Improving Bioavailability with a Novel Isotretinoin Formulation (Isotretinoin-Lidose)

Jerry Tan, MD, FRCPC[1,2] and Sanja Knezevic, BSc[1]

[1]Department of Medicine, University of Western Ontario, London, ON, Canada
[2]Windsor Clinical Research Inc., Windsor, ON, Canada

ABSTRACT

Current practice guidelines recommend administration of oral isotretinoin with high-fat meals, which may pose issues with patient compliance. Isotretinoin-Lidose (Epuris™), approved by Health Canada in November 2012 and scheduled for commercial release June 2013, is based on novel lipid encapsulation technology (Lidose®) to enclose isotretinoin, thereby increasing drug absorption during fasted states. An open label, single dose randomized crossover study demonstrated pharmacokinetic bioequivalence of isotretinoin-Lidose to standard isotretinoin formulations during fed states, with significantly greater absorption during fasting. Isotretinoin-Lidose, may lead to more consistent plasma levels of isotretinoin during variable dietary conditions, providing the potential for enhanced patient outcomes.

Key words: acne vulgaris, bioavailability, drug delivery, isotretinoin

Introduction

Since US FDA approval of the oral isotretinoin agent Accutane™ in 1982, and its subsequent approval by Health Canada in 1983, it has been and continues to be the standard of treatment for severe nodular acne in the US and Canada. As this agent is a synthetic derivative of vitamin A, it is similar to the parent compound in being fat-soluble. As a result, ingestion of oral isotretinoin with food increases bioavailability.[1] In the fasted state, ingestion of standard oral isotretinoin formulations leads to plasma levels that are approximately 60% lower compared to the fed state.[1] Accordingly, standard practice recommendations promote ingestion with food, particularly a high-fat meal, to enhance absorption.

However, patient adherence and reliability in taking isotretinoin with high-fat meals may be problematic.[2-4] Inconsistent eating habits during drug administration may result in irregular dosing and considerable variation in plasma levels of isotretinoin, within and between patients. Thus, a previous unmet need with oral isotretinoin has been a formulation less dependent on the fed state to reduce this potential for suboptimal absorption and subtherapeutic plasma levels. Hoffman-La Roche Pharmaceuticals Inc., the manufacturer of Accutane™ the incumbent branded oral isotretinoin formulation, addressed this issue through the development of Accutane-NF (new formulation). This microionized version of Accutane™ was developed to reduce particle size, thereby increasing bioavailability.[5] Accutane-NF was projected to result in therapeutic levels of isotretinoin with once-daily dosing and without the need for administration with food.[5] A randomized, double-blind clinical trial comparing these two formulations in 600 patients with severe recalcitrant nodular acne showed that the overall efficacy of Accutane-NF was statistically similar to standard Accutane™. However, the new formulation trended towards lower efficacy as demonstrated in the proportion of subjects achieving >90% reduction in nodule counts, including percentage changes with respect to nodule counts, papules/pustules, and total inflammatory lesion counts, as well as global evaluations of excellent response/clearance. At the dosages tested, a lower risk of mucocutaneous adverse event and hypertriglyceridemia were noted.[5] However, in the absence of clear advantages of the new formulation compared to standard Accutane™, when considering the balance of efficacy to adverse events (benefit:risk), there was no apparent public health benefit to marketing both formulations.[5]

Recently, this ongoing inadequacy was addressed with an innovative technology that encapsulates lipophilic drugs, such as isotretinoin, with lipid agents - thereby providing a more optimal environment for absorption within the formulation. Originally developed by SMB Laboratories, the Lidose® drug delivery system consists of a hard gelatin capsule containing liquid or semi-liquid contents composed of an active drug melted together with lipid excipients, then cooled under specific conditions.[6] This technology has already been successfully combined with a fenofibrate formulation (Lipofen™, Cipher Pharmaceuticals Inc.) to create a novel capsule used for treatment of hyperlipidemia.

Potential advantages of Lidose® over conventional capsule technology include greater tolerability with less gastric irritation, rapid absorption, and protection of drug against oxidation.[6] An application of this delivery platform encompassing oral isotretinoin-Lidose was approved by the US FDA in May 2012 (Absorica™, Cipher Pharmaceuticals Inc.) with indications for treatment of severe nodular and or inflammatory acne, acne conglobate, and recalcitrant acne. Health Canada approved isotretinoin-Lidose for the same indication in November 2012 (Epuris™, Cipher Pharmaceuticals Inc.).

Pharmacokinetic Studies

In an open label, single dose, randomized, crossover study involving 60 healthy subjects comparing isotretinoin-Lidose against standard oral isotretinoin, these preparations were shown to be pharmacokinetically bioequivalent under fed conditions (modified high-fat, high-calorie breakfast with reduced vitamin A content). However, administration of isotretinoin-Lidose resulted in significantly better absorption of isotretinoin and its metabolites under fasted conditions than did the standard isotretinoin formulation (Accutane™). Plasma levels of isotretinoin using the Lidose® formulation attained 67% of that achieved with a fatty meal compared to 40% using standard Accutane™.[7] Furthermore, while more than 75% of subjects absorbed less than 50% isotretinoin with Accutane™ during the fasting state compared to fed state, 75% of patients prescribed isotretinoin-Lidose formulation absorbed at least 60%.[7] A total of 55 adverse effects were reported, with the most common being headache. No significant difference in adverse event frequency between treatments was observed and no serious adverse events were reported.[7]

Clinical Trials

In a double-blind, randomized, controlled trial comparing isotretinoin-Lidose to a currently marketed formulation of oral isotretinoin (Accutane™), 925 subjects with severe recalcitrant nodular acne aged 12-54 years were recruited. Subjects had to have at least 10 acne nodules on the face and/or trunk. Active treatment under fed conditions with isotretinoin-Lidose or the reference marketed formulation was initiated at a dose of 0.5 mg/kg/day for the first 4 weeks, followed thereafter by 1 mg/kg/day for the subsequent 16 weeks. All participants were instructed to take the assigned isotretinoin formulation twice-daily with meals at breakfast and dinner for the full 20 weeks of treatment.[8] The number of responders, defined as those with ≥90% reduction in nodules at end of study compared to baseline, was similar in both treatment groups with overlapping 95% confidence intervals in *per protocol* (79% isotretinoin-Lidose versus 81% Accutane™) and *intent to treat* (70% versus 75%) analyses. Furthermore, the mean reduction in nodules in both groups was similar for both analyses (-17 versus -16, -16 versus -16, respectively), demonstrating clinical non-inferiority. Almost all patients experienced at least one adverse event in both groups at a similar rate (92% with isotretinoin-Lidose to 90% with Accutane™). Reported adverse events were typical for oral isotretinoin use, with the majority related to dry skin and cheilitis. No significant differences were observed in frequency of adverse events between treatment groups for psychiatric, ocular, auditory, musculoskeletal, cardiovascular, or gastrointestinal systems.[8] Rates of serious adverse events occurring with the use of both isotretinoin-Lidose and standard oral isotretinoin were low (5/464 or 1.1% and 7/464 or 1.5%, respectively). Three serious side effects possibly related to isotretinoin-Lidose were severe abdominal pain, severe upper abdominal pain, and moderate migraine, all of which resolved completely. Serious adverse events related to standard oral isotretinoin were not included in this publication. Adverse events leading to discontinuation of participation were reported in 4.1% (19/464) of patients with isotretinoin-Lidose, compared to 3.3% (15/460) of patients with standard oral isotretinoin. These were classified as psychiatric and gastrointestinal events in the isotretinoin-Lidose group, and as psychiatric and musculoskeletal/connective tissue events in the reference group.

Dosage Forms and Administration

Capsules of isotretinoin-Lidose are available in 10 mg (yellow), 20 mg (red), 30 mg (brown), and 40 mg (brown and red) doses in packages of 30 capsules (3 x 10 blister cards). Inactive ingredients in this formulation include: stearoyl macrogolglycerides, soybean oil, sorbitan monooleate, and propyl gallate. Accutane™ is currently available in 10 mg (pink), 20 mg (red; not available in Canada) and 40 mg (orange) doses in blister packages of 30 capsules, and ingredients include beeswax, black iron oxide, gelatin, glycerol, soybean and peanut oils, parabens, shellac, and titanium dioxide. To prevent potential allergic reactions, Accutane™ should particularly be avoided in patients with sensitivities to peanut oil and parabens, in addition to the aforementioned contents. Isotretinoin-Lidose dye systems vary with the dose forms: 10 mg – iron oxide (yellow) and titanium dioxide; 20 mg – iron oxide (red) and titanium dioxide; 30 mg – iron oxide (yellow, red, and black) and titanium dioxide; and 40 mg – iron oxide (yellow, red, and black) and titanium dioxide.

As with standard isotretinoin formulations, the starting dose of isotretinoin-Lidose should be administered according to the patient's weight and severity of the disease. In general, patients should initially receive isotretinoin-Lidose 0.5 mg/kg body weight daily for 2-4 weeks while monitoring their responsiveness to the drug.[8] Maintenance dose should be adjusted between 0.1 mg and 1 mg/kg body weight daily, depending on the response and tolerance. A complete course of therapy consists of 12-16 weeks of isotretinoin-Lidose administration.[8] In view of differences in bioavailability, the use of isotretinoin-Lidose is not considered interchangeable with standard oral isotretinoin formulations.

As with any oral retinoid treatment, the need for on-going pregnancy prevention and safety monitoring is of paramount concern. Generally, the side effects of oral isotretinoin have been well characterized, with the most common ones being mucocutaneous and mild. As isotretinoin-Lidose is formulated to be a more bioavailable form of oral isotretinoin under fasted conditions, rates of adverse events should not be appreciably different between the two therapies – as demonstrated by the clinical trial.[8] However, due to the specific parameters and controlled conditions of the study, this data may not directly generalize to overall rates observed in clinical practice. Therefore, it is recommended to initiate isotretinoin-Lidose treatment at a low dose of 0.5 mg/kg/day for 2-4 weeks to assess drug tolerance.

Discussion: Epuris™ and Other Recent Isotretinoin Advancements

Several current guidelines for the treatment of severe nodulocystic and conglobate acne indicate the use of isotretinoin as a monotherapy in doses ranging from 0.5-2.0 mg/kg/day over 4-6 months[9-11] to achieve a final cumulative dose of 120-150 mg/kg.[9,11] This cumulative dose has been considered to be optimal to minimize relapse requiring retreatment. Preventing the need for retreatment is a desirable prospect, as it would reduce the likelihood of fetal exposure to teratogens in women of child-bearing age with additional treatment courses, decrease the overall occurrence of adverse events, and lessen the development of permanent acne scarring resulting from incomplete resolution of acne lesions. As the isotretinoin-Lidose formulation increases isotretinoin bioavailability during fasted states, it may mitigate the obstacle of variable patient compliance, thereby increasing the probability of efficiently attaining the recommended cumulative dose. However, the evidence basis for current cumulative dose thresholds is tenuous. Recent evidence suggests that there may be less of a role for cumulative dose in the treatment of acne than previously thought, and prevention of relapse may be more directly attributable to prolonged sebosuppresion.[12] In particular, it is unclear whether prolonged remission is best achieved through prolonged sebosuppression achievable by long-term, low-dose administration, or through apoptosis and sebaceous gland atrophy requiring higher doses. Nevertheless, though it currently serves as an acceptable approximation of appropriate treatment duration, further investigation is required to provide high-level evidence for remissions with varying dosing regimens.

The reassessment of isotretinoin dosing regimens has increased in recent years, with the aim of determining the most efficient and scientifically credible means of oral isotretinoin administration. Recognition of the efficacious role of low-dose isotretinoin therapy in severe acne is compelling and emerging evidence suggests that current practice guidelines may be recommending unnecessary high doses of isotretinoin, resulting in preventable side effects. Several studies have suggested that continuous, low-dose regimens may be as effective for treatment of acne and prevention of relapse as those using higher, classic doses.[13-16] A recent randomized, double-blind, placebo-controlled trial demonstrated that doses as low as 5 mg/day isotretinoin independent of body weight, significantly reduced acne lesion count and improved Dermatology Life Quality Index (DQLI) scores after 16 weeks of treatment.[14] Patients continued to improve 10 weeks after treatment discontinuation and relapses were not observed during this post-treatment follow-up. Furthermore, in one of the largest studies evaluating low-dose isotretinoin treatment, 638 patients were successfully treated with 0.3-0.4 mg/kg/day over 6 months, with none relapsing at the 24-week follow-up.[16] Although these studies may not have had adequate follow-up durations to sufficiently assess relapse, their findings present considerable potential in improving patient satisfaction, as lower-dose regimens have been associated with fewer overall adverse events and increased cost effectiveness.[17] A prospective, randomized, controlled study investigating the clinical efficacy and tolerance of low-dose regimens reported that patient satisfaction was significantly higher in the low-dose treatment group (0.25-0.4 mg/kg/day) compared to higher dose group (0.5-0.7 mg/kg/day).[13] A major limitation of evidence for low-dose regimens is that they have not been directly compared to full-dosing (1.0 mg/kg/day). The combination of low-dose strategies with increased bioavailability formulations such as isotretinoin-Lidose could optimize the benefits of treatment with less medication.

Conclusion

The novel isotretinoin-Lidose formulation was designed to reduce variation in bioavailability during fed and fasted states compared to standard isotretinoin. In the context of clinical use, where patients may be unable to consistently take oral isotretinoin with a high-fat meal, this product enhances bioavailability and has the potential of improving clinical outcomes.

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Treatment of Infantile Hemangiomas with Beta-Blockers: A Review

Sonal Shah, MD and Ilona J. Frieden, MD

Departments of Dermatology and Pediatrics, University of California San Francisco, San Francisco, CA, USA

ABSTRACT

Infantile hemangiomas (IH) are the most common tumors occurring in early childhood, with a prevalence of approximately 5-10% of infants. While the natural history of IH is to spontaneously involute, a significant minority of IH require therapy with the aim to prevent disfigurement, functional impairment, or ulceration. In 2008, propranolol, a non-selective beta (β)-blocker, was reported to be highly effective in treating IH. Since that time there have been more than 200 articles published regarding the efficacy and potential toxicity of β-blockers, both systemic and topical, for the treatment of IH. Based on these finding, β-blockers appear to be highly effective in treating IH and are well tolerated, though side effects have been reported. When therapy is appropriately monitored, β-blockers have been proven to be a safer and superior alternative to systemic steroids.

Key words: infantile hemangioma, IH, beta-blocker, propranolol, timolol

Introduction

Infantile hemangiomas (IH) are the most common tumor occurring in early childhood, with a prevalence of approximately 5-10% of infants.[1] The vast majority of IH undergo rapid proliferation during infancy, particularly in the first weeks to months of life, followed by a slow involution period that lasts several years.[2-4] Because involution occurs spontaneously, most IH do not require treatment. Clinical characteristics including size, location, and subtype (e.g., segmental or very prominent dermal component) can predispose infants to complications including permanent disfigurement, ulceration, and functional impairment, leading to significant morbidity.[5-7] Treatment is indicated to reduce morbidity and prevent or minimize complications.

Until recently, corticosteroids in various forms, including topical, intralesional, or most commonly systemic, were the mainstay in IH treatment; however, response to therapy was varied. In addition, adverse effects with systemic steroids, such as development of Cushingoid features, gastroesophageal reflux, hypertension, growth retardation, and increased susceptibility to infection were major considerations when deciding whether or not to initiate therapy.[5,6,8,9]

In 2008, Labreze et al. reported on the serendipitous observation that propranolol, a non-selective beta (β)-blocker, was efficacious in treating 11 patients with IH.[10] Since that time, there have been more than 200 published articles regarding the use of β-blockers in IH – both systemic and topical, which has revolutionized the therapeutic approach to this common condition.

Pathogenesis of Infantile Hemangiomas

IH are neoplasms of benign endothelial cells. For decades it was assumed that these vascular tumors were manifestations of angiogenesis, i.e., the sprouting of new blood vessels from pre-existing ones. However, recent emerging evidence indicates that they may develop via vasculogenesis, the *de novo* formation of blood vessels from progenitor cells.[11,12] Local or systemic hypoxemia may be a common denominator in hemangioma growth. Both placental and perinatal abnormalities may be potentiating factors that induce increased blood vessel formation and, thus, contribute to the development of IH.[12-14]

In recent years, several review articles have summarized many of the advances in understanding the pathogenesis of IH.[11,15-17] Vascular endothelial growth factor (VEGF) regulation appears to play a central role in the proliferation of hemangiomas. Another remarkable insight is the recognition that endothelial cell precursor cells of IH represent a fetal, rather than post-natal phenotype, with the capability of transforming to adipocytes. Although much more work is needed, uncovering the pathogenesis of IH has occurred at a far greater pace in the past decade and a half than in prior history.

Mechanism of Action of β-Blockers on Infantile Hemangiomas

The exact mechanism of action of β-blockers for the treatment of IH is not yet completely understood, however, it is postulated to inhibit growth by at least four distinct mechanisms: vasoconstriction, inhibition of angiogenesis or vasculogenesis, induction of apoptosis, and recruitment of endothelial progenitor cells (EPCs) to the site of the hemangioma.[18-21] Of note, β-adrenergic receptors are expressed on endothelial cells of IH, which are found in abundance in the proliferative phase of IH.[19]

Vascular tone results from a complex interplay of a variety of chemokines in the body and their interaction with receptors located on endothelial cell surfaces. Several studies have demonstrated that activation of β-adrenergic receptors promotes vasodilation.[19,22] The use of β-blockers to mitigate the interaction of adrenaline mediated activation of $\beta2$-receptors results in vasoconstriction, which leads to reduced blood flow within the hemangioma. Clinically, propranolol can induce a noticeable change in color, as well as softening of the IH, often within the first few days or even hours after initiating therapy.[18]

Activation of β-adrenergic receptors leads to increased release of VEGF, which appears to promote both angiogenesis and vasculogenesis in IH. Inhibition of these receptors by β-blockers results in reduced VEGF production, thereby limiting proliferation of vasculature and possibly arresting growth.

β-adrenergic receptors are thought to play a role in apoptosis. Blockade of β-receptors have been shown to induce apoptosis in cultured endothelial cells,[21] which is hypothesized to contribute to the effectiveness of propranolol in the treatment of IH. In addition, newer literature also reports that beta blockage can also promote involution of IH through regulation of the renin-angiotensin pathway.[23] As well, β-blockers may decrease migration of EPCs, such that they are prevented from migrating to areas predisposed to hemangioma formation.[20]

Systemic Propranolol: Clinical Results

Although β-blockers are not (yet) US FDA-approved for the treatment of IH, there are more than 200 articles reporting their use in over 1200 patients. Many are single case reports or small series with diversified clinical settings, dosages, duration, and assessment of outcomes. To date, one randomized control trial has been published involving 40 infants with IH who received either propranolol 2 mg/kg/day divided three times daily or placebo. In the propranolol group, infants younger than 6 months and children up to 5 years of age showed reduced volume, elevation, and improved coloration in localized and segmental IH, with excellent tolerability.[24] Two comparative effectiveness studies comparing propranolol and corticosteroids have also been published. The first study, a retrospective chart review, looked at 110 patients treated with either propranolol or corticosteroids. Propranolol was shown to be more clinically effective than oral steroids, with better tolerance and less adverse effects, and also resulted in fewer surgical interventions.[5] In the second study, 12 IH patients treated with propranolol were retrospectively matched to those treated with prednisone based on type, location, and size of IH, as well as age at initiation of treatment. Propranolol was demonstrated to be superior when compared to prednisone at 1, 2, and 6 months of treatment based on evaluation of serial photographs, with all patients in the propranolol group exhibiting good to excellent response.[6]

The majority of these articles were included in two systematic reviews published in late 2012. Although slightly different methodologies were used, similar conclusions were derived, therefore supporting the significant efficacy of β-blockers in the treatment of IH. The first review assessed findings from studies of IH using corticosteroids compared with propranolol. This meta-analysis found a pooled response rate in the corticosteroid studies of 69% versus 97% for propranolol (p<0.001).[25] The second review included all case series with a minimum of 10 patients treated with propranolol. Forty-one studies were included with a total of 1264 patients analyzed. This investigation provided more details about the methods by which propranolol in currently used. Propranolol was started at a mean age of 6.6 months, at an average dose of 2.1 mg/kg/day, with a mean duration of treatment of 6.4 months. The calculated pooled response rate of 98% in this systematic review was essentially identical to the previous analysis.[26]

A relatively large retrospective study (42 patients) reported on the effectiveness of propranolol in IH patients who were beyond the proliferative growth phase (e.g., patients who were >12 months of age or had documented cessation of tumor growth). Propranolol at a mean dose of 2.1 mg/kg/day was found to be effective in reducing the clinical appearance of IH in children even up to the age of 10 years – a statistically significant finding that also serves to highlight the success of delayed propranolol initiation in promoting involution. The use of propranolol did not lead to any adverse effects that necessitated discontinuation of therapy.[27]

Hemangiomas in Special Anatomic Sites

Particular areas of IH involvement that may lead to functional impairment include the periocular region, airway, and liver. A systematic review focusing specifically on the use of propranolol for periocular involvement noted effectiveness in 96 of 97 patients.[28] A meta-analysis looking at propranolol for airway hemangiomas identified 13 studies comprising 36 patients that showed propranolol to be effective in promoting resolution of airway hemangiomas; additionally, superior efficacy was demonstrated over steroids.[29] Several case series have reported on the benefits of propranolol for the treatment of hemangiomatosis, particularly with liver involvement. One study noted improvement in 8 infants with diffuse hemangiomatosis and liver involvement. In instances where heart failure associated with hypothyroidism was also a consequence, complete resolution was noted.[30]

Ulceration

Ulceration, which is the most common complication of IH, can cause significant morbidity due to the development of severe pain, bleeding, scarring, and risk of infection. A recent study looked at 33 children with ulcerated IH (76% received previous therapy with no improvement), who were treated with propranolol at doses ranging from 2-3 mg/kg/day. Complete healing was noted at a mean of 5.7 weeks and average time to achieving pain control was 14.5 days. However, 4 infants experienced recurrence of ulceration following cessation of therapy.[31]

Rebound Growth

Upon discontinuation of propranolol, several reports have noted rebound growth or recurrence of IH. The systematic review by Marqueling et al. observed a rate of 17% for rebound growth.[26] A recent study reported rebound growth in 5 of 26 patients (19%) after discontinuation of propranolol. Time from withdrawal of medication to recurrence ranged from 0-6 months, with recurrence appearing in the deep component in the majority of IH.[32] Rebound growth has been attributed to early treatment withdrawal or a prolonged proliferative phase of IH. Predictive factors that may predispose infants to rebound growth have yet to be identified, however, studies are currently underway to better characterize these contributing factors, which may aid in determining which infants are at increased risk for recurrence.

Side Effects

Propranolol has long been used in the pediatric population for a variety of different conditions including in neonates and infants for supraventricular tachycardia, neonatal hyperthyroidism, and arrhythmias. Doses used have range from as low as 1 mg/kg/day to doses as high as 8 mg/kg/day. This experience combined with

that for treating IH have demonstrated a good safety profile and the majority of patients tolerated the doses used to treat IH (1-3 mg/kg/day) with minimal adverse events (AEs). In a recent systematic review, there were 371 total AEs reported in 1189 patients.[26] Though this review did not allow for precise percentages, as some studies failed to report them, it was possible to determine the frequency of AEs among the studies that did so. The most common AEs included sleep disturbance (136 patients), acrocyanosis (61 patients), hypotension (39 patients, although only 5 were deemed "symptomatic"), bradycardia (8 patients, 1 of which was symptomatic), and respiratory events including infections, wheezing, and stridor (35 patients). The most concerning side effect of propranolol is symptomatic hypoglycemia, which was noted in 4 patients, one of whom developed hypoglycemic seizures.[33] Blockade of β-receptors can lead to hypoglycemia due to decreased glycogenolysis, gluconeogenesis, and lipolysis. Although a rare but potentially serious side effect, patients on propranolol may be at risk for hypoglycemia during prolonged periods of fasting or poor oral intake (e.g., during an acute illness), which can occur at any point during therapy. Frequent feedings, as well as administration of the medication following feeds, and avoidance of long periods of sleep can help to minimize this risk.

Initiation of Propranolol

Consensus guidelines for initiation and monitoring of propranolol have recently been published. For infants younger than 2 months of age, brief inpatient hospitalization for monitoring during induction of treatment is generally recommended. For infants over 2 months of age, propranolol can be initiated in an outpatient setting unless there are medical co-morbidities or inadequate social support. After a careful history and physical examination to exclude any reactive airway or cardiac disease, baseline heart rate and blood pressure are obtained. Initial dosing of propranolol starts at 0.5 mg/kg/day divided three times daily, increasing slowly to a maximum of 2 mg/kg/day. Heart rate and blood pressure are monitored before and throughout the course of dose escalation, as well as at 1 and 2 hours following the initial dose. Parents should be informed of the risks of hypoglycemia and advised to feed infants every 4-6 hours.[34]

Other β-Blockers

Other β-blockers for the treatment of IH are under investigation, including atenolol, acebutolol and nadolol.[35-37] Head-to-head trials comparing the efficacy of these particular agents to propranolol are yet to be performed.

Topical β-Blockers

For superficial or small IH, in which systemic therapy may not be indicated, topical β-blockers, specifically timolol gel forming solution (GFS), have proven to be a useful alternative. In a recent multicenter retrospective study looking at the efficacy of timolol 0.5%-0.1% GFS applied twice daily for superficial IH, 72 of 73 patients exhibited some improvement, the mean duration of therapy was 3.4 months and treatment was well tolerated.[38] However, some caution must be exercised with the use of topical timolol due to its increased potency of between 4 and 10 times greater than propranolol, as well, topical absorption would bypass first-pass metabolism in the liver. To date, a small amount of topical timolol (e.g., 1 drop applied twice a day to intact skin overlying a hemangioma) appears to be safe, but the exact level of systemic absorption is not yet known. Thus, a conservative and cautious approach should be practiced in administering topical timolol while awaiting further information about potential side effects.[39]

Conclusion

Propranolol and other β-blockers have revolutionized the treatment of IH and led to new insights in the pathophysiology and management of this disease. While propranolol is undeniably effective, more studies are needed to elucidate its mechanism of action and confirm optimal dosing, duration of therapy, and safey, as well as determine risks for rebound growth.

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ERRATA

In the original article "A Look at Epidermal Barrier Function in Atopic Dermatitis: Physiologic Lipid Replacement and the Role of Ceramides" published in the July-August 2012 issue of *Skin Therapy Letter* by Dušan Sajic, MD, PhD; Rachel Asiniwasis, MD; and Sandy Skotnicki-Grant, MD, FRCPC the following correction should be made:

On page 8, right column, third paragraph under Other Non-steroidal Barrier Repair Products, the second sentence should read "Similar findings were seen in another recent study that demonstrated non-superiority of topical pimecrolimus when compared to a prescription medical device cream containing a combination of OTC components,[25] suggesting that correction of numerous epidermal barrier derangements may be an effective way of controlling AD."

Update on Drugs

Name/Company	Approval Dates/Comments
Dabrafenib mesilate capsule *Tafinlar*™ GlaxoSmithKline Inc.	In July 2013, Health Canada approved this BRAF kinase inhibitor as a monotherapy oral treatment for unresectable melanoma or metastatic melanoma in adult patients whose tumors express the BRAF V600E gene mutation. Dabrafenib is not indicated for treating patients with wild-type BRAF melanoma. A validated test to identify BRAF V600 mutation status is required to determine treatment eligibility. Dabrafenib inhibits certain mutated BRAF kinases that activate the BRAF pathway and drive tumor cell growth.
Trametinib dimethyl sulfoxide tablet *Mekinist*™ GlaxoSmithKline Inc.	In July 2013, Health Canada approved this first-in-class MEK1/MEK2 inhibitor as a monotherapy oral treatment for unresectable or metastatic melanoma in adult patients with BRAF V600E or V600K mutations. These mutations must be detected by a validated companion diagnostic to confirm treatment eligibility. It is not indicated for patients who have received prior BRAF inhibitor therapy. Trametinib specifically binds to and inhibits MEK 1 and 2, resulting in inhibition of growth factor-mediated cell signalling and cellular proliferation in various cancers.
Vismodegib capsule *Erivedge*® Curis, Inc./Roche	The European Commission has granted conditional approval to this hedgehog pathway inhibitor in July 2013 for the treatment of adult patients with symptomatic metastatic basal cell carcinoma (BCC) or locally advanced BCC inappropriate for surgery or radiotherapy. The drug is administered orally once-daily.

Drug News

In July 2013, the US FDA issued a Drug Safety Communication to healthcare professionals recommending ketoconazole oral tablets (Nizoral®) should no longer be used as a first-line treatment for any fungal infection due to the potential risk for severe liver damage, adrenal insufficiency, and drug interactions. Ketoconazole tablets should be used only for the treatment of certain life-threatening mycoses when the potential benefits outweigh the risks and alternative therapeutic options are not available or tolerated. The updated drug label for ketoconazole tablets will include:

- Use in *Candida* and dermatophyte infections is no longer indicated and should be used only when other antifungal drugs are not available or tolerated by the patient
- Not indicated for the treatment of fungal infections of the skin or nails
- Contraindicated in patients with acute or chronic liver disease

Topical formulations of ketoconazole, including creams, shampoos, foams, and gels, have not been associated with liver damage, adrenal problems, or drug interactions.

More information is available at:
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHuman MedicalProducts/ucm362672.htm

In August 2013, the US FDA issued a warning to consumers and healthcare professionals that acetaminophen is associated with rare but severe and potentially fatal skin reactions. The agency cited three published reports in which individuals developed Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalized exanthematous pustulosis (AGEP) following acetaminophen administration. From 1969 to 2012, a search of the FDA Adverse Event Reporting System database identified 91 cases of SJS/TEN and 16 cases of AGEP, which resulted in 67 hospitalizations and 12 deaths. The labels of prescription drug products containing acetaminophen will be required to indicate the risk for serious skin reactions. The FDA will also request that manufacturers add a warning about serious skin reactions to the product labels of over-the-counter acetaminophen drug products.

More information is available at:
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHuman MedicalProducts/ucm363519.htm?source=govdelivery