

COSMECEUTICAL CRITIQUE

Boldine

Boldo (*Peumus boldus* Mol.) is a slow-growing, shrubby evergreen tree native to the Chilean and Peruvian Andes. It is also found in Morocco and other parts of North Africa, and is cultivated in Europe. The plant has traditionally been used in South American folk medicine, particularly in Chile, Peru, and Brazil, to treat a wide range of conditions of the liver, bowel, and gallbladder (Pharmacol. Res. 1994;29:1-12).

The primary active constituent identified in the tree is boldine, a simple aporphine alkaloid. Several aporphine alkaloids, which are secondary metabolites, are found in boldo leaves, with boldine being the most abundant (Curr. Med. Chem. Anticancer Agents 2005;5:173-82). Boldine is extracted from the leaves and bark of the tree (Phytother. Res. 2000;14:339-43; Pharmazie 2001;56:242-3).

In Germany and other European countries, the boldo plant is used as a medi-

nal. It is the subject of a German Commission E monograph that details the acceptable uses of the plant as an herbal drug for liver, gallbladder, and gastric conditions (Blumenthal M., et al. [eds.] The Complete German Commission E Monographs: Therapeutic Guide to Herbal Medicines. Austin, Tex.: American Botanical Council and Boston: Integrative Medicine Communications, 1998, pp. 93-4).

Boldine is used worldwide in homeopathic and herbal medicine, and boldine extract is widely acknowledged as a viable herbal remedy in several pharmacopoeias (Chem. Biol. Interact. 2006;159:1-17; Pharmacol. Res. 1994;29:1-12). Indeed, boldine has been demonstrated to possess antioxidant activity in biologic as well as nonbiologic systems, and it has emerged as an ingredient of great interest for its potential in the treatment of free radical-mediated damage or conditions (Pharmacol. Res. 1994;29:1-12).



BY LESLIE S. BAUMANN, M.D.

BRIEF SUMMARY

(see package insert for full prescribing information)

Atralin™

(tretinoin) gel 0.05%

For topical use only

INDICATIONS AND USAGE

Atralin Gel is a retinoid indicated for topical treatment of acne vulgaris.

Important Limitations of Use

The safety and efficacy of the use of this product in the treatment of any other disorders have not been evaluated.

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Skin Irritation

The skin of certain individuals may become dry, red, or exfoliated while using Atralin Gel. If the degree of irritation warrants, patients should be directed to temporarily reduce the amount or frequency of application of the medication, discontinue use temporarily, or discontinue use altogether. Efficacy at reduced frequencies of application has not been established. If a reaction suggesting sensitivity occurs, use of the medication should be discontinued. Mild to moderate skin dryness may also be experienced; if so, use of an appropriate moisturizer during the day may be helpful.

Tretinoin has been reported to cause severe irritation on eczematous or sunburned skin and should be used with caution in patients with these conditions.

Topical over-the-counter acne preparations, concomitant topical medication, medicated cleansers, topical products with alcohol or astringents, when used with Atralin Gel, should be used with caution. [See Drug Interactions (7)]

Ultraviolet Light and Environmental Exposure

Unprotected exposure to sunlight, including sunlamps, should be minimized during the use of Atralin Gel. Patients who normally experience high levels of sun exposure, and those with inherent sensitivity to sun, should be warned to exercise caution. Use of sunscreen products of at least SPF 15 and protective clothing over treated areas is recommended when exposure cannot be avoided.

Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.

Fish Allergies

Atralin Gel contains soluble fish proteins and should be used with caution in patients with known sensitivity or allergy to fish. Patients who develop pruritus or urticaria should contact their health care provider.

ADVERSE REACTIONS

Clinical Studies Experience

Because clinical trials are conducted under prescribed conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two randomized, controlled trials, 674 subjects received treatment for up to 12 weeks with Atralin Gel [see Clinical Studies (14)]. In these studies, 50% of the subjects who were treated with Atralin Gel reported one or more adverse reactions; 30% of the subjects reported treatment-related adverse reactions. In the vehicle group, 29% of the 487 randomized subjects reported at least one adverse reaction; 5% of the subjects reported events that were treatment-related.

There were no serious, treatment-related adverse reactions reported by subjects in any of the treatment groups.

Selected adverse reactions that occurred in at least 1% of subjects in the two studies combined, are shown in Table 1 (below). Most skin-related adverse reactions first appear during the first two weeks of treatment with Atralin Gel, and the incidence rate for skin-related reactions peaks around the second and third week of treatment. In some subjects the skin-related adverse reactions persist throughout the treatment period.

Table 1. Number of Subjects with Selected Adverse Reactions (Occurring in At Least 1% of Subjects)

Event	Atralin Gel (n = 674)	Vehicle Gel (n = 487)
Dry Skin	109 (16%)	8 (2%)
Peeling/Scaling/Flaking Skin	78 (12%)	7 (1%)
Skin Burning Sensation	53 (8%)	8 (2%)
Erythema	47 (7%)	1 (<1%)
Pruritus	11 (2%)	3 (1%)
Pain of Skin	7 (1%)	0 (0%)
Sunburn	7 (1%)	3 (1%)

DRUG INTERACTIONS

When treating with Atralin Gel, caution should be exercised with the use of concomitant topical medication, medicated or abrasive soaps and cleansers, products that have a strong drying effect, and products with high concentrations of alcohol, astringents, spices, or lime. Particular caution should be exercised with the concomitant use of topical over-the-counter acne preparations containing benzoyl peroxide, sulfur, resorcinol, or salicylic acid. Allow the effects of such preparations to subside before use of Atralin Gel is begun.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C. There are no well-controlled trials in pregnant women treated with Atralin Gel. Atralin Gel should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Atralin Gel at doses of 0.1, 0.3 and 1 g/kg/day was tested for maternal and developmental toxicity in pregnant Sprague-Dawley rats by dermal application. The dose of 1 g/kg/day was approximately 4 times the clinical dose assuming 100% absorption and based on body surface area comparison. Possible tretinoin-associated teratogenic effects (craniofacial abnormalities (hydrocephaly), asymmetrical thyroids, variations in ossification, and increased supernumerary ribs) were noted in the fetuses of Atralin Gel treated animals. These findings were not observed in control animals. Other maternal and reproductive parameters in the Atralin Gel treated animals were not different from control. For purposes of comparison of the animal exposure to human exposure, the clinical dose is defined as 2 g of Atralin Gel applied daily to a 50-kg person.

Oral tretinoin has been shown to be teratogenic in rats, mice, rabbits, hamsters and nonhuman primates. Tretinoin was teratogenic in Wistar rats when given orally in doses greater than 1 mg/kg/day (approximately 8 times the clinical dose based on body surface area comparison). In the cynomolgus monkey, fetal malformations were reported for doses of 10 mg/kg/day, but none were observed at 5 mg/kg/day (approximately 80 times the clinical dose based on body surface area comparison), although increased

skeletal variations were observed at all doses. Dose-related increases in embryolethality and abortion also were reported. Similar results have also been reported in pigtail macaques.

Topical tretinoin in a different formulation has generated equivocal results in animal teratogenicity tests. There is evidence for teratogenicity (shortened or kinked tail) of topical tretinoin in Wistar rats at doses greater than 1 mg/kg/day (approximately 8 times the clinical dose assuming 100% absorption and based on body surface area comparison). Anomalies (humerus: short 13%, bent 6%, os parietal incompletely ossified 14%) have also been reported when 10 mg/kg/day (approximately 160 times the clinical dose assuming 100% absorption and based on body surface area comparison) was topically applied. Supernumerary ribs have been a consistent finding in rats when dams were treated topically or orally with retinoids.

With widespread use of any drug, a small number of birth defect reports associated temporarily with the administration of the drug would be expected by chance alone. Cases of temporally associated congenital malformations have been reported with use of other topical tretinoin products. The significance of these spontaneous reports in terms of risk to the fetus is not known.

Nonteratogenic effects on fetuses: Oral tretinoin has been shown to be fetotoxic in rats when administered in doses 20 times the clinical dose based on a body surface area comparison. Topical tretinoin has been shown to be fetotoxic in rabbits when administered in doses 8 times the clinical dose based on a body surface area comparison.

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Atralin Gel is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in children below the age of 10 have not been established.

A total of 381 pediatric subjects (aged 10 to 16 years), treated with Atralin Gel were enrolled into the two clinical studies. Across these two studies, comparable safety and efficacy were observed between pediatric and adult subjects.

Geriatric Use

Safety and effectiveness in a geriatric population have not been established. Clinical studies of Atralin Gel did not include any subjects over age 65 to determine whether they respond differently than younger subjects.

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Antioxidant Actions

Boldine is now considered one of the strongest natural antioxidants (Chem. Biol. Interact. 2006;159:1-17).

In the early 1990s, the traditional use of *Peumus boldus* extract prompted a team of researchers to validate some of its therapeutic properties. They found that boldine imparted significant protection in vitro against tert-butyl hydroperoxide-induced toxicity in isolated rat hepatocytes, and in vivo against carbon tetrachloride-induced hepatotoxicity in mice. A test in rats with carrageenan-induced edema also revealed significant and dose-dependent anti-inflammatory effects (Planta Med. 1991;57:110-5). The free radical-scavenging and hepatoprotective properties of this natural compound are now considered well established (Phytother. Res. 2000;14:254-60).

A 2001 study demonstrated that boldine imparts chemoprotective activity in murine liver, reducing the metabolic activation of drug-metabolizing enzymes as well as chemical mutagens (Pharmazie 2001;56:242-3).

Alkaloids semisynthesized from boldine have also been shown to inhibit activity against reactive oxygen species and are believed to represent a potential therapy for inflammatory disorders involving production of reactive oxygen species (Chem. Pharm. Bull. [Tokyo] 2004;52:696-9).

In a study in mice, boldine showed significant antioxidant activity, decreasing the oxidation of low-density lipoprotein. It also lessened atherosclerotic lesion formation in LDL receptor-deficient mice that were fed an atherogenic diet. The authors believe that antioxidant capacity, coupled with the traditional tolerance to boldine in humans, renders it a suitable alternative to vitamin E (Atherosclerosis 2004;173:203-10).

More evidence of boldine's antioxidant effects emerged from a study in which it protected intact red blood cells against hemolytic damage caused by the free radical initiator 2,2'-azobis-(2-amidinopropane) (AAPH). The effect was concentration dependent and occurred whether the herb was added simultaneously with, or 1 hour before, AAPH. Erythrocytes previously incubated with AAPH for 2 hours were largely unaffected by the addition of boldine. The investigators concluded that boldine had significant time-dependent cytoprotective as well as antioxidant activity (Phytother. Res. 2000;14:339-43).

It is noteworthy that boldine is found in plants other than the Chilean boldo. In a study of boldine and other aporphine alkaloids isolated from *Lindera angustifolia* Chen, a Chinese medicinal plant used for edema and rheumatic pain, the extract exhibited significant free radical-scavenging activity against 2,2-diphenyl-1-picrylhydrazyl. It also showed antinociceptive properties, which are thought to be associated with the capacity to scavenge free radicals (J. Ethnopharmacol. 2006;106:408-13).

Other Therapeutic Actions

Boldine has been shown to exert cytoprotective, anti-tumor promoting, anti-in-

flammatory, antidiabetic, and antiatherogenic activities, all of which may arise from its free radical-scavenging properties. This potent alkaloid also has been shown to confer significant pharmacologic benefit not related to oxidative stress, such as antitypanocidal, vasorelaxing, immun- and neuromodulatory, and choleretic and/or choleric activity (Chem. Biol. Interact. 2006;159:1-17).

In a study of carrageenan-induced edema in guinea pigs, boldine exhibited dose-dependent anti-inflammatory activity. It also acted against bacterial pyrogen-induced hyperthermia in rabbits. In addition, an in vitro arm of the same study revealed that boldine inhibited prostaglandin biosynthesis, to which investigators attributed the in vivo anti-inflammatory and antipyretic activities of boldine (Agents Actions 1994;42:114-7).

Boldine is contraindicated in people who have kidney disease, women who are pregnant or breast-feeding, and patients with liver bile duct obstruction or severe liver disease (Brinker F. Herb Contraindications and Drug Interactions. Sandy, Ore.: Eclectic Medical Publications, 1997, p. 26).

Photoprotective Action

In a recent study with the most direct dermatologic implications, boldine was shown to be photostable, with its antioxidative capacity remaining intact, thereby allowing the compound to confer photoprotection (J. Photochem. Photobiol. B 2005;80:65-9). Furthermore, in vitro tests of compounds extracted from lichens and the boldo tree revealed that their ultraviolet filtering power was similar to, or better than, that of octylmethoxycinnamate, suggesting their potential usefulness in sunscreen formulations (J. Photochem. Photobiol. B 2002;68:133-9).

Conclusions

Natural antioxidants are too plentiful, and the number under active investigation for medical and cosmetic uses too copious, to suggest that any one compound is the antioxidant du jour. That said, boldine has been studied with increasing frequency over the past 15 years, after a long history of use in folk medicine, and the evidence is ample enough to suggest that clinical trials are the next important step to determine the medical role of this natural botanical.

Direct applications in dermatology have not yet been seen, but given the antioxidant and anti-inflammatory activities exhibited by this aporphine alkaloid, there is cause to promote its use in research. Boldine is already being incorporated into several cosmeceutical moisturizers, anti-aging sera, eye and lip balms, and antioxidant masks available online.

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