The reproducibility of glyceryl trinitrate (GTN) at inducing migraine-like attacks in migraine patients

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BACKGROUND

- It has been well-characterized that administration of GTN to migraine patients induces an immediate headache which is of short duration, bilateral and throbbing. This is followed, up to 5 hours later, by a delayed headache that has features of a migraineur's spontaneous attacks.
- Although the immediate headache is generally also reported in non-migraineurs, the delayed headache is rarely observed.
- Despite GTN being used to provoke headache there is little literature available looking at the reproducibility of the delayed GTN-induced headache or whether this headache responds to treatment.
- Induction of GTN delayed headache in migraine patients may provide the basis for a model to test novel anti-migraine drugs for signals of putative efficacy[1,2,3].

OBJECTIVES

Primary Objectives

1. To assess the ability of GTN to induce migraine-like headaches in migraineurs.
2. To evaluate the within-subject reproducibility of migrainous headaches upon repeated exposure to GTN.

Secondary Objectives

1. To determine the effects of GTN on headache latency.
2. To assess the utility of 5-HT agonists to treat GTN delayed headache.

STUDY DESIGN

This was a randomized, 4-period, crossover design. 20 otherwise healthy subjects with a diagnosis of migraine without aura (IHS criteria 1.1) were recruited. In 3 periods, subjects received GTN IV 20 µg/kg for 20 min; in 1 period matched placebo.

Subjects were interviewed by a headache specialist prior to enrollment to ensure appropriate diagnosis and to characterize their usual migraine attacks. Only subjects who were responsive to triptans for the treatment of spontaneous migraine were enrolled.

Any evoked, delayed headaches, of moderate to severe intensity, on study were treated with the subject's standard-of-care triptan for spontaneously occurring migraine.

RESULTS

SUBJECT DISPOSITION

- 20 subjects were recruited, 5 males and 15 females.
- Mean age of subjects was 37.2 years (SD 10.53 years).
- All subjects completed all 4 study periods.

TOLERABILITY OF GTN MODEL

- 1 adverse event (AE) of mild intensity on placebo.
- 11 AEs reported on GTN (10 mild, 1 moderate).

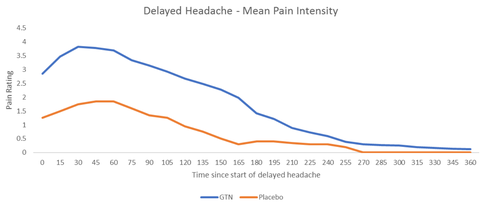
PRESENCE OF IMMEDIATE/DELAYED HEADACHE

Headache Type	GTN (n=60)	Placebo (n=20)
Immediate Headache	88%	35%
Delayed Headache	70%	45%

FREQUENCY OF DELAYED HEADACHE

Treatment	No delayed headache	Delayed headache on 1 occasion	Delayed headache on 2 occasions	Delayed headache on 3 occasions
GTN	1	4	7	8
Placebo	11	9	N/A	N/A

MEAN INTENSITY OF DELAYED HEADACHE



- Headache intensity higher for GTN treatment over placebo ($p<0.05$).
- Headache treated with triptan when reported as moderate severity.

EFFECTIVENESS OF TRIPTAN AGAINST DELAYED HEADACHE

- 46 subjects were administered their standard-of-care triptan in response to the development of a delayed headache.
- On 41 occasions significant relief of symptoms was obtained within 60 minutes of administration of standard-of-care triptan. The additional 5 subjects found relief within 4 hours following repeat administration of triptan and additional time to rest.

SIMILARITY OF DELAYED HEADACHE TO SPONTANEOUS MIGRAINE

	Delayed Headache Comparison	GTN	Placebo	Significance
1	Subject's response to CRF question "is the subject's current headache like their usual migraine"	68.3%	26.5%	p=0.006
2	Migraine specialists comparison of description of delayed headache with subjects headache history elicited at screening	53%	18%	p=0.0274
3	Comparison using ICH migraine criteria	48%	19%	p=0.0599

CONCLUSIONS

- GTN headache induction was well-tolerated, with few AEs and patients willing to return for multiple exposures.
- A delayed headache was induced more frequently following GTN than placebo, with a delayed headache present on 2 or more exposures in 75% of patients.
- The delayed headache was rapidly and effectively treated with standard-of-care 5-HT agonists.
- The delayed headache was morphologically similar to the patients spontaneous migraine attack, as judged by comparison by a migraine expert and the patients' self-reported experience.
- Overall this study has demonstrated that delayed headache following GTN exposure in migraineurs is a reasonable surrogate for spontaneous migraine attacks, in that is it well-tolerated, reproducible, migrainous in character, and treatable. As such, this technique could be used to rapidly assess putative efficacy of novel compounds under development for the treatment of migraine, using relatively modest numbers of patients.

REFERENCES

1. Iversen, HK, Olesen, J, Tfelt-Hansen, P (1989). Intravenous nitroglycerin as an experimental model of vascular headache. Basic characteristics. Pain 38, 17-24.
2. Christiansen, I, Thomsen, LL, Daugaard, D, Ulrich, V, Olesen, J (1999). Glyceryl trinitrate induces attacks of migraine without aura in sufferers of migraine with aura. Cephalalgia 19, 660-667.
3. Wienecke, T, Olesen, J, Oturai, PS, Ashina, M (2008). Prostacyclin (epoprostenol) induces headache in healthy subjects. Pain 139, 106-116.

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