

ISMP Canada Safety Bulletin

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ALERT: Clonidine Compounding Errors Continue to Harm Children

When there is a lack of commercially available pediatric formulations for particular medications, pharmacy teams may need to compound them. Clonidine suspension is one such example. Compounding is a high-risk process, and the associated complexity can increase the likelihood of medication errors. ISMP Canada has previously described reports of harm to children resulting from errors in compounded pediatric prescriptions, including clonidine.^{1,2} This bulletin describes 2 recently reported medication incidents that involved preparation of clonidine suspension by different compounding methods. These errors highlight the need for increased safety in compounding and more education about the risks, as well as the need for a commercially available pediatric formulation for clonidine in Canada.

INCIDENT EXAMPLES

- A child received 1000 times the intended clonidine dose because of a mix-up between units of measure (micrograms vs milligrams) during the process of preparing a suspension. The child required admission to a pediatric intensive care unit.
- A child experienced severe drowsiness, leading to hospitalization, after receiving a dose of compounded clonidine suspension. Testing of the prepared product determined that it was over 10 times more concentrated than intended. Inaccurate trituration of clonidine powder was reported as a contributing factor.

BACKGROUND

According to the American Academy of Pediatrics, evidence supports the use of clonidine as an adjunct to stimulant therapy in the treatment of attention-deficit hyperactivity disorder.³ Clonidine has a wide range of other off-label uses in children, such as the treatment of tic disorders (including Tourette syndrome), hypertension, pain, and sleep disorders, as well as for weaning from pain medication.⁴

A pediatric formulation of clonidine is not commercially available in Canada. Clonidine tablets are available in strengths of 0.025 mg, 0.1 mg, and 0.2 mg.^{5,6} Therapeutic doses for pediatric patients can be smaller than the lowest tablet strength (e.g., 0.5 mcg/kg per dose to treat neonate opioid withdrawal syndrome),⁷ which necessitates compounding the drug into a liquid form. Pediatric doses are often prescribed in micrograms, rather than in milligrams⁷ (as would be used for adult doses). Another complicating factor is that pharmacy weigh scales vary: many of these devices measure in grams, and some have the capability to measure in milligrams, but none are capable of measuring in micrograms.

Clonidine has a low therapeutic index in children; ingestion of just 10 mcg of clonidine per kilogram of body weight (e.g., 200 mcg or 0.2 mg for a 5-year-old weighing 20 kg) can result in a severe overdose.¹ Signs of clonidine toxicity can include bradycardia, hypotension, and central nervous system or respiratory depression; death has also been reported.⁸

DISCUSSION

Although compounding of clonidine can be carried out using the active pharmaceutical ingredient (API) in powder form, previous ISMP Canada bulletins have recommended the use of crushed tablets instead of the API powder.^{1,2} Use of crushed tablets reduces the risk of a 1000-fold error due to unit-of-weight conversion mix-ups by removing the conversion to grams needed for many weigh scales.^{1,2,9} The safeguard of using tablets has been included in compounding formulas from recognized pediatric centres, and the formulas have been shared on their websites for use by pharmacy teams.^{10,11,12} The Medication Safety Self-Assessment for Community Pharmacy also recommends this approach to help support knowledge translation of known safeguards into practice.⁹

Many community pharmacies send complex compounding requests to pharmacies that specialize in compounding. Such pharmacies typically belong to compounding networks that are sponsored by API manufacturers. One benefit of membership in such a compounding network is access to proprietary formulas. These formulas primarily use powdered APIs, both to minimize exposure to excipient ingredients to which a patient may be allergic and to allow creation of a smoother, less grainy, and better-tasting end product. However, when the API is used in preparing a pediatric clonidine suspension, the quantity of clonidine needed may be smaller than can be measured by a typical weigh scale found in a community pharmacy. As a result, trituration may be required. Trituration is the process of diluting the API powder with a filler excipient (e.g., lactose powder) to create a uniform end mixture.¹³ This allows creation of weighable aliquots, which can be measured using the pharmacy scale; however, the additional calculations and unit conversions required for trituration introduce additional risks.

Incorrect unit-conversion calculations, lack of familiarity with the trituration process, weighing errors, and distractions in the workplace are factors that have contributed to clonidine compounding errors. Dose conversions among grams, milligrams, and micrograms introduce the potential for

1000-fold errors, as in the first incident described above. Furthermore, in both of the incidents described above, as well as in other incidents described in prior ISMP Canada Safety Bulletins,^{1,2} clonidine was compounded using the API. To date, ISMP Canada has not received reports of errors related to the use of tablets in a compounded clonidine suspension.

RECOMMENDATIONS

The following strategies are shared to reduce the likelihood of compounding errors—and their associated harm—when preparing clonidine suspensions for pediatric patients.

Canadian Pharmaceutical Manufacturers

- Prioritize the development of pediatric formulations for commonly used medications that are not commercially available at present (e.g., pediatric clonidine suspension).

Prescribers

- When a compounded medication is required, discuss therapeutic alternatives with caregivers and the expected benefits and potential risks of each.
- When prescribing clonidine, indicate the dose in terms of an amount (not volume) of medication, and do not use dangerous abbreviations. For example, in describing the amount of a dose, write “microgram”, or at least “mcg”, instead of “µg”.¹⁴ The dose details may be clearer in a computer-generated, rather than handwritten, prescription.
- Include the indication and the patient’s weight on the prescription to facilitate therapeutic checks (e.g., by a pharmacist).

Pharmacy Managers, Pharmacists, and Pharmacy Technicians

- When compounding clonidine, **use a formula that incorporates commercially available tablets instead of the API powder** to reduce the risk of error in the compounding process. An exception would be when patients have known allergies to tablet excipients.

- Create a warning statement in the API-based clonidine formulas in pharmacy software programs.² For example: *Dose/concentration errors up to 1000-fold have been reported with the use of API-based clonidine formulations. Use a tablet-based clonidine formula whenever possible.*
- Require documentation of compounded products on a standardized worksheet, including a signed independent double check of the selected product, calculations, and amount/weight by a pharmacist or registered technician.¹⁵ Follow the [Guidance Document for Pharmacy Compounding of Non-Sterile Preparations](#).¹⁵
- If using a trituration, treat this as its own compound which contains its own master formula and compounding record. This should include a double check of calculations, amount/weight, and preparation accuracy.
- Any community pharmacy that is outsourcing the compounding to a specialty compounding pharmacy must request that the master formula sheet and compounding worksheet be returned with the compounded product, so that community pharmacy staff can perform their own independent double check of the calculations and amounts/weights.
- Ensure that all weighing equipment used is calibrated for accuracy either daily or before each use, and is maintained as per manufacturer's recommendations. A weigh scale that prints the weight of ingredients used in compounding is strongly recommended even if an independent double check can be conducted at the time of weighing.
- Evaluate staff members' compounding skills and competency at least annually with a standard assessment process. Support students and inexperienced staff with comprehensive training and supervision. Include examples of errors, as provided in safety bulletins,^{1,2} to increase awareness and prevent recurrences.
- Encourage parents to bring to the pharmacist's attention any refill prescription that seems to differ, in terms of appearance, taste, or instructions, from the previous prescription.¹
- Be transparent with patients and their families about the complexity of the compounding process, the safety procedures in place, and why a compounded product made with tablets may have a

slightly grainy texture. Also, inform patients and parents of the side effects that might indicate an over- or under-dose. Share the consumer newsletter [Tips for Parents When Medications Need to Be Compounded](#).¹⁶

API Manufacturers/Formula Developers

- Update formulas for clonidine suspension to recommend the use of tablets instead of API powder. Include the following warning statement: *Dose/concentration errors up to 1000-fold have been reported with the use of API-based clonidine formulations. Use a tablet-based clonidine formula whenever possible.*
- Consider developing a diluted clonidine API powder to minimize the need for pharmacies to compound triturations, and to reduce the risk of calculation and weighing errors. A commercially available diluted product can ensure uniformity and potency testing; an example of this is liothyronine sodium powder which is provided in a 1:1000 dilution.
 - Attention to labelling design for API powders (i.e., giving prominence to critical information)¹⁷ continues to be important to prevent selection errors, especially between similar products (e.g., pure and diluted versions of the same API).

CONCLUSION

The continued reports of serious harm due to 10- to 1000-fold errors with compounded clonidine products necessitated this alert. These errors meet the definition of a “never event” because they result in serious patient harm or death and can be prevented using known system safeguards.¹⁸ Although using the API powder currently available may result in a smoother-textured and better-tasting product, **use of clonidine tablets to compound clonidine suspensions is strongly recommended** to reduce the risk of known errors and serious harm.

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Oral Corticosteroid Options for Acute Respiratory Indications in Pediatrics

ISMP Canada has previously described the need for commercially available pediatric formulations to minimize the increased risk of error associated with compounding and with manipulating products intended for adults.^{1,2} One such product is dexamethasone oral liquid. Currently, dexamethasone oral liquid is only commercially available as an elixir containing alcohol 4-5% by volume^{3,4} and not appropriate for children.^{5,6} A recently reported incident involving dexamethasone for an infant again illustrates the opportunity to improve safe medication use for this vulnerable population through the development of suitable commercially available products.

Incident Description

In the reported incident, the following was prescribed for an infant:

dexamethasone tablets 4 mg
(1.25 tab as single dose)

For the prescribed dose, the commercially available elixir (dexamethasone 0.5 mg/5 mL)^{3,4} was offered as an alternative and would have required a volume of 50 mL. The caregiver conveyed a concern that this volume would not be tolerated by the infant, therefore the prescription was filled with dexamethasone 4 mg tablets. The directions for use were mistakenly labelled to give a dose of 1.25 mg, instead of the intended 1.25 tablets (equal to 5 mg).

Oral Corticosteroid Options

Dexamethasone is used to treat a variety of conditions in the pediatric population, including croup and asthma. When presented with a prescription for oral dexamethasone for a pediatric patient, review the clinical indication and patient- and parent-specific factors to determine a suitable option (Table 1).⁷

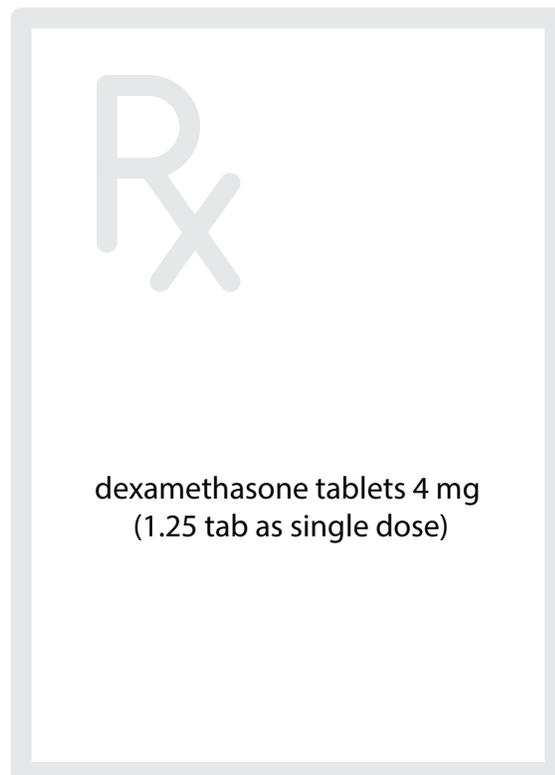


TABLE 1. Select oral corticosteroid options for acute respiratory indications in pediatric patients.

Commercially Available Pediatric Oral Solution	Commercially Available Oral Tablets	Tablets Compounded in an Oral Suspension	Injectable Solution Compounded in an Oral Suspension
Characteristic of Formulation: AVAILABILITY			
Prednisolone oral solution is commercially available in a concentration of 5 mg/5 mL. ⁸	Dexamethasone tablets are commercially available in strengths of 0.5 mg, 0.75 mg, 2 mg, and 4 mg. ^{9,10}	Dexamethasone oral suspension can be compounded from the commercially available tablet strength of 4 mg. ^{11,12}	Dexamethasone injectable solution for oral use can be compounded from the commercially available concentration of 4 mg/mL. ^{9,13}
Characteristic of Formulation: PREPARATION			
A prescription for prednisolone oral solution can be filled as usual, with no compounding or product manipulation necessary to achieve palatability and a reasonable dose volume.	If a child is unable to swallow the tablet whole, it can be split or crushed. To improve the bitter taste, tolerability, and ease of administration, it is recommended that caregivers mix the crushed tablets with a small amount of soft food (e.g., pudding) and administer immediately. ¹⁴	Compounded liquid preparations are palatable, are physically and chemically stable, and have a concentration that allows for a reasonable volume for administration. Compounding master formulation records using tablets are available from The Hospital for Sick Children and the Children's Hospital of Eastern Ontario. ^{11,12}	Compounded liquid preparations are palatable, are physically and chemically stable, and have a concentration that allows for a reasonable volume for administration. ¹⁵ A compounding master formulation record using the injectable solution is available from Nationwide Children's Hospital, a US pediatric centre. ¹³
Characteristic of Formulation: ADDITIONAL COMMENTS FOR SAFE USE			
<ul style="list-style-type: none"> • Provide caregivers with an appropriate device (e.g., oral syringe) for accurate dose measurement, and confirm their understanding of the volume to administer.¹⁶ 	<ul style="list-style-type: none"> • Incorporate an independent double check of the calculation when converting prescribed doses to number of tablets (to be specified in directions for use). • Confirm with the caregiver that they are able to split/crush the tablets and administer the medication as described. 	<ul style="list-style-type: none"> • Implement independent double-checks at each critical compounding step (e.g., calculations, verification of ingredient/strength/expiry date, weight and/or measurement of each ingredient, visual appearance of the final product).¹⁷ • Avoid returning ingredients to stock until verification of the compounded product by another team member has occurred.¹⁷ • Provide caregivers with an appropriate device (e.g., oral syringe) for accurate dose measurement, and confirm their understanding of the volume to administer.¹⁶ 	

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