ACMT Position Statement:
Alternative or Contingency Countermeasures for Acetylcholinesterase Inhibiting Agents

Disclaimer
The position of the American College of Medical Toxicology (ACMT) is as follows:

First responders and health care providers must prepare to provide care for patients poisoned by acetylcholinesterase (AchE) inhibitor chemical warfare agents or pesticides. However, pre-deployed medical countermeasures (MCMs) may not be sufficient due to production and delivery interruption, rapid depletion of contents during a response, expiration of MCM components, or lack of local availability of approved MCMs. To augment supplies of community-based and forward-deployed nerve agent countermeasures, the American College of Medical Toxicology (ACMT) supports several strategies: 1) The use of expired atropine, diazepam, and pralidoxime auto-injectors and vials if non-expired drugs are unavailable; 2) Investigation, development, and identification of alternative countermeasures-commonly stocked drugs that are not approved for nerve agent poisoning but are in the same therapeutic class as approved drugs.

While individual practices may differ, this is the position of the American College of Medical Toxicology (ACMT) at the time written, after a review of the issue and pertinent literature.

Background

First responders and health care providers must prepare to provide care for patients poisoned by acetylcholinesterase (AchE) inhibitor chemical warfare agents or pesticides. Response preparation has relied on community-based, capacity-limited, pre-deployed forward medical countermeasure (MCM) caches (e.g., "CHEMPACK."). CHEMPACK containers are specifically designated for use during mass exposures to acetylcholinesterase inhibitors ("nerve agent") (1). However, pre-deployed MCMs may not be sufficient due to production and delivery interruption, rapid depletion of contents during a response, expiration of MCM components, or lack of local availability of approved MCMs (2). Community-based, pre-deployed MCMs were never intended to be the primary (or sole) MCM capability available to a community. These stocks may be further limited as a resource due to logistical challenges (e.g., timely mobilization) or delayed recognition of an AchE-inhibitor poisoning event.

Use of Expired Medications

The American College of Medical Toxicology supports the use of expired atropine auto-injectors and vials if non-expired drug is not available. The Shelf Life Extension Program (SLEP), established in 1986, provides a mechanism where the labeled shelf life of emergency preparedness drugs can be extended based on FDA stability testing (3). Through the use of Emergency Use Authorizations, FDA can allow use of specific drugs beyond expiration in chemical, biological, radiation, and nuclear emergencies (3). If all other contingency measures have been exhausted in an AchE-inhibitor poisoning event, the use of expired antidotes such as atropine, diazepam, and pralidoxime may be appropriate even in the absence of FDA SLEP approval.

In March 2016, FDA issued a memorandum supporting use of atropine, diazepam, and pralidoxime auto-injectors for up to two years beyond the manufacturer's initial expiration date. We strongly agree with this recommendation (4). A drug is not necessarily unstable or degraded after the expiration date (5). The expiration date indicates the limit of available stability testing. Even after some drug degradation, a vial may still contain significant concentrations of active drug years after expiration (5). An expired auto-injector may deliver less than the labeled amount of drug if there is a failure of the auto-injector mechanism or degradation of drug (6). However, because anticholinergics and anticonvulsants are

titrated to clinical effect in AchE inhibitor poisoning, clinicians can simply administer more medication until the desired clinical effect is observed (7.)

Alternative Countermeasures

In a large mass casualty event, the supply of MCMs at the point of care may be insufficient, even with the authorized use of expired medications. Therefore, we also support investigation, development, and identification of alternative sources of nerve agent MCMs. Ideally, alternative MCMs are drugs that are FDA-approved for other indications and are already commonly stocked in community clinics, hospitals, pharmacies, prehospital care systems, and government agencies. Alternative MCMs should also be members of the same pharmaceutical class as traditional MCMs and have appropriate bioavailability and pharmacokinetics for use in AchE inhibitor-poisoned patients. Alternative routes of administration should be considered. For example, medications approved for intravenous (IV) route can generally be administered by the intraosseous route when IV access is delayed or impractical (8).

Another example is, sublingual or intranasal (IN) atropine. The 1% formulation may be considered as a substitute for intramuscular atropine when the latter is not available (9,10). Atropine is already formulated in this concentration for ophthalmologic use and is readily bioavailable by sublingual route. Ipratropium, approved for asthma and COPD, may be used by inhalation (inh) route as supplemental treatment for cholinergic pulmonary manifestations (11). Alternative benzodiazepines, such as lorazepam, may substitute for FDA-approved AchE inhibitor antidotes diazepam and midazolam for treating seizures in AchE inhibitor-poisoned patients. Lorazepam is FDA-approved for management of seizures, belongs to the same medication class as diazepam and midazolam, and is widely available and familiar to practitioners. At this time, there are no FDA-approved alternatives to pralidoxime, so efforts should be made to maintain availability of that drug and investigate the efficacy of other oximes, such as obidoxime.

Further work should focus on developing AchE-inhibitor treatment strategies using MCMs. We urge development of model treatment guidelines and algorithms using alternative drugs based on availability, pharmacokinetics, and bioavailability.

Table
Selected Alternative Countermeasures for Acetylcholinesterase Inhibitory Agents
(Not comprehensive)

Clinical Manifestations	Approved Measure	Alternative Countermeasure
Muscarinic-General	Atropine IM auto-injector	Atropine 1% IN
		Atropine 1% SL
		Glycopyrrolate IM/IO/IV (Arendse)
Muscarinic-Pulmonary	Atropine IM auto-injector	Ipratropium inh
		Glycopyrrolate IM/IO/IV
Seizures	Diazepam IM auto-injector	Lorazepam IM/IN(Jain)/IV

(12,13)

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