CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209260Orig1s000

CLINICAL REVIEW(S)

Division of Cardiovascular and Renal Products

NDA: 209260

Drug: Atropine Sulfate Injection, USP, 0.4 mg/mL in a 20 mL multi-dose glass vial

Sponsor: Fresnius Kabi

Type of Application: 505(b)(2)

Date of Submission: 3/28/2017

Date of Completion: 12/29/2017

Clinical Reviewer: Melanie Blank, MD

Team Leader/ CDTL: Martin Rose, MD

The purpose of this memo is to discuss and provide support for labeling changes that I propose should be made to Section 1: INDICATIONS AND USAGE; and, Section 2: DOSAGE AND ADMINISTRATION.

We have submitted most of these suggestions to the sponsor (with the exception of the specific language on organophosphate, carbamate and muscarinic mushroom poisoning) in addition to literature references and have asked the sponsor to propose new labeling.

The sponsor's proposed labeling for indications and dosing and administration (b) (4) .

The Indications and Usage section includes, among other indications, (b) (4) (b) (4). Current American Heart Association guidelines (2010) for advanced cardiac life support do not include atropine for (b) (4). AHA guidelines do recommend atropine for symptomatic bradycardia. The Dosage and Administration section included sparse dosing recommendations for adults and no proposed dosing recommendations for pediatric patients despite a plenitude of published literature addressing atropine dosing in both populations. Despite small studies, mostly uncontrolled, there has been documentation of

the successful use of atropine use over the last in adults and children since the 1950's[1], and there are clinical guidelines on atropine use from American Heart Association, the Environmental Protection Agency, the World Health Organization and other authoritative sources that help guide treatment and should be included in the label to inform current use.

1 INDICATIONS AND USAGE

The sponsor proposed the language that was in the RLD:

Atropine is indicated for temporary blockade of severe or life threatening muscarinic effects, e.g., as an antisialagogue, an antivagal agent, an antidote for organophosphorus or muscarinic mushroom poisoning, and to treat (b) (4).

This should be changed to, "Atropine is indicated for temporary blockade of severe or life threatening muscarinic effects, e.g., as an antisialagogue or an antivagal agent before or during surgery, an antidote for organophosphorus or muscarinic mushroom poisoning and to treat **symptomatic bradycardia**."

The rationale for this change is that the current AHA guidelines state that atropine is no longer indicated for asystole, pulseless electrical activity or 2nd or 3rd degree AV block and that affected patients require other drugs (epinephrine and/or dopamine) or immediate pacing.

2 DOSAGE AND ADMINISTRATION

2.2 Adult Dosage

The table that the sponsor proposed is as follows:

(b) (4)

See below for tabular recommendations for adult dosing that is more thorough and describes current evidence-based use (rationales below table).

Use	Dose (adults)	Repeat	Maximum total dose
Antisialagogue or other antivagal	0.5 mg to 1 mg (1.25 mL to 2.5 mL)	As needed every 30-60 minutes preoperatively then every 4-6 hours as needed.	3 mg**
Organophosphorus carbamate or muscarinic mushroom poisoning	2 mg to 3 mg (5 mL to 7.5 mL)	Repeat in 3-5 minutes if no change in clinical symptoms. See paragraph below table for further instructions.	See paragraph below table for further instructions.
Symptomatic bradycardia*	0.5 mg (1.25 mL)	As needed every 3 to 5 minutes;	3 mg**

*Do not rely on atropine in type II second-degree or third-degree AV block because these bradyarrhythmias are not likely to be responsive to reversal of cholinergic effects by atropine. ** Limit dose to 0.03-0.04 mg/kg in patients with coronary artery disease (see section 5.2).

Dose may be doubled with each administration until atropinization and cardiovascular and respiratory status improvement. Once adequate atropinization is achieved, maintain the patient on an atropine continuous infusion at about 10%-20% of the loading dose per hour and titrate to effect. Signs of atropinization are a goal of treatment: flushing, pupil dilation, dry mouth, and tachycardia. There should be reduced bronchospasm, improved oxygenation and drying of pulmonary secretions. Regular clinical observations are necessary to ensure that atropinization is achieved without serious toxicity such as delirium, hyperthermia, and ileus. Anticholinesterase or nerve gas poisonings may require large doses of atropine and the addition of pralidoxime.

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1. *Proposal to change "[redacted] (b) (4) " to "antisialagogue or other antivagal (preanesthesia and during surgery)". The reason for this modification is that online and printed sources all specified that the setting for this use should be the preoperative setting to inhibit salivation and secretions for improved ease of intubation[2,3] or to block cardiovagal reflexes and/or succinylcholine-induced arrhythmias during surgery[4]. A thorough review of the literature (PubMed search terms atropine, indication, antisialagogue) revealed that all the atropine use for its antisialagogue/ antivagal effect was done in the surgical setting, mostly preanesthesia.*
2. *Instructions on repeating the dose for antisialogue or other antivagal (preanesthesia or during surgery) were referenced in the Carol Taketomo reference book[2] as well as the World Health Organization resource.[5]*
3. *The recommended maximum total adult dose in the 2010 recommendations from the 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care[6] is 3 mg. This does not apply to the poisonings. Because of the life-threatening nature of organic phosphate, carbamate and muscarinic poisoning, the recommendations in those settings are to continue dosing until the patient is fully atropinized, which is generally interpreted to mean stable from a cardiovascular and respiratory system perspective (no bradycardia, no pulmonary secretions and good oxygenation).*
4. *I recommend that carbamate poisoning be added to the list of poisonings for which atropine should be indicated (also for pediatrics). Carbamate poisoning is life-*

[2] http://www.jointemsprotocols.com/atropine

[3] Taketomo CK, Pediatric & Neonatal Dosage Handbook, 21 ed., Ohio: Wolters Kluwer/ Lexicomp (official drug reference for the American Pharmacists Association), 2014, p. 234.

[4] http://www.pdr.net/drug-summary/Atropine-Sulfate-Injection-atropine-sulfate-684

[5] http://apps.who.int/medicinedocs/en/d/Jh2929e/3.html

[6] Neumar RW, Part 8: Adult advanced cardiovascular life support, 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, *Circulation.* 2010; 122(suppl 3):S729 –S767.

threatening and atropine treatment is standard treatment. Oxime therapy is also supported with data. [7,8,9] *Pralidoxime is the only oxime approved in the US.*

5. *Repeat dosing of atropine for organophosphate, carbamate and muscarinic poisoning is standard advice provided by EPA and other publications.*[9,10,11,12] *These resources instruct to "dose to atropinization" where the focus is to ensure that the patient is stable from a respiratory and cardiovascular perspective.*
6. *The advice on treating bradyarrhythmias that are symptomatic including the information in the table footnotes regarding not dosing adults with 2nd or 3rd degree AV block and lower dose recommendation for patients with cardiovascular disease is provided in the 2010 AHA recommendations*[4] *(Class IIa recommendation).*

2.3 **Pediatric Dosage:**

Current language: [redacted] (b) (4)

I propose the following table instead (rationales below table):

Use	Dose (pediatrics)	Repeat	Maximum single dose	Maximum total dose
Antisialagogue or other antivagal and in specific emergency intubations when there is higher risk of bradycardia	0.02 mg/kg IV/IO	As needed every 30-60 minutes preoperatively then every 4-6 hours as needed.	0.4 mg for a child and 1 mg for an adolescent	1 mg for a child and 2 mg for an adolescent
Organophosphate, carbamate or muscarinic	0.05 mg/kg IV	See paragraph below table for further		See paragraph below table for further

[7] https://www.epa.gov/sites/production/files/documents/rmpp_6thed_ch6_carbamates.pdf

[8] Rosman Y et al, Carbamate poisoning: treatment recommendations in the setting of a mass casualties event, *Am Jl Emer Med.* 2009; 27: 1117-1124.

[9] https://www.epa.gov/pesticide-worker-safety/recognition-and-management-pesticide-poisonings

[10] Eddleston M, et al, Early management after self-poisoning with an organophosphorus or carbamate pesticide- a treatment protocol for junior doctors, *Critical Care*. 2004; 8:R391-R397.

[11] Vale A, Lotti M, Organophosphorus and carbamate insecticide poisoning, chapter 10, Handbook of clinical Neurology, Vol 131 (3rd series) Occupational Neurology, M. Lotti and ML Bleecker, Editors, 2015 Elevier, p. 149-167.

[12] Roberts DM and Aaron CK, Manging acute organophosphorus pesticide poisoning, *BM.* 2007;334:629-34.

mushroom poisoning		instructions.		instructions.
Symptomatic bradycardia due to increased vagal tone or primary AV conduction block (not secondary to hypoxia)	0.02 mg/kg IV/IO 0.04-0.06 mg/kg via endotracheal tube**	As needed every 5 minutes.	0.5 mg for a child and 1 mg for an adolescent	1 mg for a child and 2 mg for an adolescent

IV=intravenous; IO=intraosseous; *Available evidence does not support the routine use of atropine in emergency intubation of critically ill infants and children except in in specific emergency intubations when there is higher risk of bradycardia. ** flush with 1-5 mL of normal saline depending on size and follow with 5 ventilations.

Victims of organophosphate poisoning can tolerate large doses of Atropine. May double dose and repeat every 5-10 minutes until atropinization or cardiovascular and respiratory status improvement. Signs of atropinization are a goal of treatment: flushing, pupil dilation, dry mouth, and tachycardia. There should be reduced bronchospasm, improved oxygenation and drying of pulmonary secretions. Regular clinical observations are necessary to ensure that atropinization is achieved without serious toxicity such as delirium, hyperthermia, and ileus. Anticholinesterase or nerve gas poisonings may require large doses of atropine and the addition of pralidoxime.

7. *While there should also be an indication for antisialagogue or other antivagal (preanesthesia and during surgery), according to the PALS (Pediatric Advanced Life Support) ECC (Emergency Cardiovascular Care) 2010/2015 integrated American Heart Association Guidelines for Cardiopulmoary Resuscitation and Emergency Cardiovascular Care,[13,14] atropine should be considered only in situations where there is an increased risk of bradycardia (eg, when giving succinylcholine as a neuromuscular blocker to facilitate intubation). (Class IIb recommendation).*
8. *There has been a great deal of discussion in the literature over the years about a paradoxical bradycardia when atropine is used in doses that are too low (less than 0.1mg). However, there is evidence to the contrary[15,16] and therefore, the current ECC guidelines suggest a dose of 0.02 mg/kg IV/ IO/IM or 0.04-0.06 mg/ kg via ET tube when atropine is used for premedication for emergency intubation where there is an increased risk of bradycardia. The guidelines do not specify a minimum dosage. Other authors have*

[13] https://eccguidelines.heart.org/wp-content/themes/eccstaging/dompdf-master/pdffiles/part-12-pediatric-advanced-life-support.pdf

[14] de Caen, et al, Part 12: Pediatric Advanced Life Support 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, *Circulation*. 2015;132[suppl 2]:S526–S542.

[15] Jones P, et al, Atropine for critical care intubation in a cohort of 264 children and reduced mortality unrelated to effects on bradycardia. *PLoS One*. 2013;8:e57478. doi: 10.1371/journal.pone.0057478.

[16] Jones P, et al, The effect of atropine on rhythm and conduction disturbances during 322 critical care intubations. *Pediatr Crit Care Med*. 2013;14:e289– e297. doi: 10.1097/PCC.0b013e31828a8624.

more recently published articles to discourage specifying a minimum dose of atropine in children.[17,18]

9. *Instructions on maximum single dose from several sources*[2, 10,19,20] *state that a child should receive a maximum single dose of 0.4-0.5 mg and an adolescent should receive a maximum single dose of 1 mg unless there is poisoning when there is no maximum dose.*
10. *For bradycardia, the most recent PALS*[10] *guideline advice in the bradycardia algorithm is that if bradycardia is due to increased vagal tone or primary AV conduction block (ie, not secondary to factors such as hypoxia), give IV/IO atropine 0.02 mg/kg or an endotracheal dose of 0.04-0.06 mg/kg (Class I recommendation).*
11. *The instructions on a maximum total atropine dose for children were taken from the text book Miller's Anesthesia*[21]*, in the limb describing "persistent symptomatic bradycardia-if vagal tone or primary AV block," it is recommended, that the maximum total dose for child be 1 mg. The 8th edition of Smith's Anesthesia for Infants and Children*[22] *states that the pediatric dose for atropine is 0.02 mg /kg, with a maximal dose of 2 mg.*
12. *The instructions for atropine treatment as an antidote to nerve gas, organophosphate, or carbamate poisoning were derived from a 2003 publication by Rotenberg and Newmark*[23] *published in Pediatrics and further informed by the Roberts, and Eddleston publications. I could not find any advice for pediatrics specifically on muscarinic mushroom poisoning; however, because the mechanism of toxicity is the same as the other poisons and atropine is indicated in adults with muscarinic mushroom poisoning, I thought it was reasonable to include it in the pediatric indications.*

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[17] Prakash S and Mullick P, Is a minimum dose of atropine in children justified? *Jl of Anaes Clin Pharm*. 2017; 33: 282-3.

[18] Barrington KJ. The myth of a minimum dose for atropine. *Pediatrics*. 2011;127:783-4.

[19] http://www.fpnotebook.com/Neuro/Pharm/Atrpn.htm#fpnContent-panel-id_4

[20] https://reference.medscape.com/drug/atropen-atropine-iv-im-343093

[21] McGlinch BkP, et al, Cardiopulmonary resuscitation: Basic and advanced life support. In: Miller RD, Eriksson Li, Fleisher LA, Wiener-Kronish JP, Young WL, editors. Miller's Anesthesia. 7th ed. Philadelphia, PA: Churchill Livngstone/Elsevier; 2009. P. 2996.

[22] Shaffner DH. Pharmacology of resuscitation. In: Motoyama EK, Davis PJ, editors. Smith's Anesthesia for Infants and Children. 8th ed. Philadelphia: Elsevier Publisher; 2011. P. 2794.

[23] Rotenberg J and Newmark J, Nerve Agent Attacks on Children: Diagnosis and Management. *Pediatrics*. 2003;112:648-657.

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/s/

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