The Efficacy of Gliacin, a Derivative of *Boswellia Serrata* Extract, on Indomethacin Responsive Headache Syndromes.

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OBJECTIVE

Determine the efficacy and tolerability of Gliacin, a derivative of *Boswellia serrata* extract, in the treatment of a series of subjects with confirmed indomethacin responsive headache syndromes

BACKGROUND

Indomethacin responsive headache syndromes (IRHS) are a group of heterogeneous **primary headache** disorders which **promptly** and **completely** respond to indomethacin often to the **exclusion of other treatments**. Indomethacin is a **powerful NSAID** and its effects may in part come from its ability to **block cyclooxygenase (COX) enzymes**. Prototypical examples of IRHS include both **hemicrania continua (HC) [4.7]** and the **paroxysmal hemicranias (PH) [3.2]**; each requires an absolute response to indomethacin to confirm their diagnosis based on the ICHD-II criteria. Although an absolute response to indomethacin is not required for diagnosis, there are several other conditions generally accepted to be IRHS which include: **primary stabbing headache (PSH) [4.1]**, **primary cough headache (PCH) [4.2]**, **primary exertional headache (PEH) [4.3]**, **primary headache associated with sexual activity (PHASA) [4.4]** and **hypnic headache (HH) [4.5]**. Unfortunately, responders often can't tolerate indomethacin long term because of its numerous side effects and potential serious adverse reactions. **Figure 1** summarizes the mechanisms of action and adverse reactions associated with indomethacin. In such situations, a significant therapeutic dilemma ensues often leaving the clinician with few to no alternative treatments. In fact, there is a paucity of information in the literature regarding effective alternative treatments for IRHS. The author's research suggests that blocking the **lipoxygenase (LOX) enzyme** may be an effective alternative approach to treating IRHS. Such therapeutic candidates thus include **boswellic acids** which are **pentacyclic triterpenes** shown to **inhibit leukotriene synthesis by blocking the LOX pathway [Figures 2 and 3]**. Boswellic acids are found in high concentrations in the plant ***Boswellia serrata*** which has been used in **Ayurvedic medicine** for thousands of years and is well known for its long term tolerability and safety.

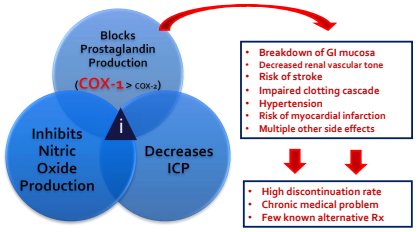

Figure 1: The mechanisms of action and adverse reactions associated with indomethacin

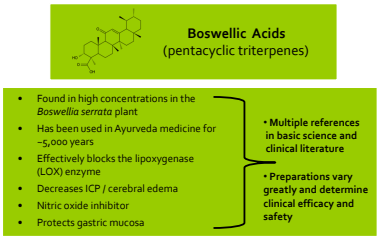

Figure 2: Boswellic acids are pentacyclic triterpenes found in high concentrations in the *Boswellia serrata plant*

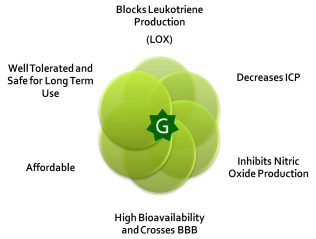

Figure 3: Gliacin, a potential indomethacin substitute, inhibits the LOX pathway and has other key characteristics

METHODS

This study was an **open label, prospective, crossover study comparing the effects of indomethacin and Gliacin in IRHS**. A total of **592 consecutive patients / potential subjects** presenting to a headache subspecialty clinic for initial consultation were evaluated for the possibility of an IRHS. Of these potential subjects, 12% (n=73) were suspected of having an IRHS. All 73 subjects were placed on indomethacin and titrated based on tolerability up to doses as high as 100 mg orally three times per day. Those with **>90% response (n=32, 5.4%) were classified as having an IRHS**. These included subjects with HC (n=16), PH (n=4), PCH (n=4), PEH (n=2), PHASA (n=4), PSH (n=1) and HH (n=1). These 32 subjects were asked to stay on the lowest effective dose of indomethacin for 90 days. They maintained headache diaries and captured information such as headache frequency, headache severity, MIDAS, HIT-6, Headache-Related Quality of Life scores and side effects experienced. After completing their indomethacin trial, subjects went through a **washout period until confirmed they returned to baseline headache status**. Subjects were then given the option to start Gliacin. Twenty-seven of the 32 subjects (84%) elected to proceed with the Gliacin trial. These subjects were started on 250 mg orally three times per day of Gliacin and titrated upwards based on tolerability and effectiveness. As with the previous trial of indomethacin, subjects took Gliacin for 90 days and recorded key outcome measures. **Gliacin responders were defined as those subjects who had >70% improvement in both their headache severity and frequency**. At the end of the Gliacin trial, all 27 subjects completed an exit interview and an analysis comparing the two therapies was conducted.

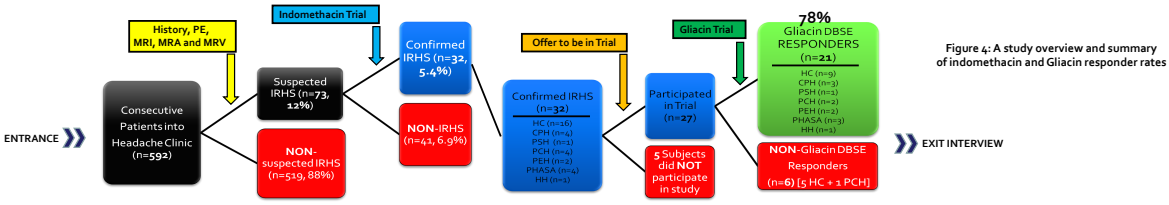

Figure 4: A study overview and summary of indomethacin and Gliacin responder rates

RESULTS

A total of 27 subjects with a confirmed IRHS went on to undergo a trial of Gliacin. The **Gliacin responder rate was 78%** (21 of 27 subjects). These subjects included those with HC (n=9), PH (n=3), PCH (n=2), PEH (n=2), PHASA (n=3), PSH (n=1) and HH (n=1). For these 21 Gliacin responders, a comparison was made between their headaches prior to indomethacin, while on indomethacin and while on Gliacin. **Figure 4 provides a study overview and summary of indomethacin and Gliacin responder rates.** The group's average headache days per month were 28 prior to indomethacin, 2.3 while on indomethacin and 1.8 while on Gliacin **[Figure 5]**. The average pain levels (0-10) were 8.2, 2.0 and 2.3 respectively **[Figure 5]**. The average HIT-6 scores were 67, 46 and 43 respectively. The average Headache Related Quality of Life scores were 56, 25 and 20 respectively. The average MIDAS scores were 80, 9, and 3 respectively. **Figure 6 summarizes the effects of indomethacin and Gliacin on headache related disability.** Sixty-seven percent of subjects rated their overall satisfaction level with Gliacin superior to indomethacin. Likewise, **67% of subjects stated that they experienced significantly fewer side effects with Gliacin as compared to indomethacin**. In fact, only 38% of subjects reported side effects with Gliacin as compared to 81% while on indomethacin. The **only side effect experienced by greater than 10% of subjects taking Gliacin was diarrhea** (n=2). **Figure 7 summarizes the common side effects experienced by subjects while on indomethacin and Gliacin.** Upon completion of the study, **86% of Gliacin responders elected to continue Gliacin instead of indomethacin**. All of the **non-Gliacin responders (n=6) noticed that they required significantly less indomethacin while concurrently taking Gliacin**. This unique combination is currently being formulated in differing doses and is known as **Gliamethacin**.

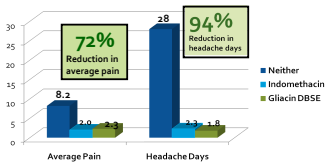

Figure 5: A comparison of average pain and headache days per month while on indomethacin and Gliacin

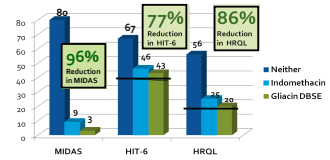

Figure 6: A comparison of the effects of indomethacin and Gliacin on headache impact and disability ratings

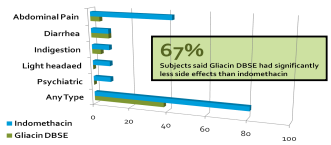

Figure 7: A comparison of the common side effects experienced by subjects while on indomethacin and Gliacin

CONCLUSIONS

The key conclusions from this study include:

- Nearly **8 out of 10** subjects with an IRHS experienced a **significant benefit from Gliacin.**
- At least **one of every type of IRHS** was shown to **respond to Gliacin**.
- **Gliacin** appears to **decrease headache frequency, intensity and related disability** in certain subjects experiencing IRHS.
- **Gliacin** is **well tolerated** with **fewer side effects** than indomethacin.
- Because of the side effects and potential serious adverse reactions associated with indomethacin, **all indomethacin responders should be considered candidates for alternative treatment with Gliacin**.
- Treatment with **Gliacin warrants further investigation** and has serious potential for extended use in various headache populations.
- A **combination of the nutraceutical Gliacin and the pharmaceutical indomethacin** may have **synergistic** and complementary benefits. The combination of these two agents, known as the **"Combiceutical" Gliamethacin**, is currently under clinical investigation and has widespread clinical implications well beyond headache alone.

DISCLOSURE

Eric J. Eross D.O. is currently a scientific and clinical advisor for Glia Sciences (Scottsdale, AZ, USA), the makers of Gliacin. Dr. Eross currently has a modest (< $10k US dollars) financial investment in the company.

CONTACT INFORMATION

Please email any questions, suggestions or comments to: **gliacin@live.com**. Please visit **www.gliacin.com** for additional information regarding Gliacin . For information regarding participating in future clinical research or to schedule a conference , please contact Glia Sciences, USA **1-602-503-9275**.