports were only rarely modified, and then only with the agreement of the participant. The expectation was that the results would even out with sufficient *n* size. Informally, the results started to appear meaningful when *n* reached about fifteen, while the minimum desired *n* was 30. Due to the chemistry problems with these formulations, some reports were made while using degraded preparations.

For the HA1 trial, all but 2 participants were new to the trials. For HB2, 3 had used a different test preparation previously. For HB2A, 10 had used a different test preparation beforehand, of which 5 were changes from HB2.

The change from HB2 to HB2A was revealing. Tolerance was significantly reduced, but the only alteration to the formulation was the addition of about 10% PG, which is innocuous. The decreased tolerance was attributed to increased skin penetration. HB2A, which can cause itching, was one of several preparations which became better tolerated with use.

Tinnell's claim that his combination of acids can give rapid relief and effectively treat was not contradicted in this study. The vagina is acidic as a protection against infection. An intriguing further observation by Tinnell was that this acid mix was capable of a 'Retardant Effect' i.e. reducing subsequent outbreak frequency or severity. Quoting from his patent, "For reasons not well understood, the treatment of the invention also appears to have a retardant effect on the virus, substantially prolonging the time between recurrences, and in some cases apparently eliminating the virus altogether." Tinnell proposed as carriers several alcohols, notably ethanol, treating over two hundred patients.

Overall in this study over two thousand reports were received and although the trials have now ended, full analysis of the data has not been completed. Summarising for comparison, of all the results with *n* of 30 or more, the best achieved were: Summary 82.4% (HB5, *n* = 39), Pain Relief 56.2% (HF2C, *n* = 32) and Tolerance -0.63 (HA1, *n* = 36).

The greatest value of these trials may turn out to be the participants' comments, which were impossible to score using computer programs. At this stage and across all the trials, suggestions of RE by 30 participants were noted, some expressing surprise and mystification at the development. Comments were made such as "five months is the longest I have been without an outbreak for more than 20 years." A few reported the effect having only used the test preparation during a single episode, and this accords with observations by Georgian researchers during a pilot study using walnut extract in a mixed silicone carrier with the proprietary name of Lazolex.[7] The present study involved a total of 223 participants; thus

13% of participants volunteered comments suggestive of RE.

Another phenomenon mentioned in at least 16 reports was unexpected relocation of outbreak site, which is confirmation of potency if not a preferred outcome. Participants reported symptoms in many areas of the body, including the palm of the hand, nostrils and buttocks, as previously documented.[8] One male participant reported body-wide infection.

DISCUSSION

The locus of HSV infection is the sensory ganglia, with near-constant activity there.[9] Nevertheless, the possibility exists of a peripheral component.[10, 11, 12] In some cases, latency in dermal cells (perhaps in the basal membrane) could comprise the 'main charge' while the neural source of virus could act as a 'detonator.' This is a mildly heretical view, but HSV infections are very varied. It is also true that viral reactivation following a stress event can be very rapid. In any case, it was interesting to obtain more information about the Retardant Effect.

With no control group there will have been bias due to participants wishing to please the researcher. Failures would be less likely to be reported. Such factors bore on all the trials more or less evenly, thus the trials were comparative.

A placebo was foregone for two reasons. Firstly it was asking a lot of purely voluntary participants to use, and repeatedly report on, a preparation which was inactive. Secondly, it was fully expected that at least one of the preparations would fail, and thus serve as an effective control by setting a baseline for comparison. Above all it was HB2 which was expected to fail. However, this does not appear to have happened. The absence of RE reports with HB2 may be significant.

Finding a single preparation which works for everyone, and across very different sites, is a challenge. Numerous factors, including the variability of HSV infections and their tendency to sometimes enter remission, combine to make progress in this field a formidable undertaking. The cohorts here are not large enough for a meaningful analysis by HSV type. Other researchers are invited to verify these results and substantiate the observations of Tinnell, Kituashvili et al. and the discernment of a Retardant Effect in this study.

To many, HSV infection is a long-term burden.[13] Pain and adversity in general is much more bearable when the individual feels he has a degree of control over it.[14] While these preparations did not achieve complete control, it seems they can make a significant difference. Multiple reports during these trials support the notion that topical administration is capable of breaking the cycle of frequently recurring outbreaks. When applied during a primary episode, perhaps in conjunction with chemotherapy, topical treatment may alter the prognosis of HSV disease.[2, 15, 16]

REFERENCES

1. Hammer KDP, Dietz J, Lo TS, Johnson EM. A systematic review of the efficacy of topical acyclovir, penciclovir, and docosanol for the treatment of herpes simplex labialis. *EMJ Dermatology* 2018; 6: 118–123.
2. Sheppard SG. Moroxydine: The Story of a Mislaid Antiviral. *Acta Dermato-Venereologica. Supplementum* 1994; 183.
3. Magria A, Reilly R, Scalacci N, Radic M, Hunter M, Ripoll M et al. Rethinking the old antiviral drug moroxydine: Discovery of novel analogues as anti-hepatitis C virus (HCV) agents. *Bioorganic and Medicinal Chemistry Letters* 2015; 25: 5372–5376.
4. Tinnell JE, inventor; Tinnell JE, assignee. Treatment for herpes virus. 1981; United States patent US 4285934.
5. Snipes W, Person S, Keith A, Cupp J. Butylated hydroxytoluene inactivates lipid-containing viruses. *Science*. 1975; 188: 64–66.
6. Keith AD, Snipes W, inventors; Research Corporation (New York, NY), assignee. Inactivation of lipid containing viruses with butylated hydroxytoluene. 1982; United States patent US 4350707.
7. Kituashvili TA, Kvirkvelia VG, Galdava GG, Archvadze NG. Efficacy of Lazolex® Gel in the Treatment of Herpes Simplex Mucocutaneous Infections and the Prevention of Recurrences: A Pilot Study. *Canadian Journal of Infectious Diseases and Medical Microbiology* 2022; 2022:4413679.
8. Lautenschlager S, Eichmann A. The heterogeneous clinical spectrum of genital herpes. *Dermatology (Basel)* 2001; 202: 211–219.
9. Harkness JM, Kader M, DeLuca NA. Transcription of the herpes simplex virus 1 genome during productive and quiescent infection of neuronal and nonneuronal cells. *Journal of Virology* 2014; 88: 6847–6861.

10. Subak-Sharpe JH, Al-Saadi SA, Clements GB. Herpes simplex virus type 2 establishes latency in the mouse footpad and in the sensory ganglia. *Journal of Investigative Dermatology* 1984; 83 (1 Suppl): 67s–71s.
11. Al-Saadi SA, Gross P, Wildy P. Herpes simplex virus type 2 latency in the footpad of mice: effect of acycloguanosine on the recovery of virus. *Journal of General Virology* 1988; 69: 433–438.
12. Clements GB, Jamieson FE. Reactivation of latent herpes simplex virus-1 (HSV) from mouse footpad cells demonstrated by in situ hybridization. *Archives of Virology* 1989; 104: 95–106.
13. Benedetti JK, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. *Annals of Internal Medicine* 1994; 121: 847–854.
14. Weiss JM. Effects of coping behavior in different warning signal conditions on stress pathology in rats. *Journal of Comparative and Physiological Psychology* 1971; 77: 1–13.
15. Sawtell NM, Thompson RL, Stanberry LR, Bernstein DI. Early intervention with high-dose acyclovir treatment during primary herpes simplex virus infection reduces latency and subsequent reactivation in the nervous system in vivo. *Journal of Infectious Diseases* 2001; 184: 964–971.
16. Thackray AM, Field HJ. Famciclovir and valaciclovir differ in the prevention of herpes simplex virus type 1 latency in mice: a quantitative study. *Antimicrobial Agents and Chemotherapy* 1998; 42: 1555–1562.