CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-146

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 21-146 **SUBMISSION DATE**: December 16, 1999

Atropine Sulfate Injection, USP

5 ml (0.05 & 0.1 mg/ml) and 10 ml (0.1 mg/ml) Plastic Syringe

Abbott Laboratories **REVIEWER**: Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: ORIGINAL NDA

BACKGROUND

Atropine sulfate has been marketed in glass containers without an approved NDA by Abbott Laboratories but they now want to market the product in plastic containers. Under 21 CFR 310.509, any parenteral drug product packaged in plastic immediate container is considered an unapproved new drug and requires an approved NDA before it could be marketed. The sponsor has requested a waiver of bioavailability test requirements per 21CFR 320.22(b)(1). The sponsor did not submit any human pharmacokinetic data or literature to this NDA but it was decided that a literature search should be conducted by the reviewer with a view to update the labeling for this drug product.

According to the sponsor Atropine Sulfate Injection, USP is indicated (1) as an antisialogogue for preanesthetic medication to prevent or reduce secretions of the respiratory tract, (2) to restore cardiac rate and arterial pressure during anesthesia when vagal stimulation produced by intra-abdominal surgical traction causes a sudden decrease in pulse rate and cardiac action, (3) to lessen the degree of atrioventricular (A-V) heart block when increased vagal tone is a major factor in the conduction defect as in some cases due to digitalis, (4) to overcome severe bradycardia and syncope due to a hyperactive carotid sinus reflex, (5) as an antidote (with external cardiac massage) for cardiovascular collapse from the injudicious use of a choline ester (cholinergic) drug, (6) in the treatment of anticholinesterase poisoning from organophosphorus insecticides, and (7) as an antidote for the "rapid" type of mushroom poisoning due to the presence of the alkaloid, muscarine, in certain species of fungus such as Amanita muscaria.

SUMMARY OF LITERATURE SEARCH (see synopsis of each article below):

Metabolism: Atropine is metabolized by the microsomal mono-oxygenase enzymes and atropine esterase to four major metabolites. Following intravenous administration of ^{3}H-atropine sulfate noratropine (24%), atropine-N-oxide (15%), tropine (2%), and tropic acid appear to be the major metabolites, while 50% of the administered dose is excreted as unchanged atropine. Stereoselective metabolism of atropine probably occurs {(-)-hyoscyamine enantiomer is selectively metabolized while the biologically inactive (+)- enatiomer is excreted}. This being the case, the excreted products should be the optically active compounds (+)-hyoscyamine, (-)-norhyoscyamine, (-)-hyoscyamine-N-oxide, and (-)-tropic acid as well as tropine. The metabolism of atropine could be inhibited by organophosphate pecticides.

Pharmacokinetics: Following i.v. administration, there was a rapid initial removal of atropine from the circulation in the first 10 minutes followed by a more slowly decrease in the plasma concentration. Following i.m. administration atropine was rapidly absorbed with peak concentration in plasma at 30 min. The plasma concentrations obtained at that time after i.m. injection were comparable to those after i.v. administration.
Atropine disappears rapidly from plasma after i.v. administration with a biexponential decay and a mean half-life of 3 to 10 hours and mean total plasma clearance of 2.9 to 6.8 ml/min/kg. The mean Vdss value of >200 l indicates that atropine is widely distributed in tissues. Atropine has a fast placental transfer with significant uptake after both the i.v. and i.m. administration. Renal plasma clearance was 660 ml/min, suggesting significant tubular secretion. The renal plasma clearance of atropine is dependent on urine flow.
Exercise both prior to and or immediately following i.m. atropine administration has the capacity to modify the PK of atropine by concomitant changes in muscle and hepatic blood flow. These changes are greatest when exercise both precedes and follows administration of the drug.

Atropine was found to be poorly bound (about 44%) to plasma protein, mainly to α-1 acid glycoprotein (AAG). Atropine binding to AAG was concentration-dependent and nonlinear *in vitro* and *in vivo*. Age no had effect on serum protein binding of atropine.

Atropine was found in human CSF after the i.m. administration but not after the i.v. injection. This is because after i.v. injection, there is a fast distribution ($t_{1/2}$ of 1-2 min) to well perfused tissues that inhibited the transfer of atropine into human CSF in significant amounts. After the i.m. injection, the slowly increasing serum levels allowed more time for the transfer of atropine through the blood-CSF barrier.

Pharmacokinetics-Pharmacodynmaics (PK-PD): Following i.m. administration, the PK of atropine were best described by a two-compartment model with very rapid first order absorption and the data suggest a nonlinear (less than dose-proportional) relationship across the four doses (0.5 to 4.0 mg). Changes in plasma atropine levels and heart rate closely overlapped for all four doses throughout most of the time course. In contrast, the differential time course of changes in atropine levels and behavioral impairment indicates that PK is not the primary rate-limiting mechanism for the CNS effect of atropine.

The kinetics of the effects of atropine on heart rate (HR) and saliva flow in three healthy male volunteers after i.v. administration (rapid, constant infusion over 3 min) of 1.35 and 2.15 mg have been determined. Both the PK and effect data were fitted to an integrated PK-PD model. The maximum HR and minimum saliva flow occurred with significant delay of 7-8 min after drug administration. Both effects were nonlinearly related to the amount of drug in the peripheral compartment. Maximum HR of 192 and 217% of the control values were observed at the lower and higher dose levels, respectively. Minimum saliva flows of 8 and 3% of the control values were measured after the lower and higher doses of atropine, respectively. The curves of effect against amount in tissue for different doses were not superimposable. The curves for HR and saliva flow had steeper slopes after the lower than after the higher dose.

This may indicate that the higher atropine dose induced increased cholinergic (or decreased adrenergic) activity through a feed-back mechanism.
Changes in plasma atropine levels following i.m. administration (0.5 to 4 mg doses) and heart rate are closely overlapped but the time course of the changes in atropine levels and behavioral impairment indicates that pharmacokinetics is not the primary rate-limiting mechanism for the central nervous system effect of atropine.

Special Populations: Dialysis did not appear to have an appreciable effect on the plasma rate decay of atropine. The ineffectiveness of dialysis in the overall elimination of atropine is probably a result of its large apparent volume of distribution and rapid metabolism and excretion by liver and kidney.

Age had significant effect on the PK of atropine: in children under 2 years and in the elderly a prolonged elimination was found. These alterations may be due to an increased distribution or to a decreased elimination of atropine and might partly explain the higher sensitivity of these age groups to the effects of atropine.

No significant differences in PK or PD were found between the sexes, which indicates that there are no sex-related alterations in the response to atropine

Drug Interaction: Metoclopramide (i.v.) enhanced and atropine (i.v.) decreased the rate of mexiletine absorption without altering the relative oral bioavailability. When the pretreatment were administered in combination, metoclopramide reversed the delay in mexiletine absorption by atropine

Request for waiver of bioavailability requirement: It is recommended that the sponsor's request for a waiver of the bioavailability test requirements per 21CFR 320.22(b)(1) be granted. This is because the drug product is intended for i.v. injection and no changes have been made to the original formulation. Additionally, the chemist said that there is no compatibility problem with atropine formulation in plastic container.

SYNOPSIS OF LITERATURE SURVEY

METABOLISM:

1. Szorady, I, Szemere, G, Magyarlaki A and Hegedus, G. "Some observations concerning atropine esterase" Acta biol Acad Sci hung 1970; 21(3):293-7.

Summary: Serum samples from 206 infants and children were examined for the presence of atropine esterase by the agar-plate and incubated *in vitro* with known amount of atropine in order to determine their atropine-degrading ability. It was only the serum of an 8-year old hospitalized child with Down's syndrone and maxillary sinusitis which showed transitory atropine esterase activity and an increased power of atropine degradation. This phenomenon, demonstrated in human serum for the first time, was presumably due to enzyme induction due to the acute disease but not due to drugs administered to the patient. Presence or absence of atropine esterase is one of the several factors responsible for atropine-sensitivity.

2. Van Der Meer, MJ, Hundt, HKL, and Muller, FO "Inhibition of atropine metabolism by organophosphate pesticides" Hum Toxicol 1983; 2(4):637-640.

Summary: Urine specimens of 8 organophosphate-poisoned patients with large doses of atropine (0.03-0.05 $mgkg^{-1}h^{-1}$) were examined by means thin-layer chromatography. Only atropine was detected and no metabolites of atropine was detected in spite of one patient having received up to 67 mg of atropine sulfate within 8 hours. Urine specimens from an organophosphate-poisoned patient were collected at various times after administration of 30 μCi of ^{3}H-atropine sulfate by intravenous injection. This patient, who had inadvertently ingested the organophosphate pesticide diazion, was receiving 2 mg atropine sulfate/h. Urine specimens were collected every hour for the first 4 h, then every 4 h until 12 h after administration of the ^{3}H-atropine sulfate, and finally one specimen between 12 and 24 h. The amount of radioactivity in each urine specimen was measured by scintillation counting and by HPLC. Other than the atropine peak, which counted for 85% of the injected radio-activity, no other fractions containing radio-activity were detectable (no glucuronide and arysulfate conjugates detected). This contrasts strongly with results obtained using a normal volunteer, when 5 metabolic products were detected using the same method. The authors concluded that the enzymes associated with atropine metabolism, namely the microsomal mono-oxygenase, must have been inhibited by the organophosphate pesticides.

3. Van Der Meer, MJ, Hundt, HKL, and Muller, FO "The metabolism of atropine in man" J Pharm Pharmcol 1986; 38(10):781-784.

Summary: Urine specimens were collected from a normal volunteer who received 2 mg of atropine sulfate and 100 μCi of ^{3}H-atropine sulfate by intravenous infusion. Total radioactivity, corrected for quenching, was measured in 100 μl aliquots of the collected urine specimens. Aliquots (100 μl) of urine were chromatographed by HPLC . The identity of each peak was established by reference to an HPLC chromatogram of the authentic compounds. No additional peaks were detected after deconjugation with glucuronidase/arylsulfatase. Based upon chromatographic retention data, noratropine (24%), atropine-N-oxide (15%), tropine (2%), and

tropic acid appear to be the major metabolites, while 50% of the administered dose is excreted as unchanged atropine.
The possibility that only one isomer of atropine was selectively metabolized was investigated using urine samples from a patient who was hospitalized after accidentally ingesting an unknown amount of an organophosphate pecticide (demeton-S-methyl). The patient received 67 mg of atropine by continuous infusion. Analysis of the urine specimen by circular dichroism spectroscopy showed that the spectrum for atropine obtained from urine of the patient was a mirror image of the spectrum obtained from authentic (-)-hyoscyamine i.e. it was (+)-hyoscyamine. This suggests that stereoselective metabolism of atropine probably occurs {(-)-hyoscyamine enantiomer is selectively metabolized while the biologically inactive (+)-enatiomer is excreted}. This being the case, the excreted products should be the optically active compounds (+)-hyoscyamine, (-)-norhyoscyamine, (-)-hyoscyamine-N-oxide, and (-)-tropic acid as well as tropine.

PHARMACOKINETICS AND PHARMACOKINETICS-PHARMACODYNAMICS:

1. Berghem, L, Bergan, U, Schildt, B, Borbo, B. "Plasma atropine concentrations determined by radioimmunoassy after single-dose I.V. and I.M. administration" Br J Anaesth 1980; 52(6):597-601.

Summary: Single doses of atropine (1 mg) were given as premedication to (a) six male patients i.v. immediately before induction of anesthesia and (b) i.m. 30 min before the start of anesthesia to two male and two female patients. Blood samples were taken immediately before atropine administration and at various time intervals and the plasma concentrations of atropine were determined by radioimmunoassay. Following i.v. administration, there was a rapid initial removal of atropine from the circulation in the first 10 minutes followed by a more slowly decrease in the plasma concentration (Figure 1). Following i.m. administration atropine was rapidly absorbed with peak concentration in plasma at 30 min (Figure 2). The plasma concentrations obtained at that time after i.m. injection were comparable to those after i.v. administration.

Figure 1

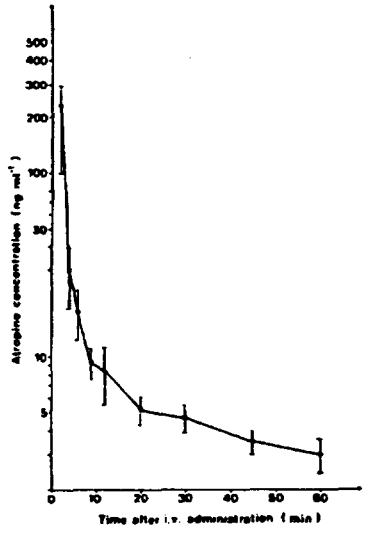
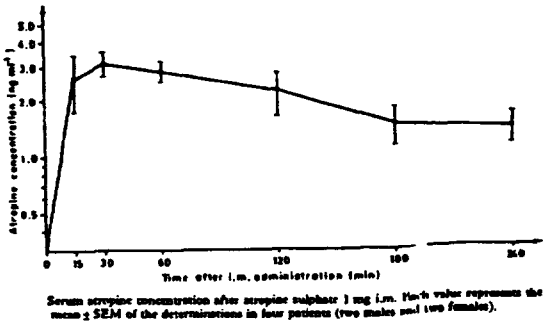


Figure 2



2. Adams, RG, Verma, P, Jackson, AJ and Miller, RL. "Plasma pharmacokinetics of intravenously administered atropine in normal subjects" J Clin Pharmacol 1982; 22(10):477-481.

Summary: Six healthy male volunteers (age 27 to 39 years) received a single 1 mg dose of atropine injection over 2 minutes. Blood samples were collected immediately before atropine administration and at 2, 4, 8, 12, 16, 20, 30, 45 minutes, and 1, 2, 3, 4, 8, and 24 hours and the plasma concentrations of atropine were determined by radioimmunoassay. Pulse rates were monitored at each sampling interval of the study. Atropine disappears rapidly from plasma after i.v. administration with a biexponential decay and a mean half-life of 4.13 hours and mean total plasma clearance of 533.35 ml/min. Subject 6 demonstrated a total plasma clearance twice that of other subjects and had minimal changes in the PD parameters measured and the authors were not certain if this was due to genetic effects on the disposition of atropine. The mean Vdss value of 230.79 l indicates that atropine is widely distributed in tissues. PK parameters were estimated for each subject with PCNONLIN (Table 1). The pulse rate values were expressed as a percent of the control value taken prior to drug administration. The mean maximal increase in pulse rate occurred between 12 and 16 minutes after i.v. injection consistent with maximal tissue levels of atropine (Figure 3).

TABLE I
Estimated Pharmacokinetic Parameters for Subjects Receiving 1 mg Atropine Intravenously

Pharmacokinetic parameters	1	2	3	4	5	6	Mean ± S.D.
α (min^{-1})	0.3910	0.453	0.116	0.536	0.296	0.0789	0.311 ± 0.184
β (min^{-1})	0.0028	0.0024	0.00041	0.0043	0.00144	0.0554	0.0028 ± 0.0019
k_{12} (min^{-1})	0.2500	0.344	0.102	0.412	0.248	0.0382	0.232 ± 0.141
k_{21} (min^{-1})	0.1350	0.100	0.0084	0.107	0.0367	0.0329	0.070 ± 0.050
k_{10} (min^{-1})	0.0082	0.0110	0.0057	0.0213	0.0166	0.0133	0.0118 ± 0.0053
$V_{c_{ss}}$ (liters)	15.845	162.77	525.05	141.62	165.81	191.07	230.79 ± 145.38
V_d (liters)	56.86	41.54	39.95	29.96	25.63	61.89	45.97 ± 20.66
Total plasma clearance (ml/min)	460.31	457.66	237.02	659.22	297.05	1088.87	533.36 ± 309.57
R for plasma data	0.984	0.996	0.974	0.993	0.959	0.984	

Figure 3

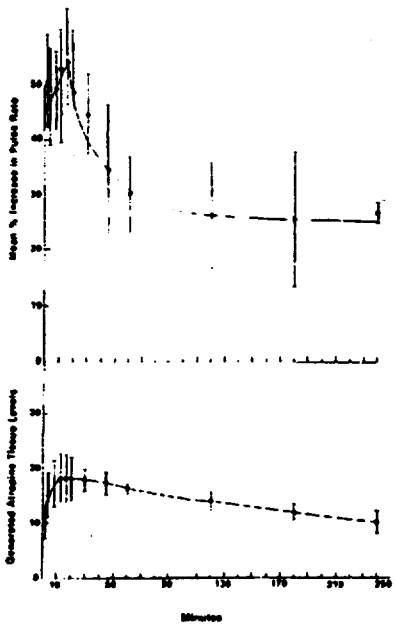


Fig. 2. Apparent correlation between mean per cent increase in pulse rate (upper graph) at 1 mg atropine and the mean amounts of generated atropine in the tissue compartment (lower graph). The resting pulse rates prior to drug administration served as control values. Vertical bars indicate ± S.E.M. The correlation coefficient between the increase in pulse rate and generated tissue levels was 0.84 and was statistically significant at $P \leq 0.01$.

3. Kivalo, I and Saarikoski, S. "Placental transmission of atropine at full-term pregnancy" Br J Anaesth 1977; 49(10):1017-1021.

Summary: Twenty-five pregnant patients received ^{3}H-atropine 0.5 $\mu g.kg^{-1}$ i.v. 1-30 min before delivery. Blood was sampled from the antecubital vein of the mother before anesthesia and at the time of delivery of the infant, simultaneous with the sampling of umbilical vein and artery blood. The total radioactivity was determined by liquid scintillation counting. The study showed that there may be rapid placental transmission of atropine. The mean ^{3}H concentrations

in the umbilical vein 1 and 5 min after injection were respectively 12% and 93% of the corresponding maternal value and it remained at 71% for the next 25 min. During the period from 1 to 5 min after administration of the drug, the concentration in the umbilical artery was approximately 50% of that in the umbilical vein.

4. Scheinin, H, Helminen, A, Huhtala, S, Gronroos, P, Bosch, JA, Kuusela, T, Kanto, J, and Kaila, T, "Spectral analysis of heart rate variability as a quantitative measure of parasympatholytic effect – integrated pharmacokinetics and pharmacodynamics of three anticholinergic drugs" Therapeutic Drug Monitoring 1999; 21(2):141-51.

Summary: In this double-blind, cross-over, placebo-controlled study, three different anticholinergic drugs or placebo were given at 1 week intervals to eight healthy volunteers. Each subject received single i.v. bolus doses of 10 $\mu g.kg^{-1}$ atropine sulfate, 5 $\mu g.kg^{-1}$ glucopyrronium, 5 $\mu g.kg^{-1}$ scopolamine and physiological saline (placebo). Blood samples were drawn at various time intervals and ECG measurements were made at the same time. Atropine plasma concentrations were determined using radioreceptor assay methods. PK and PK-PD analyses were performed using PCNONLIN. A linear two-compartment model with bolus input was used for PK model and a sigmoid inhibitory effect model with baseline effect was used for the PK-PD model. Table 2 summarizes the main two-comparment PK parameters for atropine. After i.v. administration, atropine was fastly distributed with mean (±SD) $t_{1/2\alpha}$ value of 4.5 (±3.6) min, and also rapidly eliminated with CL value of 1.74 (±0.26) L/h/kg and $t_{1/2\beta}$ value of 1.89 (±0.39) h. Table 3 summarizes the PK-PD parameters based on a sigmoidal Emax PD model and an equilibration delay between plasma and the effect site. The average (±SD) k_{e0} was 11.0 (±5.28) L/h and the corresponding equilibration half-life ($ln2/k_{e0}$) was 4.7 (±2.3) min.

Table 2

Pharmacokinetic parameters of single IV doses of atropine (10 μg/kg).

Parameter	Atropine
A [ng/mL]	8.69 (7.16)
B [ng/mL]	2.00 (0.39)
α [1/h]	17.3 (14.0)
β [1/h]	0.38 (0.08)
AUC [ng·h/mL]	5.86 (0.78)
k_{21} [1/h]	3.40 (1.65)
V_c [L/kg]	1.31 (0.72)
CL [L/h·kg]	1.74 (0.26)
V_{ss} [L/kg]	4.23 (0.79)

Values expressed as mean (SD). A, zero-time intercept of the distribution phase; B, zero-time intercept of the elimination phase; α, rate constant for distribution; β, rate constant for elimination; AUC, area under the concentration-time curve; k_{21}, rate constant for transfer from compartment 2 to 1; V_c, volume of the central compartment; CL, total plasma clearance; V_{ss}, volume of distribution at steady state.

Atropine induced average increase in heart rate (HR) of 22%, maximum effect being observed 10 min after drug administration. The concentration-effect curve was very steep ($\gamma = 6.07$) and there was no physiological or pharmacological explanation for the unexpectedly steep slope but modeling the data without sigmoidicity factor yielded inferior fits. The study showed that spectral analysis of heart rate variability appears to be a powerful tool in monitoring parasympatholytic activity.

Table 3

Pharmacokinetic-pharmacodynamic model parameters for atropine

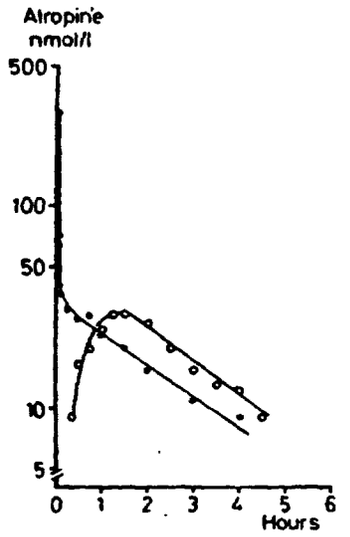
	EC_{50} [ng/mL]	E_{max}	E_0	γ	k_{e0} [1/h]
Atropine	1.35 (0.27)	39.9 (11.4)	45.4 (10.7)	6.07 (1.98)	11.0 (5.28)

Values given as mean (SD). EC_{50}, concentration at 50% of E_{max}; E_{max}, maximal drug effect; E_0, baseline affect; γ, sigmoidicity (Hill) factor; k_{e0}, equilibration rate constant.

5. Kanto, J, Virtanen, R, Isalo, E, Maenpaa, K and Liukko, P. "Placental transfer and Pharmacokinetics of atropine after single maternal intravenous and intramuscular administration" Acta Anaeth Scand 1981; 25(2):85-88.

Summary: Placental transfer and PK of atropine was studied after i.v (n=32) or after i.m. (n=12) administration of 0.01 mg/kg in 44 healthy parturients undergoing caesarian section. Blood samples were drawn from the maternal antecubital vein, umbilical vein and artery from selected groups at time points shown in Figure 4. A sample from the amniotic fluid was taken in five cases, 45-70 min after the i.m. administration. The atropine concentrations in plasma were determined by radioimmunoassay. The maternal PK of i.v. atropine obeyed a two-compartment open model (Table 4) with a fast distribution phase (mean $t_{1/2\alpha} = 1.02$ min) and a fast elimination phase ($t_{1/2\beta} = 2.56$ h) The total apparent volume of distribution was 1.01 l/kg and total plasma clearance was 6.36 ml/min/kg (Table 4). Table 5 presents the levels in the fetal and maternal circulations and the fetal-maternal ratios of atropine after i.v. or i.m. injection (similar to those from ref 3 above). The mean maternal plasma levels after i.m. atropine administration were found at 1.59 h and mean $t_{1/2}$ was 2.1 h. No atropine was found in the amniotic fluid. The data from this study show that atropine has a fast placental transfer with significant uptake after both the i.v. and i.m. administration.

Figure 4



The mean concentrations of atropine in the plasma after a single 0.01 mg/kg intravenous (O, n = 10) and intramuscular (●, n = 8) injection in connection with caesarean section.

Table 4

Pharmacokinetic parameters derived from the plasma concentrations of atropine after a single 0.01 mg/kg intravenous injection (mean ± s.e. mean, n = 10).

α	= 0.903 ± 0.211 min^{-1}
$t^{\alpha}_{1/2}$	= 1.02 ± 0.18 min
V_1	= 0.13 ± 0.03 l/kg
β	= 0.378 ± 0.086 h^{-1}
$t_{1/2}$	= 2.56 ± 0.46 h
V^{β}	= 1.00 ± 0.09 l/kg
Cl	= 6.36 ± 1.84 ml/min/kg

α = slope of the distribution phase;
$t^{\alpha}_{1/2}$ = distribution phase half-life;
V_1 = volume of the central compartment ($= \frac{dose}{A+B}$);
β = slope of the elimination phase;
$t_{1/2}$ = elimination phase half-life;
V^{β} = total apparent volume of distribution ($= \frac{dose}{\beta \cdot AUC}$);
Cl = total plasma clearance ($= \beta \cdot V^{\beta}$);
AUC = area under the plasma curve

Table 5.

The concentrations of atropine (nmol/l, mean±s.e. mean) in the maternal and foetal plasma after a single 0.01 mg/kg intravenous or intramuscular administration.

Time	n	Maternal vein	Umbilical vein	Umb. vein mat. vein	Umbilical artery	Umb. art. mat. vein	Umb. art. umb. vein
Intravenous administration							
<1 min	3	198.3 ±76.3	<9	–	<9	–	–
1-2 min	5	100.4 ±23.0	24.1 ±6.3	0.27 ±0.11	9.1 ±3.6	0.16 ±0.06	0.42 ±0.03
3-4 min	7	22.4 ±2.7	18.1 ±3.0	0.88 ±0.12	13.5 ±3.7	0.72 ±0.15	0.86 ±0.17
~ 5 min	7	38.2 ±7.9	17.8 ±1.5	0.54 ±0.10	15.5 ±1.7	0.39 ±0.08	0.85 ±0.10
~ 6 min	5	17.0 ±2.2	21.6 ±2.0	1.27 ±0.12	14.8 ±2.3	0.87 ±0.15	0.69 ±0.12
~ 7 min	2	16.8 and 18.2	11.9 and <9	0.71 –	9.8 and 22.4	0.58 and 1.23	0.82 –
8.5 min	1	18.6	23.1	1.24	13.0	0.70	0.56
11 min	1	16.1	17.5	1.09	20.0	1.24	1.14
Intramuscular administration							
~ 40 min	4	18.3 ±4.3	9.0 ±1.3	0.50 ±0.10	7.8 ±1.5	0.43 ±0.09	0.87 ±0.13
~ 60 min	7	22.0 ±5.2	10.6 ±3.3	0.48 ±0.11	8.4 ±3.6	0.38 ±0.10	0.80 ±0.16
2.5 h	1	10.5	<9	–	<9	–	–

6. Kamimori, GH, Smallridge, RC, Redmond, DP, Belenky, GL and Fein, HG. "The effect of exercise on atropine pharmacokinetics" Eur J Clin Pharmacol1990; 39(4):395-397.

Summary: Because atropine is used by the U.S. military as treatment for organophosphate poisoning, it is important to document the effect of physical exercise on the PK of atropine. Seven healthy males underwent each of four separate conditions in a repeated measures design. Five of these underwent additional trial. In four of the five trials subjects received 2 mg atropine sulfate i.m. at rest (T1); following completion of a single exercise (EX) bout (T2), (each bout consisted of 25 min of stationary cycling at 40% VO2max with 5 min of seated rest), prior to three Ex bouts (T3) and following one and prior three Ex bouts (T5). Trial 4 (T4) was the same as T3 with the substitution of a saline placebo. Atropine plasma levels were determined over 12 h period. The results obtained from the study showed that compared to T(1) (Table 6):

- Ex prior to atropine (T2) significantly decreased the mean volume of distribution, Vz
- Ex in T3 significantly decreased the $t_{1/2}$, Vz, CL and significantly increased the Cmax (Cp)
- In T5, Ex significantly decreased the $t_{1/2}$, Vz, and CL, and significantly increased the Ka (98% increase), Cmax (Cp), and AUC

Ex both prior to and following atropine administration increased the Ka possibly due to an increase in the perfusion rate in the muscle following initiation of Ex. An increase in blood

flow in the area of atropine administration could account for the changes observed in the Cmax and the Tmax (Tp). Atropine is described as a high clearance, flow dependent drug. Thus, its metabolism and removal can be modified by a change in delivery of the drug to the site of metabolism (liver) or in the activity of the metabolizing enzymes. The data from this study suggests that exercise both prior to and or immediately following atropine administration has the capacity to modify the PK by concomitant changes in muscle and hepatic blood flow. These changes are greatest when exercise both precedes and follows administration of the drug.

Table 6.

Atropine pharmacokinetic data (Mean ± SD)

Trial	k_a (min^{-1})	k_e (min^{-1})	$t_{1/2}$ (h)	C_p ($ng \cdot ml^{-1}$)	T_p (min)	V_c (l)	AUC ($ng \cdot h \cdot ml^{-1}$)	CL ($ml \cdot min^{-1} \cdot 70\ kg^{-1}$)
Part I ($n = 7$)								
1 $\bar{x}$	0.482	0.0012	4.2	6.7	41	278	44.1	738
(SD)	(0.194)	(0.0002)	(0.8)	(0.9)	(38)	(33.0)	(4.5)	(142)
2 $\bar{x}$	0.672	0.0014	3.8	8.7	29	237*	44.1	751
(SD)	(0.254)	(0.0003)	(0.6)	(1.4)	(28)	(32.0)	(7.5)	(209)
3 $\bar{x}$	0.401	0.0014	3.5*	12.3*	32	198*	53.1*	619
(SD)	(0.117)	(0.0015)	(0.4)	(2.6)	(10)	(26.7)	(7.6)	(107)
Part II. ($n = 5$)								
1 $\bar{x}$	0.561	0.0012	4.4	6.9	28	277	45.7	670
(SD)	(0.106)	(0.0001)	(0.6)	(0.9)	(16)	(34.0)	(3.0)	(59.4)
5 $\bar{x}$	1.10*	0.0015*	3.4*	14.0*	14	182*	53.5*	575*
SD)	(0.238)	(0.0002)	(0.3)	(2.6)	(10)	(11.9)	(4.6)	(77.0)

* $P < 0.05$ (compared to trial 1)

7. Ellinwood, EH, Nikaido, AM, Gupta, SK, Heaterly, DG and Nishita JK. "Comparison of central nervous system and peripheral pharmacodynamics to atropine pharmacokinetics" J Pharmacol Exp Ther 1990; 255(3):1133-1139.

Summary: Two experiments were designed to examine the PK-PD relationship for the central nervous system (CNS) and peripheral effects of atropine. According to a random Latin square design, healthy young male volunteers were given i.m. injections containing single doses of placebo or 0.5, 1.0, 2.0 or 4.0 mg of atropine. The CNS tests included wheel tracking, a coordination task, and digit symbol substitution, a memory-psychomotor speed task; the physiological variable was heart rate. Protein binding (both *in vitro* and *in vivo* methods) of atropine (0-20 ng/ml) in plasma, serum, human albumin (40 g/l), human α-1 acid glycoprotein (AAG, 0.7 g/l) and AAG spiked plasma and serum was determined using both ultrafiltration and equilibrium dialysis methods. The PK of atropine were best described by a two-compartment model with very rapid first order absorption and the data suggest a nonlinear relationship across the four doses (Table 7).
Changes in plasma atropine levels and heart rate closely overlapped for all four doses throughout most of the time course. In contrast, the differential time course of changes in atropine levels and behavioral impairment indicates that PK is not the primary rate-limiting mechanism for the CNS effect of atropine.

Table 7.

Average* pharmacokinetic parameters of atropine after i.m. dosing

Parameters	Dose (mg)			
	0.5	1.0	2.0	4.0
$T_{1/2}k_a$ (hr)	0.08 ± 0.01	0.06 ± 0.01	0.07 ± 0.10	0.06 ± 0.01
Lag time (hr)	0.11 ± 0.02	0.10 ± 0.02	0.11 ± 0.03	0.12 ± 0.02
C_{max} (ng/ml)*	2.40 ± 0.32	4.62 ± 0.49	7.20 ± 0.63	13.52 ± 0.85
Dose normalized C_{max} (ng/ml)	2.40 ± 0.32	2.31 ± 0.49	1.80 ± 0.63	1.69 ± 0.85
$T_{1/2}\alpha$ (hr)	0.35 ± 0.01	0.30 ± 0.01	0.52 ± 0.03	0.44 ± 0.02
$T_{1/2}\beta$ (hr)*	3.30 ± 0.05	2.96 ± 0.04	2.34 ± 0.06	1.62 ± 0.04
CL_p/F (l/hr)*	38.67 ± 8.15	40.10 ± 7.23	49.28 ± 8.95	64.38 ± 10.50
V_{area}/F (l)*	157.36 ± 14.19	162.31 ± 15.70	172.50 ± 17.61	191.08 ± 15.44
V_{area}/F, free (l)	267.33 ± 14.19	226.72 ± 12.70	269.53 ± 17.61	264.81 ± 15.44

* Mean ± S.D.
* Differed significantly between dose levels (Duncan test, $P < .05$).

Atropine was found to be poorly bound (about 44%) to plasma protein, mainly to AAG. Atropine binding to AAG was concentration-dependent and nonlinear *in vitro* and *in vivo* (Table 8). Since AAG levels may be elevated by physiological stress, trauma or other conditions and result in higher protein binding and less free atropine in plasma, individuals in a stressful situation may not have the same dose as individuals who are not experiencing any stress. The concentration-dependent (nonlinear) binding may in part explain the decrease in elimination half-life as a function of dose.

Table 8

Comparison of plasma unbound fractions of atropine between *in vitro* and *in vivo* studies

Studies	Plasma Atropine Concentration (μg/l)			
	2	5	10	20
In Vitro	0.56	0.61	0.65	0.71
In Vivo	0.55	0.62	0.63	0.73

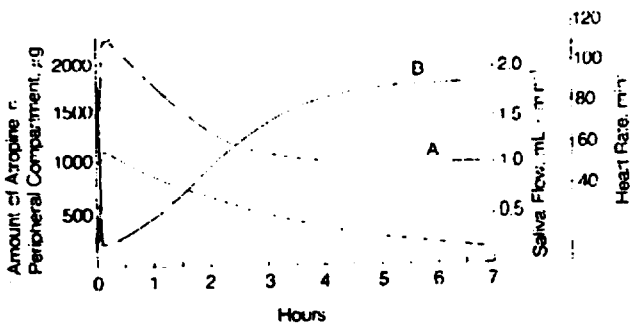
8. Hinderling, PH, Gundert-Remy, U, Schmidlin, O. "Integrated pharmacokinetics and pharmcodynamics of atropine in healthy humans I: Pharmacokinetics" J Pharm Sci 1985; 74(7):703-710.

Summary: The PK of atropine in three healthy male volunteers after i.v. administration (rapid, constant infusion over 3 min) of 1.35 and 2.15 mg was determined. Pharmacodynamic effects of atropine were measured simultaneously. Plasma concentrations of atropine and urinary levels of atropine and tropine were measured by GC-MS assay. A two-compartment model was

fitted to the data and the apparent half-lives for the two phases were 1 ± 0.2 ($t_{1/2\alpha}$) and 136 ± 25 ($t_{1/2\beta}$) min. The urinary excretion of unchanged drug and tropine were 57% and 29% of the dose respectively. The steady-state volume of distribution was 210 L, implying extensive tissue binding and/or partitioning. Renal plasma clearance was 660 ml/min, suggesting significant tubular secretion. The renal plasma clearance of atropine is dependent on urine flow.

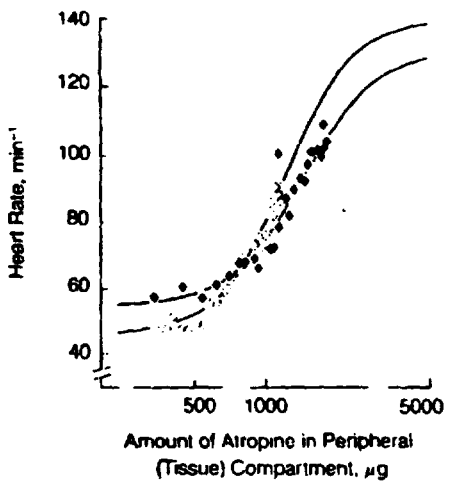
9. Hinderling, PH, Gundert-Remy, U, Schmidlin, O. "Integrated pharmacokinetics and pharmcodynamics of atropine in healthy humans I: Pharmacodynamics" J Pharm Sci 1985; 74(7):711-717.

Summary: The kinetics of the effects of atropine on heart rate (HR) and saliva flow in three healthy male volunteers after i.v. administration (rapid, constant infusion over 3 min) of 1.35 and 2.15 mg were determined. The PK of atropine and tropine were determined simultaneously. Both the PK and effect data were fitted to an integrated PK-PD model (Figures 5-7). The maximum HR and minimum saliva flow occurred with significant delay of 7-8 min after drug administration. Both effects were nonlinearly related to the amount of drug in the peripheral compartment (Figures 6 and 7). Maximum HR of 192 and 217% of the control values were observed at the lower and higher dose levels, respectively. Minimum saliva flows of 8 and 3% of the control values were measured after the lower and higher doses of atropine, respectively. The curves of effect against amount in tissue for different doses were not superimposable. The curves for HR and saliva flow had steeper slopes after the lower than after the higher dose. This may indicate that the higher atropine dose induced increased cholinergic (or decreased adrenergic) activity through a feed-back mechanism.
Figure 5



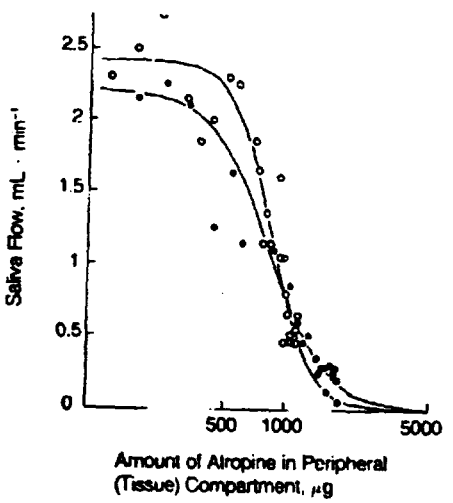
Fit of the experimentally measured heart rate (A) and saliva flow (B) data after administration of 1353 µg of atropine to subject B. Both effects depend nonlinearly on the amounts of atropine in the peripheral (tissue) compartment (– · · · –). The pharmacokinetic and pharmacodynamic data were fitted simultaneously to the integrated kinetic–dynamic model of Scheme I using the digital computer program TOPFIT. Only the fits of the pharmacodynamic data and the amounts of drug in the peripheral compartment generated by the computer are shown.

Figure 6



Plots of the effect of the drug on heart rate against the logarithm of the amounts of drug in the peripheral compartment, generated by the computer. Data were obtained in subject A after administration of 1383 μg (◇) and 2290 μg (◆) of atropine. The fitted lines are sigmoidal and imply a nonlinear relationship between the effect and amount of drug in the peripheral compartment.

Figure 7



Plots of the effect of the drug on saliva flow against the logarithm of the amounts of drug in the peripheral compartment, generated by the computer. The curves originate in the upper left corner and have negative slopes. Data were obtained in subject A after administration of 1383 μg (○) and 2290 μg (●) of atropine. The fitted lines are sigmoidal and imply a nonlinear relationship between the effect and amount of drug in the peripheral compartment.

10. Worth, DP, Davidson, AM, Roberts, TG, and Lewins, AM. "Ineffectiveness of hemodialysis in atropine poisoning" Br Med J (Clin Res Ed) 1983; 286(6383):2023-2024.

Summary: A 27 year old woman who accidentally ingested about 300 mg atropine underwent hemodialysis. Dialysis did not appear to have an appreciable effect on the plasma rate decay of atropine. The ineffectiveness of dialysis in the overall elimination of atropine is probably a result of its large apparent volume of distribution and rapid metabolism and excretion by liver and kidney.

SPECIAL POPULATIONS

A. Age and Gender

1. Virtanen, R, Kanto, J, Iisalo, E, Iisalo, EUM, Salo, M and Sjovali, S. "Pharmacokinetics of atropine with special reference to age" Acta Anaeth Scand 1982; 26(4):297-300.

Summary: The effect of age on the PK of atropine was studied in 31 patients (age 0.08-75 years) undergoing major surgery. At the beginning of a combination of anesthesia, atropine was injected i.v. as a bolus, 0.02 mg/kg, and blood samples were drawn over 24 hours. Age had significant effect on the PK of atropine:in children under 2 years and in the elderly a prolonged elimination was found (Tables 9 and 10, Figure 8). These alterations may be due to an increased distribution or to a decreased elimination of atropine and might partly explain the higher sensitivity of these age groups to the effects of atropine. Age no had effect on serum protein binding of atropine. Another group of 21 patients received i.v. atropine (0.010 mg/kg) and i.m. (0.015 mg/kg). A single blood and cerebrospinal fluid (CSF) sample was withdrawn 8-80 min after the i.v. and 45-105 min after the i.m. administration. Atropine was found in human CSF after the i.m. administration but not after the i.v. injection. This is because after i.v. injection, there is a fast distribution ($t_{1/2}$ of 1-2 min) to well perfused tissues that inhibited the transfer of atropine into human CSF in significant amounts. After the i.m. injection, the slowly increasing serum levels allowed more time for the transfer of atropine through the blood-CSF barrier.

Table 9

The pharmacokinetic parameters of atropine derived from the serum concentrations after a single 0.02 mg/kg intravenous injection given at the beginning of a combination anaesthesia. Due to a significantly lower clearance value (healthy adults versus the elderly: $P<0.01$; children versus the elderly: $P<0.05$), the elimination phase half-life was significantly prolonged in the elderly in comparison with the two other groups ($P<0.05$) (mean ± s.d.).

Age (years)	Weight (kg)	N	$t^{\alpha}_{1/2}$ (h)	$t_{1/2}$ (h)	V_1 (l/kg)	V^{β} (l/kg)	Cl (ml/min/kg)	Serum protein binding %
0.08–10 (2.9)	3.6–29 (12.1)	13	0.046±0.030	4.8±3.5	0.27±0.17	2.2±1.5	6.4±3.9	22.5±20.6
16–58 (35.7)	60–94 (68.6)	8	0.028±0.027	3.0±0.9	0.09±0.05	1.6±0.4	6.8±2.9	14.0±9.1
65–75 (69.3)	55–100 (76.3)	10	0.017±0.006	10.0±7.3	0.11±0.06	1.8±1.2	2.9±1.9	22.2±16.7

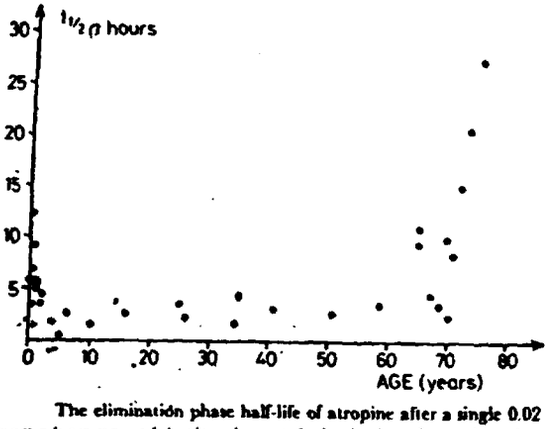
$t^{\alpha}_{1/2}$ = distribution phase half-life; $t_{1/2}$ = elimination phase half-life; V_1 = volume of the central compartment; V^{β} = total apparent volume of distribution; Cl = total serum clearance.

Table 10

Due to a significantly increased apparent total volume of distribution, a significantly longer elimination phase half-life of atropine was determined in children under 2 years of age in comparison with those over 2 years of age ($P<0.05$) (mean±s.d.).

	Children under 2 years of age N=7	*P*-value	Children over 2 years of age N=6
$T_{1/\beta}$ (h)	6.9±3.3	<0.05	2.5±1.2
V^{β} (l/kg)	3.2±1.5	<0.05	1.3±0.5
Cl (ml/min/kg)	6.8±5.3	N.S.	6.5±1.6

Figure 8



The elimination phase half-life of atropine after a single 0.02 mg/kg intravenous injection given at the beginning of a combination anaesthesia was significantly prolonged both in the elderly (over 65 years of age) and in children under 2 years of age in comparison with older children and adults.

2. Kanto, J, Pihlajamaki, K, and Hovi-Viander, M. "Elimination of and heart rate response to atropine in the elderly are independent of sex " Acta Anaeth Scand 1987; 31:202-204.

Summary: The changes in the PK and the PD (HR) of atropine were studied in female (n=9) and male (n=9) elderly patients after a single 0.02 mg/kg i.v. injection at the beginning of a combination anesthesia. Serum concentrations of atropine were determined by a radioimmunoassay over 36 after drug injection. No significant differences in PK or PD were found between the sexes, which indicates that there are no sex-related alterations in the response to atropine (Table 11).

Table 11

A. Pharmacokinetic parameters of atropine based on serum levels measured with RIA following a single 0.02 mg/kg i.v. injection of the drug at the beginning of combination anaesthesia (mean ± s.d.).

	$T_{1/2\alpha}$ (min)	$T_{1/2\beta}$ (h)	AUC (ng/ml·h)	Cl (l/kg/h)	$V_{d_{area}}$ (l/kg)
Group 1 males, n = 9	1.60 ± 1.50	6.56 ± 4.43	147.8 ± 97.1	0.195 ± 0.092	1.19 ± 0.48
Group 2 females, n = 9	1.61 ± 1.32	6.29 ± 3.08	164.8 ± 100.5	0.207 ± 0.177	1.44 ± 0.68

B. Pharmacodynamic response to atropine 0.02 mg/kg i.v. measured as heart rate changes

	Before drug injection	3 min	5 min	10 min	15 min
Group 1	81.9 ± 18.1	84.2 ± 16.7	82.0 ± 17.3	82.6 ± 16.8	81.3 ± 18.0
Group 2	77.6 ± 11.9	79.4 ± 13.7	81.3 ± 11.8	81.6 ± 12.8	79.7 ± 11.3

$T_{1/2\alpha}$ = distribution phase half-life; $T_{1/2\beta}$ = elimination phase half life; AUC = area under serum curve; Cl = total serum clearance; $V_{d_{area}}$ = distribution volume (area method).

B. Pediatric Population:

1. Pihlajamaki, K, Kanta, J, Aaltonen, L, Iisalo, E and Jaakkola, P. "Pharmacokinetics of atropine in children " Int J Clin Pharmacol Ther Toxicol 1986; 24(5):236-239.

Summary: The serum concentration of atropine was determined both by radioreceptor assay and RIA following single 0.02 mg/kg i.v. injection of 7 girls (age 6-15 years) and 16 boys (age 4-15 years at the beginning of a combination anesthesia. As reported by previous workers, a biexponential serum decay curve was demonstrated by RIA with a very rapid distribution phase ($t_{1/2\alpha}$ = 1-2 min) and a high tissue distribution $V_{d\beta}$ = 2.6 l/kg), but due to effective clearance of the drug (mean CL_{total} = 0.310 – 0.384 l/kg/h) the mean elimination phase half-life was around 6.5 hours. No age or gender dependency was found in the PK of atropine in this patient population (age 4-15 years).

DRUG INTERACTIONS

1. Wing, LMH, Meffin, PJ, Grygiel, JJ and Smith, KJ. "The effect of metoclopramide and atropine on the absorption of orally administered mexiletine" Br J Clin Pharmacol 1980; 9(5):505-509.

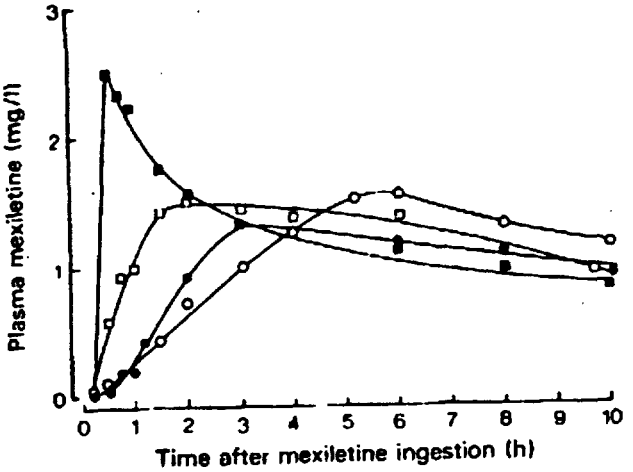
Summary: The effect of pretreatment with i.v. metoclopramide (10 mg) and atropine (0.6 mg), both separately and combined, on the absorption rate and relative bioavailability of mexiletine (400 mg) was studied in eight fasting healthy male subjects using a 4 x 4 Latin Square design for order of pretreatment administration. On each of the four occasions (separated by 72 hours), oral mexiletine was ingested 5 min after i.v. administration of the following:

(i) sodium chloride 154 nM (S)
(ii) metoclopramide 10 mg + sodium chloride 154 nM (M)
(iii) atropine 0.6 mg + sodium chloride 154 nM (A)
(iv) metoclopramide 10 mg + atropine 0.6 mg (A + M)

The data obtained from the study showed that (Table 12, Figure 9):

- Tmax of mexiletine was reduced by metoclopramide ($P<0.01$) and was increased by atropine ($P<0.01$) compared to normal saline
- Atropine pretreatment was associated with a significant reduction of Cmax ($P<0.05$) and of elimination half-life ($P<0.05$).
- The AUC of mexiletine was not affected by any of the pretreatments.
- The results suggested that metoclopramide enhanced and atropine decreased the rate of mexiletine absorption without altering the relative oral bioavailability. When the pretreatment were administered in combination, metoclopramide reversed the delay in mexiletine absorption by atropine.

Figure 9



Mexiletine plasma concentrations (mg/l) with respect to time (h) after ingestion of mexiletine 400 mg in a healthy male. The four separate curves were obtained following different intravenous pretreatments as indicated – saline (●), atropine 0.6 mg (○), metoclopramide 10 mg (■), and combined atropine 0.6 mg + metoclopramide 10 mg (□). For clarity, data from 10–32 h have been omitted from the figure.

Table 12

Mean kinetic parameters for orally administered mexiletine following saline, atropine, metoclopramide and atropine + metoclopramide pretreatments ($n = 8$).

Pretreatment	*Tmax (h)*	*Cpmax (h)* ($mg\ l^{-1}$)	*AUC* $_{0\ \infty}$ ($mg\ l^{-1}\ h$)	$T_{\frac{1}{2}}$ (*h*)
Saline	1.97	1.45	15.77	9.49
Atropine	3.32**	1.17*	17.65	8.02*
Metoclopramide	1.03***	1.79	16.68	8.88
Atropine + metoclopramide	1.70	1.36	15.75	8.48
Residual s.e. mean for each pretreatment (from ANOVA)	±0.26	±0.15	±0.86	±0.40

* $P < 0.05$
** $P < 0.01$
*** $P < 0.001$ from ANOVA and factorial analysis

FORMULATION: The quantitative compositions of formulations are shown on Table 13.

Table 13

A comparison of the formula of Abbott Laboratories' Abboject® product in glass container and the proposed fomula in Ansyr™ plastic syringe as follows:

0.1mg/mL Atropine Sulfate Injection, USP:

Ingredients Per mL	Abbott Labs Abboject® Glass Syringe	Abbott Proposed Ansyr™ Plastic Syringe
Atropine Sulfate, USP	0.1 mg	0.1 mg
Sodium Chloride, USP	9 mg	9 mg
Sulfuric Acid*	q.s.	q.s.
Sodium Hydroxide*	q.s.	q.s.
Water for Injection, USP	q.s.	q.s.

0.05mg/mL Atropine Sulfate Injection, USP:

Ingredients Per mL	Abbott Labs Abboject® Glass Syringe	Abbott Proposed Ansyr™ Plastic Syringe
Atropine Sulfate, USP	0.05 mg	0.05 mg
Sodium Chloride, USP	9 mg	9 mg
Sulfuric Acid*	q.s.	q.s.
Sodium Hydroxide*	q.s.	q.s.
Water for Injection, USP	q.s.	q.s.

*Used for pH adjustment

WAIVER OF BIOAVAILABILITY / BIOEQUIVALECE STUDY
The sponsor has requested a waiver of the bioavailability test requirements per 21CFR 320.22(b)(1). Because the drug product is intended for i.v. injection and/or injection directly into the ventricular cavity in cardiac resuscitation and no changes have been made to the original formulation, it is recommended that the waiver request be granted. Additionally, the chemist said that there is no compatibility problem with atropine formulation in plastic container.

LABELING COMMENTS The clinical pharmacology section of the labeling is deficient. The labeling should be updated as indicated (addition italicized and underlined) on the attached draft labeling (see appendix).

RECOMMENDATION:
The Division of Pharmaceutical Evaluation I has conducted a literature search on the clinical pharmacology of atropine and recommends a labeling update for this drug product. It is also recommended that the sponsor's request for a waiver of the bioavailability test requirements per 21CFR 320.22(b)(1) be granted. Please, forward the comments above to the sponsor.

/S/ 10/12/2000

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

/S/ 10/12/2000

FT Initialed by P. Marroum, Ph.D. ----------

CPB on 10/11/200 attended by: MEHTA, SAHAJWALLA, MARROUM, FADIRAN

cc: NDA 21-146, HFD-110, Fredd (HFD-110), HFD-860 (Fadiran, Mehta), BIOPHARM - CDR

7 pages redacted from this section of the approval package consisted of draft labeling

(23 - 29)