Thiamidol: A Breakthrough Innovation in Treatment of Hyperpigmentation

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Abstract

Skin hyperpigmentation, including melasma, solar lentigines, and post-inflammatory hyperpigmentation, results in a significant impact on patient quality of life. Unfortunately, to date, many over-the-counter (OTC) options have often been limited by efficacy, safety and tolerability concerns. Additionally, limited education on disease manifestation and root causes of hyperpigmentation often leaves patients undiagnosed and untreated. Melanogenesis is driven by a complex pathway resulting in the ultimate production and deposition of melanin in skin. The major rate-limiting step of melanogenesis centers on the conversion of L-Dopa to melanin mediated by a cellular tyrosinase, resulting in overproduction of melanin in cases of hyperpigmentation. Recently, Thiamidol (isobutylamido thiazolyl resorcinol) has been identified as the most effective inhibitor of human tyrosinase out of 50,000 compounds screened *in vitro*, and thus, a novel ingredient for inclusion in OTC hyperpigmentation products. Here, we describe the current pre-clinical and clinical safety and efficacy data on Thiamidol formulations, aimed at educating the dermatology community on a safe and effective OTC option for use as part of the overall management of hyperpigmentation in patients.

Materials and Methods

A comprehensive literature review was conducted to summarize currently available pre-clinical and clinical safety and efficacy data on isobutylamido thiazolyl resorcinol (Thiamidol) for treatment of hyperpigmentation mediated by melasma, solar lentigines, and post-inflammatory hyperpigmentation (acne-, UV-, and laser-induced), with the goal of providing insights for dermatologists on this novel human tyrosinase inhibiting small molecule and its potential use as part of an overall hyperpigmentation treatment regimen.

Results

FIGURE 1. Types of Hyperpigmentation.

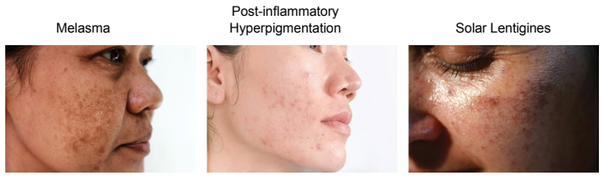


FIGURE 2. Schematic Overview of Role of Tyrosinase in Melanogenesis. A. Melanogenesis pathway. **B.** Pathway converting tyrosine to eumelanin and pheomelanin. The conversion of tyrosine to L-Dopa is a key rate-limiting step in the melanogenesis pathway and a validated target (tyrosinase inhibitor) for treatment of pigmentary disorders.

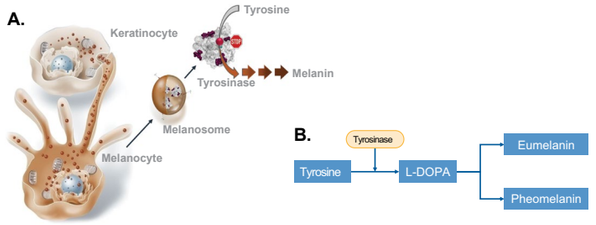
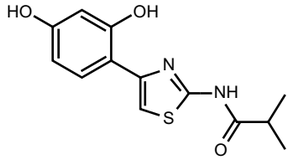


FIGURE 3. Chemical Structure of Thiamidol (isobutylamido thiazolyl resorcinol).



N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)isobutyramide
Isobutyl**amido**-**Thi**azolyl-Resorcin**ol**
THIAMIDOL

FIGURE 4. Inhibition of Melanin Production in MelanoDerm Skin Model System. The melanin content of each MelanoDerm (MatTek Corporation, Ashland, MA) skin model was determined after 13 days of cultivation in the presence of various inhibitors (Thiamidol, 4-Butylresorcinol, Kojic Acid, Rhododendrol, Hydroquinone, and Arbutin) at the concentrations noted. Data represents mean ± standard deviation of five independent experiments. (Mann et al).

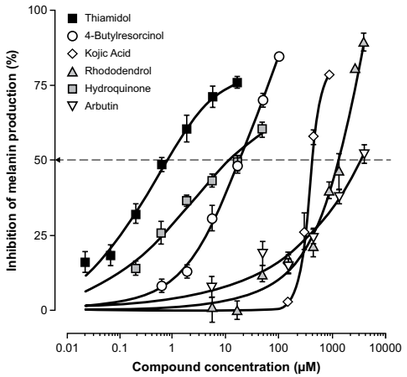


TABLE 1. Kinetic Data for Inhibition of Human and Mushroom Tyrosinase. (Modified from Mann et al).

Compound	IC_{50} (μmol/L)	
	Human Tyrosinase	Mushroom Tyrosinase
Thiamidol	1.1	108
4-Butylresorcinol	21	0.6
4-Hexylresorcinol	94	1.2
4-Phenylethylresorcinol	131	0.3
Kojic Acid	500	6.0
Hydroquinone	>4,000	1.1
Arbutin	>4,000	40

FIGURE 5. Changes in Melasma Area and Severity Index (MASI) Score. A. Modified Hemi-MASI score (mean ± standard error of the mean) pre- and post-treatment in mild-moderate Melasma. (***P ≤ 0.001). **B.** MASI score (mean ± standard error of the mean) versus baseline at every time point measured after treatment with Thiamidol regimen or vehicle in subjects with moderate-severe Melasma. Significant improvement in comparison to baseline for Thiamidol-treated group and vehicle at all points in time. Significant differences between Thiamidol-treated group and vehicle as indicated (*P < 0.05, **P < 0.01, ***P < 0.001). After 13-20 weeks of cessation of all treatment (regression), including sunscreen use, there was a significant difference for both treatments compared to baseline (P < 0.005). (Arrowitz et al; Roggenkamp et al).

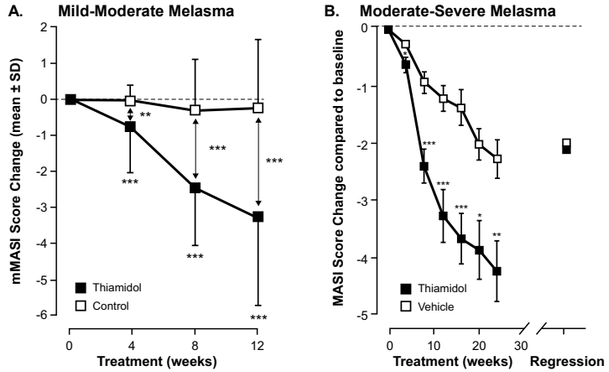


FIGURE 6. Improvement in Hyperpigmentation Following a 12-Week Thiamidol-based Regimen. Selected digital images of two subjects before and after treatment with the combination Thiamidol-based serum and Thiamidol day care SPF 30 applied twice daily (1x in the morning and 1x at night) during a Thiamidol regimen study. (Philipp-Dormston et al).

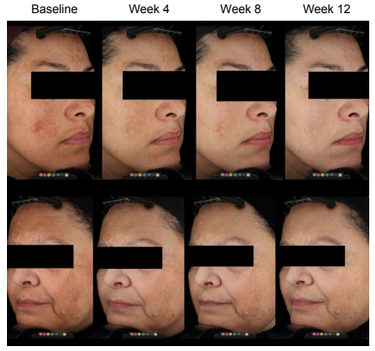


FIGURE 7. Change in Hemi-MASI Score (mean ± SD) from Baseline to Week 12 in a Split-face Thiamidol Regimen Study. Scores were assessed after 4, 8 and 12 weeks of treatment. *Significant improvement (P < 0.001) compared with baseline and with treatment with Thiamidol day care SPF 30 cream only; ⁺Significant improvement compared with baseline (P < 0.001). (Philipp-Dormston et al).

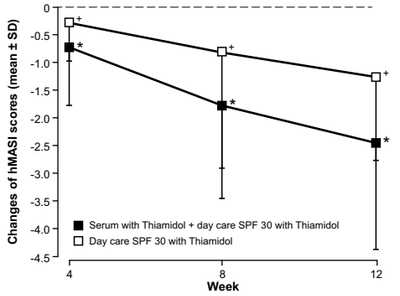
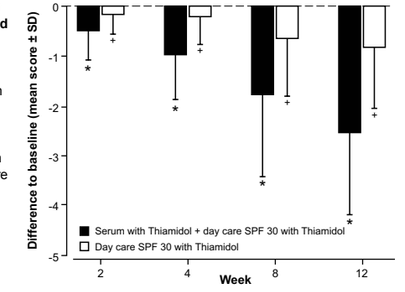


FIGURE 8. Self-assessment of Hyperpigmentation by Modified Griffiths' Score (0-9) in a Split-face Thiamidol Regimen Study. Differences of the mean hyperpigmentation scores (mean ± SD, n = 34) at each time point versus baseline. *Significant improvement (P < 0.001) compared with baseline and with treatment with Thiamidol day care SPF 30 cream only; ⁺Significant improvement compared with baseline (P < 0.001). (Philipp-Dormston et al).



Summary and Conclusions

- Skin hyperpigmentation, including melasma, solar lentigines, and post-inflammatory hyperpigmentation (e.g., UV-, laser-, and acne-induced post-inflammatory hyperpigmentation), results in significant impact on patients' quality of life
- The major rate-limiting step of melanogenesis centers on the conversion of L-Dopa to melanin mediated by a cellular tyrosinase (Figure 2), resulting in overproduction of melanin in cases of hyperpigmentation
- To-date, many over-the-counter (OTC) options are limited by efficacy, safety and tolerability concerns
- Recently, isobutylamido thiazolyl resorcinol (Thiamidol, Figure 3) has been identified as an effective inhibitor of human tyrosinase and melanin production (Figure 4), with an IC_{50} = 1.1 μmol/L as compared to Hydroquinone's IC_{50} > 4000 μmol/L (Table 1)
- In clinical studies, Thiamidol has been shown to reduce hyperpigmentation in mild-to-severe melasma (Figure 5), and acne-, UV-, or laser-induced post-inflammatory hyperpigmentation (data not shown)
- Thiamidol regimens including Thiamidol-based serum and day cream with SPF 30 enhance effects on hyperpigmentation (Figures 6-8)
- These results demonstrate that Thiamidol is a safe and effective ingredient that should be considered when recommending an OTC option as part of the overall treatment regimen for patients with hyperpigmentation

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