Adverse Reaction to Atropine and the Treatment of Organophosphate Intoxication

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Abstract

Atropine is the drug of choice for treatment of organophosphate nerve agent and insecticide intoxication and has been used for this indication for several decades. Adverse reactions to atropine may occur, and are of two types: toxic and allergic. Toxic reaction, the most common form, results from the anti-muscarinic effects of the drug. Since it is most probably related to interpersonal variation in sensitivity to atropine, toxic effects may appear at the usual therapeutic doses. The second type, allergic reaction, includes local manifestations, usually after the administration of eyedrops, and systemic reaction in the form of anaphylaxis. Since most patients manifest only a mild reaction, allergy testing is not performed and the prevalence of allergy to atropine is therefore not known. Severe allergic reaction to atropine is rare, as evidenced by the small number of case reports in the literature despite the drug's extensive use. Alternative anti-muscarinic drugs recommended for OP poisoning include glycopyrrolate and scopolamine. Glycopyrrolate is a peripheral anti-muscarinic drug that has been studied in comparison to atropine for many clinical indications, while scopolamine is an anti-muscarinic drug with both peripheral and central effects. An acceptable alternative regimen for patients with proven allergy to atropine is a combination of glycopyrrolate with centrally active drugs such as benzodiazepines or scopolamine.

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Organophosphate nerve agents and insecticides are extremely toxic chemicals that exert their biologic effects by inhibition of the enzyme acetylcholinesterase. The inhibited enzyme cannot hydrolyze acetylcholine, resulting in the accumulation of the neurotransmitter in the nicotinic and muscarinic cholinergic synapses, and overstimulation of the cholinergic system [1].

Atropine is considered the drug of choice for nerve agent intoxication, since the late 1940s. It continues to be the standard treatment despite the fact that many cholinergic blocking substances have since been tested and found active. Atropine is a competitive inhibitor of the muscarinic acetylcholine receptor. It blocks the effect of excess acetylcholine and protects the receptor from further stimulation. It has a minimal effect at nicotinic receptor sites [1,2]. Although atropine does not readily cross the blood-brain barrier, the drug has some central beneficial effects in OP poisoning. The central nervous system effects observed in atropine overdose demonstrate that it is capable of crossing the blood-brain barrier to some extent.

Experience with atropine for treatment of OP insecticide poisoning in humans is considerable [3], while experience with the drug for treatment of nerve agent intoxication comes mainly from animal studies. The known existence of hypersensitivity toward atropine, albeit rare, requires a medical solution for treating OP-poisoned atropine-sensitive patients.

Adverse reactions to atropine

The available literature on systemic adverse reactions to atropine is limited, with most reports relating to the use of eyedrops containing atropine. There are two types of adverse reactions to atropine: toxic (atropine toxicity) and allergic [4,5].

Toxic reaction

Toxic reaction to atropine results from its anti-cholinergic action and includes a variety of peripheral and central manifestations. This reaction is related to the considerable interpersonal variation in susceptibility to atropine (idiosyncrasy), so that toxic effects may occur at the usual therapeutic doses [6]. Thus, a toxic reaction is manifested by signs of an overdose, even though the doses used were not deemed excessive. The interpersonal variation in relation to atropine toxicity is demonstrated by cases of death that have been reported following doses of 100 mg or less for adults (and 10 mg for children), while on the other hand, people have recovered from intoxication with a 1 g dose of atropine [5]. Patients with Down's syndrome are abnormally sensitive to atropine [7].

Local reaction to atropine may derive from both toxic and allergic origins, which are not easily distinguishable by the clinical presentation alone [8]. In contrast to local reactions, the systemic reaction due to atropine toxicity has features that are clearly different from those stemming from anaphylactic reaction, thus the cause of the reaction can be more easily determined. Local toxic reaction to atropine includes conjunctival injection and periorbital dry, red skin. Atropine systemic toxicity causes tachycardia, tachypnea, elevated body temperature, and CNS stimulation marked by restlessness, confusion, psychotic reactions, delirium and occasionally seizures. A rash may appear on the face or upper trunk. In severe intoxication, central stimulation may cause CNS depression, coma, circulatory and respiratory failure, and death.

Gallasch et al. [9], evaluating the adverse reactions to atropine eyedrops among children (age 1–14), noted 31 reports of toxic reactions that resulted in elevated body temperature and dry, warm

OP = organophosphate

CNS = central nervous system

skin. In two cases with red eyes and periorbital dermatitis, allergic reactions were suspected but skin allergy tests were negative. In a study by Stokes [10], the members of the South Carolina Ophthalmological Society were asked to report all known reactions to topical diagnostic drugs used in their office practice during the preceding 2 years (1982–1984). Reported reactions to atropine eyedrops included 26 local ocular reactions, 31 mild systemic reactions, and 4 severe reactions that included 2 cases of asthmatic attack, one case of convulsions and one of tachycardia [5]; it was not noted whether allergy tests were performed in these cases.

There are several case reports of severe toxic reactions following the use of atropine. Economacos and Kanakis [6] reported a toxic reaction in a 65 year old patient after intramuscular administration of 0.5 mg atropine. The patient developed tachycardia, hypertension and mydriasis. A severe toxic reaction in a 12 year old girl after the use (probably ingestion) of atropine eyedrops was reported in 1985 [5]. A lethal dose of as low as 1.6 mg in a 2 year old boy was also reported [11]. Acute, non-fatal toxic reactions have been observed after the instillation of only a few drops of atropine for cycloplegic refraction [12].

According to these studies and case reports, toxic reactions to atropine, especially when administered topically, are not rare. Local reactions are usually mild and are not reported because of their low clinical significance. They resolve after the cessation of atropine use. In cases of systemic toxicity, treatment includes supportive care, and in severe cases physostigmine and diazepam. Patients who manifest an adverse reaction of the toxic type – e.g., Down syndrome patients – can still be treated with a reduced dose of atropine, with appropriate care.

Allergic reaction

The literature contains few reports of allergic reactions to atropine. These include one prospective study and several case reports. The most common manifestation of atropin allergy is local reaction after instillation of eyedrops. The allergic reaction usually includes dermatitis over the eyelids, with erythema, itching and local edema. Reports of anaphylaxis due to atropine are extremely rare [4].

A prospective study by Vadot and Piasentin [8] evaluated the incidence of adverse reactions to eyedrops among hospitalized patients. The incidence of allergic reaction was 3% for eyedrops containing atropine, most of which were mild reactions proven as allergy by patch tests. This incidence of atropine allergy is higher than that in the study by Gallasch et al. [9], who found no positive allergy tests in 31 patients with local reactions. In both studies a patch test was used for allergy testing. A possible explanation for this discrepancy relates to differences in atropine sensitivity between populations (one study was conducted in France and the other in Germany) [8,9]. A case report from Japan describes a patient who developed severe dermatitis after the use of atropine eyedrops [13]. The patient was extremely sensitive, and had a positive patch test even with dilution of 1:1,600 of the clinically used concentration (1%).

In the last 20 years there was only a single reported case of proven hypersensitivity to atropine given intravenously during anesthesia [4]. A 38 year old woman developed symptoms of anaphylactic shock after administration of intravenous atropine and required adrenaline to maintain perfusion pressure. The patient had no history of allergy or atopy. An intradermal test to 1% atropine solution 1 month after the event proved strongly positive. The patient reported having taken an oral analgesic compound that contained 0.25 mg atropine, less than 1 year before the event. This prior exposure to the drug is important because for an anaphylactic reaction to occur, previous exposure to the drug (or similar agent) is necessary.

Although cases of severe systemic reaction to atropine that are proven to be of the allergic type are very rare, patients with an allergic reaction, even if mild, have an increased risk for severe reaction in the future. Thus, in these patients, another anti-muscarinic drug should be used.

Alternative anti-muscarinic drugs

There are several anti-muscarinic drugs, other than atropine, that can be used to treat OP intoxication. Of those, the two that have been suggested as a replacement for atropine are glycopyrrolate and scopolamine [4].

Glycopyrrolate

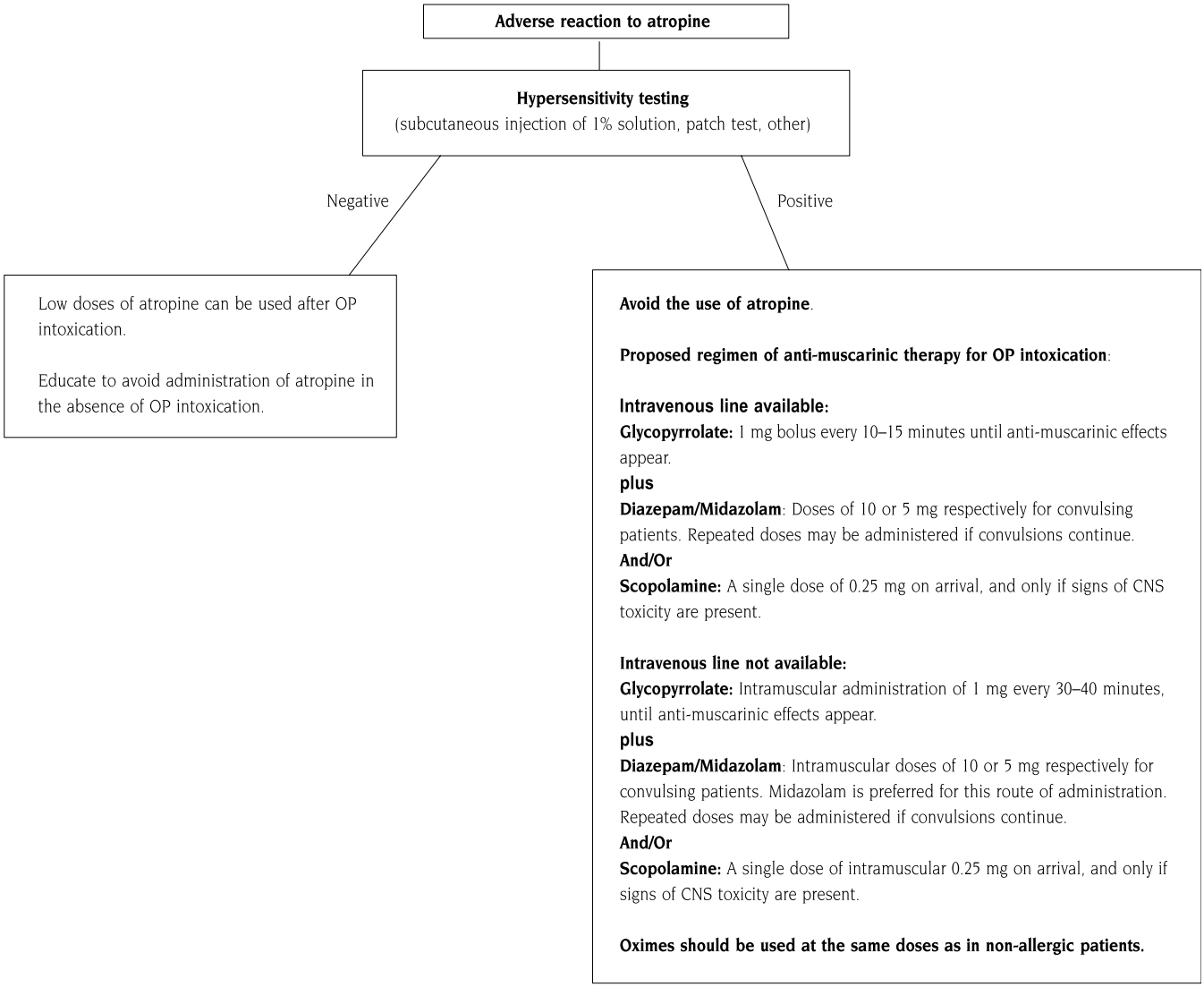
Glycopyrrolate (glycopyrronium bromide) is a quaternary ammonium anti-cholinergic agent, with anti-muscarinic activity and peripheral action similar to that of atropine. Because of the marked differences in the chemical structure of atropine and glycopyrrolate, patients allergic to atropine will most probably not be allergic to glycopyrrolate.

Indications for the use of glycopyrrolate include: reduction of gastric secretion volume and acidity in patients undergoing surgical procedures, as an adjunct in the treatment of peptic ulcer, secretion reduction during anesthesia, and reversal of the effect of muscle relaxants [14]. It can also be used during pregnancy instead of atropine because it does not cross the blood-placenta barrier. Glycopyrrolate is twice as potent as atropine for peripheral effects, therefore half the dosage should be given for comparable response [15]. Penetration of glycopyrrolate across the blood-brain barrier is low [16]. It does not have detectable central anti-cholinergic effects at doses capable of blocking peripheral cholinergic receptor sites.

Glycopyrrolate may be administered orally, intramuscularly or intravenously. Absorption from the gastrointestinal tract is poor, with 10–25% absorbed after oral intake. Peak effects occur within 30–45 minutes following intramuscular administration, and within 1 minute following intravenous administration [14,17]. It is excreted in bile and urine, and should be used with caution in patients with renal failure. The mean elimination half-life after intramuscular administration is 75.4 minutes, and almost half of the drug is excreted in pharmacologically active form in the urine within 3 hours [17].

Bardin and Van Eeden [15] compared the treatment of insecticide OP poisoning in humans with atropine versus glycopyrrolate. The ratio of atropine and glycopyrrolate was 2:1 and treatment was by continuous infusion. Treatment with atropine and glycopyrrolate was equally effective, except for a trend (not statistically significant) of fewer respiratory infections in the

Figure 1. Treatment algorithm for patients with a history of adverse reaction to atropine



glycopyrrolate group. Tracey and Gallaghar [18] reported the use of glycopyrrolate to treat patients with insecticide OP poisoning. Both patients were treated with glycopyrrolate, atropine, pralidoxime and benzodiazepines. The use of a combination therapy of atropine and glycopyrrolate provided adequate control of secretions and heart rate, while avoiding the central toxic effects that can occur when very large dosages of atropine are used. Nevertheless, it is important to note that in nerve agent intoxication as well as in some insecticide OP intoxications, the central anti-muscarinic effects of atropine are beneficial.

In a study by Lau et al. [19], the therapeutic efficacy of some anti-muscarinic drugs against the nerve agent soman was evaluated in rats. Atropine and glycopyrrolate were tested alone or in combination with the oxime HI-6. When given alone, both drugs offered only mild protection against soman poisoning. Inclusion of HI-6 significantly enhanced the efficacy of atropine, whereas the combination therapy with glycopyrrolate and HI-6 only marginally improved outcome. In this study, no centrally active drug was given as part of the treatment regimen, which may explain the difference in the efficacy of the drugs. Further study is needed to evaluate the efficacy of glycopyrrolate when given together with centrally active drugs, such as benzodiazepines, or centrally active anti-cholinergic drugs.

The comparative efficacy of glycopyrrolate and atropine was evaluated in various other medical conditions, including airway obstruction, premedication, labor, exercise-induced asthma, neuromuscular blockade reversal, gastric acidity, lower esophageal sphincter pressure reduction, neuromuscular blockade, and prevention of oculocardiac reflex [20]. Glycopyrrolate was found to be as good as atropine for these indications, when given in equivalent doses.

Based on these reports, and although there are only limited data on its efficacy in nerve agent intoxication, glycopyrrolate seems to be an acceptable alternative for treatment of the peripheral effects

of OP intoxication. Other drugs that are centrally active should be given together with glycopyrrolate for patients with signs of CNS toxicity.

Scopolamine

Scopolamine (hyoscine methonitrate) is an anti-muscarinic agent with central and peripheral actions. It crosses the blood-brain barrier, and its central action differs from that of atropine in that it depresses the cerebral cortex, especially the motor areas, and produces drowsiness and amnesia. It is well absorbed from the gastrointestinal tract, and may be given orally, intramuscularly, intravenously, subcutaneously or by dermal patch. It is effective in the prevention and control of motion sickness and has also been given as an anti-emetic in the prophylactic treatment of other forms of nausea [21].

Scopolamine has been studied for the treatment of seizures caused by nerve agent intoxication because it crosses the blood-brain barrier and has central anti-muscarinic activity. It has been shown that nerve agents induce seizures that rapidly progress to status epilepticus and may cause profound brain damage [22]. Recent works by McDonough and Shin [23] demonstrate the ability of scopolamine to prevent or stop seizures only during the first 5–10 minutes of epileptic activity. Administration of the drug during later stages of the intoxication may cause CNS effects due to its anti-muscarinic action, without providing sufficient protection. Therefore, other drugs, mainly benzodiazepines, should be used at these later stages [22].

Treatment of patients with history of adverse reaction to atropine

The approach to a patient with an atropine-allergic reaction is different to that regarding a patient who has a history of toxic reaction. Hence, when preparedness programs are being developed against chemical warfare, it is important to identify patients allergic to atropine and to provide treatment regimens with alternative drugs.

Performing skin tests on patients with a history of adverse reaction to atropine, even if mild, will help to identify allergic patients who will need other drugs, and is thus recommended. However, since the prevalence of severe allergy to atropine is probably very low, screening of large populations in order to trace patients with this allergy is not warranted. Allergy testing for atropine can be done by subcutaneous injection of atropine solution, patch tests, or other testing methods.

If a patient with a history of adverse reaction to atropine has a negative allergy test, atropine for the treatment of nerve agent poisoning is not contraindicated but should be used with caution and in small doses. As the dosage of anti-cholinergic drugs in nerve agent intoxication is titrated by the clinical response and not by prefixed values, the risk for overdose is small. In the case of atropine toxicity (due to overdose or due to the use of atropine in a patient who was not intoxicated), treatment is usually supportive. Physostigmine has been used for anti-muscarinic poisoning [24] and may be useful for patients with coma, arrhythmias, hallucinations, severe hypertension, or seizures. Diazepam may also be given to control marked excitement and seizures. If the patient is allergic to atropine (by positive allergy test), further treatment with this drug is contraindicated and alternative drugs should be used. Glycopyrrolate is an acceptable alternative for treating the peripheral effects of the intoxication. Centrally active drugs, such as benzodiazepines or scopolamine, should be added for patients with signs of CNS toxicity. These centrally active drugs should be administered under medical supervision. Treatment regimens are presented in Figure 1.

Conclusion

Atropine is a widely used drug in the form of eyedrops, solutions for intravenous administration, and auto-injectors for nerve agent intoxication. This drug has been in use for many years and the frequency of systemic allergic reactions is very low, but the exact prevalence is not known. The administration of atropine to a large population for treatment of nerve agent intoxication carries the risk of allergic or toxic reactions in a small number of patients. Performing skin tests on patients with even a mild adverse reaction to atropine will enable better medical treatment in the case of organophosphate poisoning.

References

1. Sidell FR, Borak J. Chemical warfare agents. II. Nerve agents. *Ann Emerg Med* 1992;21:865–71.
2. Gunderson CH, Lehmann CR, Sidell FR, Jabbari B. Nerve agents: a review. *Neurology* 1992;42:946–50.
3. Sungur M, Guven M. Intensive care management of organophosphate insecticide poisoning. *Crit Care* 2001;5(4):211–15.
4. Aguilera L, Martinez-Bourio R, Cid C, et al. Anaphylactic reaction after atropine. *Anesthesiology* 1988;43:955–7.
5. O'Connor PS, Mumma JV. Atropine toxicity. *Am J Ophthalmol* 1985;99:613–14.
6. Economacos G, Kanakis J. A case of hypersensitivity to atropine. *Anesth Analg Reanim* 1981;38:748.
7. Cramp J. Reported cases of reactions and side effects of the drugs which optometrists use. *Aust J Optom* 1976;59(1):13–25.
8. Vadot E, Piasentin D. Incidence of allergy to eyedrops – results of a prospective survey in a hospital milieu. *J Fr Ophtalmol* 1986;9:41–3.
9. Gallasch G, Schutz R, Gotz ML, Kraus-Mackiw E. Side effects of atropine: pharmacological, allergic, pseudo-allergic or toxic reactions? *Klin Monatsblatter Augenheilk* 1982;181:96–9.
10. Stokes HR. Drug reactions reported in a survey of South Carolina. *Ophthalmology* 1979;86:161–5.
11. Heath WE. Death from atropine poisoning. *Br Med J* 1950;2:608.
12. Hoefnagel D. Toxic effects of atropine and homatropine eyedrops in children. *N Engl J Med* 1961;264(4):168–71.
13. Yoshikawa K, Kawahara S. Contact allergy to atropine and other mydriatic agents. *Contact Dermatitis* 1985;12:56–7.
14. Mirakhur RK, Dundee JW. Glycopyrrolate: pharmacology and clinical use. *Anesthesiology* 1983;38:1195–204.
15. Bardin PG, Van Eeden SF. Organophosphate poisoning: grading the severity and comparing treatment between atropine and glycopyrrolate. *Crit Care Med* 1990;18:956–60.
16. Proakis AG, Harris GB. Comparative penetration of glycopyrrolate and atropine across the blood-brain and placental barriers in anesthetized dogs. *Anesthesiology* 1979;48:333–44.
17. Ali-Melkkila TM, Kaila T, Kanto J, Iisalo E. Pharmacokinetics of I.M. glycopyrronium. *Br J Anaesth* 1990;64:667–9.
18. Tracey JA, Gallaghar H. Use of glycopyrrolate and atropine in acute organophosphorus poisoning. *Hum Exp Toxicol* 1990;9(2):99–100.

19. Lau WM, Lewis KJ, Dawson RM. Evaluation of the therapeutic efficacy of some antimuscarinics against soman in vivo. *J Appl Toxicol* 1996;16(5):423–30.
20. DRUGDEX System. Atropine: Clinical Application, Comparative Efficacy, Glycopyrrolate. In: Klasco RK, Gelman CR, eds. DRUGDEX System. MICROMEDEX, Greenwood Village, Colorado.
21. Reynolds JEF, ed. Martindale: The Extra Pharmacopoeia. 31st edn. London, The Pharmaceutical Press, 1996:499–500.
22. Lallement G, Dorandeu F, Filliat P, Carpentier P, Baille V, Blanchet G. Medical management of organophosphate-induced seizures. *J Physiol (Paris)* 1998;92:369–73.
23. McDonough JH, Shin TM. Pharmacological modulation of soman-induced seizures. *Neurosci Biobehav Rev* 1993;17(2):203–15.
24. Lapan D, Smith JW. Atropine coma: physostigmine reversal. *Ariz Med* 1977;34:159–60.

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One of the first duties of the physician is to educate the masses not to take medicine.

William Osler (1849–1919), Canadian physician considered the "father" of modern medicine, and the first author of Harrison's Principles of Internal Medicine

Such is the blindness, nay, the insanity of mankind, that some men are driven to death by the fear of it.

Seneca, Greek philosopher (first century A.D.)