ISSN: 2577 - 8005

Review Article

Medical & Clinical Research

Germicidal (Bactericidal) Power of Phytorelief (On Group A β -Hemolytic Streptococcus) a Concept, Pilot Registry

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Submitted:04 July 2020; **Accepted**: 07 July 2020; **Published**: 01 Aug 2020

Abstract

This concept, pilot study evaluated the effects of some bactericidal products in vivo to evaluate the presence of Group A β-hemolytic streptococcus (GAS) in throat swabs. With this model, if an asymptomatic subject is swab-positive, bactericidal products can be used (i.e., for 3 to 7 days) and the positivity re-evaluated to define the direct killing power of the product.

Results: A progressive decrease in positivity in the swab samples was observed. Bactericidal products (Phytorelief, in 2 formulations, baicalin, rifampin and benzydamine produced the disappearance of positivity in most subjects at 3-7 days. All oral bactericidal used in this pilot registry resulted effective in killing bacteria in >85% of cases. The pharmaceutical form (gummy, slow release lozenges) of Phytorelief seems to be important to assure persisting traces of the bactericidal/virucidal in the mouth. Phytorelief lozenges in 2 formulations, possibly, produced the longest action (>3 hours) due to the slower release of the substances (mainly pomegranate and ginger) in the product.

Conclusions: These preliminary observations indicate a significant effect on Group A β-hemolytic streptococcus as previously seen on the viral contamination of the mouth (in COVID-positive subjects) with a relatively simple, cost-effective human model. The lower presence of a bacterial and virus charge (load) and its decrease may reduce contagiousness of most of these patients and possibly, the spread of bacterial/viral material from the mouth. The effects on the evolution of infections on single patients is, at the moment, not fully predictable with this model but oral bactericidal and virucidals may assume a significant community value in preventing and controlling spreading.

Introduction

Group A β-hemolytic streptococcus causes common infections of the throat and skin (from mild, asymptomatic conditions to severe infections). It is not clear what elements cause different diseases or clinical conditions as a result of GAS infection with the same bacteria; patient's characteristics and individual factors – including the immunity status- may produce a large clinical variability. The virulence factors related to GAS may influence the evolution of infections and their gravity. Generally, individuals with altered immunity are very susceptible to diseases caused by GAS (1-4).

GAS's may 'confuse' an immune detection; this is facilitated by protein S, an extracellular, cell wall-associated protein that enables it to camouflage itself by binding fragments of lysed red blood cells. Humans may carry the GAS on the skin or in the throat and show no symptoms. These carriers are possibly, less contagious than symptomatic carriers. Minimal infections caused by GAS tend to be less severe and more frequent. They occur when the bacteria colonize the throat where it recognizes the specific epithelial-mucosal cells. The two most significant infections of GAS are both clinically limited: strep throat (pharyngitis) causes 15–30% of the childhood cases and 10% of adult cases: impetigo Is also relatively common in different clinical forms (3, 4).

These common infections may be effectively treated with antibiotics. Scarlet fever is also a limited infection caused by GAS

although it recently becomes quite rare. Invasive, more severe infections caused by Group A β-hemolytic streptococcus tend to be less frequent and confined to specific individuals. These infections occur when the bacteria infect areas where these bacteria are not usually present and found (blood and organs). The diseases that may be caused as a result of this spread include streptococcal toxic shock syndrome (STSS), necrotizing fasciitis (NF), pneumonia and bacteremia (now, relatively uncommon in advanced medical systems). Infection of GAS may lead to further complications and health conditions, namely acute rheumatic fever and poststreptococcal glomerulonephritis.

In this concept registry the throat swabs were performed with a rapid test, in the morning before breakfast. The oral oral lozenge formulation Phytorelief has recently shown a significant activity as a virucidal in COVID, swab-positive, asymptomatic subjects [5-7]. Virucidals that can be used orally, may reduce the viral charge and control viral spread to other individuals [8, 9]. Some natural extracts (particularly from plant sources) may be considered as natural, safe virucidal/bactericidal products applicable in the mouth [10-12]. The subjects followed in this non-clinical registry were asymptomatic and otherwise healthy (range 35-45 years, all males). Subjects with positive swabs were advised to use one of the germicidal solutions (4 times daily) or complexes; the swab test was repeated at 3 and 7 days to evaluate the specific *germicidal power* of the oral compound on GAS.

Methods, Subjects

Asymptomatic 'patients' (found as positive at the swab during a screening program) who were otherwise fully healthy were evaluated. Their age was <55. No drugs had been used, a normal oral hygiene was regularly observed, their body temperature was normal. The test was made before 10 am, without washing mouth or teeth and before breakfast. The same tests were repeated at 3 days under similar conditions. No specific systemic or local drugs were used during the observation period and no significant symptoms occurred or were reported.

All subjects remained fully asymptomatic during the observation period. Progression to significant symptoms and to the need for management of infections (or any other condition) was considered exclusion items. All subjects respected hygienic measures and the necessary measures (mask, hygiene, distancing) during the COVID-19 period and used Vitamin C (400 mg/day) and a normal diet. Over the Counter (OTC) were used to evaluate their 'germicidal' power.

Phytorelief® (5): (Alchem Life, Germany) includes pomegranate (as the main local virucidal/antiviral) in association with ginger and turmeric. Pomegranate extract is one of the most powerful natural antivirals. The lozenge is slowly dissolved in the mouth; its effects may last more than 3 hours.

Its virucidal power has been recently shown [6, 7].

Benzydamine: (also known as Tantum Green, branded in some countries as Difflam or Septabene), is usually available as the hydrochloride salt in a green solution. It is a very common, locally acting as nonsteroidal anti-inflammatory drug (NSAID) associated with local anesthetic and analgesic properties determining pain relief. It is used for the management/treatment of mild conditions of the mouth and upper throat.

Phytorelief-CC®: (product formulation 2), (Alchem Life, Germany) includes pomegranate (as the main local virucidal/antiviral) in association with licorice, ginger and turmeric. Pomegranate extract is one of the most powerful natural antivirals. The gummy lozenge is slowly dissolved in the mouth; its effects may last more than 3 hours. The new composition (CC) includes, with pomegranate, a standardized licorice extract and selenium: these natural products are considered both virucidals and antivirals (if used for systemic administration) and germicidal.

Baicalin (85%): (obtained by InXi, Shanghai). This product (alone or in combinations) has been diffusely used in Wuhan during the viral epidemic (however clinical data are not accessible) [10-12]. It is a flavone glycoside (the glucuronide of baicalein). This product is an Inhibitor of 5- and platelet 12-lipoxygenases (IC50 values are 9.5 and 0.12 μM respectively). It also inhibits Raf-mediated MEK-1 phosphorylation in glioma cells and induces G1 and G2 cell cycle arrest by decreasing cdk1, cdk2, cyclin D2 and cyclin A expression. Baicalin inhibits the production of inflammatory cytokines by inhibiting NF-κB activation. It also inhibits erastin-induced ferroptosis. Baicalin is found in several species in the genus *Scutellaria*, including *Scutellaria baicalensis* and *Scutellaria lateriflora*. There are 10 mg/g baicalin in Scutellaria galericulata leaves. It is one of the chemical ingredients of Sho-Saiko-To, a traditional Chinese medicine.

Baicalin is also present in the bark of *Oroxylum indicum* tree. Baicalin, along with its aglycone baicalein, is a positive allosteric modulator of the benzodiazepine site and/or a non-benzodiazepine site of the GABAA receptor. Baicalin produces anxiolytic effects without sedative or myorelaxant effects. It is thought that baicalin, along with other flavonoids, may underlie the anxiolytic effects of S. baicalensis and S. lateriflora. Baicalin is also a prolyl endopeptidase inhibitor [10-12].

Rifampin is an antibiotic used to treat several types of bacterial infections, including tuberculosis, *Mycobacterium avium* complex, leprosy, and Legionnaires' disease. It is generally used with other antibiotics, except when given to prevent *Haemophilus* influenzae type b and meningococcal disease in people exposed to those bacteria. A significant antiviral activity of Rifampin has been described [13]. The registry evaluated the germincidal effects of these compositions at inclusion, 3 and 7 days.

Statistical Analysis: Statistical analysis was performed with a Sigma-Plot software package; the analysis of the variance and the

Mann–Whitney U-test were used (considering results as non-parametrical data). The proportion of included samples in the management group was calculated in groups of at least 15 patients to detect significant variations in the measurements before-after periods. Spontaneous intra-individual and inter-individual variations (5–10% in most measurements) are possible as a consequence of spontaneous variations. An arbitrary cut-off point (at least a >10% variation) in parameters was considered to be valid to define significant changes due to management. The presence absence of bacteria in swabs values is not regularly distributed and measurements variations were evaluated (including % of positivity) by non-parametric tests.

Results

The subjects (all males) in the different groups were comparable (as seen in Table 1).

No side effects of these products were reported.

The tolerability was optimal (no subject has to stop the managements).

Their BMI was <26.

Results (positivity) at 3 and 7 days are shown in Table 2 and in Figure 1.

Results are useful to define these products as oral germicidal/bactericidal as they appear to decrease positivity of at least 75% in these patients.

A prospective, more complex evaluation, looking at other blood parameters may be needed.

A clinical evaluation on the evolution of infections to clinical stages may be needed.

Table 1: groups composition.

Group 1	18	Age 36.2;2
2	18	35.3;2.2
3	18	35.5;2.1
4	18	36.1;1.6
5	16	36.5;2.6

Table 2: data concerning the positivity of swabs in the 5 groups at different times.

Arbitrarily, it is possible to define as germicidal products that reduce of >80% the positivity of swabs in a week of 'standard' management.

TIME	phyrelief	benz	phrelief-CC	BAICA	RIFAMP
Inclusion	18	18	18	18	16
3 days	1	3	2	2	2
7 days	1(5.5%)*	2(11.1%)*	2(11.1%)*	2(11.1%)*	1(6.25%)*

*= P<0.05; ANOVA

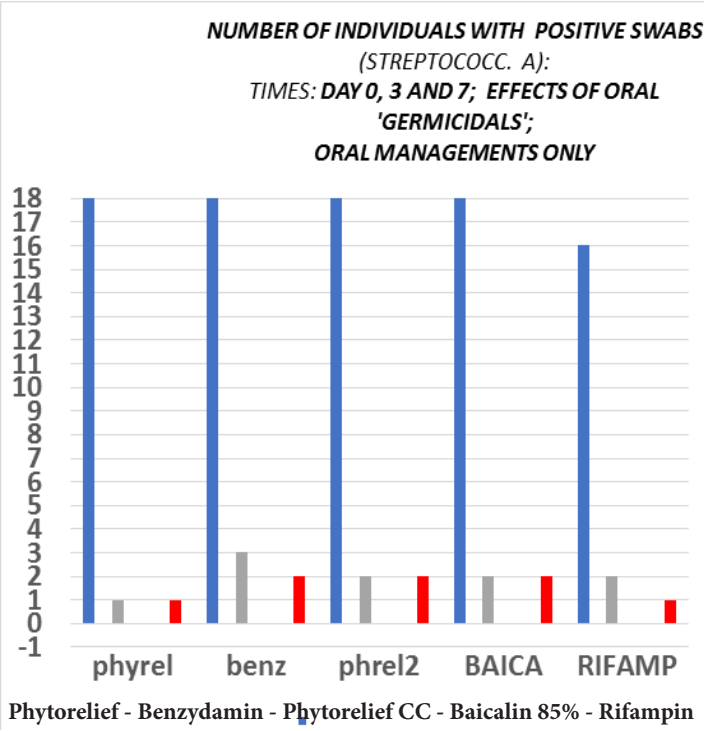

Figure 1: variations in positivity with the 5 oral 'germicidals'.

Discussion

A bactericidal product is a drug or substance which kills bacteria. A virucidal has the capacity to destroy or inactivate viruses. A substance, drug or agent that kills germs, especially pathogenic microorganisms can be defined as a germicidal; a disinfectant is a different product that cannot be used in the mouth or ingested [14, 15]. Antiviral drugs and antibiotics are the key drugs used for treating bacterial and viral infections. Most antibiotics and antivirals target specific bacteria or viruses; however, some broad-spectrum antibiotics and antivirals may be effective against a wide range of bacteria/viruses both in systemic administration and in local applications.

Antivirals do not directly destroy their target virus but, generally, inhibit their development. At the moment – studies are in progress - there are no specific antivirals, strongly active i.e., against the Wuhan viruses. Virucidals are not used as systemic drugs but deactivate or destroy many viruses inside or outside the body and specifically in 'border' anatomical areas (mouth, nose) when it is possible to apply them without causing damages or side effects.

Some of the most common virucidals (but these products also affect most bacteria) are produced from natural plant extracts (pomegranate, eucalyptus and Australian tea tree oil, licorice, Baicalin). Most of these products can be also used by inhalation. Eucalyptus extracts (as Calyptol, Sanofi) has been the first product (and the most common product) used with WHV (warm humid

vaporization) in our studies aimed to control the COVID virus. Phytorelief has shown remarkable activity against the aggressive COVID-19 virus.

This registry had the aim of evaluating a possible bactericidal-germicidal activity on a very common micro-organism (GAS) present, in asymptomatic form, in many subjects. The fast, but possibly, temporary negativization of swabs in this concept, registry may be considered a model to study the germicidal and virucidal activity of locally-acting oral compounds (that can also be ingested). Germicidals and virucidals have been neglected: they are cheap, generally not protected by patents and basically, have an adjuvant role in a low-cost market.

The real target is to kill bacteria and viruses (including the COVID virus) without side effects and in early phases of contamination. Killing bacteria and any virus early, in a preventive phase, could be the best option to avoid spreading. Advanced diseases, with all its clinical complications (both for bacterial infections and viral problems) appear much more difficult to manage [16]. The combination of virucidals to block the viral spread (particularly for the COVID) and low-dose antivirals with other treatments may be possible solutions to control viral spread [17-19].

A comparable model can be applied for common bacteria, present in a large number of asymptomatic subjects, when an antibiotic treatment may solve the problem but cause side effects and induce resistance. This preliminary experience shows that Phytorelief, in particular, can be considered virucidanl and bactericidal (germicidal). Clinical implications should be evaluated in larger, prospective studies. Predictive statistical models (based on this simple, human real-life, model) indicate that the potential bactericidal-virucidal power of these products may reduce the number of severe clinical complications of some 35% [18, 19].

References

1. Vakkila J, Koskinen J, Brandt A, Muotiala A, Liukko V (2015) Detection of Group A Streptococcus from Pharyngeal Swab Samples by Bacterial Culture Is Challenged by a Novel mariPOC Point-of-Care Test. J Clin Microbiol 53: 2079-2083.
2. Thompson TZ, McMullen AR (2020) Group A Streptococcus Testing in Pediatrics: the Move to Point-of-Care Molecular Testing. J Cl Microbiol 58: e01494-19.
3. O Luiz FB, Alves KB, Barros RR (2019) J Prevalence and long-term persistence of beta-haemolytic streptococci throat carriage among children and young adults. Med Microbiol 68: 1526-1533.
4. Naik TB, Nadagir SD, Biradar A (2016) J Prevalence of Beta-Hemolytic Streptococci Groups A, C, and G in Patients with Acute Pharyngitis. Lab Physicians 8: 45-49.
5. Luzzi R, Belcaro G, Pellegrini L, Cornelli U, Feragalli B, et al. (2015) Phyto-relief CC: prevention of cold episodes. Control of signs/symptoms and complications. Minerva Gastroenterol Dietol.
6. Belcaro G, Bombardelli E, Cornelli U, Cesarone MR, Cotellese R, et al. (2020) Virucidals Control the Presence of Covid in Mouth/Saliva. Med Clin Res 5: 76-79.
7. Belcaro G, Cornelli U, Cesarone MR, Feragalli B, Cotellese R, et al. (2020) Decrease in Covid-19 Contagiousness: Virucidals Control the Presence of Covid in Saliva and Salivary Glands. Med Clin Res 5: 55-58.
8. "The definition of virucide" (2017) Reference.com.
9. Xu J, Li Y, Gan F, Du Y, Yao Y (2020) Salivary Glands: Potential Reservoirs for COVID-19 Asymptomatic Infection. J Dent Res 22034520918518.
10. Wang H, Hui KM, Xu S, Chen Y, Wong JT, et al. (2002) "Two flavones from Scutellaria baicalensis Georgi and their binding affinities to the benzodiazepine site of the GABAA receptor complex". Pharmazie 57: 857-858
11. Boyce JM, Pittet D (2002) Healthcare Infection Control Practices Advisory Committee, HICPAC/SHEA-APIC/IDSA Hand Hygiene Task Force. "Guideline for Hand Hygiene in Health-Care Settings 51: 1-45.
12. Tarrago T, Kichik N, Claasen B, Prades R, Teixidó M, et al. (2008) "Baicalin, a prodrug able to reach the CNS, is a prolyl oligopeptidase inhibitor". Bioorganic & Medicinal Chemistry 16: 7516-7524.
13. Sodeik B, Griffiths G, Ericsson M, Moss B, Doms RW (1994) Assembly of vaccinia virus: effects of rifampin on the intracellular distribution of viral protein. J Virol 68: 1103-1114.
14. Sauerbrei A, Wutzler P (2010) Virucidal efficacy of povidoneiodine- containing disinfectants. Letters in Applied Microbiology 51: 158-163.
15. Horhammer L (1928) Hager's Handbuch der Pharmazeutischen Praxis. The Journal of the Amer Pharmac Association 17: 318-319.
16. Thomas L, Sekhar Miraj S, Surulivelrajan M, Varma M, Sanju CSV, et al. (2020) Influence of Single Nucleotide Polymorphisms on Rifampin Pharmacokinetics in Tuberculosis Patients. Antibiotics (Basel) 9: E307.
17. McMurray RL, Ball MEE, Tunney MM, Corcionivoschi N, Situ C (2020) Antibacterial Activity of Four Plant Extracts Extracted from Traditional Chinese Medicinal Plants against Listeria monocytogenes, Escherichia coli, and Salmonella enterica subsp. enterica serovar Enteritidis. Microorganisms 8: E962.
18. Siegel E (2013) Predictive analytics. Wiley, Hoboken, NJ.
19. Cox Dr (1961) Planning of Experiments. Wiley, Oxford.