CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

17-558

MEDICAL REVIEW

NDA 17-558 4/15/74

MEDICAL OFFICER'S REVIEW OF NDA 17-558

NDA 17-558

DATE COMPLETED: 4/15/74

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

NAME OF DRUG: Trade: Robinul Injectable

Generic: Glycopyrrolate

DOSAGE FORM: Liquid, available in 1 ml, 5 ml and 20 ml vials.

ROUTE OF ADMINISTRATION: Subcutaneous, intramuscular or intravenous

CATEGORY OF DRUG: Anticholinergic

DATE OF SUBMISSION OF NDA: January 4, 1974

RELATED NDA's: 14-764 Glycopyrrolate injectable for gastrointestinal indications.

CHEMICAL NAME: 1-methyl-e-pyrrolidyl alpha-phenyl-cyclpentane glycolate methobromide

COMPOSITION:

Glycopyrrolate	0.2 mg	)
Water for injection, U.S.P.	q.s.	) per ml.
Chlorobutanol	0.5%	)

PRECLINICAL BASIS:

1. Pharmacology: NDA 14-764, and one published paper plus a preliminary report on distribution and metabolism. This material to be reviewed by the pharmacologist.

2. Chemistry: NDA 14-764 and manufacturing controls. See chemist's review.

CLINICAL STUDIES:

Studies were performed to support the following in anesthesia indications: "In anesthesia, Robinul injectable is indicated for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; and to block cardiac vagal inhibitory reflexes during induction of anesthesia and intubation.

During anesthesia, it counteracts the potent parasympathomimetic effects of general anesthetics such as cyclopropane, methoxyflurane, halothane, etc.; and at reversal of neuromuscular blockage, due to nondepolarizing muscle relaxants, it protects against the peripheral muscarinic effects (e.g. bradycardia and excessive secretions) of cholinergic agents, such as neostigmine and pyridostigamine."

Studies are separated into Special Studies (1), Dose-range Studies (1), Controlled Clinical Studies (7), Other Clinical Studies (3), plus published and unpublished reports.

There were nine investigators, the majority being heads of departments of anesthesiology in University or teaching hospitals. All are well qualified to conduct clinical investigations.

In the controlled and special studies 122 children received the test drug and 129 received atropine (control drug); Of the adults studied, 247 received the test drug and 165 received atropine. These are as follows:

INVESTIGATOR	AGE GROUP	TYPE STUDY	TEST	ATROPINE
( )	Adult	Special	12 cross-over	
	Adult	Dose Range	85	
	Adult	Controlled Blinded	49	50
	Pediatric	" "	47	54
	Pediatric	" "	25	25
	Adults	" "	24	25
	Adults	" "	49	50
	Adults	" "	28	28
	Pediatric	" "	50	50

In the above listed studies six cases were dropped for various acceptable reasons.

OTHER STUDIES

( )	Pediatric	150
	Adult	100
	Adult	49

Every clinical study was deliberately dissimilar in one or more aspects, such as the time of administration of the test drug, the measurements carried out, the anesthetic used, and so forth. These variations were all for appropriate reasons.

Of the eight anesthetics used only halothane was used in both pediatric and adult studies. No children received methoxyflurane or balanced anesthesia, and only one child received Innovar. No adults received cylcopropane, ether, ketamine or nitrous oxide (although presumably those receiving balanced anesthesia did receive nitrous oxide).

Measurements included blood pressure, pulse, temperature, ECG, pupil size, blurring of vision, skin color and moisture and secretions (subjective dry mouth and noted secretions).

Patients excluded from the studies include those with pre-existing cardiac arrhythias, glaucoma or any patient in whom an anticholinergic drug would be contraindicated.

The usual adult dose was 0.004 mg/lb of atropine and 0.002 mg/b of glycopyrrolate. The usual pediatric dose was 0.005 mg/lb of atropine and 0.0025 mg/lb of glycopyrrolate.

RESULTS IN PEDIATRIC CASES (Note: not all measurements done in all cases)

Pulse Rate: (Notable decrease means more than 10 beats)

247 cases Pre-induction to Post-induction - notable decrease

25% Atropine
23% Glycopyrrolate

180 cases Pre-intubation to Post-intubation - notable decrease
23% Atropine
15% Glycopyrrolate

110 cases Pre-reversal to Post-reversal - notable decrease
56% Atropine
35% Glycopyrrolate

The sponsor submits that this is evidence that glycopyrrolate is superior to atropine in protecting the heart from cholinergic overactivity.

Secretions:

204 cases Dry Mouth 73% Atropine
88% Glycopyrrolate

246 cases Post-induction tracheobronchial secretions
absent 73% Atropine
80% Glycopyrrolate

181 cases	Pre-intubation pharyngeal secretions absent	51% Atropine 63% Glycopyrrolate
179 cases	Post-intubation pharyngeal secretions absent	52% Atropine 64% Glycopyrrolate
127 cases	Pre-extubation pharyngeal secretions absent	45% Atropine 71% Glycopyrrolate
128 cases	Post-extubation pharyngeal secretions absent	52% Atropine 71% Glycopyrrolate

The sponsor suggests that this shows glycopyrrolate is superior to atropine in controlling secretion during anesthesia in children.

Blood Pressure: (Note: Notable decrease means ANY decrease)

Measurements before pre-medication to pre-induction, pre-induction to post-induction, and pre-intubation to post-intubation showed no significant difference between those receiving glycopyrrolate and those receiving atropine. For the time period of pre-muscle relaxant to post-muscle relaxant those having a notable decrease were:

Systolic - 42% Atropine
33% Glycopyrrolate

Diastolic - 42% Atropine
36% Glycopyrrolate

Measurements taken before reversal to after reversal and before extubation to after extubation showed no significant change. The sponsor concludes that glycopyrrolate is superior to atropine in preventing a decrease in blood pressure during anesthesia. Presumably this is the pre-muscle relaxant to post-muscle relaxant time period. At no other time period of measurement was there any significant difference.

Adverse Reactions:

This information is presented in 3 different ways in 3 different sections, making evaluation difficult. On page 395 is a list of adverse experiences in children during anesthesia (not cited as side effects of the test drug).

	Atropine	Glycopyrrolate
Tachycardia	24	24
Bradycardia	12	5
BPincrease	0	0
Temperature increase	4	0
Blurred vision	1	0
Pupils dilated	2	0
Dry mouth	1	0
Secretions	1	0

Arrhythmias	22	6
Facial flush	8	3
Vomiting	1	0
Tonic seizure	0	1
Dry hot skin	5	0
Total	81	39
Total number patients	52	32

On page 408 there is the total number of patients with side effects (NOT number of side effects):

Atropine	Glycopyrrolate
57	66

On page 412 there is a list of all side effects per each investigator. The ones noted for those doing pediatric studies show:

Atropine	Glycopyrrolate
228	108

The effects reported for atropine and glycopyrrolate are the same in nature and severity. Larger numbers of side effects were reported for children than for adults. It is noted that Deming reported 194 side effects in 47 of the 50 children receiving atropine, and 76 side effects in 46 children receiving glycopyrrolate. Corssen had a similar percentage in reporting side effects. However, Salem reported only 1 side effect in 1 patient receiving atropine. The sponsor states that this degree of investigator difference is unexplained. In view of this and the rather confusing manner of presenting this material one can only conclude that glycopyrrolate is as safe as atropine. An explanation of investigator difference would be necessary in order to conclude that the test drug is superior to atropine.

RESULTS IN ADULTS

Pulse Rate:

300 cases Pre-induction to Post-induction - notable decrease	39% Atropine 38% Glycopyrrolate
294 cases Pre-intubation to Post-intubation - notable decrease	19% Atropine 16% Glycopyrrolate
185 cases Pre-reversal to Post-reversal - notable decrease	43% Atropine 38% Glycopyrrolate

The sponsor states that this data shows the test drug to be superior to atropine in protecting the heart from cholinergic activity.

Secretions:

252 cases Pre-induction dry mouth	70% Atropine 73% Glycopyrrolate
279 cases Tracheobronchial secretions absent	87% Atropine 95% Glycopyrrolate
285 cases Pharyngeal secretions absent pre-intubation	80% Atropine 93% Glycopyrrolate
274 cases Pharyngeal sections absent post-intubation	81% Atropine 89% Glycopyrrolate
294 cases Pharyngeal secretions absent pre-extubation	33% Atropine 47% Glfycopyrrolat
287 cases Pharyngeal sections absent post-extubation	34% Atropine 50% Glycopyrrolate

The above is said to demonstrate the superiority of glycopyrrolate in controlling secretions during anesthesia. It should be noted that the differences pre and post-extubation may demonstrate the longer duration of action of glycopyrrolate.

Blood Pressure:

Measurements at various times from before pre-medication to post-extubantion showed no significant differences between patients receiving the test drug on control drug.

Adverse Reactions:

As with the pediatric studies this information is presented 3 different ways. On page 403 is a list of adverse reactions which are <u>not</u> cited as drug related.

	Atropine	Glycopyrrolate
Tachycardia	9	3
Bradycardia	3	1
Blood pressure increase	1	0
Pupils dilated	0	0
Dry mouth	3	0
Secretions	5	0
Arrhythmias	26	15
Facial flush	1	0
Dry not skin	2	0
Headache	1	0
Fuzzy	1	0
	52	21
Number of patients	39	32

On page 407 is a list of adverse reactions which are said to be drug related.

	Atropine	Glycopyrrolate
Tachycardia	97	66
Bradycardia	16	6
Cardiac arrhythmia	4	3
Decrease in blood pressure	1	1
Dryness (mouth or other)	50	12
Blurred vision	4	1
Secretions noted	18	9
Pupils dilated	41	6
Elevated body temperature	5	10
Decreased body temperature	0	2
Facial flush	34	10
Failure to counter BP drop at induction	1	0
Difficulty voiding	1	0
Trasient hypotension	1	0
Increased pulse rate	4	10
Decreased pulse rate	3	1
	280	138

It is not clear whether the above table represents adults and children, but from other figures it apparently is a combined list. On page 411 the side effects thought to be drug relatd is given as 54 in 153 atropine adult patients and 49 in 150 glycopyrrolate adult patients.

Further information regarding patients who developed cardiac arrhythmias is as follows:

1. 4 year old - irregular pulse and dropped beats after pre-medication and prior to induction. Glycopyrrolate

2. 35 year old - wandering pacemaker. Glycopyrrolate

3. 25 year old - nodal rhythm. Glycopyrrolate

4. 74 year old - unifocal PVC's. Atropine

5. 7 year old - tachycardia after gallamine, marked slowing followng reversal. Atropine

6. 15 year old - T wave inverted lead 2 - reverted after reversal and extubation. Atropine

7. 13 year old - marked changes in pulse rate - PVC's during extubation. Atropine.

The adverse reactions occurred in approximately even distribution among those receiving the various anesthetic agents, in proportion to the number of cases done with each agent, except for the group receiving Ketamine. In the pediatric patients receiving ketamine there were 33 reactions in 25 patients who received atropine and 32 reactions in 25 patients who received glycopyrrolate. 41 of these 50 patients were ophthalmology cases.

COMMENTS ON INDIVIDUAL STUDIES

(Note: Protocl numbers for an individual study are different in various sections of NDA)

Study

This was a single blind, cross-over, randomized study in 12 normal volunteers for efficacy and duration of action of the drug.

The saliva inhibiting properties were tested by comparing 0.1 mg. of glycopyrrolate, 0.2 mg of glycopyrrolate, 0.4 mg atropine and saline (placebo). Saliva was collected from the parotid duct by a suction cup following stimulation by administration of carbamylcholine chloride, and recorded as ml of saliva.

The investigator concluded that the 3 test drugs all have significant antisialogogue effect. 0.4 mg of atropine and 0.2 mg of glycopyrrolate are equal in magnitude of effect. The duration of action of atropine is 2 to 3 hours while the duration of action of glycopyrrolate is 7 to 10 hours.

Other observtions were interesting. There was a marked difference in the volume of saliva secretion between individuals, and a variation in the time to respond following administration of the saliva stimulant. Some individuals had a rather constant flow of saliva while others secreted saliva in spurts.

Subjectively there was intense dryness for more than 7 hours following administration of glycopyrrolate - to the point of pharyngeal soreness. The sensation of dryness was more intense with glycopyrrolate. There were no significant changes in blood pressure, pulse or ECG readings in these patients.

This was a three part study (85 patients) to determine the proper ratio of glycopyrrolate to neostigmine to minimize side effects during reversal of curare; to compare efficacy of the glycopyrrolate-neostigmine mixture to atropine-neostigmine mixture with regard to cardiovascular side effects; to determine optimal sequence of administration of neostigmine and glycopyrrolate for reversal of curare. This was a single investigator, partially controlled sutdy. Subject selection was healthy adults scheduled for elective surgery, and the anesthesia was halothane, nitrous oxide and curare. Changes in cardiac rate, blood pressure, pulse, ECG and arrhythmias were recorded.

The results are submitted as a published paper from the Canadian Anesthetists Society Journal V.19, page 399, 1972. The conclusions are:

1. Gl-ycopyrrolate is identical to atropine in the protection afforded against severe bradycardia following administration of neostigmine.

2. Glycopyrrolate produces less tachycardia than atropine.

3. The optimum dose is 0.2 mg of glycopyrrolate per 1 mg of neostigmine.

4. The preferable sequence of administration of glycopyrrolate and neostigmine is simultaneous.

Study # [redacted]
and Pharmacology, University of Tennessee. This study was to test the effectiveness of glycopyrrolate as pre-anesthetic medication and the effectiveness of use with neostigmine for reversal of [redacted] muscular blockade.

Ninety-nine patients were first separated, 49 receiving halothane and 50 receiving methoxyflurane, and then randomized. Of those receiving halothane 25 received atropine and 24 received glycopyrrolate. Patients receiving methoxyflurane were evenly divided as to the anticholinergic they received. All patients received gallamine as the muscle relaxant. For reversal the anticholinergic was used ONLY to counteract any bradycardia which might occur after administration of neostigmine.

41 patients were given enostigmine for reversal and 26 of these required no anticholinergic drug. These 26 were evenly divided between patients receiving atropine and those receiving glycopyrrolate. There were 3 patients who received [redacted] halothane and were given neostigmine followed by glycopyrrolate. All 3 have M 91 (test symbol) on the patient record sheet, but 2 have Robinul written on the anesthesia chart (the third anesthesia chart is of illegible Xerox copy). It might be noted that approximately one third of all anesthesia charts could not be read because of poor copying while the other two thirds from the same investigator were quite clear. In the group receiving methoxyflurane plus glycopyrrolate following neostigmine there were 5 anesthesia charts which stated "Robinul". In the group of patients who received atropine following neostigmine there were 3 anesthesia charts with no notation, 2 stated Robinul and 1 the test symbol (M 89). -In veiw of these confusing notations on patient record forms and anesthesia charts one cannot be sure of [redacted] blinding of this study.

There were 24 adverse reactions which were said to be drug related and these were primarily dry mouth, flush, tachycardia or blurred vision. There were 34 reactions said to be NOT drug related and these were primarily arrhythmias. This is a total of 58 reactions.

The sponsor concludes that glycopyrrolate is as effective as atropine in the reduction of the incidence of neostigmine induced bradycardia and the prevention of cardiovascular effect. There were no differences in temperature changes between the group receiving atropine and those receiving glycopyrrolate. Superiority is claimed for glycopyrrolate in that 12 patients who received their pre-medication 90 minutes prior to induction, 5 who received atropine said they had no dry mouth and 1 who received glycopyrrolate reported no dry mouth. Those who reported dry mouth were 3 for atropine and 3 for glycopyrrolate.
Since this group of patients had the pre-medication more than 90 minutes before induction this most likely represents the longer action of glycopyrrolate, and 12 patients ~~x~~ are too few to support a claim of superiority.

This was a controlled, blinded study in 101 patients ages one month to 14 years. General anesthesia with endotracheal tube and curare were used. Patients were first separated by agent, 10 pateints receiving halothane, 10 receiving cyclopropane, 10 receiving nitrous oxide and 11 receiving either.

The results showed that glycopyrrolate is as effective as atropine in reducing salivary, pharyngeal and tracheobronchial secretions as well as in preventing the adverse cardiovascular effects of anesthesia. No differences in changes in body temperature between the two groups were noted. Again superiority of glycopyrrolate is claimed in that 23 patients who received premedication 60 minutes or more before induction had a higher incidence of subjective dry mouth. The only adverse reaction noted in all cases was one instance of bradycardia in a patient receiving ether and atropine.

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of Alabama. This study was conducted in 50 patients 15 years of age or younger. Ketamine was used for premedication and anesthesia, and 41 of the cases were for ophthalmic surgery. Glycopyrrolate .0025 mg per lb or atropine .005 mg per lb. was used for premedication.
Results indicate that glycopyrrolate was no different than atropine in reducing salivary secretions, or preventing adverse cardiovascular effects (particularly bradycardia from activation of the oculocardiac reflex).
There were no differences in temperature variations between those receiving atropine or glycopyrrolate.

Glycopyrrolate is said to be superior to atropine in that pharyngeal secretions appear later than do those in patients given atropine. There were a total of 9 patients where phyngeal secretions were noted, 6 of whom received glycopyrrolate and 3 received atropine. On the basis of these numbers one might also say that there were more cases of phyngeal secretions with the test drug. The length of time from premedication to appearance of secretions was indeed longer following administration of glycopyrrolate.

There was a higher incidence of "flush" and of increased pulse rate in those receiving atropine. The summary states there were no significant adverse reactions. The investigator lists those not considered drug related as 13 for atropine and 17 for glycopyrrolate; these were primarily tachycardia, secretions, flush, bradycardia and dilated pupils. Of those said to be drug related there were 14 for atropine and 3 for glycopyrrolate; primarily tachycardia.

Study # [redacted] In this study glycopyrrolate or atropine was used as premedication in connection with Innovar. Succinylcholine was used for intubation and curare for maintenance of muscular blockage. The study was randomized and blind, and 49 adults were in the group. The induction dose of Innovar was 1-2 cc per 25 lb, and followed by Fentanyl 0.05 to 0.1 mg every 45 to 60 minutes.

The sponsor concludes that glycopyrrolate is as good as atropine in controlling salivary, pharyngeal and treacheobronchial secretions, and in prevention of cardiovascular effects. Pharyngeal secretions were noted in 8 patients who received atropine and in 4 who received glycopyrrolate. Of interest is that the description of secretions nearly always used the word "thick"/

The adverse reactions were said to be not significant. There were a total of 19 reactions in the atropine group and 24 in the glycopyrrolate group. These were sub-divided into drug related and not drug related. However, since both of these latter groups included such reactions as blurred vision, tachycardia, secreations, PVC's and arrhythmias, such a sub-division is not clear.

It should be noted that in 12 of these 49 patients glycopyrrolate was also used intra-operatively.

Study # [redacted]

In this study glycopyrrolate or atropine was used for premedication and preceding neostigmine used for reversal of neuromuscular blockade. 99 cases were first separated so that 40 patients received halothane and 50 received methoxyflurane, following which the study was randomized. Curare was the blocking agent used.

The investigators concluded that glycopyrrolate is as good as atropine for premedication and for use preceding administration of neostigmine. One adverse reaction is noted - PVC's in a patient who received atropine and methoxyflurane. The investigator feels that the only side effects of anticholinergic drugs are in the areas of cardiovascular changes and secretions, and that alterations in these may be due to many other things rather than the specific anticholinergic agent used. This investigator also said (in a letter to the sponsor) that the study sheets were too repetitious and confusing. The sheet for investigators rating is based on any difference the investigator noted vs. what he might have expected from atropine. This is said to be rather pointless. This reviewer agrees that the investigators evaluation sheets were of little or no value and hence they have not received any specific comments throughout this review.

Study # ——————— This study differed from the previous ones in that balanced anesthesia was used and the investigator was asked to attempt to identify the anticholinergic from observation of the patient. 56 adult patients were randomly assigned to receive the test drug or atropine, and the study was blinded.

As with the other studies the glycopyrrolate was found equal to atropine with regard to suppression of secretions and adverse cardiovascular reactions. In this particular study glycopyrrolate was said to be superior to atropine in that there was a lower incidence of elevated temperatures with the test drug as opposed to atropine. Further, it was said to better in suppressing tracheobronchial secretions.

There were 2 adverse reactions when glycopyrrolate was used following reversal with neostigmine. There was one instance of nodal rhythm and one patient had junctional rhythm.

The investigator correctly identified the anticholinergic 66% of the time, and was correct 58% of the time when atropine was given vs. 75% of the time when glycopyrrolate had been administered.

No summary of temperature changes was presented. Review of the individual patient records shows that the greatest temperature change was from 98' to 96' - no attempt was made to statistically evaluate differences between the atropine and the test group.

Study # [redacted] There were 100 children between the ages of 1 and 12 years in this study. The study was randomized and blind. 97 of the children received halothane and of these 84 received gallamine. Others received pancuronium, succinylcholine and curare.

This study is said to support the statements that glycopyrrolate is superior to atropine in that there was more pupil dilatation with atropine; more flush with atropine; more temperature elevations with atropine; more pharyngeal and tracheobronchial secretions after extubation with atropine; and more instances of decreased pulse rate after reversal when atropine was used. As was pointed out earlier in the review under RESULTS IN PEDIATRIC CASES, [redacted] eported 194 reactions in 47 of the 50 children receiving atropine, and 76 reactions in 46 reactions in those receiving glycopyrrolate. [redacted] reported 1 reaction in 101 cases. This wide investigator variation leaves claims of superiority unsubstantiated.

OTHER CLINICAL STUDIES:

Study [redacted]
General. This was a retrospective, open, randomized study in children 12 years old or younger. The effects of atropine, glycopyrrolate, or glycopyrrolate plus antacid on gastric acidity were determined.

Since the incidence and severity of Mendelson's syndrome (asthmatic-like reaction to aspiration of gastric contents) is said to be reduced if gastric pH is above 2.5, it might be useful to use a premedicant which increases gastric pH.

Gastric content samples were taken at the time of surgery. The group receiving atropine had a mean pH of 1.74, those receiving glycopyrrolate a mean pH of 4.02 and those receiving glycopyrrolate plus antacid a mean pH of 5.72. The difference between the atropine and glycopyrrolate groups was significant ($p < 0.0005$); with further significance between glycopyrrolate and glycopyrrolate and antacid ($p < 0.005$).

This study supports the fact that glycopyrrolate will significantly elevate gastric pH, and that the addition of an antacid will further elevate the pH. The antacid used in this study was Mylanta (aluminum hydroxide, magnesium hydroxide and simethicone). It would have been more complete to also study the effects of Mylanta plus atropine, and supplied information regarding the effect of Mylanta alone.

Study [redacted] This was a study to determine the cardiovascular effects of glycopyrrolate administered intravenously to awake patients and to those receiving either halothane, methoxyflurane, ether or cyclopropane.

In 20 awake volunteers glycopyrrolate was administered intravenously, either 0.2 mg or 0.3 mg, and blood pressure and ECG were recorded as well as notations regarding dryness of the mouth. There were no blood pressure changes greater than 15 mm of murcury systolic and 10 diastolic following the glycopyrrolate. One patient had A-V dissociation for 50 seconds after 0.3 mg of the test drug.

In the group of 21 patients who were anesthetized with halothane 5 had arrhythmias before the test drug, and after administration of glycopyrrolate 2 of these reverted to normal rhythm. Two other patients developed nodal rhythm after administration of the test drug.

Of the 20 patients anesthetized with methoxyflurane 2 had nodal rhythm prior to the test drug, and one of these reverted to normal after administration of glycopyrrolate. One other patient developed nodal tachycardia after glycopyrrolate and this lasted for 2 minutes and 21 seconds. All of the patients in this group showed an increase in heart rate.

Two of 17 patients receiving ether had nodal rhythm prior to glycopyrrolate, and one of these persisted after administration of the test drug. Two patients developed arrhythmias (A-V dissociation - tachycardia) after administration of glycopyrrolate.

From these studies it was concluded that it is safe to give glycopyrrolate intravenously. The total incidence of arrythmias was 4.8% and almost no change in heart rate after intravenous administration of glycopyrrolate. HOWEVER, while it was originally planned to include cyclopropane, basic data on this portion of this study was not included. There is a letter from Dr. Klingenmaier to the sponsor reporting on results with intravenous administration of glycopyrrolate to patients anesthetized with cyclopropane. He reported a high incidence of both atrial and ventricular arrhythmias (30% incidence for ventricular) and so stopped this portion of the study and stated that the drug is NOT recommended for use with cyclopropane.

Study [redacted] This was a retrospective study of 49 adults to determine any advantages of glycopyrrolate for reversal of neuromuscular blockade by curare. The test drug was given simultaneously with neostigmine and changes in heart rate or incidence of arrythmias were noted. There was little change in heart rate. The incidence of arrhythmias was 4.1%. The investigator postulates that the low incidence of arrhythmias is due to the fact that glycopyrrolate and enostigmine have similar rates of onset and duration of action.

REVIEW OF LABELING:

The format of the package insert was discussed with _____ HFD-110, and it was determined that separation of the labeling for gastrointestinal use and that for use in anesthesia would be desirable. The package insert may be one sheet of paper with one side designed to be read by the gastroenterologist and the other side to be read by the anesthesiologist.

The package insert requires revisions as follows:

DESCRIPTION: Delete "companion...potent" and "developed...Company."

ACTIONS: Separate gastronintestinal and anesthesia information. In several instances indications are implied in the description of actions. Indications should be confined to the section entitled INDICATIONS. This section is excessively long, and should be revised accordingly. The description of the duration of action of the drug is confusing, and should be clarified.

The intraoperative use of glycopyrrolate with cyclopropane should be stated as a contraindication or warning.

Note should be made of the fact that if glycopyrrolate is used for reversal at the end of anesthesia the sensation of dry mouth will last for up to 7 hours, and is said to be intense.

CONCLUSIONS:

Studies were performed to substantiate the safety and efficacy of glycopyrrolate for use as a premedicant, to reduce acidity of gastric secretions, for antimuscarinic activity during anesthesia and for use with neostigmine for reversal of neuromuscular blockade.

There were nine investigators, the majority being heads of departments of anesthesiology in University or teaching hospitals. All are well qualified to conduct clinical investigations.

In the controlled and special studies 122 children received glycopyrrolate, and 129 received atropine. In these studies 247 adults received the test drug and 165 received atropine. There were 299 patients in other studies, of which 150 were pediatric patients.

In general the dose of glycopyrrolate was 0.002 mg/lb for adults and 0.0025 mg/lb for children. The usual dose of glycopyrrolate is 1/2 that of atropine.

One special study was a crossover in normal volunteers and the other special study was a dose range study. There were 7 controlled, blinded, randomized studies. There were 3 "other" studies, 2 of which were retrospective and one was an open study.

While all commonly used anesthetics were included in these studies it should be noted that only halothane was used in both children and adults. No pediatric patients received methoxyflurane or balanced anesthesia and only one child received Innovar. No adults received cyclopropane, ether or ketamine.

Observations included changes in blood pressure pulse, temperature, ECG, pupil size, blurring of vision, skin color and moisture and amount of secretions.

The studies support the indications and show glycopyrrolate is as safe and effective as atropine for use in anesthesia. It is superior to atropine in reduction of gastric acidity. The approximate cost of atropine for

The adverse reactions are approximately the same for glycopyrrolate and for atropine. The sensation of dry mouth is stated to be more intense, to the point of pharyngeal soreness, for glycopyrrolate and may last for more than 7 hours.

Labeling requires revisions.

RECOMMENDATIONS: NDA 17-558 is approvable under Section 505(b)(1) of the Act (clinical). The NDA is not approvable under Section 505(b)(6) of the Act (labeling).

Recommendations of Respiratory and Anesthesia Drugs Advisory Committee to be obtained at May 6, 1974, meeting.

Firm be advised to prepare revised labeling(preliminary notice of this made to sponsor in phone conversation of April 12, 1974).

Margaret Clark MD
Margaret A. Clark, M.D.

cc: INDA 17-558 Orig., Dup.
HFD-100, HFD-160
R/D MClark(HFD-160)4/15/74
R/D Init JWinkler 4/16/74
Final typed nm 4/17/74.

MEDICAL OFFICERS REVIEW OF NDA AMENDMENT

NDA 17-558

DATE COMPLETED: 7/3/74

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

NAME OF DRUG: Trade: Robinul Injectable

Generic: Glycopyrrolate

DOSAGE FORM: Liquid, available in 1 mo, 5 ml and 20 ml vials.

ROUTE OF ADMINISTRATION: Subcutaneous, intramuscular or intravenous

CATEGORY (USE) OF DRUG: Anticholinergic

DATE OF SUBMISSION OF AMENDMENT: May 28, 1974

REASON FOR AMENDMENT: Submission of revised package insert, per advice of Respiratory & Anesthetic Drugs Advisory Committee and HFD-160 staff.

CLINICAL EVALUATION:

NOTE: This revised insert was sent to all members of the Respiratory & Anesthetic Drugs Advisory Committee for comment. All members have commented. The following suggestions take into account these comments.

The proposed package insert should be further revised as follows:

1. Page 1: Place in the top left hand corner the statement "Date of Issuance: (add date)".
2. Page 1: Label heading should be as it will be in final print, deleting phrases such as "Proposed Labeling - 5/21/74".
3. Page 1: Add missing bond from formula.
4. Page 1: Under the formula add the sentence, "Unlike atropine, glycopyrrolate is permanently charged."

5. Page 2: Line 4, change "cholinoreceptors" to "cholinergic receptors".

6. Page 2: Line 9, delete "and does so to an extent greater than atropine."

7. Page 2: Lines 13 and 14, delete "but producing significantly less initial tachycardia and fewer arrhythmias."

8. Page 2: Lines 16 and 17, replace "the belladonna alkaloids," with "atropine sulfate and scopolamine hydrobromide".

9. Page 3: Line 5, delete "potent".

10. Page 3: Line 6, rephrase to read "cyclopropane, methoxyflurane and halothane."

11. Page 3, Line 7, begin with "At reversal.."

12. Page 3, Line 17, Is there evidence that it is the anticholinergic action of the drug that causes the diminished rates of conception? Clarify this point.

13. Page 3: Add to the WARNINGS section,"This drug should be used with great caution, if at all, in patients with glaucoma or asthma."

14. Page 4: Lines 6 and 7, revise to read "Investigate any tachycardia before giving glycopyrrolate since an increase in the heart rate may occur."

15. Page 4: Line 8, revise to read "..a curare-like action or ganglionic block may theoretically..".

16. Page 4: Lines 10 and 11, Recent work indicates that children with monogolism may tolerate the usual doses of atropine. Do you have evidence that such children do not tolerate glycopyrrolate? Please clarify this point.

17. Page 4: Lines 12 and 13, Delete "Symptoms of central nervous system... ...Robinul (glycopyrrolate) Injectable."

18. Page 4: Line 16, after "xerostomia" add "(dry mouth)".

19. Page 4: Line 17, is there evidence that mydriasis and cycloplegia do occur? Please document.

20. Page 5: Line 18 (fourth from bottom of page), replace "should" with "may".

21. Page 6; lines 1 and 2, be specific about the pediatric dosage.

22. Page 6: line 4, glucose and dextrose are redundent.

23. Page 6: lines 5 and 6, use generic names.

24. Page 6: line 9, state the reason why the drug should not be added to these solutions.

25. Page 6: Add a statement about Clinical Incompatibility, making reference to cyclopropane.

CONCLUSION: The proposed package insert requires further revisions as noted above.

RECOMMENDATION: Sponsor should be notified of our recommendations and comments and requested to furnish a revised package insert.

Margaret Clark, M.D.

Margaret Clark, M.D.

cc: NDA 17-558 Orig.
HFD-100, HFD-160
R/D MClark(HFD-160)7/3/74
Final xeroxed 7/3/74

AUG 2 3 1974

MEDICAL OFFICER'S REVIEW OF NDA AMENDMENT

NDA 17-558

DATE COMPLETED: August 15, 1974

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

NAME OF DRUG: Trade: Robinul Injectable
Generic: Glycopyrrolate

DOSAGE FORM: Liquid, available in 1, 5 and 20 ml vials.

ROUTE OF ADMINISTRATION: Subcutaneous, intramuscular or intravenous.

CATEGORY (USE) OF DRUG: Anticholinergic

DATE OF SUBMISSION OF AMENDMENT: August 5, 1974

REASON FOR AMENDMENT: Submission of revised labeling in response to our letter of July 10, 1974.

CLINICAL EVALUATION:

The following revisions are required:

1. Delete "ANESTHETIC USE" from the heading of the insert.
2. Delete "PACKAGE INSERT" from the heading of the insert.
3. The package insert should be headed by the trade name. The generic name should be under the trade name, and in letters at least one-half the size of the trade name. The modifying phrase "Anticholinergic for Anesthetic Use" may be placed under the generic name.
4. The information concerning the contents of each ml should be within the DESCRIPTION section instead of above this section.

CONCLUSIONS: The revised package insert is satisfactory except for the required revisions noted above.

RECOMMENDATIONS: Request FPL with the above noted revisions.

Margaret Clark, M.D.

cc: NDA 17-558 Orig.
HFD-100, HFD-160
R/D MClark (HFD-160)8/15/74
Final typed nm 8/15/74.

AUG 2 2 1974

NDA 17-558

MEDICAL OFFICER'S REVIEW OF NDA AMENDMENT

Date Completed: August 21, 1974

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

NAME OF DRUG: Trade: Robinul Injectable
Generic: Glycopyrrolate

DOSAGE FORM: Liquid, available in 1, 5, and 20 ml. vials

ROUTE OF ADMINISTRATION: Subcutaneous, intramuscular or intravenous

CATEGORY (USE) OF DRUG: Anticholinergic

DATE OF SUBMISSION OF AMENDMENT: August 20, 1974

REASON FOR AMENDMENT: Revised labeling to correct deficiencies of August 5, 1974 submission.

CLINICAL EVALUATION:

The proposed package insert corrects the deficiencies noted in the M.O. review of August 15, 1974, and provides for the safe and effective use of the drug.

In a conversation with Mr. Alan Young of A. H. Robins and Margaret Clark, M.D. of FDA on August 20, 1974, it was agreed that the words "PACKAGE INSERT COPY" at the top of the insert will not appear on the final printed labeling.

It should be noted that this labeling was drafted with the advice and suggestions of the members of the Respiratory and Anesthetic Drug Advisory Committee.

CONCLUSIONS:

The revised package insert provides for the safe and effective use of this drug.

RECOMMENDATIONS:

This application is recommended for approval under section 505(b)(1) and (6) of the Act.

cc:
NDA 17-558 Orig.
HFD-100
HFD-160
R/D MClark/HFD-160
Final typed by: MTR/8-21-74

Margaret A. Clark, M.D.
Margaret A. Clark, M.D.

MEDICAL OFFICERS REVIEW OF NDA AMENDMENT

NDA 17-558

DATE COMPLETED: September 26, 1974

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

NAME OF DRUG: Trade: Robinul Injectable
Generic: Glycopyrrolate

DOSAGE FORM: Liquid, availabel in 1, 5, and 20 ml vials

ROUTE OF ADMINISTRATION: Subcutaneous, intramuscular or intravenous

CATEGORY (USE) OF DRUG: Anticholinergic

DATE OF SUBMISSION OF AMENDMENT: September 18, 1974

REASON FOR AMENDMENT: Revised labeling

CLINICAL EVALUATION:

The package insert reflects the changes requested in the phone call of September 17, 1974, between Mr. Alan Young and Margaret Clark, M.D.

CONCLUSIONS: The revised package insert provides for the safe and effective use of this drug.

RECOMMENDATIONS: This application is recommended for approval under Section 505(b) (1) and (6) of the Act.

Margaret Clark, M.D.

Margaret Clark, M.D.

cc:
NDA 17-558 Orig.
HFD-160
HFD-108
R/D by MClark 9/26/74
R/X 9/26/74:jw

NDA 17-558
Robinul Injectable
A. H. Robins Co.

August 22, 1974

RECOMMENDATIONS OF DIVISION DIRECTOR

This application is recommended for approval under Section 505(b) (1), (2), (3), (4), (5), and (6) of the Act. The supervisory staff concur with the reviewing personnel with regard to this recommendation.

Robinul injectable is an anticholinergic which is indicated for use as an adjunct in anesthesiology. This drug is similar to atropine in its properties, but with a longer duration of action than atropine. Clinical studies were conducted in 122 children and 247 adults. There were six controlled and blinded studies as well as dose range and special studies. Safety and efficacy were established in these studies. The animal studies support the safe use in humans. There are no adverse comments regarding chemistry, and there was a satisfactory establishment inspection on May 22, 1974.

Labeling as originally proposed was reviewed by members of the Respiratory and Anesthetic Drugs Advisory Committee, and has been revised in accord with their suggestions. The present draft labeling provides for the safe and effective use of the drug.

Margaret Clark M.D.

Margaret Clark, M.D.

cc: NDA 17-558 Orig.
HFD-100
HFD-160
R/D MClark(HFD-160)8/22/74
Final typed nm 8/23/74.