

# Taurine bromamine: a new therapeutic option in inflammatory skin diseases

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## KEY WORDS

acne vulgaris, inflammation, myeloperoxidase, *Propionibacterium acnes*, taurine bromamine

## ABSTRACT

Acne vulgaris is a multifactorial inflammatory skin disease. One of the pathogenic factors in acne is *Propionibacterium acnes* (*P. acnes*). Traditional treatment of acne lesions involves topical application of antibiotics with anti-bacterial and anti-inflammatory properties. However, a failure of this therapy is widely associated with emergence of resistant bacteria. Therefore, a search for alternative topical anti-acne drugs is necessary.

Taurine bromamine (TauBr), the physiological product of hypobromous acid reaction with taurine, shows antioxidant, anti-inflammatory, and anti-bacterial properties. Importantly, *P. acnes*, a potential pathogenic agent for acne vulgaris, is extremely sensitive to TauBr. In addition, TauBr inhibits the generation of  $H_2O_2$  by activated neutrophils, which seems to be crucial for reducing the number and severity of inflammatory acne lesions. All these data strongly support the concept of using TauBr for topical anti-acne therapy. In our pilot clinical study, we have compared the efficacy of TauBr cream with clindamycin gel, one of the most common topical agents used in the treatment of acne. After 6 weeks, both treatments produced comparable, beneficial results. More than 90% of patients improved clinically with similar reductions in a number of acne lesions (~65%). Therefore, the results from clinical studies are consistent with previous in vitro data and strongly suggest that TauBr could be considered a new therapeutic option in inflammatory acne.

## Taurine haloamines (taurine chloramine, taurine bromamine) – properties and biological functions

Activated neutrophils and eosinophils generate a variety of reactive oxygen species (ROS) at the site of infection and inflammation. Most importantly, they generate hypohalous acids (HOCl, HOBr) from the oxidation of halide ions (Cl<sup>-</sup>, Br<sup>-</sup>) by myeloperoxidase (MPO) and eosinophil peroxidase in the presence of  $H_2O_2$ .<sup>1,2</sup> These oxidants are potent antimicrobial agents, but excessive production can result in a host tissue damage.<sup>3-5</sup> In physiological conditions, this effect is controlled by antioxidants, primarily by taurine. Taurine (2-aminoethane sulphonate), the most abundant free amino acid in leukocyte cytosol, is the major scavenger of hypohalous acids.<sup>6</sup> Physiological products of reaction between taurine and HOBr or HOCl are taurine bromamine (TauBr) and taurine chloramine (TauCl), respectively.<sup>1,6,7</sup> TauCl and TauBr, the major haloamines generated at the site of inflammation,

have anti-inflammatory and microbicidal properties.<sup>3,8,9</sup> TauBr, similarly to TauCl, decreases the production of inflammatory mediators such as nitric oxide, prostaglandin  $E_2$ , tumor necrosis factor- $\alpha$ , interleukin (IL)-6, IL-12, and chemokines in both rodent and human leukocytes.<sup>10,11</sup> Anti-inflammatory activity of taurine haloamines is also associated with their antioxidant properties. TauCl and TauBr reduce generation of ROS. However, only TauBr neutralizes  $H_2O_2$ , the major oxygen species generated at the site of inflammation.<sup>12</sup> Both TauBr and TauCl can induce generation of heme oxygenase-1 (HO-1), a stress-inducible enzyme, which also has an antioxidant and anti-inflammatory capacity.<sup>13</sup> Therefore, it may be suggested that taurine haloamines and HO-1 cooperate in the regulation of inflammatory response and attenuation of oxidative stress. However, it is not clear whether endogenous TauCl and TauBr support HOCl and HOBr in microbial killing. On the other hand, it has been demonstrated

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Conflict of interest: Prof. Janusz Marcinkiewicz is the owner of European patent during validation No. EP 1 663 195:

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that exogenous TauCl exerts microbicidal activity at concentrations well tolerated by human tissue but higher than that achieved by endogenous TauCl.<sup>3</sup> Importantly, a number of clinical studies have confirmed that TauCl might be useful in treating various topical infections due to its combined microbicidal and anti-inflammatory properties.<sup>3,14</sup> Much less is known on potential therapeutic application of TauBr. Recently, we have reported that TauBr shows strong anti-bacterial activity at physiological non-cytotoxic concentrations.<sup>15</sup> Interestingly, in vitro, at the same concentrations TauBr killed tested bacteria (*Escherichia coli*, *Propionibacterium acnes* [*P. acnes*], *Staphylococcus epidermidis*) and reduced ROS generation by neutrophils.<sup>5,12,16</sup> Because bacterial infections and ROS generation are closely associated with the pathogenesis of many inflammatory skin diseases<sup>17,18</sup>, these data suggest that TauBr may be a good candidate for topical therapy in dermatology.

### Perspectives for TauBr application in dermatology

Is TauBr a good candidate in acne topical therapy? In dermatology, medications containing a mixture of anti-inflammatory agents (steroids) and antibiotics are widely used. Therapies which allow to achieve the same result without side effect of steroids seem to be the future in the treatment of various inflammatory skin diseases, including acne vulgaris. Acne is a multifactorial inflammatory skin disease affecting pilosebaceous follicles. Acne is not an infectious disease, although the role of *P. acnes* is outlined in many studies.<sup>19,20</sup> *P. acnes* and *S. epidermidis* belong to bacterial flora of the skin, but only *P. acnes* is considered to be involved in the pathogenesis of chronic skin inflammation in acne. During proliferation *P. acnes* secretes various inflammatory mediators that initiate and perpetuate the local inflammatory response.<sup>21,22</sup>

A variety of agents for the treatment of acne vulgaris are available today. Current clinical strategy in the case of mild to moderate inflammatory acne involves combination with typical topical antibiotics, retinoid, and benzoyl peroxide to achieve a simultaneous anti-bacterial, anti-oxidant, and anti-inflammatory therapeutic effect.<sup>23,24</sup> During the last few years, clindamycin and benzoyl peroxide have become the most widely prescribed topical drugs for acne.<sup>24,25</sup> However, resistance of *P. acnes* to anti-acne antibiotics is considered a therapeutic failure of topical treatment.<sup>26-28</sup> These findings indicate the need to develop strategies to minimize the use of antibiotics in acne therapy.

Based on our knowledge on the biological properties and functions of taurine haloamines, we have decided to examine clinical efficacy of TauBr in the treatment of acne. We suggest that TauBr may be a good candidate for topical therapy, without the risk of inducing bacterial resistance, the major problem of topical antibiotic therapy in acne.<sup>29</sup> From a clinical point of view,

it is interesting that susceptibility of *P. acnes* to TauBr appeared to be significantly higher than that of *S. epidermidis*, as we have shown recently.<sup>15</sup> Therefore, due to its ability to selectively kill *P. acnes*, TauBr seems to be a promising candidate as a topical agent in acne therapy.

In our double blind study, the efficacy and safety of 0.5% TauBr in a cream formulation was compared with 1% clindamycin gel, one of the most common topical agents in the treatment of acne vulgaris. Forty patients with mild to moderate inflammatory facial acne vulgaris were randomly treated with either TauBr or clindamycin for 6 weeks, twice a day. More than 90% of patients improved after both treatments. No adverse effects were observed. Both TauBr and clindamycin produced significant reduction of inflammatory skin lesion counts (papules/pustules). After 6 weeks, comparable reduction in acne lesions have been observed in the TauBr and clindamycin groups – 65% and 68%, respectively.<sup>30</sup>

**Conclusions** Our in vitro studies and a pilot clinical investigation suggest that TauBr can be used in monotherapy or in a combination with other drugs as a topical agent in the treatment of acne vulgaris. TauBr at non-cytotoxic concentrations demonstrates bactericidal activity in vitro, being significantly stronger than that of TauCl. *P. acnes*, a potential pathogenic agent in acne, is more susceptible to TauBr than *S. epidermidis*, which supports the concept of using TauBr as a selective topical disinfectant in the treatment of acne vulgaris. Moreover, TauBr showed the capacity to reduce generation of ROS by neutrophils, which seems to be crucial for reduction of the number and severity of inflammatory acne lesions. Finally, TauBr may be a desirable alternative treatment for acne vulgaris, especially in patients who have already developed antibiotic resistance (Patent No. EP 1 663 195). We also suggest that TauBr and TauCl, because of their ability to stimulate heme oxygenase-1 expression<sup>13</sup>, may be used as novel players in cutaneous wound repair and psoriasis<sup>31</sup>.

### REFERENCES

- 1 Thomas EL, Bozeman PM, Jefferson MM, et al. Oxidation of bromide by the human leukocyte enzymes myeloperoxidase and eosinophil peroxidase. *J Biol Chem.* 1995; 270: 2906-2913.
- 2 Henderson JP, Byun J, Williams MV, et al. Production of brominating intermediates by myeloperoxidase. *J Biol Chem.* 2001; 11: 7867-7875.
- 3 Nagl M, Hess MW, Pfaller K, et al. Bactericidal activity of micromolar N-chlorotaurine: evidence for its antimicrobial function in the human defense system. *Antimicrob. Agents Chemother.* 2000; 44: 2507-2513.
- 4 Yazdanbakhsh M, Eckmann CM, Roos D. Killing of schistosomula by taurine chloramine and taurine bromamine. *Am J Trop Med Hyg.* 1987; 37: 106-110.
- 5 Klebanoff SJ. Myeloperoxidase: friend and foe. *J Leukoc Biol.* 2005; 77: 598-625.
- 6 Learn DB, Fried VA, Thomas EL. Taurine and hypotaurine content of human leukocytes. *J Leukoc Biol.* 1990; 48: 174-182.
- 7 Weiss SJ, Klein R, Slivka A, et al. Chlorination of taurine by human neutrophils: evidence for hypochlorous acid generation. *J Clin Invest.* 1982; 70: 598-603.
- 8 Marcinkiewicz J. Neutrophil chloramines – missing link between innate and acquired immunity. *Immunol Today.* 1997; 18: 677-680.

- 9 Marcinkiewicz J, Chain B, Nowak B, et al. Antimicrobial and cytotoxic activity of hypochlorous acid: interactions with taurine and nitrite. *Inflamm Res.* 2000; 49: 280-289.
- 10 Park E, Schuller-Levis G, Jia JH, et al. Preactivation exposure of RAW 264.7 cells to taurine chloramines attenuates subsequent production of nitric oxide and expression of iNOS mRNA. *J Leukoc Biol.* 1997; 61: 161-166.
- 11 Marcinkiewicz J, Grabowska A, Bereta J, et al. Taurine chloramine down-regulates the generation of murine neutrophil inflammatory mediators. *Immunopharmacology.* 1998; 40: 27-38.
- 12 Marcinkiewicz J, Mak M, Bobek M, et al. Is there a role of taurine bromamine in inflammation? Interactive effects with nitrate and hydrogen peroxide. *Inflamm Res.* 2005; 54: 42-49.
- 13 Olszanecki R, Marcinkiewicz J. Taurine chloramines and taurine bromamine induce heme-oxygenase-1 in resting and LPS-stimulated J774.2 macrophages. *Amino Acids.* 2004; 27: 29-35.
- 14 Nagl M, Nguyen VA, Gottardi W, et al. Tolerability and efficacy of N-chlorotaurine in comparison with chloramine T for treatment of chronic leg ulcers with a purulent coating: a randomized phase II study. *Br J Dermatol.* 2003; 149: 590-597.
- 15 Marcinkiewicz J, Biedroń R, Bialecka A, et al. Susceptibility of *Propionibacterium acnes* and *Staphylococcus epidermidis* to killing by MPO-halide system products. Implication for taurine bromamine as a new candidate for topical therapy in treating acne vulgaris. *Arch Immunol Ther Exp.* 2006; 54: 61-8.
- 16 Tokunaga S, Kanayama A, Miyamoto Y. Modification of IκBα by taurine bromamine inhibits tumor necrosis factor α-induced NF-κB activation. *Inflamm Res.* 2007; 56: 479-486.
- 17 Akamatsu H, Horio T. The possible role of reactive oxygen species generated by neutrophils in mediating acne inflammation. *Dermatology.* 1998; 196: 82-85.
- 18 Akamatsu H, Horio T, Hattori K. Increased hydrogen peroxide generation by neutrophils from patients with acne inflammation. *Int J Dermatol.* 2003; 42: 366-369.
- 19 Burkhart CG, Burkhart CN, Lehmann PF. Acne: a review of immunologic and microbiologic factors. *Postgrad Med J.* 1999; 75: 328-331.
- 20 Jeremy AH, Holland DB, Roberts SG, et al. Inflammatory events are involved in acne lesion initiation. *J Invest Dermatol.* 2003; 121: 20-27.
- 21 Bialecka A, Mak M, Biedroń R, et al. Different pro-inflammatory and immunogenic potentials of *Propionibacterium acnes* and *Staphylococcus epidermidis*: implication for chronic inflammatory acne. *Arch Immunol Ther Exp.* 2005; 53: 79-85.
- 22 Jappe U, Ingham E, Henwood J, et al. *Propionibacterium acnes* and inflammation in acne; *P. acnes* has T-cell mitogenic activity. *Br J Dermatol.* 2002; 146: 202-209.
- 23 Gans EH, Kligman AM. Comparative efficacy of clindamycin and benzoyl peroxide for *in vivo* suppression of *P. acnes*. *J Dermatolog Treat.* 2002; 13: 107-110.
- 24 Leyden J, Kaidbey K, Levy SF. The combination formulation of clindamycin 1% plus benzoyl peroxide 5% versus 3 different formulations of topical clindamycin alone in the reduction of *Propionibacterium acnes*. An *in vivo* comparative study. *Am J Clin Dermatol.* 2001; 2: 263-266.
- 25 Guay DR. Topical clindamycin in the management of acne vulgaris. *Expert Opin Pharmacother.* 2007; 8: 2625-2664.
- 26 Eady EA, Cove JH, Holland KT, et al. Erythromycin resistant propionibacteria in antibiotic treated acne patients: association with therapeutic failure. *Br J Dermatol.* 1989; 121: 51-57.
- 27 Leyden JJ. Antibiotic resistance in the topical treatment of acne vulgaris. *Cutis.* 2004; 73: 6-10.
- 28 Dreno B. Topical antibacterial therapy for acne vulgaris. *Drugs.* 2004; 64: 2389-2397.
- 29 Tan HH. Topical antibacterial treatments for acne vulgaris: comparative review and guide to selection. *Am J Clin Dermatol.* 2004; 5: 79-84.
- 30 Marcinkiewicz J, Wojas-Pelc A, Walczewska M, et al. Topical taurine bromamine, a new candidate in the treatment of moderate inflammatory acne vulgaris: a pilot study. *Eur J Dermatol.* 2008; 18: 433-439.
- 31 Hanselmann C, Mauch C, Werner S. Haem oxygenase-1: a novel player in cutaneous wound repair and psoriasis? *Biochem J.* 2001; 353: 459-466.

# Bromamina tauryny – nowa strategia w leczeniu chorób skóry o podłożu zapalnym

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### SŁOWA KLUCZOWE

bromamina tauryny,  
mieloperoksydaza,  
*Propionibacterium  
acnes*, trądzik  
pospolity, zapalenie

### STRESZCZENIE

Trądzik pospolity (*Acne vulgaris*) jest chorobą zapalną skóry, powodowaną przez wiele czynników. Jednym z nich jest *Propionibacterium acnes* (*P. acnes*). Klasyczne leczenie polega na miejscowym podawaniu antybiotyków wykazujących właściwości bakteriobójcze i przeciwzapalne. Jednakże częste niepowodzenia takiej terapii są związane z narastającą antybiotykoopornością bakterii skórnych. Istnieje zatem konieczność poszukiwania alternatywnych leków.

Bromamina tauryny (TauBr), fizjologiczny produkt reakcji HOBr z tauryną, wykazuje właściwości przeciwbakteryjne, przeciwzapalne i antyoksydacyjne. Co ważne, *P. acnes*, potencjalny czynnik patogenny trądziku pospolitego jest wysoce wrażliwy na TauBr. Wykazano ponadto, że TauBr hamuje produkcję H<sub>2</sub>O<sub>2</sub> przez zaaktywowane neutrofile, co wydaje się być kluczowe dla redukcji ilości i natężenia zapalnych zmian trądzikowych. Powyższe dane potwierdzają, że TauBr jest dobrym kandydatem do miejscowego leczenia trądziku pospolitego. W naszych pilotowych badaniach klinicznych porównaliśmy efektywność kremu z TauBr z żelem z klindamycyną, jednym z najpowszechniejszych leków w leczeniu zmian trądzikowych. 6-tygodniowe obserwacje wykazały podobny efekt terapeutyczny w obu badanych grupach. Poprawę zaobserwowano u >90% pacjentów, z podobną redukcją ilości zmian skórnych wynoszącą ~65%. Badania kliniczne potwierdziły zatem wyniki poprzednich badań *in vitro* nad właściwościami TauBr i sugerują wyraźnie, że TauBr powinna być rozpatrywana jako nowa opcja terapeutyczna w leczeniu zapalnego trądziku.

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