Monograph on Atropine

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1. Introduction

Atropine is the best-known member of a group of drugs known as muscarinic antagonists, which are competitive antagonists of acetylcholine at muscarinic receptors. This naturally occurring tertiary amine was first isolated from the *Atropa belladonna* plant by Mein in 1831 (Weiner, 1985). Although atropine earlier enjoyed widespread use in the treatment of peptic ulcer, today it is mostly used in resuscitation, anaesthesia, and ophthalmology, usually as the more soluble sulphate salt. By competitively blocking the action of acetylcholine at muscarinic receptors, atropine may act as a specific antidote. As such, it may also be used to counteract adverse parasympathomimetic effects of pilocarpine, or neostigmine administered in myasthenia gravis. It is a specific antidote for the treatment of poisoning with organophosphorus and carbamate insecticides and organophosphorus nerve agents. Although other anticholinergic agents (such as dextemidside) with different distribution kinetics may have advantages in rodent models (Lullmann et al., 1982), the role of atropine in the treatment of organophosphate poisoning is essentially unchallenged, though there is controversy concerning the dose of atropine necessary for optimal therapy in organophosphate poisoning.

Atropine is also useful in treating muscarine poisoning following ingestion of fungi of the *Clitocybe* and *Inocybe* species.

If the dose of atropine is titrated correctly, it has few serious side effects when used in organophosphate poisoning. Patients who are hypoxic, however, are at risk of developing ventricular tachycardia or fibrillation if given atropine. It is important, therefore, to correct hypoxia by clearing airways, administering oxygen and, if necessary, mechanically ventilating the patient before giving atropine (Hase et al., 1984; Matthew & Lawson, 1970; Heath & Meredith, 1992).

2. Name and chemical formula

2.1 Names:

Atropine and atropine sulphate

2.2 Synonyms

*atropine*

Atropin (German); eyeules; DL-hyoscyamine (atropine consists of a mixture of equal parts of D- and L-hyoscyamine); atropinum; 2-phenylhydracrylic acid-3-alpha-tropanyl ester; beta-phenyl-t-oxypropionsaure-tropyl-ester (German); 1-alpha-H,5-alpha-tropan-3-alpha-OL(±)tropate (ester); DL-tropanyl-2-hydroxy-1-phenylpropionate; tropic acid–3-alpha-tropanyl ester; DL-tropyltropate; (1R,3r,5S,8r)-Tropan-3-yl(RS)-tropate, tropine tropate
atropine sulphate

Atropina solfato (Italy); atropina sulfato (Spain, Argentina); atropine sulphate (USA); atropin siran (Czech); atropinsulfas; atropinsulfat (Germany); sulphate d’atropine (France); 1-\(\alpha\)-H,5-\(\alpha\)-H-tropan-3-\(\alpha\)-OL-(±)-tropate (ester), sulfate (2:1) salt; dl-tropanyl-2-hydroxy-1-phenylpropionate sulphate

(atropine, Sax, Lewis 1992)

2.3 IUPAC name

atropine

benzeneacetic acid, alpha-(hydroxymethyl)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester endo-(±)-

atropine sulphate

benzeneacetic acid, alpha-(hydroxymethyl)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl ester endo-(±)-, compounds, sulfate (2:1) (salt)

2.4 CAS number:

51-55-8 (atropine)

55-48-1 (atropine sulphate anhydrous) (USP, 2002).

5908-99-6 (atropine sulphate monohydrate) (Parfitt, 1999)

2.5 Empirical formula

\begin{align*}
\text{atropine} & : \text{C}_{17}\text{H}_{23}\text{NO}_3 \\
\text{atropine sulphate monohydrate} & : (\text{C}_{17}\text{H}_{23}\text{NO}_3)_2\text{H}_2\text{SO}_4\cdot\text{H}_2\text{O} \quad \text{(Parfitt, 1999)}
\end{align*}

2.6 Relative molecular mass

\begin{align*}
\text{atropine} & : 289.38 \\
\text{atropine sulphate monohydrate} & : 694.82 \quad \text{(Budavari, 1996)} \\
\text{atropine sulphate anhydrous} & : 676.82
\end{align*}

2.7 Conversion tables

atropine

3. Physico-chemical properties

3.1 Melting point

*atropine:*

Atropine sublimes under high vacuum at 93 to 110 °C and has a melting point of 114 to 116 °C. (Budavari, 1996)

*atropine sulphate monohydrate:*

This salt has a melting point of 190 to 194 °C (Budavari, 1996).

3.2 Physical state

*atropine:*

Atropine occurs as white crystals or crystalline powder.
**atropine sulphate:**

Atropine sulphate occurs as odourless, very bitter, colourless crystals or white crystalline powder (Parfitt, 1999, Budavari, 1996).

### 3.3 Solubility

**atropine:**

Atropine has low solubility in water (approximately 1g atropine in 455ml water and 1 g atropine in 90ml water at 80 °C). One gram is soluble in 2 ml alcohol, 2.5ml alcohol at 60°C, 27 ml of glycerol, 25ml ether and 1 ml chloroform (Budavari, 1996)

**atropine sulphate monohydrate**

Atropine sulphate is very soluble in water. One gram dissolves in 0.4 ml water. One gram dissolves in 5 ml cold alcohol and 2.5 ml boiling alcohol, in 2.5 ml glycerol, 420 ml chloroform and 3,000 ml ether. (Budavari, 1996)

### 3.4 Optical properties:

**atropine**

atropine is optically inactive.

**atropine sulphate**

atropine sulphate is almost inactive optically (Budavari, 1996).

### 3.5. pK\textsubscript{a}

**atropine:**

9.8 (McEvoy, 2002)

### 3.6. pH

**atropine:**

A saturated solution of atropine in water is alkaline (Parfitt, 1999).

**atropine sulphate:**

A 2% solution in water has a pH of 4.5 to 6.2 (Parfitt, 1999).

### 3.7. Stability in light

**atropine:**

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Atropine should be protected from light, and stored in airtight containers (Parfitt, 1999).

**atropine sulphate:**

Atropine sulphate is slowly affected by light (McEvoy, 2002). It should be protected from light and stored in airtight containers (Parfitt, 1999).

### 3.8. Reactivity

**atropine:**

When heated to decomposition, toxic fumes of oxides of nitrogen are emitted (Sax, Lewis, 1992).

**atropine sulphate:**

Atropine sulphate effloresces when exposed to dry air (McEvoy, 2002). When heated to decomposition, toxic fumes of oxides of nitrogen and sulphide are emitted (Sax, Lewis 1992).

### 3.9. Pharmaceutical incompatibilities

**atropine:**

No information available

**atropine sulphate**

Atropine sulphate is reported to be physically incompatible with noradrenaline bitartrate, metaraminol bitartrate and sodium bicarbonate injections. A haze or precipitate may form within 15 minutes when the injection is mixed with methohexital sodium solution (McEvoy, 2002). Immediate precipitation occurs when cimetidine and pentobarbital sodium together are mixed with atropine sulphate in solution, while a precipitate will form within 24 hours if atropine sulphate is mixed with pentobarbital sodium alone (Trissell, 2001). Thiopental sodium and atropine sulphate injected together at Y-sites will form white particles in the solution immediately (Trissell, 2001). A haze will form in 24 hours then a precipitate at 48 hours if flucloxacillin sodium and atropine sulphate are stored together at 30 °C, while no change is seen at 15°C (Trissell, 2001).

Incompatibilities between atropine sulphate and hydroxybenzoate preservatives have occurred, with a total loss of atropine in 2-3-weeks (Parfitt, 1999). Atropine sulphate is incompatible with other alkalis, tannin, salts of mercury or gold, vegetable decoctions or infusions, borax, bromides and iodides (Budavari, 1996).

### 3.10. Proprietary names and manufacturers

**atropine:**

Atropen® (Meridian, USA) (McEvoy, 2002);

Atropinol® (Winzer, Denmark) (Index Nominum 2000)
**atropine sulphate:**

Atropair® (Pharmafair, USA); Atropine Aguettant® (Aguettant, France),

Atropine Meram® (Cooper, France); Atropine Ophthadose® (Ciba-Geigy, Belgium); Atropine SDU Faure® (Ciba Vision, Suisse); Atropinium sulfuricum Streuli® (Streuli, Suisse);

Atropinum sulfuricum AWD® (ASTA Medica, Denmark); Atropisol® (Ciba Vision, Canada, Iolab, USA);

Atropocil® (Edol, Portugal); Atropt® (Sigma, Australia);

Atrosol® (Adilna Turkey); I-Tropine® (Americal, USA);

Isopto Atropine® (many countries); Liotropina® (SIFI, Italy);

Midrisol® (Abdi Ibrahim, Turkey); Noxenur S® (Galenika, Denmark);

Sal-Tropine® (Hope, USA); Skiatropine® (Cjauvin, France, Suisse); Stellatropine® (Stella, Belgium, Luxembourg); Tropyn Z® (Zafiro, Mexico)

**3.11. Other**

There are no data available concerning the specific gravity or refractive index of atropine or its salt.

**4. Pharmaceutical formulation and synthesis**

**4.2. Manufacturing processes**

Atropine is usually prepared by extraction from the plants *Atropa belladonna* (deadly nightshade), *Datura stramonium* (Jimson weed) or *Duboisia myoporoides* (McEvoy, 2002). This extracted atropine is a combination of D and L hyoscyamine. Both these isomers may bind to muscarinic receptors (Berghem et al., 1980) although the pharmacological activity is thought to be due almost entirely to L hyoscyamine (McEvoy, 2002).

**4.3. Pharmaceutical formulation**

**atropine**

Atropine is available as a sterile solution with a citrate buffer, glycerin and phenol as preservative, in a self-injecting device for administration into the muscular tissue of the outer thigh. It can be administered through clothing if necessary. The content is 1.67 mg atropine (equivalent to 2 mg atropine sulphate) in 0.7 ml (Atropen Meridian Technologies) (Byrd, 2002, Copenhaver, 1994).

**atropine sulphate**

Atropine sulphate is available as a sterile solution in normal saline or water for injection from several manufacturers (including Astra, Abbott, Elkins-Sinn and IMS) (McEvoy, 2002). The preservatives parabens and sulphites, (McEvoy 2002) may be found in injectable products. Atropine sulphate is
usually available in concentrations of 0.25-0.5 mg/ml, although some countries, such as Portugal and Germany, have a 10 mg/ml solution for use in organophosphate poisoning. Atropine sulphate injections may be adjusted to a pH of 3 to 6.5 with sulphuric acid (McEvoy 2002).

Oral forms (tablets) are also available (McEvoy, 2002).

**4.1. Synthesis**

*atropine*

The alkaloid, atropine, is an organic ester which may be prepared synthetically by combining tropine and tropic acid (McEvoy 2002), but is usually obtained by extraction from some solanaceous plants (Parfitt, 1999).

### 5. Analytical methods

#### 5.1. Quality control of antidote.

*atropine*

**Assay (USP, 2002)**

400 mg of atropine, accurately weighed, is dissolved in 50 ml of glacial acetic acid and one drop of crystal violet TS is added. This is titrated with 0.1 N perchloric acid VS to a green endpoint. A blank determination is performed and any necessary correction made. Each ml of 0.1N perchloric acid should be equivalent to 28.94 mg of \( C_{17}H_{23}NO_3 \).

**Limit of foreign alkaloids and other impurities (USP, 2002)**

A solution of atropine in methanol is prepared containing 20 mg per ml, and, by quantitative dilution of a portion of this solution with methanol, a second solution of atropine is prepared containing 1 mg per ml. Then, 25 µL of the first (20 mg per ml) atropine solution, 1 µL of the second (1 mg per ml) atropine solution and 5 µL of a methanol solution of USP Atropine Sulfate RS containing 24 mg per ml is applied to a suitable thin layer chromatographic plate, coated with an 0.5 mm layer of chromatographic silica gel. The spots are allowed to dry, and the chromatogram developed in a solvent system consisting of a mixture of chloroform, acetone and diethylamine (5:4:1), until the solvent front has removed about three quarters of the length of the plate. The plate is removed from the developing chamber, the solvent front is marked and the solvent allowed to evaporate. The spots on the plate are located by spraying with potassium iodoplatinate TS: the \( R_f \) value of the principal spot obtained from each test solution should correspond to that obtained from the Reference Standard solution: no secondary spot obtained from the first atropine solution should exhibit intensity equal or greater than the principal spot obtained from the second atropine solution (0.2%).

*atropine sulphate*

**Assay (USP, 2002)**

1 g of atropine sulphate, accurately weighed, is dissolved in 50 ml of glacial acetic acid, then titrated with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. A blank determination is
performed and any necessary corrections made. Each ml of 0.1 N perchloric acid should be equivalent to 67.68 mg of \((C_{17}H_{23}NO_3)_2 \cdot H_2SO_4\).

Assay (BP, 2000)

0.500 g of atropine sulphate is dissolved in 30 ml of anhydrous acetic acid R, warming if necessary. The solution is cooled then titrated with 0.1M perchloric acid and the end-point determined potentiometrically (2. 2. 20). 1 ml of 0.1M perchloric acid should be equivalent to 67.68 mg of \(C_{34}H_{48}N_2O_{10}S\).

Assay (PPRC, 2000)

0.5 g of accurately weighed atropine sulfate is dissolved in a mixture of 10 ml of glacial acetic acid and 10 ml of acetic anhydride, one to two drops of crystal violet IS is added and the solution titrated with perchloric acid (0.1 mol/L) VS until the colour is changed to pure blue. A blank determination is performed and any necessary corrections made. Each ml of perchloric acid (0.1 mol/L) VS should be equivalent to 67.68 mg of \((C_{17}H_{23}NO_3)_2 \cdot H_2SO_4\).

Limit of other alkaloids (USP, 2000)

150 mg atropine sulphate is dissolved in 10 ml water. To 5 ml of this solution is added a few drops of platinic chloride TS: no precipitate should be formed. To the remaining 5 ml of the solution, 2 ml of 6 N ammonium hydroxide is added and shaken vigorously: a slight opalescence may develop but no turbidity should be produced.

Limit of foreign alkaloids and decomposition products (BP, 2000)

The substance should be examined by thin-layer chromatography (2. 2. 27) using silica gel G R as the coating substance. Solutions should be made up as follows:

Test solution. 0.2 g of the substance to be examined is dissolved in methanol R and diluted to 10 ml with the same solvent.

Reference solution (a). 1 ml of the test solution is diluted to 100 ml with methanol R.

Reference solution (b). 5 ml of reference solution (a) is diluted to 10 ml with methanol R.

To the plate is applied separately 10 µl of each solution. These are developed over a path of 10 cm using a mixture of 90 volumes of acetone R, 7 volumes of water R and 3 volumes of concentrated ammonia R. The plate is dried at 100 °C to 105 °C for 15 minutes. It is allowed to cool then sprayed with dilute potassium iodobismuthate solution R until the spots appear. Any spot in the chromatogram thus obtained with the test solution, apart from the principal spot, should not be more intense than the spot in the chromatogram obtained with reference solution (a) (1.0 per cent) and not more than one such spot should be more intense than the spot in the chromatogram obtained with reference solution (b) (0.5%).

Limit of apoatropine (BP, 2000)

0.10 g atropine sulphate is dissolved in 0.01M hydrochloric acid and diluted to 100 ml with the same acid. The absorbance is determined (2. 2. 25) at 245 nm. The specific absorbance should not be greater
than 4.0, calculated with reference to the anhydrous substance (about 0.5 per cent).

**atropine sulphate injection**

Chromatographic methods of assay are described in USP, 2002 and BP, 2000.

The pH of atropine sulphate injection USP, 2002 should be between 3.0 and 6.5. It should contain not more than 55.6 USP Endotoxin units per milligram of atropine sulfate and it should meet the standard requirements for USP, 2002 injections.

### 5.2. Methods for identification of antidote

**Atropine**

*(USP, 2002)*

Infrared absorption spectrophometric identification testing is one method by which atropine can be identified:

Atropine 30 mg then 36 mg of USP atropine sulphate RS are dissolved in individual 60 ml separators with the aid of 5 ml portions of water. To each separator is added 1.5 ml of 1 N sodium hydroxide solution and 10 ml of chloroform. This is shaken for 1 minute, the layers allowed to separate and the chloroform extracts filtered through separate filters of about 2 g of anhydrous granular sodium sulfate supported on pledgets of glass wool. Each aqueous layer is extracted with two additional 10 ml portions of chloroform. These are filtered and combined with the respective main extracts. The chloroform solutions are evaporated under reduced pressure to dryness, then each residue is dissolved in 20 ml of carbon disulfide. The infrared absorption spectrum, determined in a 1 mm cell of the solution obtained from the test specimen, should exhibit maxima only at the same wavelengths as that of the solution obtained from the Reference Standard.

**Atropine sulphate**

*(BP, 2000)*

First identification tests A, B and E

Second identification tests C, D, E and F.

A. An aqueous solution should show almost no optical rotation

B. The sample is examined by infrared absorption spectrophotometry (2. 2. 24) then compared with the spectrum obtained with atropine sulphate CRS

C. About 50 mg of the test specimen is dissolved in 5 ml of water R, then added to 5 ml picric acid solution R. The precipitate, when washed with water R, then dried at 100 °C to 105 °C for 2 hours, should melt (2. 2. 14) at 174 °C to 179 °C.

D. To about 1 mg of test specimen is added 0.2 ml of fuming nitric acid R, which is evaporated to dryness in a water bath. The residue is dissolved in 2 ml of acetone R. Then, 0.1 ml of a 30 g/L solution of potassium hydroxide R in methanol is added. A violet colour should develop.
E. Reactions of sulphates (2.3.1) is given by the test specimen

F. Reaction of alkaloids (2.3.1) is given by the test specimen

**Atropine sulphate injection**

**(BP, 2000)**

A The method for thin-layer chromatography, Appendix 111 A, using silica gel G as the coating substance and a mixture of 50 volumes of chloroform, 40 volumes of acetone and 10 volumes of diethylamine as the mobile phase is carried out. Applied separately to the plate are 5 µl of each of the following solutions:

For solution (1), a volume of the injection containing 5mg of Atropine Sulphate is evaporated to dryness on a water bath, the residue is triturated with 1 ml of ethanol (96%), allowed to stand and the supernatant liquid used.

Solution (2), containing 0.5% w/v of atropine sulphate BPCRS in ethanol (96%) is heated at 105 °C for 20 minutes after removal of the plate, allowed to cool and sprayed with dilute potassium iodobismuthate solution.

The spot in the chromatogram obtained with solution (1) should correspond to that in the chromatogram obtained with solution (2).

B In the Assay, the chromatogram obtained with solution (1) should exhibit a peak with the same retention time as the peak due to atropine sulphate in the chromatogram obtained with solution (2)

**5.3. Methods for analysis of atropine in biological samples**

Atropine may be assayed accurately in plasma using a radioimmunoassay technique (Wurzburger et al., 1977; Berghem et al., 1980). Atropine concentrations down to 0.1-0.9 mg/L can be measured with good accuracy and reliability using reversed phase liquid chromatography (Fell et al., 1979), GC-MS assay (Hinderling et al., 1985), mass fragmentography (Palmer et al., 1981), or radioreceptor assay (Metcalfe, 1981; Aaltonen et al., 1984).

**5.4. Methods for analysis of the toxic agent in biological samples**

Various methods have been described for the detection of organophosphates in biological fluids. However, most often, measurement of erythrocyte (or plasma) acetylcholinesterase activity is used as an indirect measurement of the degree of enzyme inhibition (see section 4 in overview chapter).

**6. Shelf life**

**atropine**

When stored protected from light, atropine in a self-injecting kit can have a shelf life of 5 years. (Byrd, 2002). The self-injector kit should be stored between 15 and 30 °C (McEvoy, 2002) and may freeze at temperatures below 29 °F. Frozen injectors are still usable after being thawed if they do not appear to be frozen or cracked (Copenhaver, 1994). Atropine should be preserved in airtight, light-resistant
Atropine sulphate should be stored in single or multiple-dose containers, preferably glass, at a temperature of less than 40 °C (preferably between 15 to 30 °C). It should be protected from light (McEvoy, 2002) and stored in airtight containers. Freezing should be avoided (McEvoy, 2002). The shelf-life is 24 months from the date of manufacturing if kept under the above conditions (personal communication, Abbott Laboratories, 1989).

7. General properties

7.1. Mode of antidotal activity

Atropine is a muscarinic cholinergic blocking agent. It competitively blocks parasympathetic, postganglionic nerve endings from the action of acetylcholine and other muscarinic agonists. Atropinic drugs have little effect at nicotinic receptor sites. Large doses of atropine produce only partial block of autonomic ganglia and have almost no effect at the neuromuscular junction.

Small doses of atropine depress sweating and salivary and bronchial secretion. Atropine is particularly useful in relieving bronchoconstriction and salivation induced by anticholinesterases. Doses required to inhibit gastric secretion are invariably accompanied by dry mouth and ocular disturbances. At higher doses, the heart rate increases as the effects of vagal stimulation are blocked (Kentala et al., 1990). When given alone atropine has little effect on blood pressure, although it can block completely the hypotensive and vasodilatory effects of choline esters. Larger doses decrease the normal tone and amplitude of contractions of the bladder and ureter, thereby inhibiting micturition. Atropine inhibits both the tone and motility of the gut, reducing peristalsis.

Unlike scopolamine, small doses of atropine have little depressant action on the central nervous system. However, in toxic doses, atropine initially causes central excitation (exhibited as restlessness, confusion, hallucinations, and delirium) followed by central depression with coma and death. Both atropine and scopolamine shift the EEG to slow activity, reducing the voltage and frequency of the alpha rhythm. Atropine normalizes increased EEG activity due to isofluorophate (Longo, 1966). For many years, the central anticholinergic effects of the belladonna alkaloids in reducing tremor were the mainstay of therapy for Parkinson's disease.

Large doses of atropine impair accommodation, causing dilation of the pupil and blurred vision. The normal pupillary response to light or upon convergence may be completely abolished. These ocular effects may be seen after oral, systemic, or local administration of the drug (Weiner, 1985).

The peripheral antimuscarinic effects of atropine may not be the only antidotal property of the drug in organophosphate poisoning. Atropine may also be of value in treating acute dystonic reactions occasionally observed in acute organophosphate poisoning (Joubert et al., 1984; Joubert & Joubert, 1988; Smith, 1977; Wedin, 1988). Patients with extrapyramidal signs have been noted to have abnormally low plasma and red blood cell cholinesterase activities, producing an excess of acetylcholine relative to dopamine (Wedin, 1988). However, there is little clinical evidence available on the possible anticonvulsive effects of atropine in man.

8. Animal studies
8.1. Pharmacodynamics

This section will review briefly animal work relevant to the use of atropine, whether administered alone or in combination with an oxime, in the management of organophosphate poisoning. It is necessary, when reviewing animal data, to ensure that the dose of atropine given was sufficient to influence outcome. Another problem in extrapolating animal data to man is that many animal models evaluate mortality up to 24 hours, after only one injection of an antidote or antidotes given immediately following exposure to an organophosphorus compound, a model not likely to be mimicked in clinical practice.

Given the importance of adequate supportive therapy in the clinical setting, and particularly the importance of a patent airway, it is surprising that many studies do not state whether such treatment was employed, even when large animals such as buffalo calves (weighing 100-150 kg) were used (Gupta, 1984).

8.1.1. Antidotal effect of atropine

Sanderson (1961) studied the effect of intraperitoneally administered atropine (17.4 mg/kg) given alone, or combined with oximes, on the survival of rats poisoned orally by ten different organophosphates, excluding dimethoate. Atropine alone prevented the development of toxicity. Although the numbers of rats in each group were small (n = 6) and statistical analysis was not performed, this study demonstrated that atropine treatment alone did reduced mortality.

Stein & Neill (1985) studied the survival rate of rats poisoned orally by dimethoate (600 mg/kg) after treatment with either atropine or hyoscine, 1 mg/kg intraperitoneally (i.p.) and repeated hourly for up to 12 h. Compared to non-treated controls, no effect on survival was observed and the authors concluded that atropine and hyoscine were equally ineffective. However, their conclusions were most probably invalid, since the dose of atropine used was inadequate for the species studied (Sanderson, 1985). In a previous study, Sanderson & Edson (1959) had demonstrated that atropine (17.4 mg/kg i.p. every 4 hours) was effective in reducing the mortality in dimethoate-poisoned rats.

Schoene et al. (1988) studied the efficacy of atropine administered prior to dosing with paraoxon in mice. Atropine was administered 5, 20, 40 and 60 minutes before organophosphate administration and was found to reduce mortality significantly. The "efficacy half-life" of the antidote was approximately twice the half-life of the antidote in blood. Although the sensitivity of the atropine assay used in this study was not satisfactory, this does not detract from the significant life-saving effect of atropine in this experimental study.

In calves poisoned with intravenous dichlorvos, atropine was shown to reverse the respiratory effects of the organophosphate (Likeux et al., 1986). The organophosphate-induced reduction in dynamic lung compliance, arterial oxygen tension, increase in total pulmonary resistance, work of breathing and alveolar arterial oxygen gradient were reversed by atropine. Atropine may therefore, reverse changes in ventilation-perfusion inequalities resulting from uneven distribution of ventilation, caused by acetylcholine-mediated airway constriction (Slocombs & Robinson, 1987). Atropine had no effect on muscle fasciculation or plasma cholinesterase inhibition.

In monkeys, Lipp (1976) investigated the effect of atropine on soman-induced respiratory depression. An immediate increase in heart rate was accompanied by a gradual increase in respiratory rate. Only after low doses of organophosphate is a relationship demonstrable between the antimuscarinic and protective effects of atropine pre-treatment (Green et al., 1977). Large doses of atropine counteract the
convulsive effects of massive organophosphate poisoning. This effect is not related to the degree of mусcarinic blockade.

In a study in rats, Pazdernik et al. (1986) investigated the effect of atropine pre-treatment on local cerebral glucose utilization during seizures induced with soman. High-dose atropine (10 mg/kg) was found, like diazepam, to reduce local cerebral glucose utilization and thus reduce brain damage. The protective effect of atropine in organophosphate poisoning may therefore be far more than simple mусcarinic blockade.

Support for an anticonvulsant action of atropine has been presented by McDonough et al. (1987) who found that atropine pre-treatment prevented the development of convulsions and brain damage induced by soman or VX injected directly into the amygdala. The results indicated that the nerve agents were not directly neurotoxic, that peripherally induced hypoxia or anoxia were unlikely mechanisms of the neuropathology, and that the brain damage produced by these compounds was primarily seizure-mediated.

Chronic exposure to certain organophosphates may induce changes in the pharmacodynamics of atropine, thus influencing the response of the animal to atropine therapy. Atropine has been shown to produce myoclonus and stereotyped responses in rats (related to enhanced serotonergic and dopaminergic activity) following DFP (isoflurophate) exposure (Fernando et al., 1985). In rats challenged 6 to 72 hours after single doses of sarin or soman, myoclonus was markedly enhanced (Fernando et al., 1986), suggesting rapid development of hypersensitivity to antimuscarinic agents. Furthermore, repeated DFP administration caused a specific decrease in mусcarinic receptors and $^{14}$C choline uptake in the striatum and ileal longitudinal muscle of guinea pigs (Yamada et al., 1983), a change associated with a more than 50% depression of tissue acetylcholinesterase activity. The concept of a down regulation of mусcarinic receptors after chronic soman administration has also been corroborated by Modrow & McDonough (1986), who, using a behavioural model in rats, found supersensitivity to atropine.

Matsubara & Horikoshi (1983) observed that atropine alone increased the survival rate by 20 to 40% in rats given a normally lethal dose of fenitrothion.

8.1.2. Atropine and oximes

Although the role of atropine in organophosphate poisoning is clear, our knowledge of the kinetics and dynamics of atropine and oximes when employed in combined therapy is very limited. In one study in mice, Clement et al. (1988) noted that soman increased the terminal half-life and volume of distribution (Vd) of the oxime HI-6 (asoxime chloride). Atropine increased the clearance of HI-6 with no effect on Vd. These changes in oxide kinetics were probably the result of haemodynamic changes.

In fenitrothion-poisoned rats, Matsubara and Horikoshi (1983) studied the effect of various antidotes on 72-hour lethality. When using 100% lethal doses of this organophosphate (800 mg/kg orally), atropine (20 mg/kg i.p.) alone was more effective than oxime (pralidoximine (2-PAM), 50 mg/kg i.p.) alone, and significantly ($p < 0.05$) increased the survival ratio up to 40% (survival of 6/10 compared with 0/10 in controls). The effect of 2-PAM alone was not significant (survival of 2/10) at this dose of fenitrothion. At the 500 mg/kg dose of the organophosphate (OP), the effect of both antidotes alone upon survival was significant as compared to controls. The optimal therapy (800 mg/kg of OP), however, was the repeated and combined administration of atropine and 2-PAM resulting in 90% survival and considerable alleviation of the features of toxicity (survival of 9/10; 0/10 in controls).
Gupta (1984) studied the effect of atropine, 2-PAM and diazepam in buffalo calves poisoned orally with sublethal (100 mg/kg) or minimal lethal doses (125 mg/kg) of malathion, which produced severe tremors and convulsions within 40 to 60 minutes. The antidotes were administered parenterally either alone or in combination at the time of peak malathion toxicity (within 1 hour) and were assessed for their ability to reduce signs of cholinergic toxicity. A combination of atropine (0.5 mg/kg, 1/4 IV and 3/4 IM) and 2-PAM (20 mg/kg IV) reversed the clinical evidence of malathion toxicity within 15 minutes. Atropine alone was less effective (survival - 4/5; survival with the combination - 5/5; survival of controls - 0/3) and did not reverse malathion-induced biochemical changes. In contrast, administration of 2-PAM (10-30 mg/kg IV) or diazepam (0.5-1.0 mg/kg IV) alone accentuated malathion toxicity when sublethal doses were given (0/9 and 0/12 survived, respectively, compared to 3/3 in controls). In this experimental setting, the combination of atropine sulphate and 2-PAM was claimed to be the most effective antidotal treatment in acute malathion poisoning (sublethal doses) as judged from the rapid disappearance of toxic features. The survival ratio for the latter combination (5/5) was the same as for the combination of atropine and diazepam (5/5, controls - 0/3).

In the experimental study by Sanderson (1961) discussed in section 8.1.1, no beneficial potentiation between oxime and atropine could be demonstrated for the ten organophosphate insecticides tested when the organophosphate was given orally, and the combination was less effective than atropine alone in azinphos-methyl (gusathion), azinphos-ethyl (ethyl-gusathion), demeton and morphothion poisoning. Beneficial potentiation between oxime and atropine did occur when morphothion was given intraperitoneally. Sanderson (1961) suggested that combined treatment with atropine and oxime may be deleterious when the animals are given the organophosphate orally because reduced peristalsis slows the absorption of the organophosphate beyond the most effective concentrations of the antidotes given parenterally. The study by Gupta (1984), described above did not, however, demonstrate this negative effect of combined oxime and atropine therapy.

Ligtenstein & Moes (1991) studied the synergism of atropine (37.5 mg/kg ip) and oxime (HI-6) pre-treatment (50 mg/kg ip) in rats administered two different cholinesterase inhibitors subcutaneously, one with a mixed central/peripheral mode of action (S-diethylaminoethyl-0-cyclohexylmethylphosphonothioate) and its methiodide derivate with an almost entirely peripheral effect. LD50 was assessed after 24 hours. In both cases, HI-6 alone was found to be more effective than atropine alone, significantly reducing convulsions and lethality (factor of 5 and 70, highest for the peripheral agent). Atropine alone had only a slight protective effect against the mixed central/peripheral agent and no beneficial effect against the other. The explanation offered for this observation was that the beneficial effect of atropine was mediated through central mechanisms, the peripheral parasympatholytic effect being negligible in counteracting lethality. The combination of atropine and oxime had an extremely significant synergistic effect on reducing lethality (LD50 increased from 16 ug/kg to no deaths at 5 mg/kg) when the toxicant had a mixed central/peripheral action, whereas no significant synergistic effect was observed when the toxicant had a peripheral action. The authors’ explanation for this observation was that under the former circumstances, the acetylcholinesterase reactivation in the respiratory neuromuscular synapse by the oxime, was supplemented by the central action of atropine, which improved respiratory control at the level of the central nervous system.

Clement (1994) studied the effect of atropine (17.4 mg/kg, i.p.) alone, or combined with 2-PAM, obidoxime and HI-6, administered 5 min before mice were poisoned by a combination of sarin and cyclohexyl methylphosphonofluoridate (cyclosarin or GF) administered subcutaneously. Atropine alone failed to reduce lethality but combined with either oxime the lethality was significantly reduced as judged by 24 hour ED50 values.

An experimental study of sarin poisoning in rats (Shiloff & Clement, 1987) compared the efficacy of
HI-6, obidoxime and pralidoxime as antidotes when combined with atropine. HI-6 was found to be most efficacious, followed by pralidoxime and obidoxime. These conclusions were however based on a single dose regimen of sarin and of atropine. This may be important, since the optimal combination of atropine with an oxime may depend upon the severity of the poisoning. Response surface methods, which provide an assessment of the entire dose-response surface for all inherent variables, were used to optimize treatment therapies in soman intoxication (Carter et al., 1985). These workers showed in guinea pigs that the level of soman exposure altered the nature of the atropine/pralidoxime interaction. At low exposure levels, optimal treatment was with atropine alone. As soman toxicity increased, pralidoxime became important and the optimal dose of atropine required initially decreased slightly, but then again increased when soman was given in high doses.

8.1.3. Atropine and oxime synergy with other therapeutic agents

8.1.3.1. Physostigmine and Pyridostigmine (Carbamates)

In animal experiments, both physostigmine (Albuquerque et al., 1985; Deshpande et al., 1986; Harris et al., 1978 & 1980) and pyridostigmine (Berry & Davies, 1970; Dellinger, 1988; Jones et al., 1985) pre-treatment has been shown to reduce atropine and pralidoxime requirements. Carbamates, such as physostigmine, that pass the blood-brain barrier may protect from organophosphate toxicity by reducing the organophosphate-induced rise in total brain acetylcholine, thereby restoring neural function (Harris et al., 1980). The optimal atropine/pralidoxime dose combination has been shown to be a function of the challenge level of soman and pyridostigmine (Jones et al., 1985). The protective effect of these carbamates may involve several mechanisms other than cholinesterase inhibition. It is of interest that, for example, physostigmine, in addition to its anticholinesterase activity, interacts with multiple sites at the acetylcholine receptor (Albuquerque et al., 1985). Deshpande et al. (1986) studied the synergistic effect of atropine following pre-treatment with physostigmine in an experimental study in the rat. These workers found that physostigmine pre-treatment 30 minutes prior to injection of sarin reduced mortality to 28%. When it was co-administered with atropine, mortality fell to 4%.

Prophylactic use of these carbamates may be important for defence forces expecting to be attacked with nerve agents. Pre-treatment, or treatment, with these carbamates has no present place in the treatment of organophosphate insecticide poisoning in man.

8.1.3.2. Diazepam

The anticonvulsant effect of diazepam has been demonstrated in rats treated with soman (Pazdernik et al., 1986) and in the monkey (Lipp, 1973). In quinalphos-poisoned rats, pre-treatment with atropine and diazepam decreased the acute toxicity of the insecticide 3.3 times (Bokonjic et al., 1987). This positive effect was further enhanced by a continuous infusion of pralidoxime, which maintained pralidoxime concentrations between 1- 5.4 µg/L. In a study of rats poisoned with fluostigmine and pre-treated with atropine and diazepam, the subsequent administration of diazepam had no effect on the course of the poisoning (Rump et al., 1976). In the study by Gupta (1984) using minimal lethal doses of malathion, the combination of atropine and diazepam (0.75 mg/kg IV) prevented death (5/5 animal survived compared to 0/3 of controls) and the development of cholinergic signs of toxicity, except for weak muscular fasciculation persisting for 30 to 60 minutes. Diazepam alone accentuated toxicity.

8.1.3.3. Clonidine

In a study in mice, Buccafusco & Aronstam (1986) showed that pre-treatment with the centrally-acting alpha-C-2 adrenergic agonist clonidine protected against several of the centrally-mediated toxic effects
of soman, increasing survival rates. Furthermore, there was a synergistic effect on survival rates when clonidine was combined with atropine. At protective doses, clonidine not only blocked acetylcholine release but non-competitively inhibited acetylcholinesterase activity. It also inhibited ligand binding to cortical muscarinic receptors. Clearly, clonidine has multiple effects and should be the subject of further experimental study.

8.1.3.4. Calcium channel blockers

This group of drugs, together with phenytoin (but not other anticonvulsants used in the study), may also offer protection against organophosphate toxicity (Dretchen et al., 1986). In mice, pre-treatment with phenytoin, verapamil, nifedipine, nitrendipine or nimodipine increased the LD$_{50}$ of DFP. This may be due to a protective action on central respiratory centres and peripheral nicotinic sites.

8.1.3.5. Other agents

The effects of antidotal therapy on neuronal RNA content have been studied by Doebler et al. (1983). Soman produced a virtually complete inhibition of acetylcholinesterase activity and moderate decline in neuronal RNA content. Atropine pre-treatment together with pralidoxime reduced RNA levels but increased acetylcholinesterase activity. Thus, no precise relationship exists between the restoration of neuronal acetylcholinesterase (AChE) and AChE activity. The effects on neuronal RNA metabolism may, rather, reflect alterations in acetylcholine sensitivity; if this is so, then manipulation of acetylcholine responsiveness may be a further mechanism for therapeutic intervention. Sterling et al. (1988) studied two drugs found to inhibit presynaptic acetylcholine synthesis in vitro. In a rat model, pre-treatment with N-hydroxyethylnaphthylvinylypyridine (NHENVP) or N-allyl-3 quinuclidinol was found to protect rats from soman toxicity, enhancing the effects of atropine and pralidoxime.

Thus the effects of atropine, pralidoxime and other drugs that synergistically decrease organophosphate toxicity are complex and as yet, not elucidated fully. Although there are promising new therapeutic approaches, the clinical usefulness of clonidine, calcium channel blockers and presynaptic blockade of acetylcholine synthesis is not yet known.

8.2. Pharmacokinetics

The extensive information obtained from clinical studies, and the problems of extrapolating data obtained from different animal species, limits the need for animal data on pharmacokinetics.

Studies in anaesthetized monkeys show that mean plasma concentrations after intraosseous administration correspond to those found two minutes after intravenous administration. Both the intraosseous and endotracheal routes are acceptable alternatives if intravenous access is delayed or unavailable (Prete et al., 1987).

8.3. Toxicology

The following LD$_{50}$ values are given for acute toxicity (Sax, Lewis 1992)

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>Atropine LD$_{50}$ (mg/kg)</th>
<th>Atropine sulphate LD$_{50}$ (mg/kg)</th>
</tr>
</thead>
</table>

8.3.1. Mutagenicity testing

Atropine caused non-specific aggregation of chromosomes, considered to be of no cytogenetic danger (Vrba, 1971, Davies 1985).

Atropine sulphate was assessed as negative in the Ames assay, using one or more *Salmonella typhimurium* standard strains (TA98, TA100, TA1535, TA1537 and TA1538) (Ramel et al, 1986).

8.3.2. Carcinogenicity testing

Atropine may promote experimental carcinogenesis in rat stomach caused by N-methyl-N’-nitro-N-nitrosoguanidine (Tatsuka et al.1989). In a long-term trial of 858 rats by Schmahl and Habs, (1976) atropine was not found to be carcinogenic.

8.3.3. Teratogenicity testing

Chick eggs were injected with 0.6 to 1.5mg atropine during the interval of 4 to 12 days incubation. No defects were produced (Shepard, 1980).

Atropine given to rat dams from days 7 to 19 of gestation resulted in avoidance learning deficits in their pups compared to controls. Findings suggested that prenatal exposure to sympatholytic drugs may produce adverse effects on the behavioural development of pups (Matsuhashi et al.1984).

8.3.4. Behavioural toxicology

In microencephalic rats, compared to normal controls the magnitude of deficits in learning the Morris water maze increased as a function of atropine dose, suggesting that learning and memory may be related to changes in the number and/or function of muscarinic cholinergic receptors (Lee et al 1990). Behavioural alterations have been noted amongst the offspring of rats treated during pregnancy with atropine (Watanabe et al 1985).

9. Volunteer studies

The pharmacokinetic data and basic pharmacodynamic data in man are given in this section although some information may be derived from case reports.
**9.1. Pharmacodynamics**

There is a clear temporal relationship between the plasma concentrations of atropine after intramuscular injection (Berghem et al., 1980), and the time course of the cardiac accelerating effect of the drug (Sidell et al., 1970). This does not hold true for all pharmacological effects; for example, the saliva reducing effect is more delayed, peaking at 100 minutes after an intramuscular injection (Murrin, 1973). The effect of atropine on pupillary dilation and near point vision reaches a maximum only six hours after administration (Mirakhur, 1978). Furthermore, studies in both adults (Sjovall et al., 1984a) and children (Sjovall et al., 1984b) report no correlation between a single serum atropine concentration and both subjective and objective responses.

**9.2. Pharmacokinetics**

**9.2.1. Absorption**

*Oral absorption.* Atropine is absorbed irregularly from the gastrointestinal tract, and more slowly than with parenteral dosing (Dollery, 1991). In adults, atropine is absorbed mainly from the duodenum and jejunum rather than the stomach. Maximum radioactivity, using $^3$H-atropine, was found one hour after an oral dose (Beermann et al., 1971). Absorption of orally administered atropine may be delayed if atropine has been previously administered, as shown by Hardison et al (1979): a 38% increase in small bowel transit time was observed following intramuscular injection of atropine.

In children, who received atropine 0.03mg/kg orally, peak plasma concentrations occurred at 90 minutes with only 10-20% occupancy of muscarine-2 subtype receptors. By contrast, after 0.02mg/kg intramuscular administration, peak was at 25 minutes with 60-70% receptor occupancy (Gervais et al., 1997). Following an oral dose of 0.03mg/kg atropine, a mean maximum serum concentration of 6.7nmol/L occurred at two hours in children, compared with 5.7 nmol/L at 30 minutes after intramuscular administration (Saarnivaara et al, 1985).

*Rectal absorption.* In children, rectal absorption of atropine is slower than absorption from the intramuscular route. Peak plasma concentrations of 0.7µg/L occurred after 15 minutes, following rectal administration of atropine, compared with 2.4 µg/L, five minutes after intramuscular dosing (Olsson et al., 1983). Peak plasma concentrations after rectal dosing in children below 15kg in weight were lower than in older children (but not to a clinically significant degree) and plasma concentrations declined faster (Bejersten et al, 1985).

*Sublingual absorption.* Oral sublingual atropine absorption was considered to be "of minor clinical significance" compared to absorption after intramuscular or subcutaneous administration. Absorption from the sublingual route was variable and low in pregnant women at full term given 0.02mg/kg to 0.07mg/kg compared to intramuscular or subcutaneous administration of 0.02mg/kg (Kanto & Pihlajamaki, 1986). A 7-month child in asystole received a sublingual injection of atropine 0.15mg (with adrenaline) with return of sinus rhythm and pulse (Rothrock et al, 1993).

*Inhalation.* Inhalation of atropine sulphate from a pressurized metered-dose inhaler resulted in peak serum concentrations of 4.9 µg/L, 6.1 µg/L and 7.9 µg/L from administration of 1.7mg, 3.4mg and 5.2mg respectively. By comparison, a 1.67mg intramuscular injection of atropine free base (equivalent to 2mg atropine sulphate) gave a mean peak concentration of 8.4 µg/L (Kehe et al, 1992).

*Ocular absorption.* Some absorption of atropine can occur from the lower cul-de-sac of the eye (Lahdes et al, 1988). Peak plasma concentration was reached within 8 minutes after instillation of a 1% atropine
solution.

**Dermal absorption.** Limited absorption occurs from the intact skin (Hardman, 1996).

**Intramuscular absorption.** Intramuscular absorption of atropine and atropine sulphate depends on the method of injection, the site of injection (Friedl et al, 1989) and the pharmaceutical form. Exercise may increase the rate of absorption (Kamimori et al, 1990). Atropine and atropine sulphate reach peak plasma levels when injected intramuscularly in about 30 minutes (Berghem et al, 1980, Saarnivaara et al, 1985, Gervais et al, 1997). In pregnant women at full term, however, mean peak plasma levels were reached at 1.59 hours, following a dose of 0.01mg/kg (Kanto et al, 1981). Absorption may be faster if atropine is injected into the deltoid muscle rather than the gluteal or vastus lateralis muscles (Ali-Melkkila et al, 1993). A study using time to peak heart rate to seek differences between routes of administration and pharmaceutical forms, found that intravenous administration was most rapid (5? 5 minutes) compared to intramuscular administration of citrate buffered atropine in a modified syringe (26 + 13 minutes [sic]), citrate buffered atropine ( 40 + 15 minutes[sic]), or atropine sulphate (56? 20minutes) (Martin et al, 1980).

**Subcutaneous absorption.** There was no significant difference in the rate of absorption of doses (0.02mg/kg atropine) given intramuscularly or subcutaneously to full term pregnant women (Kanto & Pihlajamaki, 1986).

**Endotracheal absorption.** Optimal drug doses and absorption parameters for administration by the endotracheal route are unknown (The American Heart Association, 2000) but medications should be administered at 2 to 2.5 times the recommended intravenous dose, and diluted before use in 10ml saline or distilled water in adults (Emergency Cardiac Care Committee, 1992). In children with normal cardiac status, Howard & Bingham (1990) found that there was no difference between effect on heart rate or speed of onset with either intravenous atropine sulphate 0.025mg/kg dilute in 2ml saline, given at the same time as 2ml saline endotracheally or twice the dose (ie 0.05mg/kg) of atropine given endotracheally at the same time as 2ml intravenously. After studying 50 patients using dose titration with endotracheal atropine, it was considered that if atropine must be given by the endotracheal route in an emergency, then 0.03mg/kg or more may be comparable to the effect of 0.01mg/kg given intravenously (Lee et al, 1989). Any route of vascular administration was considered preferable to the endotracheal route (The American Heart Association, 2000).

**Intraosseous administration.** Animal studies with atropine (Prete et al, 1987) have shown similar actions and drug concentrations after intraosseous administration to those after intravenous administration (Emergency Cardiac Care Committee, 1992). Establishment of an intraosseous route in children 6 years old or younger has been suggested, if venous access cannot be achieved. Intraosseous administration has been used in older children & adults, and has also been considered preferable to the endotracheal route (The American Heart Association, 2000).

**9.2.2. Distribution**

After intravenous dosing, atropine distributes rapidly with only 5% remaining in the blood compartment after five minutes (Berghem et al., 1980). Initial distribution half-life is approximately one minute (Kanto & Klotz, 1988). Elimination kinetics can be fitted to a two-compartment model after therapeutic doses. The apparent volume of distribution (Vd) is 1-1.7 L/kg with a clearance of 5.9-6.8 ml/kg/minute and a half-life of 2.6-4.3 hours in the elimination phase (Kanto et al, 1981; Aaltonen et al., 1984; Virtanen et al., 1982).
Atropine rapidly crosses the placenta, with apparent fetal uptake. No distribution into the amniotic fluid was found in one study (Kanto et al, 1981) but significant distribution in another (Kanto et al. 1987). In one study, concentrations in the umbilical vein were 93% of the maternal level five minutes after an intravenous injection (Kivalo & Saarikoski, 1977). Small quantities of atropine are stated to appear in breast milk but there is little data to support this (atropine may also impair milk production, although this is not conclusively documented) (Dollery, 1991)

Penetration into human lumbar cerebrospinal fluid was less complete, particularly after a single intravenous injection (Virtanen et al., 1982). It has been speculated that the cerebrospinal fluid (CSF) represents a "deep" compartment with slow drug penetration (Kanto & Klotz, 1988). Nonetheless, atropine penetration is assumed to be greater into the central nervous system than into lumbar cerebrospinal fluid (CSF), compatible with the well-known central anticholinergic effects of the drug.

Penetration of atropine into the eye after both local and systemic administration is slow and incomplete. (Morton Grant W, 1986, Friedl et al 1988)

9.2.3. Elimination

After intravenous dosing, atropine elimination fits a two-compartment model with an intrinsic clearance of 5.9-6.8 ml/kg/min and a plasma half-life of 2.6-4.3 hours in the elimination phase (Kanto et al., 1981; Aaltonen et al., 1984; Virtanen et al., 1982).

The elimination half-life of atropine is longer in children less than two years of age, and in the elderly. In children, this is due to an increased volume of distribution (Vd), increasing the half-life up to 5-10 hours in the neonate. In the elderly (70 years and older), the half-life may be prolonged from 10 to 30 hours due to reduced clearance. These changes do not appear to be sex-related. Not only the kinetics, but also the dynamics may change with age, making both the younger and older patient more sensitive to a given dose (Berg et al., 1959; Smith et al., 1979). Patients with Down’s syndrome may exhibit abnormally greater cardioaccelerator response to intravenously administered atropine (Harris & Goodman 1969) while patients with albinism may have decreased susceptibility to some of the actions of atropine (Parfitt, 1999; Maciejasz, 1971). The mechanisms for these differences are unclear.

Atropine is metabolized in the liver by microsomal monooxygenases. HPLC separation of urine has identified 5 compounds: atropine, noratropine, tropine, atropine-N-oxide(equatorial isomer), and tropic acid (Van der Meer et al., 1983). Thus, atropine is partly metabolized and partly excreted unchanged in the urine, the unchanged portion being approximately 50% (Van der Meer et al, 1986). Since biliary excretion is negligible, the hepatic plasma clearance of 519±147 ml/min represents metabolism. Hepatic blood clearance and extraction ratio were 476±136 ml/min and 0.32, respectively. The elimination of atropine is, therefore, partly flow-dependent (Hinderling et al., 1985). Following an intravenous injection, 57% of the dose is found in the urine as unchanged atropine and 29% as tropine. Since the renal plasma clearance (656±118 ml/min) was found to approach the renal plasma flow (712±38 ml/min), tubular excretion may occur. Thus, both liver and renal disease can be expected to influence the kinetics of atropine (Hinderling et al., 1985).

10. Clinical studies - clinical trials

The first report of atropine being used as an antidote for acetylcholinesterase inhibitors was by Fraser in 1870 (Holmstedt, 1972; 1985), who used atropine to counteract the effect of physostigmine on the pupil. Although the clinical efficacy of atropine in organophosphate poisoning is well known (Bardin et al., 1987; Chew et al., 1971; DuToit et al., 1981; Hayes et al., 1978; Hirschberg & Lerman, 1984; Kipling &
Cruickshank, 1985; Minton & Murray, 1988; Namba et al., 1971; Richards, 1964; Senanayake & Karalliedde, 1987; Zilker & Hibler, 1996; Zweiner & Ginsburg, 1988), no controlled prospective studies have been published. This evaluation is therefore based mainly on case reports and retrospective case studies as presented in section 11. Two non-controlled clinical studies are discussed briefly below.

Finkelstein et al. (1989) performed a non-controlled prospective study of severe organophosphate poisoning. In this study of 53 adult patients, relatively low doses of atropine (2 mg intravenous bolus, then the same dose at intervals of 10 min or more) were administered, adjusted as necessary to the severity of tracheobronchial secretions and bronchospasm. All 53 patients were mechanically ventilated and obidoxime was also given. Although it is not possible to quantitate any beneficial effect from atropine administration alone in these severely poisoned patients, atropine treatment appeared to counteract the muscarinic features and thereby the pulmonary complications.

De Silva et al. (1992) compared the treatment of moderate to severe organophosphate poisoning from a period when pralidoxime was not available in Sri Lanka (atropine given alone to 21 patients) with a period when both atropine and pralidoxime were available (24 patients). Their conclusion, that atropine alone may be sufficient in such cases, was heavily criticized by Johnson et al. (1992). The observed beneficial effect of atropine, however, remained unchallenged.

11. Clinical studies - case reports

There are numerous case reports on the use of atropine in organophosphate poisoning. To provide a better overview of the data, this section is divided into subheadings as follows.

11.1. Dose and duration of atropine sulphate therapy

The optimal dose of atropine sulphate required to manage moderate and severe organophosphate poisoning is controversial. Recommendations for initial intravenous dosing range from 1 mg in adults and 0.01 mg/kg in children as a "test dose" up to 5 mg in adults, (Ganendran, 1974; Kipling & Cruickshank, 1985; LeBlanc et al., 1986), and 0.05 mg/kg in children (Borowitz, 1988; Dutta et al., 1977; Lund & Monteagudo 1986; Mortenson, 1986). Larger doses may, however, be necessary: in a retrospective study of 37 paediatric patients, Zweiner & Ginsburg (1988) found that one third of patients required at least 0.05 mg/kg before any decrease in cholinergic activity was observed. In one adult, up to 15 mg was given as a single bolus (Worrell, 1975). Most cases of mild-moderate organophosphate poisoning require no more than a total of 5-50 mg atropine.

A small number of patients appear to have required massive quantities of atropine, sometimes for prolonged periods, in particular those poisoned with highly lipid-soluble compounds, such as fenthion (Borowitz, 1988). Total doses of atropine as high as 3911 mg (Warriner et al., 1977), 11 443 mg (Hopmann & Wanke, 1974) and 19 590 mg (Goulsoussidis & Kokkas, 1985) have been given to patients, who recovered from their severe poisoning. LeBlanc et al (1986) describe a case treated with 30 000 mg of atropine over 5 weeks (LeBlanc et al., 1986). Relapse during therapy also appears to be more common with highly lipophilic organophosphates (Borowitz, 1988; DuToit et al., 1981; Hayes et al., 1978; LeBlanc et al., 1986; Milby, 1971; Warriner et al., 1977; Worrell, 1975; Yoshida et al., 1987). Because of the risk of relapse, patients should be weaned off atropine slowly (Ganendran, 1974). If large quantities of atropine sulphate are given, care should be taken to avoid using formulations containing preservatives such as chlorobutanol or benzyl alcohol.

11.2. Route of administration
In order to cater for the sometimes large doses of atropine required to treat organophosphate poisoning some manufacturers produce larger ampoules, containing 10-100 mg of atropine (Berman & Bertoldi, 1985). It may be more practicable to administer large doses by intravenous infusion rather than by intermittent bolus injections (Bardin et al., 1987; Borowitz, 1988; Chew et al., 1971; DuToit et al., 1981; LeBlanc et al., 1986). Intravenous infusion may save time, produce less fluctuation in plasma atropine concentrations and make weaning much easier. On the other hand, because administration by infusion may result in less frequent assessments, it is much easier for a patient to develop atropine toxicity while on an infusion than when receiving bolus injections. Moreover, it should be remembered that the half-life of atropine (up to 4 hours or longer in children and the elderly) necessitates using a bolus dose as well as adjusting the drip rate if a rapid increase in the degree of atropinization is required.

In an emergency situation, it may be necessary to give atropine before intravenous or intraosseous access can be established. The endotracheal route has therefore been used, when vascular access was not available. Atropine was given endotracheally to a 16-month-old child with a carbamate overdose (Garbner, 1987). The child responded rapidly to 1.0mg, and a total of 2.5 mg atropine was given by this route. The optimal dose requirements for the endotracheal route have not yet been established, however.

Oral administration of atropine has been reported as being useful for stable patients on intravenous therapy for several days or weeks, who need slow weaning (Worrell, 1975).

Atropine given intramuscularly in some specialized injectors may have faster onset of action than other forms of intramuscular injection. The recommended dose for nerve agent exposure in adult, otherwise healthy patients with mild to moderate symptoms is 2 to 4 mg (McEvoy, 2002).

Initial doses of both atropine and atropine sulphate administered to adults and children by the intramuscular route appear to be similar to those given intravenously (McEvoy 2002, Copenhaver 1994, Parfitt 1999, Dollery 1991), although onset of action will be slower after intramuscular injection (Martin et al 1980).

11.3. Assessment of optimal atropinization

An evaluation of adequate atropine dosing is made clinically, by noting a decrease in cholinergic (muscarinic) signs or symptoms. Atropine has no effect on red blood cell or plasma cholinesterase activity.

The decision as to whether more atropine is required, or whether the patient can be weaned, is essentially clinical. The degree of atropinization may be indicated by dryness of the mouth and tracheobronchial secretion, pupil size, heart rate, and flushing (Milby, 1971; Senanayake & Karalliedde, 1987). Tachycardia and mydriasis can be unreliable indicators, however, since both may also result from nicotinic stimulation in severely poisoned patients (Ganendran, 1974; Hirschberg & Lerman, 1984; Worrell, 1975). Tachycardia may also reflect hypoxia caused by pulmonary hypersecretion and bronchospasm. The use of atropine is not, therefore, contraindicated in a patient with tachycardia: as the patient’s oxygenation improves the pulse rate will usually slow (Fjarli et al., 1998, Zweiner & Ginsburg, 1988).

Mann (1967) noted that 10% of organophosphate-poisoned patients did not have miosis. Pupil constriction that reverses following atropine administration, however, does appear to be a reliable indicator (Garbner, 1987).

The most sensitive measure of adequate atropinisation appears to be repeated evaluation of the quantity

of secretions (Bardin et al., 1987; Dean et al., 1967; DuToit et al., 1981).

When weaning patients who have been treated for several days, atropine should be continued for at least 24 hours after symptoms have subsided (Bardin et al., 1987).

11.4. Adverse effects of atropine therapy

Atropine toxicity was noted on at least one occasion in 16 of 61 patients (26%) (Bardin et al., 1987). Hirschberg & Lerman (1984) in a retrospective, multicentre study noted over-atropinization in three of 232 cases. The dose of atropine should be reduced if the patient shows signs of atropine toxicity such as fever, or delirium.

If atropine is administered to hypoxic patients there is a risk of ventricular tachycardia or fibrillation (Hase et al., 1984; Matthew & Lawson, 1970). In this situation, atropine should be given at the same time as the patient is oxygenated (Zavon, 1974).

Prolonged atropinization may cause paralytic ileus (DuToit et al., 1981). Paralytic ileus was also reported in an infant with Down’s syndrome who was being treated with topical atropine (Marshall et al., 1989).

In a case reported by LeBlanc et al. (1986), rigidity was observed for up to 10 days following weaning after a five-week period of therapy. Mydriasis, but no other pharmacological effects, was noted in a neonate, whose mother had been given atropine for organophosphate poisoning before the birth (Shah et al., 1995).

Other adverse effects of atropine, not necessarily associated with treatment of organophosphorus insecticide poisoning, include precipitation of glaucoma (Berdy et al. 1991) and hypersensitivity reactions (anaphylaxis) (Aguilera et al., 1988).

11.5. Role of other anticholinergic agents

Both n-methylatropine and glycopyrrolate bromide have been used in organophosphate poisoning in man. De Kort et al., (1988) reported a case where 69 mg of n-methylatropine nitrate was used. Gerkin & Curry (1987) gave 5850 mg of atropine sulphate and 124 g pralidoxime in a case of methyl parathion poisoning. In an attempt to use an anticholinergic with a longer duration of action, 510 mg glycopyrrolate bromide was then given. The large amount of bromide involved resulted in an elevated plasma bromide concentration. Thus the risk of bromide intoxication may restrict the use of large quantities of glycopyrrolate bromide in organophosphate poisoning.

A single case has been described of an adult male who had ingested chlorpyrifos and was treated with ipratropium when six days of intravenous atropine had failed fully to control respiratory distress. Ipratropium was given by endotracheal administration of an aerosol mist of 0.5mg diluted to 2 ml. A total of 409 mg of atropine had been given before commencement of ipratropium. The patient received a total of 7mg of ipratropium over a period of 5 days, commencing at 0.5mg every six hours for the first day. Tachycardia and mydriasis were observed as side effects at the beginning of treatment. Respiratory distress was alleviated, but intraoral salivary secretions continued unabated (Shemesh et al, 1988). Ipratropium has less of an inhibitory effect on mucociliary clearance, compared with atropine, thus, its use avoids the increased accumulation of lower airways secretions in patients with airways disease (Hardman, 1996).
All of the above drugs are quaternary derivatives that do not penetrate the blood-brain barrier. Thus they are ineffective against the CNS toxicity of organophosphates.

**11.6. Clinical atropine toxicity**

Poisoning can occur following oral, ocular, respiratory or parenteral exposure. There are numerous case reports of atropine poisoning from plants from antiquity through to the present. In a case of jimsonweed poisoning (*Datura stramonium*), a four-year-old boy presented with confusion, hallucinations, ataxia, and tachycardia. Symptoms developed three hours after ingestion, recovery took two days (Schumacher, 1965). In a 65-year-old man, 3 mg of atropine from *Atropa belladonna* leaves mistaken for burdock (*Arctium lappa*) leaves, produced not only peripheral atropinization but also a central anticholinergic syndrome with restlessness, hyperactivity, and dysphasia. Symptoms resolved within 24 hours with symptomatic therapy (Wood & Haq, 1971).

Mild atropine toxicity, with a central anticholinergic syndrome, may also occur after "normal" dosing, as the prolonged half-life of atropine with increasing age puts the older patient at risk (Beech et al., 1987).

Arthurs & Davies (1980) reported three children overdosed with atropine following a thousand-fold error in dosage. During the first 12 hours, the children were sedated and disoriented. They became increasingly restless as a central anticholinergic syndrome persisted for two days, requiring large quantities of diazepam for sedation; the pupils remained dilated for a week.

In a review of nine cases of accidental poisoning with oral drops (Eumydrin, atropine methonitrate), Meerstadt (1982) reported toxicity with atropine dosages ranging from 0.39-3.55 mg/kg. One patient, a 6-week-old boy, presented with fever, irritability, warm dry skin, inspiratory stridor, cyanosis of the hands and feet, and dilated and unresponsive pupils. Recovery was uneventful.

Following an accidental oral overdose of 0.3 mg/kg atropine in two small children, Saarnivaara et al. (1985) reported maximum serum levels of 29 and 15.6 mg/L at 2 to 2.5 hours, concentrations normally found in the distribution phase following an intravenous bolus of a therapeutic dose. Symptoms of toxicity resolved uneventfully within eight hours. In three-year old children, deaths have been reported following ocular applications as low as 1.6 and 2 mg (Heath, 1950; Morton, 1939) and oral doses of 100 mg (Legroux, 1962), although one patient recovered following an estimated ingestion of 1 g (Alexander et al., 1946).

**11.7. Drug interactions**

Intramuscular atropine may slow small bowel transit time by approximately 38% (Hardison et al 1979), which in turn determines enterohepatic cycling frequency. Gastric emptying may also be delayed by atropine (Dollery, 1991). Thus, the pharmacokinetics and/or efficacy of oral drugs co administered with atropine may be changed, as may the response of drugs that undergo enterohepatic circulation.

Changes in drug efficacy have occurred with levodopa (decreased effect) (Algeri et al., 1976) and amantidine (hallucinations) (Postma & Tilburg, 1975), when anticholinergics were given concomitantly. Pre-treatment with the calcium channel blocker, verapamil has increased the tachycardia produced by atropine in healthy volunteers.(Meyer et al, 1991).

Other drugs with anticholinergic effects, such as tricyclic antidepressants, some antihistamines, phenothiazines, disopyramide and quinidine, will have additive peripheral and central nervous system anticholinergic activity if given with atropine (Dollery, 1991). Tertiary amine muscarinic receptor
antagonists used as antispasmodics, such as dicyclomine, oxyphencyclimine, flavoxate and oxybutynin will also act similarly, as will quaternary ammonium muscarinic receptor antagonists, for example, ipratropium, methscopolamine and homatropine (Hardman, 1996).

The muscarinic actions of parasympathomimetic drugs such as carbachol, bethanecol and pilocarpine are blocked by atropine (Hardman, 1996).

The action of anticholinesterase agents such as physostigmine, neostigmine, edrophonium, ambenonium and pyridostigmine can be antagonised at muscarinic receptor sites by atropine (Hardman, 1996) and vice versa, according to dose size.

12. Summary of evaluation and recommendations

Atropine is the drug of choice for the treatment of the muscarinic symptoms and signs of poisoning with anticholinesterase agents (organophosphate or carbamate), particularly excessive salivation and lacrimation, bronchoconstriction and hypersecretion, pulmonary oedema and bradycardia. Animal studies have shown that atropine alone significantly reduces mortality and counteracts features of toxicity due to most anticholinesterase insecticides. In several clinical case reports the administration of atropine is clearly associated with a reduction of cholinergic features and a favourable outcome.

In most experimental studies, a reduction in cholinergic features has been demonstrated by the concomitant administration of atropine and an oxime, although a significant further reduction in mortality has not always been demonstrated from the use of combined therapy. An unequivocal synergism from combination therapy in reducing mortality can be achieved experimentally following exposure to organophosphorus insecticides with a mixed central/peripheral mode of action. In clinical case reports the combination of atropine and an oxime has usually, but not always, been associated with a favourable outcome.

12.1. Indications

Based on experimental studies and clinical case reports, atropine sulphate is the anticholinergic drug of choice for the initial management of organophosphate poisoning whenever cholinergic features are present. The decision to treat should be based on the clinical evaluation of the patient, especially the bronchial hypersecretion, rather than on any laboratory tests.

12.2. Advised routes and doses

Based on clinical evidence, atropine is best given intravenously as bolus injections to dry the secretion as quickly as possible. The initial adult dose in an unknown or mild anticholinesterase poisoning is 1-2 mg repeated every 5 to 10 minutes until the desired clinical response is achieved. In a severe organophosphate poisoning atropine must be given at much higher doses to dry the secretion. Atropine may then be repeated or increased in increments at 15 to 30 minute intervals to maintain the signs of atropinization. Since repeated dosing is required, a constant infusion of atropine to maintain atropinization is more practical. When a constant atropine infusion is used the patient should be examined at least very 1 to 2 hours

For diagnosis in children, an intravenous dose of 0.015mg/kg can be administered, while watching for signs of atropinization (mouth dryness, dilated pupils, tachycardia). For a therapeutic intravenous dose in symptomatic children, 0.015 to 0.05mg/kg can be given every fifteen minutes as needed.
If intravenous access is not available, the drug can be given by the intraosseous, endotracheal, intramuscular, or subcutaneous routes. If a rapid effect is required, case reports have shown that atropine sulphate can be given effectively by the endotracheal route. The dose requirements are unclear, however, and may be at least 2 to 2.5 times the intravenous dose. Based on pharmacokinetic studies in monkeys, the intraosseous route may also be considered in children. The intraosseous dose of atropine is similar to the intravenous dose. Doses of intramuscular or subcutaneous atropine sulphate are similar to intravenous doses also, but onset time is longer (about 30 minutes), and more variable.

The dose of atropine should be titrated against a reduction in secretions, especially bronchial secretions, rather than against heart rate (tachycardia) or pupil size (miosis). No maximum atropine dose per hour or per 24 hours can be given as this depends entirely on the severity of the intoxication (dose and type of organophosphate). Atropine treatment may have to be continued for many days.

For patients who develop CNS signs of atropine toxicity such as agitation, hallucination and confusion, treatment should be discontinued until the CNS signs disappeared. Patients should be weaned from atropine treatment slowly, particularly if they have received atropine over several days.

12.3. Other consequential or supportive therapy

There is evidence from many animal studies of a significant synergistic effect from combination therapy with an oxime and atropine. Animal data also indicate that the addition of diazepam is beneficial for the control of seizures, though significantly reduced lethality has not been demonstrated.

Sodium bicarbonate infusion to induce blood alkalinization (maintain arterial blood pH between 7.45 and 7.55) in a controlled clinical trial of human organophosphate poisoning revealed significant therapeutic effects (Balali-Mood et al, 2002).

12.4. Controversial issues and areas of use where there is insufficient information to make recommendations

There appears to be no controversy as to the benefit of atropine in reversing cholinergic features in organophosphate poisoning. Although the optimal dose of atropine (see section 12.2) is the dose which prevents bronchial hypersecretion, there appears to be little evidence, as yet, to confirm which route of administration is the most effective in an emergency if venous access is not available.

12.5. Proposals for further studies

Very little is known regarding the optimal dose and pharmacokinetics of atropine in relation to the dose of oximes, the severity of poisoning, and the properties of a particular organophosphate. This is clearly a field worthy of further study.

No controlled clinical study has documented the effect of atropine in human organophosphorus insecticide poisoning. Based on the data reviewed in this monograph, such a study would be considered unethical to perform. Further studies are, however, warranted to confirm the optimal route of administration if venous access is not available.

12.6. Adverse effects

Signs of over-atropinization are infrequent but may include mydriasis, tachycardia and a central
anticholinergic syndrome with restlessness, hyperactivity and delirium.

**12.7. Restrictions for use**

There appear to be no restrictions for the use of atropine in organophosphate-poisoned patients with excess cholinergic features. However, special care must be taken under the following circumstances:

In the hypoxic patient clearing the airway and sufficient oxygenation of the patient must be ensured to avoid clinically significant cardiac arrhythmias.

In warm environments, the body temperature should be monitored because of atropine inhibition of sweating. External cooling measures may be necessary.

**13. Model information sheet**

**13.1. Uses**

Atropine sulphate is indicated for the treatment of anticholinesterase agents (organophosphate and carbamate poisonings) and whenever cholinergic features need to be counteracted.

**13.2. Dosage and route**

**Adults:** 1-2 mg bolus given intravenously in an unknown or mild anticholinesterase poisoning. Repeated as often as every 5-10 minutes as required to reduce (bronchial) secretions. In moderate and severe organophosphate poisonings, much larger doses are required.

**Children:** At least 0.015 mg/kg bolus should be given intravenously; then 0.015 to 0.05 mg/kg every 15 minutes as needed. Intraosseous, endotracheal, intramuscular or subcutaneous routes should be used if venous access is not available.

No maximum dose of atropine can be given as this depends on the severity of the organophosphate poisoning.

**13.3. Precautions/contraindications**

Cyanotic (hypoxic) patients should be oxygenated and if necessary intubated at the same time as atropine is administered, to avoid ventricular tachyarrhythmias.

If an infusion is used, the risk of over-atropinization should be avoided by regular review of the rate of infusion, particularly in patients with liver or kidney disease, in children and in the elderly.

In warm environments, patients should be kept cool and body temperature monitored as atropine inhibits sweating.

**13.4. Pharmaceutical incompatibilities and drug interactions**

Anti-AChE agents, such as the organophosphorus insecticides, are synergistic with the depolarizing blocking agents, such as succinylcholine. The latter is therefore best avoided in these patients as is also other parasympathomimetic therapy.
13.5. Adverse Effects

Atropine administration should be discontinued if over-atropinization is observed.

Possible hypersensitivity to cholinergic stimulation (tremors, rigidity) after prolonged atropine therapy may occur.

13.6. Use in pregnancy and lactation

Pregnancy is no contraindication to therapy as the organophosphate poisoning represents a greater threat to the fetus than atropine.

13.7. Storage

Atropine sulphate injection preparations should be stored at 15-30°C and protected from light. Under these conditions, the shelf life of atropine sulphate for injection is two years. Atropine in autoinjectors, protected from light and stored between 15 and 30 °C, have a shelf life of 5 years.

14. References


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