CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-558

PHARMACOLOGY REVIEW

NDA 17-558

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PHARMACOLOGIST REVIEW OF NDA 17-558

AUG 2 2 1974

AMENDMENT OF AUGUST 5, 1974

APPLICANT: A. H. Robins Company
1407 Cummings Drive
Richmond, Virginia 23220

DRUG: Robinul Injectable

CATEGORY: Synthetic anticholinergic

EVALUATION: Applicant has modified precautionary labeling, in response to our question concerning the relationship between the anticholinergic action of the drug and diminished rate of conception, in the following manner: "studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate".

CONCLUSION: Modified labeling is satisfactory from the pharmacologist's standpoint.

Clyde G. Oberlander

cc: NDA 17-558 orig.
HFD-100
HFD-160
HFD-102 (W.D'Aguanno)
R/D C.G.Oberlander
R/D Init. J.K.Inscoe 8/20/74
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April 1, 1974

PHARMACOLOGIST REVIEW OF NDA 17-558
Original Summary

Applicant: A.H. Robins Company
1407 Cummings Drive
Richmond, Virginia 23220

Organization Performing Toxicity Studies:
(1) Applicant

[redacted]

Drug: Robinul Injectable

Category: Synthetic anticholinergic

Composition:

	Per ml.
Glycopyrrolate	0.2 mg.
Chlorobutanol, Anydrous plus 5%	0.5 %
Water for Injection U.S.P. q.s.	

(available in 1 ml., 5 ml. and 20 ml. vials)

Related INDs: [redacted]
NDAs:

Pre-NDA Conference: September 21, 1971

Proposed Dosage:

Preanesthetic Medication

Adults: 0.002 mg (0.01 ml) per pound of body weight IM, 30 minutes to one hour prior to induction of anesthesia or during administration of preanesthetic narcotic and/or sedative.

Children: (up to 12 years of age) 0.002 to 0.004 mg per pound of body weight. Children with disorders such as Down's syndrome should not have anticholinergics; or, if necessary, the usual dose should be reduced by half.

Intraoperative Medication

Adults: 0.1 mg (0.5 ml) IV to counteract drug-induced or vagal traction reflexes with associated arrhythmias.

Children: Same as adults.

Reversal of Neuromuscular Blockade

Adults: 0.2 mg (1.0 ml) IV for each 1.0 mg (1.0 ml) of neostigmine or equivalent dose of pyridostigmine.

Children: Same as adults.

Gastrointestinal Disorders

Adults: 0.1 (0.5 ml) to 0.2 mg (1.0 ml) SC, IM or IV, at 4-hour intervals, 3 or 4 times daily.

Proposed Indications: Preoperative antimuscarinic to reduce salivary, tracheobronchial and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation.

During anesthesia to counteract parasympathomimetic effects of general anesthetics and at reversal of neuromuscular blockade to protect against peripheral muscarinic effects of cholinergic agents.

Management of gastrointestinal disorders amenable to anticholinergic therapy when oral medication is not tolerated or a rapid anticholinergic effect is desired.

Toxicity Studies - Glycopyrrolate
Acute

Reference Firm: 2

Species	Sex	Route	LD_{50} (mg/kg)	95% Confidence Limits
Mouse	M	I.V.	14.7	11.9-18.4
Mouse	M	I.P.	112	93-134
Mouse		P.O.	550	430-704
Rat	F	I.V.	14.6	13.9-15.3
Rat	F	P.O.	1280	1180-1389
Rabbit	Either	I.V.	25*	
Dog	Either	I.V.	15-30*	
Cat	Either	I.V.	15-30*	

*Approximations

Observations (3 Days):

Mouse & Rat: Mydriasis observed consistently. Most rats at lower oral dose levels (500 to 1000 mg/kg) were inactive but responded to tactile stimuli, usually with an exaggerated response. At higher levels by any route (1500 to 2000 mg/kg) tremors, clonic and tonic convulsions and labored respiration were observed before death, apparently due to respiratory failure. Gross pathology showed no significant changes.

Rabbit: Mydriasis, tachycardia and prostration. Death due to respiratory failure. Survivors appeared essentially normal within 2 minutes.

Dog: Mydriasis, xerostomia and tachycardia. At 20 mg/kg, respiratory rate increased and then decreased at higher doses. At 80 mg/kg ataxia, convulsive twitches and emesis occurred. Survivors at high dose levels were sluggish and did not eat. Deaths were due to respiratory failure. Pulmonary hyperemia was noted in several animals. Liver was very firm in 2/4 survivors (20-30 mg/kg).

Four-Week Repeated Dose Toxicity — Reference Firm: 1

I.V. administration of glycopyrrolate (0.4 or 2.0 mg/kg/day) 5 days per week for 4 weeks caused no signs of toxicity in beagle dogs. Parameters monitored included: body weight gain, hemograms, gross and microscopic examination of tissues. BUN, serum Alk. Phos., SGOT and qualitative urinalysis. Clinical observations included: light, dry encrusted nares and dryness of oral and nasal mucosa at 2 mg/kg.

Irritation Studies — Reference Firm: 3

Intramuscular: Concentrations up to 25 mg/ml of glycopyrrolate injected into the sacrospinalis muscles of rabbits were no more irritating than positive controls (Dimetane (10 mg/ml) and Robaxin Injectable), during 72 hours.

Dermal: Glycopyrrolate solution (400 mg/ml) was applied to intact and abraded skin of rabbits at dose levels of 200, 600 and 2,000 mg/kg and covered with a rubber dam. Five day observations included: slight erythema for 24 hours at 200 mg/kg, and slight edema and more persistent erythema at the higher levels. Lower doses produced mydriasis lasting 48 hours while the high dose prolonged mydriasis for 72 hours.

Subcutanous: Rabbits injected s.c. with 0.5 ml glycopyrrolate aqeuous solutions containing 0.2 mg/ml and 2 mg/ml showed no histological evidence of inflammation during 3 days. Blood extravasation was seen in areas around the site of one of the lower dose injections and in areas of all of the higher levels.

Reproduction Studies
Rat - Multigeneration — Reference Firm: 3

Young male and female albino rats were given glycopyrrolate in their diet. Drug concentration was 0.13% (about 65 mg/kg) for 56 days prior to mating and through 2 matings (28 weeks), and 0.035% thereafter until termination of the study. There were four matings and all litters were evaluated on the basis of litter size, pup survival rate, malformations, etc.

Results: No abnormalites were seen among the offspring of treated animals; however there was a dose-related decrease in the rate of conception and survival at weaning.

Rabbit - Segment II

Reference Firm: 4

Robinul Injectable was administered I.M. to 15 mated female New Zealand White rabbits from Day 7 - Day 19. Dose levels were 0.05 and 0.5 mg/kg/day. Controls received vehicle alone. Rabbits were sacrificed on Day 30 and examined. All fetuses were examined for external and visceral malformations and then cleared and their skeletons stained with Alizarin Red for visualization of skeletal anomalies

Results:

	Control Vehicle Group I	Robinul Injection mg/kg/day 0.05 Group II	0.5 Group III
No. pregnant dams/pregnancy rate %	14/93.3	10/67.7	11/73.3
Maternal deaths	0	0	0
Mean no. corpora lutea	10.1	10.2	9.7
Mean no. resorptions	1.4	0.6	1.4
Mean no. implants	8.9	9.4	8.4
Implant efficiency %	88.1	92.2	86.6
Resorptions/No. implants (%)	19/125(15.2)	5/85(17.0)	15/92(16.3)
Live fetuses/Dead fetuses	125/0	85/0	92/0
Mean no. live fetuses	7.6	8.9	7.0
Mean live fetal weight (gm)	42.43	39.64	41.66
Sex ratio (M/F)	0.83	0.87	0.79
Fetal malformations %	0.0	1.1*	0.0
Incidence of ossification variations %	40.6	48.4	41.6

*Slight hydronephrosis in one animal.

Maternal body weight gains were depressed during the dosing period (Days 7-19) in Group II (about 63%) and Group III (about 85%) compared to controls. A decreased body weight gain of approximately 59.5% observed overall (Days 7-30) was seen in Group III compared to the control group.

Pharmacodynamics Reference Firm: 2

General - Anesthetized Dogs:

In anesthetized dogs, I.V. doses (5-10 µg/kg) or oral doses (0.5-5 mg/kg) of glycopyrrolate markedly reduced intestinal tone and moderately inhibited amplitude of intestinal contractions, but they had essentially no effect on respiration, carotid arterial blood pressure, or cardiac rate. Depressor response, changes in intestinal activity, and responses of the urinary bladder to parasympathetic stimulating agents were inhibited. These doses reduced the bradycardia, hypotension and the intestinal hyperactivity resulting from peripheral vagal stimulation. In general, larger I.V. or oral doses either greatly inhibited or abolished symptoms of parasympathetic stimulation. Glycopyrrolate did not significantly affect transmission of the nerve impulse at autonomic ganglia or at the somatic neuromuscular junction. The effect of large I.V. doses (5-10 mg/kg) on the pressor response to 1,1-diphenyl-4-piperazinium iodide (DMPP) were variable. In some experiments the blood pressure increase was augmented slightly, and in other experiments it seemed to be inhibited. The pressor response to bilateral carotid occlusion was not affected by the [illegible] glycopyrrolate. As indicated by the responses of the gastrocnemius muscle to electrical stimulation of the sciatic nerve, relatively high I.V. doses (5-10 mg/kg) were minimal for exhibiting impairment of nervous transmission at the somatic neuromuscular junction. Pressor responses to epinephrine or norepinephrine were slightly augmented particularly by high I.V. doses of glycopyrrolate. The depressor response to histamine was not altered by glycopyrrolate.

Isolated Guinea Pig Ileum

Glycopyrrolate and atropine appeared to be equipotent in antagonizing standardized contractions of the guinea pig ileum. Both drugs were more effective against the ileum response to acetylcholine than to histamine.

Test Meal Progression in Rats

Glycopyrrolate was effective in restricting gastrointestinal propulsive activity in the unanesthetized rat. The effect of glycopyrrolate was comparable to that of isopropamide iodide and significantly less than atropine sulfate.

Unanesthetized Thiry-Vella Loop Dogs

Glycopyrrolate (25 µg/kg, I.V.) inhibited intestinal motility and tone. Orally administered glycopyrrolate (1-5 mg/kg) had essentially the same qualitative effects in these dogs. Doses in the minimal effective range with regard to inhibition of intestinal activity, did not cause mydriasis or grossly observable dryness of the oral mucous membrane.

Gastric Antisecretory and Anti-ulcer Effect in Pyloric-ligated Rats

Glycopyrrolate (5 mg/kg, p.o.) significantly lowered both volume and free acidity of gastric secretion in pyloric-ligated rats. This antisecretory potency is equivalent to that of atropine sulfate. This dose also decreased ulcer formation. Higher doses (up to 40 mg/kg, p.o.) prevented ulcer formation.

Effect on Basal Gastric Secretion in Chronic Fistula Rats

Intragastric glycopyrrolate (1 mg/kg as the base) effectively reduced the volume and acidity of basal secretion in rats.

Effect on Gastric Secretion in Chronic Pouch Dogs

Glycopyrrolate (0.5 - 1.0 mg/kg, p.o.) significantly decreased gastric hypersecretion induced by histamine and likewise diminished insulin-stimulated gastric secretion. These doses also inhibited meal-stimulated gastric secretion in pouch dogs. On a weight basis the gastric antisecretory activity of glycopyrrolate appeared equivalent to atropine sulfate.

Tests for Parasympathetic Inhibition

1. Mydriatic Activity in Mice - Glycopyrrolate (20 µg/ml, applied topically to mouse eye) was comparable in effect to atropine sulfate.

2. Antilacrimation Activity in Rats - Methacholine-induced lacrimal hypersecretion was antagonized by glycopyrrolate (26 mg/kg, p.o.)

3. Effect on Salivary Secretion in Dogs - Glycopyrrolate (5 µg/kg, i.v.) diminished the volume of salivary secretion, which was stimulated by methacholine.

4. Antitremorine Activity in Mice - Glycopyrrolate (0.6-57 mg/kg, p.o.) protected mice from the peripheral effects of tremorine but not from the central effects.

EEG Studies in Cats

An accumulated I.V. dose of 15.9 mg/kg glycopyrrolate was required in order to obtain electroencephalogram central responses similar to those produced by 0.9 mg/kg, IV of atropine sulfate.

Local Anesthetic Activity in Guinea Pigs and Rabbits

Glycopyrrolate produced intradermal anesthesia in guinea pigs at local anesthetic concentration $_{50}$ (7.6%) and corneal anesthesia in rabbits at local anesthetic concentration $_{50}$ (10.3%).

Distribution and Metabolism of AHR-504-^{14}C Reference Firm: 1

Three rats (#1, 180 gm. each) were ~~each~~ given an oral dose (aqueous solution) by stomach tube of 15 mg/kg glycopyrrolate (AHR-504-^{14}C) (4.40 x 10^6 DPM/rat). Feces and urine were analyzed for radioactivity at 24 hour intervals for 3 days.

Results:

	Radioactivity Recovered at 72 Hours		
	Rat # 1	Rat #2	Rat #3
Urine	5.2%	3.0%	4.1%
Feces	69.8%	75.2%	90.2%
Total	75.0%	78.2&	94.3%

Radioactivity in the urine was determined not to be AHR-504. Structure of the radioactive metabolites has not been worked out. The bulk of the radioactivity in the feces was determined to be unchanged AHR-504.

#2
A female Sprague-Dawley rat (199 gm) was orally dosed with AHR-504-^{14}C (20 mg/kg) for $^{14}CO_2$ and excretion recovery through 96 hours.

Results:

A total of 99.36% of the radioactivity was recovered in the urine (3.59%) and feces (95.77%) at 96 hours. No radioactivity was recovered in the exhaled carbon dioxide.

Reference Firm: 1

Glycopyrrolate as a Substitute for Atropine in Anesthesia

Seven adult mongrel cats of either sex (wt. range: 2.0-5.4 kg) were anesthetized with ketamine hydrochloride (44 mg/kg, I.M.) or pentobarbital sodium (35 mg/kg, I.P.). The trachea was intubated and carotid artery and cephalic veins were cannulated. Each cat was paralyzed with gallamine triethiodide and artificial respiration was instituted. Following partial recovery, neostigmine (0.15 mg/kg, I.V.) was administered. After recovery from effects of neostigmine (usually 30-120 minutes) the above procedure was repeated except that atropine (0.05 mg/kg, I.V.) or glycopyrrolate (0.05 mg/kg, I.V.) was administered concomitantly with neostigmine. In addition, neostigmine was administered 30 minutes after atropine and glycopyrrolate to determine the duration of action of each agent in preventing slowing of the heart.

Results: Neostigmine alone: Within 1-2 minutes after administration, respiratory function was markedly improved and was accompanied by a marked reduction in heart rate.

Neostigmine plus atropine or glycopyrrolate:
Atropine or glycopyrrolate prevented a marked decrease in heart rate while having essentially no effect on respiration.

Neostigmine administration after atropine or glycopyrrolate:
Glycopyrrolate's effect was greater than 2 hours, while atropine's action lasted only 45 minutes.

Six cats were anesthetized with pentobarbital and prepared for recording heart rate. Drugs were administered I.V. via the cephalic vein and the trachea was intubated. Glycopyrrolate (4 cats) or atropine (2 cats) was given at 0.05 mg/kg, I.V. and stimulation of the exposed vagus nerve was performed at 15 minute intervals until slowing of the heart rate, comparable to the degree seen prior to drug administration, was recorded.

Results: Glycopyrrolate prevented vagal effects in all 4 animals for over 4 hours, while the inhibitory action of atropine was gone in approximately 1½ hours.

Human Studies

Abbott, William E. et al "The Effect of Glycopyrrolate (Robinul) on Basal and Histamine - or Insulin-induced Gastric Secretion". Ann. N. Y. Acad. Sci. 99: 163-73, 1962.

In approximately 2/3 of patients studied, 5-14 mg of glycopyrrolate given by mouth daily, produced a significant decrease in gastric acidity as quantitatively measured by a basal secretory test, but the decrease following histamine or insulin stimulation was not of sufficient magnitude to be significant in most cases.

Moeller, Hugo C. "Physiological Effects and Clinical Evaluation of Glycopyrrolate in Peptic Ulcer Disease". Ann. N. Y. Acad. Sci. 99: 158-62, 1962.

Glycopyrrolate was found to be an effective antisecretory agent. Side effects were not encountered at the oral dose level of 4 mg per day.

Sun, David C. H. "Comparative Study on the Effect of Glycopyrrolate and Propantheline on Basal Gastric Secretion". Ann. N. Y. Acad. Sci. 99:153-7, 1962.

A comparative study on the effect of glycopyrrolate and propantheline on basal gastric secretion in 64 patients with chronic duodenal ulcer was made. Glycopyrrolate, in oral doses of 1, 2 and 4 mg, produced a significant depression in volume, acid concentration, and output of basal gastric secretion. The degree of inhibition increased with an increase in the dose of the drug. When an equitoxicity dose was compared with an "optimal effective dose", propantheline was effective in suppressing acidity to pH 4.5 or higher in 13/18 patients while glycopyrrolate was effective in all 16 patients.

Young, Robert, Sun, David C. H. "Effect of Glycopyrrolate on Antral Motility, Gastric Emptying, and Intestinal XR Transit". Ann. N. Y. Acad. Sci. 99:174-78, 1962.

Glycopyrrolate (0.5 mg. S.C.) completely suppressed Type II antral waves in 5 cases and Type I wave in 4/5 cases. At 0.2 mg S.C., complete suppression of Type II wave was observed in 4/5 patients without effect on the Type I wave. Glycopyrrolate (2 mg, orally) did not effect gastric emptying or intestinal transit time. Side effects were minimal and limited to slight dryness of the mouth noted only on subcutanous injection.

Evaluation:

Robinul Injectable is the parenteral form of the potent synthetic anticholinergic drug, glycopyrrolate (0.2 mg/cc), which has been commercially available in the U. S. since 1967 (NDA 14-764 - approved 3-29-67) and has been indicated for controlling gastric hyperacidity and hypermotility of the gastrointestinal tract. This NDA provides for a new 20 ml multiple dose vial (also available in 1 cc ampuls and 5 cc multiple dose vials) and for a new indication, preoperative, intraoperative and postoperative use in anesthesia. Glycopyrrolate (Mol. Wt.: 398.34) is designated chemically as 1-methyl-3-pyrrolidyl-a-phenyl-cyclopentane glycolate methobromide.

Advantages claimed for the drug are:

(1) Greater protection to the heart against excessive vagal stimulation and less tachycardia than atropine.

(2) Prolonged duration of action (antisialogogue activity lasts 7-10 hours compared to 2-3 hours for atropine).

(3) Greater drying effect on tracheobronchial secretions.

(4) Diminishes volume and acidity of gastric secretions and helps to maintain gastric pH above the critical level of 2.5, thereby decreasing the risk of complication from gastric fluid aspiration.

(5) Since the drug is a quaternary ammonium compound it does not easily penetrate the blood brain barrier and thus lacks the adverse central effects of atropine (delirium, excitement) and peripheral effects (flushing and fever).

(6) Has the ability to control excessive secretions after the induction of anesthesia without causing disturbing dryness of the mouth prior to induction.

[redacted]

Acute toxicity studies with glycopyrrolate showed the following:

		LD_{50} (mg/kg)
mouse	i.v.	14.7
mouse	i.p.	112
rat	i.v.	14.6
rabbit	i.v.	25 (approximate)
dog & cat	i.v.	15 - 30 (approximate)

The i.v. dose is approximately 50 times as potent as the oral dose in mice and 80 times as potent in rats. Toxic effects are those seen with other anticholinergics namely, mydriasis, rapid respiration, convulsions, respiratory failure and death.

Intravenous administration of glycopyrrolate (0.4 and 2.0 mg/kg/day,5 days per week) for 4 weeks caused no toxic effects in beagle dogs.

In rabbits intramuscular injections of glycopyrrolate (25 mg/ml) were no more irritating than Dimetane Injection or Robaxin Injection. Topical applications of glycopyrrolate solution (400 mg/ml) to intact and abraded skin of rabbits caused slight edema and erythema. Subcutaneous injections of glycopyrrolate (2 mg/ml) showed no histological evidence of inflammation.

Multigeneration reproduction studies in rats with glycopyrrolate (up to 65 mg/kg in the diet) produced no teratogenic effects although there was a dose-related decrease in the rate of conception and survival at weaning.

Segment II reproduction studies in rabbits with Robinul Injectable (0.05 and 0.5 mg/kg) caused no teratogenic effects. Maternal body weight was depressed at both levels during the dosing period.

Pharmacological studies with glycopyrrolate showed:

1. Inhibition of gastric secretion in rats and dogs
2. Inhibition of salivary secretion in dogs
3. Blocked lacrimation in rats
4. Decreased intestinal tone and motility of intestinal contractions in dogs but no effect on blood pressure or respiration.
5. Lack of central effect in mice and cats

Metabolism studies in rats indicate 70-90% of the drug is excreted unchanged in the feces during 72 hours.

Studies in anesthetized cats show that glycopyrrolate is effective in blocking the muscarinic effects produced by neostigmine and that its effects lasted more than twice as long (4 hours) as those of atropine (1.5 hours).

Conclusion:

Animal studies support the safe use of this drug in man.

cc: NDA 17-559, Orig., Dup
HFD-100
HFD-160
P/D/ Oberlander HFD-160
Typed/ets/4/11/74
Zerox/ts/4/11/74
Init. Inscoe 4-3-74

Clyde G. Oberlander
Pharmacologist

NDA 17-559

May 24 1977

SUMMARY OF BASIS FOR APPROVAL

Toxicology - Pharmacology:

Acute studies, i.v., in mice, rats, rabbits, dogs and cats showed an adequate margin of safety.

Subacute study, 4 week, i.v., in dogs caused no drug-related toxicity.

Irritation study, i.m., in rabbits showed no more irritation than Dimetane Injection or Robaxin Injection.

Reproduction studies in rats (multigeneration) and rabbits (Segment II) produced no teratogenic effects.

Metabolism studies in rats indicate 70-90% of the drug is excreted unchanged in the feces during 72 hours.

Pharmacological studies show: (1) inhibition of gastric secretion in rats and dogs, (2) inhibition of salivary excretion in dogs, (3) blocked lacrimation in rats, (4) decreased intestinal tone and motility of intestinal contractions in dogs but no effect on blood pressure or respiration, (5) lack of central effect in mice and cats, and (6) blocking of muscarinic activity of neostigmine in cats lasting twice as long as atropine.

Conclusion: Animal studies support safety in man.

Prepared by: Clyde G. Oberlander

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