CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-146

Pharmacology Review(s)

D. Willard

APR 19 2000

NDA 21-146

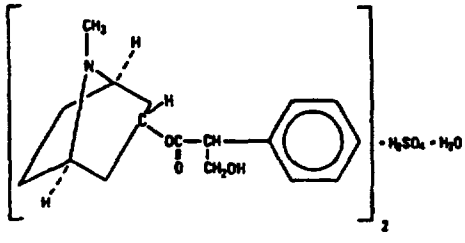
PHARMACOLOGY REVIEW OF ORIGINAL APPLICATION

C.A. Resnick, Ph.D.

SUBMISSION DATE: 16 December 1999
CENTER RECEIPT DATE: 20 December 1999
REVIEWER RECEIPT DATE: 02 January 2000

SPONSOR: Abbott Laboratories **DRUG PRODUCT**: Atropine Sulfate Injection, USP, Plastic Syringe

ACTIVE INGREDIENT: Atropine Sulfate



A naturally occurring belladonna alkaloid, a racemic mixture of equal parts of d- and l-hyocyamine.

FORMULATION and ROUTE OF ADMINISTRATION: A sterile, nonpyrogenic solution of atropine sulfate monohydrate in water for injection (0.1 mg/mL in 5 and 10 mL plastic syringes; 0.05 mg/mL in 5 mL plastic syringe) with sufficient NaCl to render the solution isotonic. It is to be administered parenterally by the subcutaneous, intramuscular or intravenous routes.

PHARMACOLOGICAL CLASS: Anti-muscarinic agent (antagonizes the muscarine-like actions of acetylcholine and other choline esters; activity primarily due to the levo isomer).

PROPOSED INDICATIONS

1) 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 antrioventricular (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*.

PROPOSED DOSAGE REGIMEN: Varies with indication and age of patient. In children at least 12 years of age, and in adults, doses range up to 0.6 mg when used as an antisialogogue (subcutaneous administration 30 minutes before surgery). For treatment of bradyarrhythmias, (intravenous) doses as high as 2mg every 2 hours may be required (up to 0.03 mg/kg in children). In anticholinesterase poisoning from exposure to insecticides, doses of at least 2-3 mg are recommended with repetition (at unspecified intervals) until signs of atropine intoxication appear. In the "rapid type" of mushroom poisoning, doses sufficient to control parasysmpathomimetic signs before coma and cardiovascular collapse supervene are recommended.

NONCLINICAL PHARMACOLOGY/TOXICOLOGY DATA: None.

LABELING: The package insert for this product is similar to the insert for Abbot's grandfathered (glass container) product. One change is the addition of a Carcinogenesis, Mutagenesis, Impairment of Fertility subsection under PRECAUTIONS. The proposed text of that section reads as follows:

DRAFT

EVALUATION: Abbott Laboratories currently markets atropine sulfate injection in an Abbojject® glass container. There is no approved NDA for this product, which was grandfathered under the 1938 Food, Drug and Cosmetic Act. The company now wishes to market the same solution in a plastic syringe. An application to do so has been submitted under section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The sponsor notes in their application that a supplemental application for another grandfathered drug, 25% Dextrose Injection (NDA 19-445), packaged in the same plastic container, was approved by the Division of Metabolic and Endocrine Drug Products in November 1998. They further provide a listing of other approved products packaged in the same syringe (apparently all the subjects of supplemental NDAs or ANDAs).

Section 505(b)(2) of the act permits reliance for approval on literature or on an Agency finding of safety and/or efficacy for an approved product. Approval of the 505(b)(2) application is subject to patent or exclusivity protections covering the approved product.

The only currently approved injectable atropine product is Meridian's AtroPen Auto-Injector, which is approved for only one of the seven (acute use) indications sought by Abbott (treatment of anticholinesterase poisoning from organophosphorus insecticides). Although we would like to see some non-clinical safety data generated in support of Abbott's application, specifically genetic toxicity and developmental toxicity data, which appear not to have been provided in support of the approved Meridian product, it would certainly be inconsistent on the part of the Agency to deny approval of the pending NDA on the basis of the absence of non-clinical safety data while permitting the continued use of the marketed product in the absence of similar data.

RECOMMENDATION: Approvable from the perspective of Pharm/Tox (i.e., additional studies in animals, *in vitro* or *in vivo*, not required) with recommended changes in labeling; see LABELING, above.

Charles A. Resnick
Pharmacology Team Leader
Division of CardioRenal Drug Products

cc:
Orig.NDA 21-146
HFD 110
HFD 110/CSO
HFD 110/CAResnick 15 April, 2000