A Unique Preparation and Delivery Method for Acitretin for Neonatal Harlequin Ichthyosis

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Harlequin ichthyosis is a rare form of congenital ichthyosis with a distinct phenotypic appearance. We describe a case of a newborn baby with harlequin ichthyosis who was treated with an oral formulation of acitretin. The treatment resulted in a satisfactory improvement in the skin condition of the patient. The tolerance to the drug was good with no side effects in the patient. The aim of this case report is to highlight an extemporaneous preparation of acitretin from the commonly available capsule form, which is effective for use in neonates with harlequin ichthyosis. It also highlights the risk of exposure to health care providers to acitretin.

ABBREVIATIONS ASHP, American Society of Health-System Pharmacist; BUD, beyond-use date; HI, harlequin ichthyosis; NICU, neonatal intensive care unit; PPE, personal protective equipment; USP, United States Pharmacopeia

KEYWORDS acitretin; drug delivery; drug preparation; harlequin ichthyosis; neonates

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Introduction

Harlequin ichthyosis (HI), also known as “harlequin baby” or “harlequin fetus,” is a rare disorder of keratinization. Harlequin ichthyosis is inherited in an autosomal recessive fashion and arises secondarily to mutations in the *ABCA12* gene. Infants with HI are typically born premature, encased in a thickened, hard stratum corneum, which is often described as armor-like. Acetretin, isotretinoin, and in the past etretinate, have provided the most effective therapy for ichthyosiform conditions.^{1,2} However, the efficacy of acitretin and other retinoids in pediatric patients is based on isolated case reports and their pediatric safety profile is not well established.³ Of the various side effects of retinoids, one of the most serious one is teratogenicity. Use of acitretin in pregnant women has been associated with malformations such as meningomyelocele, multiple synostoses, and facial dysmorphism as well as cardiovascular malformations. While this may not affect neonatal patients, the exposure of drug particles to health care workers in the reproductive age group may pose a serious harm. Also, as the drug is only available in capsule form in fixed dosages, its use in neonates requires it to be formulated for every patient as per body weight and be delivered in a manner that exposes the caregivers to the medication. We describe a case of HI that was treated with an extemporaneous compounding of an oral preparation of acitretin.

Case

A 1.98-kg male baby was delivered by normal vaginal delivery to a 34-year-old woman with history of systemic

lupus erythematosus. The mother had a prior history of a baby born at 28 weeks who was diagnosed with HI. This baby was homozygous for the W129 4X mutation of the *ABCA* gene and expired soon after birth. The course of the current pregnancy had been uneventful with no medical issues until it was complicated by premature rupture of membranes and onset of labor at 33 weeks. The baby upon delivery was wrapped in sterile cloth with saline and placed in a polyethylene bag and transferred to the neonatal intensive care unit (NICU). The baby had ichthyosis of the scalp, face, and neck with outward pouting of lips or fish mouth (eclabium), compressed ear pinna, and slightly open eyes because of outward turning of eyelids from the eyeball (ectropion). The extremities had tight thickened skin with deep fissures and were erythematous. There was associated neck rigidity due to thickened skin. The rest of the systemic examination was normal.

A dermatology consult was done with advice to remove excess skin, which was raised so it does not get entangled with clothing. He was placed in an isolette, and umbilical arterial and venous catheters were inserted. The humidity in the isolette was kept at 100% but was difficult to maintain owing to frequent nursing care. The baby was placed on room air, a blood culture was drawn, and vancomycin (10 mg/kg/dose every 12 hours) and piperacillin/tazobactam (75 mg/kg/dose every 12 hours) were started, which were stopped after 2 days owing to negative blood culture results. A basic metabolic panel including blood urea nitrogen (BUN) and creatinine was performed daily to follow renal functions; BUN (11 to 15 mg/dL) and creatinine (0.4 to 0.9 mg/dL) remained within normal limits until the time

he developed septicemic shock. Because the umbilical catheters were difficult to maintain owing to inability to put tape on the abdominal skin, they were removed and enteral feeds were started.

The neonatal team, as advised by dermatology, applied emollient in the form of petroleum jelly over different parts of the skin, thereby avoiding complete coverage and allowing the skin to breathe. Attention was given to prevent maceration of the skin. Bacitracin ointment was applied over fissured areas. Artificial tears were also administered. Acitretin therapy was started on day 3, after baseline hematologic, metabolic, and hepatic panel findings were normal. The dose was 1 mg/kg/day administered enterally through the orogastric tube for an initial period of 30 days. There was consistent improvement with the shedding of the thick plates of skin, which were constantly removed. After 30 days, the dose was reduced to 0.5 mg/kg/day. The baby continued to improve and the dose was finally reduced to 0.5 mg/kg/dose 3 times per week. There was marked improvement of the skin with shedding of hyperkeratotic plaques.

Despite close monitoring for signs of sepsis, on day of life 45 the baby became apneic and developed bradycardia with heart rate down to 50 beats per minute and oxygen saturation dropping to 30%. Blood culture confirmed *Pseudomonas* sepsis, which is the usual organism found in high humidity conditions⁴ and the baby was started on meropenem (40 mg/kg/dose every 8 hours). Despite aggressive management, he developed polyuric acute renal failure and severe hypernatremic dehydration associated with free water loss from the skin and as urine. A head ultrasonogram was notable for periventricular leukomalacia, possibly related to hypotensive episodes of infectious origin. The baby had no movement or reactivity with lack of spontaneous brain activity in the electroencephalograph. The family was updated about the baby's critical condition and they opted to withdraw care. Owing to a positive family history of ichthyosis in the older sibling of the patient, a genetic test was performed and showed that the patient was homozygous for the W129 4X mutation of *ABC12* gene, which is a nonsense mutation leading to RNA decay.

Details of Acitretin Preparation

The acitretin oral solution used to treat the patient was prepared under a chemotherapy hood with masks and gloves. Five milliliters of Ora-Plus solution was measured with a graduated cylinder and added to an amber-colored glass bottle of 1-oz capacity. The contents of 1 acitretin 10-mg capsule was added to the amber bottle containing Ora-Plus and mixed thoroughly. The bottle was shaken well and labelled with information detailing the storage conditions and beyond-use date (BUD). The bottle was refrigerated with a BUD of 5 days. The final concentration of the solution was 2 mg/mL. It is known

that drug concentrations vary for the drugs that use Ora-Plus as a vehicle of delivery.⁵ Because our patient weighed 1.98 kg, we decided to constitute the 10 mg of acitretin in 5 mL to achieve a final concentration of 2 mg/mL to allow us to administer 1 mL every 24 hours. Although BUD for a water-containing oral formulation should not be longer than 14 days,⁶ different periods of BUD are described with Ora-Plus.⁵ The lowest BUD of 5 days was chosen for the acitretin to be sure the compound remains stable. The drug was dispensed to the NICU by the pharmacy in prefilled syringes and was administered by nurses who had personal protection equipment (PPE) in the form of caps, mask, and gown. All efforts were made for male nurses to take care of this baby but this was not possible at all times. The importance of PPE for both female and male nurses, along with side effects of the medications, was stressed during the medical rounds, which were attended by all the health care staff taking care of the baby.

Discussion

We describe a case of HI that was treated with acitretin in our NICU. Harlequin ichthyosis is a rare occurrence and it has been previously described as case reports.^{2,3} Although there are reports on the efficacy of acitretin for the treatment of HI, there are no case studies that have described the preparation and administration of acitretin in neonates diagnosed with HI.

In neonates with HI, early use of systemic retinoids promotes accelerated shedding of the hyperkeratotic plates, and continued use reduces scales and improves the ectropion and eclabium. Retinoids should therefore be started as soon as possible after delivery. Acitretin has become the preferred retinoid because of its shorter half-life than that of its parent drug etretinate, which has not been available in the United States since 1998. Acitretin provides a better safety profile than etretinate, with decreased severity of side effects such as mucocutaneous dryness and skin irritation.³ Despite these advantages, the efficacy and safety profile of acitretin are not well established in children and there are no commercially available preparations of the drug for use in children. Another hindrance associated with the use of acitretin is the lack of details on the preparation, delivery, and administration of the medication to the neonates with HI. It must be formulated on an as-needed basis for use in individual patients, hence requiring extemporaneous compounding.

Our report provides several details on acitretin preparation. Acitretin was prepared under a chemotherapy hood while using PPE to prevent risk of exposure to pharmacy staff associated with cutting, crushing, or otherwise manipulating medicine.⁷ Similar exposures are a concern for health care workers administering the medication to the patient and can be avoided with appropriate use of PPE. We also report in detail the use of Ora-Plus, which has been successfully used for

compounding a liquid preparation of acitretin.⁸

Ora-Plus solution, an aqueous-based vehicle consisting of suspending agents with high degree of colloidal activity, is a commonly used excipient for the preparation of many drugs including acitretin.⁸ The suspending agents form a structured, gel-like matrix that suspends particles and allows for slight settling. Further, Ora-Plus is buffered to a slightly acidic pH to help reduce degradation of medicinal agents through oxidation. In addition, an antifoam agent is incorporated into Ora-Plus to allow for vigorous shaking to mix medications with minimal foaming. It retains its suspending properties, even when diluted with up to 50% water or flavoring agents, making it ideal for pediatric suspensions and nasogastric preparations. Further, as acitretin degrades on exposure to photolytic stress with an increase in degradation products and impurities,⁹ the preparation of the solution and its long-term storage must be done to minimize exposure to photolytic stress, which is achieved by storing the solution in amber-colored glass bottles.

Assigning the correct BUD as established by United States Pharmacopeia (USP) <795> guidelines on pharmaceutical compounding is an important aspect of making such preparations. The maximum BUD for water-based oral preparations is 14 days when stored at controlled cold temperatures.⁶ Because BUD may differ from case to case depending on the storage conditions, we were cautious and used the lowest BUD for acitretin to ensure maximum efficacy of the medication for our patient. In light of the studies that have focused on the occupational exposure hazards of chemotherapeutic drugs, it is now well recognized that several drugs have a toxicity profile, like the teratogenicity of acitretin,⁹ which is of concern. There is also evidence that health care workers are exposed to chemotherapeutic agents and other hazardous drugs at delivery sites, while pharmacists are exposed during the preparation of these drugs.^{10,11} Inhalation and skin contact/absorption are the most likely routes of exposure, but unintentional ingestion from hand to mouth contact and unintentional injection through a needle-stick or sharps injury are also possible.¹² Administration of drugs via aerosolization can lead to measurable air concentrations in the breathing zone of workers providing treatment. For example, concentrations of 18 mcg/m³ have been reported by personal air sampling of workers administering pentamidine.¹³

The major side effect associated with the use of acitretin is teratogenicity. While this may not be an issue to neonatal and pediatric patients, it poses a serious risk to health care workers who may have accidental exposure to acitretin. The mechanism of the exposure and production of the toxicity are determined by the size of particle of the active agent, as it determines to what extent the agent may get absorbed into the body.

In addition, these particles are released in the air during preparation of medication or dried spills of prepared medication. It may also be directly dispersed into the air from the powder suspended in the excipient. Drug particles larger than 10 μm are deposited in the oropharyngeal region when the drug is inhaled, while those 5 to 10 μm in size are deposited in the large airways and particles smaller than 5 μm are deposited in the alveoli. Acitretin particles in the commonly available capsule forms have a d90 (size of 90% of drug particles) ranging from 2.5 μm to 5 μm . Hence the drug may get absorbed into the body through the large airways or from the alveoli. Furthermore, owing to the long half-life of acitretin, once exposed it may remain in the body for long periods. Hence, additional PPE precautions must be taken by any health care staff handling acitretin with a special emphasis on those who are of reproductive age. The handling of the formulation must be avoided by those staff members who may be pregnant or are planning to conceive. Documented reproductive effects of chemotherapeutic drug exposure have been reported in nurses working at oncology sites. Although there was no difference in the incidence of abortions and congenital malformations of the neonates born to nurses working in medical and surgical wards, the nurses working at oncology sites had a 4.7 times higher odds of having children with congenital malformations.¹⁴ These findings support the need of PPE for nurses and other health care providers handling hazardous drugs.

Acitretin was included in the hazardous drug category after the 1990 American Society of Health-System Pharmacists (ASHP) definition of hazardous drugs was revised by the National Institute of Occupational Safety and Health working groups on Hazardous Drugs for the Alert in 2012.¹⁵ The ASHP recommends guidelines for drug preparation precautions such as the use of Biological Safety Cabinets for preparation with high-efficiency particulate air filters, gloves with increased thickness, use of protective disposable gowns, and eye and face protection. Safe work practices as outlined by ASHP must be followed to minimize exposure to workers.

In summary, acitretin is an important therapeutic agent in the management of HI patients. Because the drug is not available in an appropriate dosage and formulations for doses required for neonatal and pediatric use, it must be compounded for individual patients. We have described a compounding method that is efficient and safe for the preparation and administration of the drug to neonates and children. We also highlight the importance of avoiding the chance of accidental exposure to health care providers by use of appropriate preparation techniques and PPE. Because HI management is complex, a multidisciplinary approach and robust communication between the medical team and other health care providers, including family members, are needed for long-term care of these patients.

ARTICLE INFORMATION

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