REDACTIONS ARE MADE UNDER SECTION 41 AND 43

MODULE 2.5

CLINICAL OVERVIEW

NAME OF PRODUCT:	GLYCOPYRRONIUM BROMIDE TABLETS 1 MG / 2 MG
ACTIVE SUBSTANCE:	GLYCOPYRRONIUM BROMIDE
FORMULATION:	TABLETS 1 MG / 2 MG

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List of Abbreviations

%	Percent
±	Plus/minus
µg	Microgram (s)
AACG	Acute angle closure glaucoma
ASA	American Society of Anaesthesiologists physical status
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from zero (0) hours to infinity (∞).
AUC_{0-t}	Area under the plasma concentration-time curve from zero (0) hours to time (t).
b.i.d	Two times a day
CDER	Center for drug evaluation and research
CL	Clearance
C_{max}	Maximum blood/plasma/serum concentrations
CSF	Cerebrospinal fluid
e.g.	Exempli gratia
FDA	Food and drug administration
g	Gram (s)
h(r)	Hour (s)
i.m.	Intramuscular
i.v.	Intravenous
IC_{50}	Half maximal inhibitory concentration
I_{max}	Maximum percent inhibition
KCl	Potassium chloride
kg	Kilogram (s)
L	Litre (s)
LLOQ	Lower limit of quantification
m^2	Meter square
mg	Milligram (s)
min	Minute (s)
mL	Millilitre (s)
MR	Medical review
n/N/No.	Number
NA	Not available
ng	Nano gram (s)
OED	Optimal effective dose
p.o.	Per oral
pA_2	Equilibrium dissociation constant
pK_i	Log inhibitory constant
q.i.d	Four times daily
SCI	Spinal cord injury
SD	Standard deviation
SmPC	Summary of Product Characteristics
t.i.d	Ter in die (three times daily)
$t_{½}$	Half-life
T_{max}	Time to maximum concentration
UK	United Kingdom
USFDA	United states food and drug administration
V_d	Volume of distribution
vs	Versus
V_{ss}	Volume of distribution at steady state
WHO	World health organization

2.5.1 PRODUCT DEVELOPMENT RATIONALE

The applicant Kinedexe limited UK intends to file an application for marketing authorisation of Glycopyrronium Bromide 1 and 2 mg tablets for "**use in adults as add-on therapy in the treatment o f p eptic u lcer**", in accordance with Article 10a of Directive 2001/83/EC, as amended.

Since glycopyrrolate has been marketed for many years worldwide, comprehensive information exists on its biochemistry, pharmacology, safety, and clinical use. The aim of this clinical overview is to provide concise and up-to-date information, referring to medicinal products containing glycopyrronium bromide as their active ingredient. Hence forth in this document, glcopyrronium bromide has been written as glycopyrrolate. The overview will address the recently published literature (up to July 2015) so that any new information on the safety and efficacy of the drug can be taken into account. The degree of scientific interest allowing detailed assessment of the compound's safety and efficacy is reflected in numerous publications enclosed with this application leading to coherent findings as discussed in detail in this clinical overview.

The applicant has drawn up a SmPC reflecting the current scientific knowledge and the characteristics specified for the reference product. Throughout this clinical overview, it will be critically assessed whether the stipulations given in the SmPC are sufficient to ensure the safe and effective use of the preparation under review in the indications claimed. A critical evaluation of the findings will be printed in italics at the end of the various sections.

Glycopyrrolate is a quaternary ammonium compound which is used for many years orally (p.o.) and via intravenous (i.v.) route for its anticholinergic properties. In the operating room setting it is used as part of the pre-anaesthesia procedure to decrease oral secretions prior to intubation. In the clinic, it was used as a treatment for ulcers prior to the development of H_2 and proton pump inhibitors both of which have supplanted its use for this indication (Glycopyrrolate, CPBR, CDER, USFDA Review, 2010).

Glycopyrrolate is used in the management of gastrointestinal disorders. In clinical studies on patients with duodenal ulcer, dosage was varied for each patient from one tablet twice daily to two tablets four times a day, on the basis of clinical response produced a significant decrease in volume, acid concentration and output of basal gastric secretion and dosage of three to eight mg per dayhave been reported to be well tolerated ([redacted]).

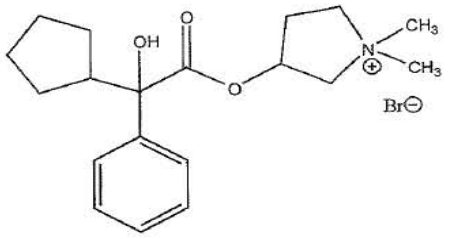
Glycopyrronium bromide is 3-[(cyclopentylhydroxyphenylacetyl) oxy]-1,1-dimethylpyrrolidinium bromide. Glycopyrrolate exists in four distinct stereo isometric forms due to the presence of two chiral centres in the Glycopyrrolate molecule. One of the two enantiomeric pairs of diastereomers of glycopyrrolate is (R,R)-glycopyrrolate and (S,S)-glycopyrrolate, and the other enantiomeric pair is (R,S)-glycopyrrolate and (S,R)-glycopyrrolate ([redacted]).

Glycopyrrolate occurs as a white, odourless crystalline powder. It is soluble in water and alcohol and practically insoluble in chloroform and ether. It is completely ionised at physiological pH values (Glycopyrrolate, CPBR, CDER, USFDA Review, 2010).

Molecular formula: $C_{19}H_{28}BrNO_3$

Molecular weight: 398.33

Structural formula:



2.5.2 OVERVIEW OF BIOPHARMACEUTICS

Not applicable.

2.5.3 OVERVIEW OF CLINICAL PHARMACOLOGY

2.5.3.1 Pharmacokinetics

2.5.3.1.1 Method of Analysis

A quantitative electrospray ionisation-liquid chromatography-mass spectrometry method was used for the absolute quantification of glycopyrrolate in human plasma in a concentration range from 0.101 to 101 ng/mL. The lower limit of quantification (LLOQ) was 0.101 ng/mL, total precision was under 20% (18.0% (n = 6) at the LLOQ) and maximum accuracy was 112% (88.9% for the LLOQ, n = 6) ([redacted]).

2.5.3.1.2 Absorption

Oral glycopyrrolate had low oral bioavailability, a median of 3.3% was found in plasma. Oral glycopyrrolate produced low plasma concentrations (C_{max} 190-440 pg/mL) lasting up to 12 h (Glycopyrrolate, MR, CDER, USFDA Review, 2010).

Table 1 : Summary of pharmacokinetic parameters for glycopyrrolate after oral administration of 2 mg as glycopyrrolate liquid under fasted and fed conditions and as Robinul (glycopyrrolate) tablet under fasted conditions (Glycopyrrolate, MR , CDER, USFDA Review, 2010)

Parameter*	Glycopyrrolate liquid 2 mg (1 mg/ 5 mL) fasted	Robinul® tablet 2 mg (2 × 1 mg) fasted	Glycopyrrolate liquid 2 mg (1 mg/ 5 mL) fed
C_{max} (ng/mL)	0.318±0.189(37)	0.406±0.197(37)	0.084±0.081(36)
T_{max} (h)	2.53(37) (0.50-6.00)	3.00(37) (1.50-6.00)	2.50(36) (1.00-6.08)
$AUC_{(0-t)}$ (h × ng/mL)	1.74±1.07(37)	2.34±1.03(37)	0.38±0.14(36)
$AUC_{(0-\infty)}$ (h × ng/mL)	1.81±1.09(37)	2.45±1.15(36)	0.46±0.13(35)
λz (/h)	0.2626±0.0965	0.2528±0.1025(36)	0.2325±0.0551(35)
$t_{1/2}$ (h)	3.02±1.20(37)	3.31±1.57(37)	3.21±1.05(35)
*Arithmetic mean±standard deviation (N) except for T_{max} for which the median (N)(range) is reported			

In an open study with eight healthy male volunteers, after single i.v. bolus glycopyrrolate (5 µg/kg) the C_{max} was 198±137 (ng/mL) and AUC was 5.16±0.97 (ng×h/mL) [redacted]

The pharmacokinetics of glycopyrrolate after a single intramuscular (i.m.) dose are observed as very rapid absorption rate was found, with C_{max} of 6.3 (1.5) ng/mL and mean time to C (T_{max}) 10 (3.8) min. The respective AUC value from 0 to 8 h was 5.61 (1.27) ng×h/mL ([redacted]

Effect of food

The food effect data indicate the mean C_{max} under fed high fat meal conditions is about 74% lower than the C_{max} observed under fasting conditions. Similarly, the mean AUC of treatment given under fed conditions was 3 to 4 times lower than those observed for the treatment given under fasted conditions. These data indicate that a high fat meal reduces the oral bioavailability of glycopyrrolate, if taken shortly after a meal. Glycopyrrolate should be dosed at least one hour before meals as reasonably feasible (Glycopyrrolate, MR, CDER, USFDA Review, 2010).

2.5.3.1.3 Distribution

In an open study with eight healthy male volunteers, after single i.v. bolus glycopyrrolate (5 µg/kg) the volume of distribution at steady state (V_{ss}) was 0.37±0.26 (L/kg) ([redacted] .

After i.v. injection of 0.006 mg/kg, the mean distribution phase half-life was 2.22±1.26 min (Glycopyrrolate, MR, CDER, USFDA Review, 2010).

2.5.3.1.4 Metabolism

Specific *in v itro* and *in vi vo* testing was not performed on glycopyrrolate to identify enzymatic pathways responsible for clearance of the drug. The anticholinergic activity of glycopyrrolate is well characterized and its general effects on all muscarinic receptors are known (Glycopyrrolate, MR, CDER, USFDA Review, 2010).

[redacted] reported that only 20% of the drug is metabolised and 80% is excreted unchanged in urine and bile in man.

In a study, the metabolism of scopolamine and glycopyrrolate was studied in 11 healthy subjects having undergone caesarean section. Glycopyrrolate concentrations increased only slightly between 1 and 3 h after the drug injection. Thus, it was suggested that β-glucuronide or sulphate conjugation plays only a minor part in the metabolism of glycopyrrolate ([redacted]).

In adult patients who underwent surgery for cholelithiasis and were given a single i.v. dose of titrated glycopyrrolate, approximately 85% of total radioactivity was excreted in urine and < 5% was present in T-tube drainage of bile. In both, urine and bile > 80% of the radioactivity corresponded to unchanged drug. These data suggest that a small proportion of i.v. glycopyrrolate is excreted as one or more metabolites (Glycopyrrolate, CPBR, CDER, USFDA Review, 2010).

2.5.3.1.5 Elimination

Glycopyrrolate is excreted largely unchanged in the urine (Glycopyrrolate, MR, CDER, USFDA Review, 2010).

In a study glycopyrrolate was labelled in one methyl group with tritium and its fate was studied in six patients with T-tube drainage by determining serum levels as well as the biliary and urinary excretion of radioactivity after i.v. injection. More than 90 % of the radioactivity had disappeared from serum in 5 min and after 30 min almost no radioactivity could be found. The highest radioactivity in bile was found in samples taken 30 or 60 min after the injection. However, measurable radioactivity was found in most cases after 48 h. The first urine samples (0-3 h) showed the greatest radioactivity, and in 48 h, 85% of the total radioactivity was excreted into the urine. Paper chromatography showed that in both, in bile and in urine, over 80 % of the radioactivity corresponded to unchanged glycopyrrolate. The excretion of appreciable amounts of glycopyrrolate into the bile suggests that the spasmolysis achieved with glycopyrrolate could be based partly on a local action on the bile ducts ([redacted], [redacted] .

2.5.3.1.6 Pharmacokinetics in Special Populations

Renal Impairment

[redacted]) studied the pharmacokinetics of glycopyrrolate in 11 uraemic patients undergoing cadaveric renal transplantation and in seven ASA I control patients undergoing general surgery. Glycopyrrolate 4 µg/kg was given i.v. before induction of anaesthesia. Volume of distribution (V_d) in the elimination phase was similar in both groups, the

elimination half-life ($t_{1/2}$) was longer ($P < 0.05$), AUC larger ($P < 0.01$) and plasma clearance (CL) smaller ($P < 0.01$) in the uraemic patients. In 3 h, mean 0.7 (range 0-3) % and 50 (21-82) % of glycopyrrolate was excreted in the urine in the uraemic and healthy patients, respectively ($P < 0.001$). The 24 h renal excretion was 7 (0-25) % in uraemic and 65 (30-99) % in control patients ($P < 0.001$). The authors concluded that the elimination of glycopyrrolate was severely impaired in uraemic patients.

Hepatic Impairment

Pharmacokinetic information in patients with hepatic impairment is unavailable (Glycopyrrolate, CPBR, CDER, USFDA Review, 2010).

Glycopyrronium is cleared predominantly from the systemic circulation by renal excretion (see 2.5.3.1 Pharmacokinetics – 2.5.3.1.5 Elimination). Impairment of the hepatic metabolism of glycopyrronium is not thought to result in a clinically relevant increase of systemic exposure

Elderly People

In a study the basic pharmacokinetic properties of glycopyrrolate were evaluated through radioreceptor assay (RRA) in elderly patients (59-79 years) . The patients in Group I were premedicated with glycopyrrolate 4 mg orally and those in Group 2 with glycopyrrolate 8 µg/kg i.m., group 3 the patients received a combination anaesthesia (thiopentone 3-5 mg/kg, vecuronium 0.1 mg/kg, $N_2O + O_2$, fentanyl 3 µg/kg and neostigmine as an anticurarizing agent in incremental doses up to 1.25 mg) and glycopyrrolate 6 µg/kg was injected i.v. just before the induction of anaesthesia. Based on the plasma levels after a single i.v. injection, 6 pg/kg ($n = 6$), the distribution phase $t_{1/2}$ (2.22±1.26 SD min) and the elimination phase $t_{1/2}$ (0.83±0.29 h) of glycopyrrolate were short due to the low distribution volume during the elimination phase (0.64±0.29 L/kg) and the respectively high total plasma clearance value (0.54±0.14 L/kg/h). An intramuscular injection, 8 pg/kg ($n = 6$) was followed by a fast and predictable systemic drug absorption and clinical effects (heart rate increase, dry mouth). In this group, the time to maximum plasma concentration (T_{max}) was 27.48±6.12 min and the C_{max} was 3.47±1.48 pg/L. After oral drug intake of 4 mg ($n = 6$), an apparently low and variable gastrointestinal absorption was found (T_{max} = 300.0±197.2 min, C_{max} = 0.76±0.35 pg/L), thus indicating that the oral route of drug administration is of no value as a routine premedication ([redacted] However, the oral glycopyrrolate produced significant antisialogogue effect.

Furthermore, the applicant's formulation (Glycopyrronium bromide tablets 1 mg / 2 mg) is indicated for add-on therapy in the treatment of peptic ulcer and not as premedication. Many studies (refer Module 2.5.4) which also included elderly patients, have shown that oral glycopyrrolate is effective in the treatment of peptic ulcer. Also in the above study ([redacted] oral glycopyrrolate produced significant antisialogogue effect. Hence, it can be said that oral glycopyrrolate can be prescribed in elderly patients for the treatment of peptic ulcer.

Children

In a study in six healthy children operated twice during a several weeks and receiving a single p.o. (50 µg/kg) and i.v. (5 µg/kg) dose of glycopyrrolate, plasma levels were determined with a radio receptor assay and resulted in the pharmacokinetic parameters displayed in Table 2 [redacted]).

Table 2: Pharmacokinetic parameters glycopyrrolate in children ([redacted]).

Parameter	Intravenous (5 µg/kg)	Oral (50 µg/kg)
V_{ss} (L/kg)	1.37 (0.75-2.64)	--
Cl (L/kg/h)	1.09 (0.60-1.43)	--
$AUC_{(0-\infty)}$ (µg/L×min)	276.3 (210.2-502.8)	106.6 (38.5-287.7)
$t_{1/2}$ (h)	139 (73-239)	--
T_{max} (min)	--	90 (30-480)
C_{max} (µg/L)	--	0.37 (0.19-0.44)
Bioavailability (%)	--	3.3 (1.3- 13.3)
Data presented as [Median (Range)]		

Vaginal Hysterectomy Patient

Inanother pharmacokinetics study of glycopyrrolate nine surgical patients undergoing vaginal hysterectomy received a a single i.m. injection of 8 µg/kg . Rapid absorption was found, with a mean peak plasma concentration after 16.1 min and mean elimination $t_{1/2}$ of 75.4 min. Almost half (49.3%) of the drug was excreted in pharmacologically active form in the urine within 3 h. There was no measurable glycopyrrolate in lumbar cerebrospinal fluid (CSF) samples (n = 9) taken 40 min after administration of drug [redacted]

Parturient

In a pharmacokinetics study of glycopyrrolate 6 µg/kg after i.m. (deltoid muscle) administration in eight caesarean section patients, a fast absorption rate was found with a mean (C_{max} of 6.3 (SD 1.5) ng/mL, a mean time to C_{max} (T_{max}) of 10.0 (3.8) minutes and a elimination half-life ($t_{1/2}$) of 33.4 (1.92). The respective AUC_{0-8} value was 5.61 (1.27) h × ng/mL. Almost half of drug (48.3%) was excreted into the urine within 3 h. There were no measurable levels of glycopyrrolate in the lumbar CSF 60 min after drug injection. The concentrations of glycopyrrolate in the umbilical venous (0.28 (0.25) ng/mL) and in the umbilical arterial (0.18 (0.11) ng/mL) plasma after 86 min of drug injection were low and clinically insignificant, as it was the case in the amniotic fluid (0.15 (0.08) ng/mL) [redacted]

2.5.3.1.7 Pharmacokinetic Drug Interactions

Digoxin

Patients received glycopyrrolate and digoxin as slow-dissolution tablets which resulted in increased serum levels and enhanced action of digoxin [redacted] .

Atenolol

Glycopyrrolate co-administered with atenolol, may increase bioavailability of atenolol [redacted]

Metformin

Metformin plasma levels may be elevated, when metformin was co-administered with glycopyrrolate.Therefore, dose reductions of glycopyrrolate and metformin may be required if both are simultaneously administered [redacted]).

Haloperidol

The concentrations of haloperidol may decrease when haloperidol was co-administered with glycopyrrolate ([redacted]).

Levodopa

The concentrations of levodopa may decrease when levodopa was co-administered with glycopyrrolate. Therefore, in patients receiving glycopyrrolate and levodopa, an increase in levodopa dosage may be required ([redacted] .

Cimetidine

In an open-label, two-period, two-sequence, crossover study, 20 healthy subjects received two treatments. A single dose of 100 µg glycopyrrolate was inhaled alone and on day 4 of a 6-day treatment with p.o. cimetidine 800 mg b.i.d. Plasma concentrations and urinary excretion of glycopyrrolate were determined up to 72 h post glycopyrrolate dose. Inhalation of glycopyrrolate in the presence of cimetidine resulted in an increase in total systemic exposure of glycopyrrolate by 22%. This exposure increase correlated with a slight decrease of 23% in CL. C_{max} was not affected. Both treatments were safe and well tolerated without any deaths or severe adverse events. Therefore, it was concluded that glycopyrrolatecan be co-administered with cimetidine or other inhibitors of the organic cation transport ([redacted] .

Ethambutol

In a study of thirteen tuberculous in-patients and two groups of healthy volunteers with six subjects each, the effect of aluminium hydroxide and/or of glycopyrrolate on the absorption of a single oral 50 mg/kg dose of ethambutol was investigated. It was concluded that aluminium hydroxide and glycopyrrolate, alone or in combination, clearly retarded the ethambutol absorption. ([redacted]

2.5.3.2 Pharmacodynamics

2.5.3.2.1 Pharmacodynamics Related To Proposed Indication

Mechanism of Action

Glycopyrrolate inhibits parasympathetic nerve impulses by selectively blocking the binding of the neurotransmitter acetylcholine. Glycopyrrolate competitively inhibits the actions of acetylcholine or other cholinergic stimuli at muscarinic receptors and has little effect on cholinergic stimuli at nicotinic receptors, on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sino-atrial node, the atrioventricular node, exocrine glands, and, to a limited degree, in the autonomic ganglia. By this mechanism, glycopyrrolate diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions (Glycopyrrolate, MR, CDER, USFDA Review, 2010).

An *in vitro* study reported that glycopyrrolate had high affinity and potency towards the M_3 muscarinic receptor, with an equilibrium dissociation constant (pA_2) of 9.7. The dissociation $t_{1/2}$ from the M_3 receptor was 6.1 h. Glycopyrrolate binding affinities against all five human muscarinic receptor subtypes were similar to each other; the log inhibitory constant (pK_i) for the human M_1, M_2, M_3, M_4 and M_5 receptors were respectively 10.09, 9.67, 10.04, 10.26 and 9.74 ([redacted]).

Effect on Gastric Secretion

A comparative study was undertaken in two groups in patients with duodenal ulcer. In the first group of 30 patients, the effect of glycopyrrolate and propantheline on basal gastric secretion and their dose-response relationships were studied. In a second group of 34 patients, the effects of an optimal effective dose (OED) of glycopyrrolate and of propantheline on basal gastric secretion were studied. Glycoyrrolate in a dose of 1.0, 2.0, and 4.0 mg produced a significant suppression of volume and acidity of the basal gastric secretion patients with chronic duodenal ulcer. When the dose of drug was increased to the OED, significant suppression of acidity to pH 4.5 or higher was observed in all patients [redacted]).

A study was undertaken in twenty seven patients (aged 17 - 55 years), out of which twenty four had duodenal ulcers, one had gastric ulcer and two had functional dyspepsiaThe study was conducted to investigate the effect of glycopyrrolate (1, 2 or 3 mg. b.d.) and a combined oxyphencyclimine-hydroxizine preparation (5 mg oxyphencyclimine and 10 mg hydroxizme in a 1, 2 or 3 mg b.d.). Glycopyrrolate and oxyphencyclimine-hydroxizine preparation suppressed, both basal secretion and the maximum acid output.. Glycopyrrolate and oxyphencyclimine-hydroxizine reduced the basal and histamine-induced acid secretion with little or no side-effects ([redacted] .

A study on the antisecretory effect of glycopyrrolate in active duodenal ulcer was conducted in 12 in-patients. After 2 mg p.o. of glycopyrrolate, six patients showed a prolonged suppression of acidity, the pH rose from 1.6 to 5.7, in three patients the pH rose from 2.05 to 3.25 and in three patients there was little or no effect on pH ([redacted]).

[redacted]) evaluated the effect of glycopyrrolate on gastric acid secretion in man. Ten patients were treated with glycopyrrolate 1 mg tablets four times daily (q.i.d). Nine patients showed a marked reduction in hydrochloric acid secretion while one patient showed an unchanged acid secretion during treatment period. The average decrease of basal secretion in these patients was reported to be 67 %. Glycopyrrolate also inhibited histamine stimulated gastric acid secretion by 45%.

A study investigated the effectiveness of glycopyrrolate in suppressing gastric acidity. In this study, 21 patients with a duodenal ulcer were treated under basal conditions, 17 patients were treated after stimulation with histamine and 8 patients after stimulation with insulin.Each patient underwent 2 to 5 studies including a control test and a test under one or more of the following conditions: placebo, glycopyrrolate, atropine and following an ulcer operation. Glycopyrrolate 5 to 14 mg of daily produced a significant drop in gastric acidity as quantitatively measured by a basal secretory test, thus indicating that this is an effective anticholinergic drug. The average decrease in basal secretion rate after glycopyrrolate was quite pronounced but the decrease following histamine or insulin stimulation was not of sufficient magnitude to be significant in most cases. Perhaps a greater reduction in acid might had occurred following histamine or insulin stimulation if larger amounts of glycopyrrolate had been given ([redacted] .

The antisecretory effect of glycopyrrolate 2 mg p.o. was tested in 8 patients with peptic ulcer. The effect of glycopyrrolate on basal nocturnal secretions was measured over a 10 h period in all 8 patients. Glycopyrrolate decreased total acid by 65 %, free acid by 78 % and the volume of gastric secretion by 62 % ([redacted]).

In a study 34 unselected patients with roentgenographic evidence of peptic ulcer were the subjects of a clinical evaluation of glycopyrrolate. The group consisted of 16 women and 18 men ranged in age from 20 to 79 years. The diagnoses were as follows: duodenal ulcer 25,

gastric ulcer 7, and marginal ulcer 2. Patients were studied for periods of 2 to 12 months. A reduction of around 67.7 % in pepsin was reported after 1 h while a 63.9 % reduction was reported after 2 h of administration of 4 mg of glycopyrrolate. After administration of 2 mg, there is 49.4 % reduction in the first h and 51.3 % reduction in the second h. Results were excellent in 24 patients (71 %) of the group. These 24 patients became asymptomatic and remained so while under observation and continuing therapy. The results were regarded as good in 9 (26 %) of the patients and fair in 1 patient (3 %) ([redacted]).

2.5.3.2.2 Pharmacodynamics Not Related To Proposed Indication

Antisialogogue Effect

A study was conducted in six adult volunteers to evaluate the anticholinergic actions of glycopyrrolate bromide. Glycopyrrolate was given by three routes: 0.1, 0.2 and 0.4 mg i.m., 0.1, 0.14 and 0.2 mg i.v. and 2, 4 and 8 mg p.o. Glycopyrrolate was found to be an effective antisialogogue of long duration of action by all three routes. When given p.o. the effects were delayed in onset and persisted for too long. Glycopyrrolate 0.2 mg i.m. was found to be the optimal dose as an antisialogogue ([redacted]).

Effect of Glycopyrrolate on Sialorrhea

[redacted] and colleagues conducted a small double-blind, placebo-controlled crossover study in 39 children with sialorrhea associated with developmental disabilities. A glycopyrrolate dose of 0.1 mg/kg was effective in controlling sialorrhea ([redacted]

Adjunctive Therapy for Anesthesia

Anticholinergics are frequently used to reduce the bradycardia produced by anesthetic agents. In a efficacy study of glycopyrrolate and atropine in 90 children between 1 month and 12 years of age undergoing surgery, after induction with halothane and succinylcholine children were randomized to receive either 0.005 mg/kg glycopyrrolate or 0.01 mg/kg atropine given i.v. None of the patients developed bradycardia ([redacted]

Antispasmodic Effect

Fifty patients with various disorders of the gastrointestinal tract were treated with glycopyrrolate. A positive therapeutic response was observed in 46 (92 %) of the patients. Glycopyrrolate appeared to have antisecretory and marked antispasmodic action. Two patients had dermatological reactions: one a rash and one urticaria. Both were considered as possibly drug-related ([redacted]).

2.5.3.2.3 Pharmacodynamics Drug Interaction

Glycopyrrolate effects may be intensified by administration with other anticholinergics, including amantadine, phenothiazines or tricyclic antidepressants. The slower gastrointestinal passage produced by glycopyrrolate may increase the risk for hyperkalemia from sustained-release potassium chloride products and reduce the effectiveness of digoxin. Glycopyrrolate may increase plasma levels of atenolol or metformin if given concomitantly with these agents. Administration with glycopyrrolate may reduce plasma levels of haloperidol or levodopa ([redacted]).

Potassium Chloride

In a controlled multicentre investigation the effects of p.o. potassium chloride (KCl) 60 mEq/day (20 mEq t.i.d) supplements on the gastrointestinal mucosa in 120 healthy men for 18

days were evaluated. All subjects were given glycopyrrolate concomitantly to delay gastric emptying. After treatment was completed, mild to moderate gastrointestinal irritation, characterised by erythema and edema, was found with similar frequency in all four treatment groups (different types of formulations of KcL. Two of 30 subjects given the microencapsulated KCl had a single erosion each. Single or multiple erosions were also observed in 14/30 men given the wax/polymer matrix tablet, in 7/30 given the powder, and in 1/30 given placebo. One subject given the wax/polymer matrix tablet had a gastric ulcer. The incidence of gastrointestinal injury with the microencapsulated form was significantly less ($P < 0.01$) than that with the wax/polymer matrix tablet and was not significantly different from that seen with either the powder or placebo [redacted]).

In a double-blind, randomized, placebo-controlled clinical trial, 30 healthy subjects took either one of two potassium chloride preparations or placebo t.i.d. for 1 week with concomitant oral glycopyrrolate. The upper digestive tract was endoscopically examined immediately before and after the treatment period. One subject in both of the KCl treatment groups and six subjects in the placebo group developed submucosal lesions. All lesions were minor and of limited clinical significance. It was concluded that there may be reason to believe that glycopyrrolate plays a role in the production of such lesions. If so, the concomitant use of glycopyrrolate in clinical trials of KCl preparations may cloud the results of such studies ([redacted]).

Phenobarbital

Combination of glycopyrrolate with phenobarbital may be used safely and effectively, particularly in the advanced stage of chronic duodenal ulcer with nocturnal pain and in ulcerative colitis ([redacted]).

[redacted]) evaluated the clinical efficacy of orally administered glycopyrrolate tablets in 50 out-patients with a wide range of gastrointestinal disorders characterized by hypersecretion and / or hypermotility. In 31 cases, glycopyrrolate alone was used and in 19 cases it was combined with Phenobarbital. Depending upon the severity of symptoms, initial dosage ranged from 1 mg to 8 mg glycopyrrolate a day. Concomitant therapy such as antacids and sedatives were used as and when indicated. The therapeutic response was reported to be excellent in 52 % of the patients while 26 %, 12 % and 10 % patients reported to show good, fair and poor response.

Chlorothiazide and Reserpine

A hypertensive patient suffering from splenic flexure syndrome obtained excellent relief of gastrointestinal symptoms with 2 mg glycopyrrolate daily while her hypertension was adequately controlled with chlorothiazide and reserpine ([redacted]).

Neostigmine

In a cross-over study patients with spinal cord injury (SCI) and defecatory disorders received i.m. injections of neostigmine 2 mg and glycopyrrolate 0.4 mg or two placebo injections . Neostigmine was a cholinergic agonist that had been shown to increase gastrointestinal motility and had been used to treat intestinal pseudoobstruction. In order to attenuate the cardiovascular effects of neostigmine anesthesiologists routinely co-administer glycopyrrolate. Results demonstrated that the combination of i.m. neostigmine and glycopyrrolate accelerate bowel care in patients with SCI-related defecatory disorders. Furthermore, this combination did not result in any clinically significant bradycardia or change in blood pressure. Glycopyrrolate was effective in attenuating the adverse cardiovascular side effects of neostigmine ([redacted] .

Glycopyrrolate is poorly absorbed after oral administration. Administration of a high fat meal further reduces oral absorption. Following oral administration, the anti-cholinergic effects of glycopyrrolate may persist for up to 8-12 h. Glycopyrrolate is widely distributed with an average volume of distribution at steady state of 0.37± 0.26 (L/kg) Only a small portion of absorbed glycopyrrolate is metabolised and excreted as one or more metabolites. Approximately 65 -80% of orally administered glycopyrrolate is recovered in urine as unchanged drug. The remaining portion is believed to be metabolised and excreted in bile. Glycopyrrolate increased serum levels of digoxin and haloperidol. Glycopyrrolate, alone or in combination with aluminium hydroxide, clearly retarded the thambutol absorption. Glycopyrrolate may increase the bioavailability of atenolol. Glycopyrrolate inhibits the action of acetylcholine on peripheral acetylcholine (muscarinic M_3) receptors on smooth muscle, cardiac muscle, the sinoatrial and atrioventricular nodes, exocrine glands, and to a lesser degree, autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal, and bronchial secretions. Glycopyrrolate effects may be intensified by administration with other anticholinergics, including amantadine, phenothiazines or tricyclic antidepressants. The slower gastrointestinal time produced by glycopyrrolate may increase the risk for hyperkalemia from sustained-release potassium chloride products and reduce the effectiveness of digoxin. Glycopyrrolate with phenobarbital may be used safely and effectively, particularly in the advanced stage of chronic duodenal ulcer with nocturnal pain and in ulcerative colitis.

2.5.4 OVERVIEW OF EFFICACY

2.5.4.1 Dose Ranging Studies

In a clinical evaluation of glycopyrrolate 50 patients with various gastrointestinal complaints were included. Glycopyrrolate was prescribed at dosage levels ranging from three to eight tablets (3 to 8 mg) daily, depending upon the severity of the condition and the therapeutic response noted. A positive therapeutic response was observed in 46 (92 %) of the patients. Glycopyrrolate appeared to have marked antisecretory and antispasmodic effects. It was shown to be effective in patients with acute and chronic duodenal ulcers ([redacted]

The efficacy of glycopyrrolate was studied in 39 ambulatory patients with uncomplicated peptic ulceration. The majority of patients tolerated dosages of 4-8 mg a day. All patients became asymptomatic on glycopyrrolate and the ulcer healed in 31 of the 39 patients. Two ulcers were found to be active, but smaller, when rechecked. Three patients presented duodenitis after therapy and 3 failed to report for follow-up. An excellent reduction of gastric acidity was found in 12 of 15 patients studied experimentally. A diminished acid volume was noted in all 15 patients. Glycopyrrolate exerts minimal or no effect on gastrointestinal motility following oral administration. Due to the excellent acid inhibition coupled with minimal suppression of motility glycopyrrolate was considered as a useful anticholinergic agent ([redacted]).

2.5.4.2 Placebo-Controlled Studies

In another study efficacy of glycopyrrolate was determined in patients with duodenal ulcer utilising a double-blind method. Patients with chronic duodenal ulcer with complete healing of the ulcer after the acute phase were selected for study and received either placebo or 1 mg tablet of glycopyrrolate q.i.d. At the end of an 18 month follow-up study, incidence of recurrence of ulcer disease was 15 % in the glycopyrrolate group compared with 71 % in the placebo group. Results indicated that the use of glycopyrrolate in long-term therapy can minimise the recurrence of episodes in patients with duodenal ulcers [redacted]

A comparative double-blind efficacy trial was conducted in 120 peptic ulcer patients comparing glycopyrrolate and propantheline bromide along with placebo enrolling 40 subjects in each group. One group received propantheline, another glycopyrrolate and the third served as the control. The dosage was one tablet t.i.d (before meals) for at least two months. Glycopyrrolate was found to be more effective than propantheline and both drugs were superior to the placebo. Patients on glycopyrrolate showed symptomatic relief after an average of 3.5 days as compared with 7.5 days when propantheline bromide was used. Side-effects were less frequent with glycopyrrolate as compared with propantheline ([redacted]).

2.5.4.3 Verum-Controlled Studies

[redacted]) evaluated the efficacy of glycopyrrolate 1 mg in comparison with atropine 0.2 mg for management of gastrointestinal disorders in patients suffering from active or recurrent symptoms of peptic ulceration (gastric ulcer, duodenal ulcer and recurrent ulcer), reflux esophagitis due to hiatus hernia and functional bowel distress (irritable bowel and excessive flatus) in a randomized, double-blind trial. Thirteen of the 16 patients with peptic ulcer complaints had an excellent or good response to either glycopyrrolate, atropine, or both, and only one could be considered a therapeutic failure. Glycopyrrolate appeared to be well tolerated in the dosage of 3 to 8 mg/day and produced fewer side-effects than atropine.

A controlled single-blind trial was carried out to determine the value of long-term therapy of glycopyrrolate with 1-hyoscyamine in duodenal ulcer. A total of 106 male patients with duodenal ulcer were enrolled in the trial out of which 91 completed the study. Patients were divided randomly into three groups, receiving either glycopyrrolate or 1-hyoscyamine in a sustained-release form or inert placebo tablets for one year. Progress was judged on the basis of frequency and severity of symptoms, monthly assessments by patients, antacid consumption and radiology. By all criteria, almost 79% of subjects in glycopyrrolate group reported better response as compared to 65% in 1-hyoscyamine group and 72 % in placebo group ([redacted] .

2.5.4.4 Non-Controlled Studies

[redacted]) evaluated the clinical efficacy of glycopyrrolate in 62 patients with gastrointestinal disorders. Patients were treated with 1 mg tablets of glycopyrrolate on a q.i.d dosage schedule. Symptoms such as acute discomfort, gnawing pain, epigastric pain, belching and other symptoms of duodenal ulcer were relieved within 16-72 h following. Excellent results were obtained in 57 patients as evidenced by complete remission of symptoms. The drug was well tolerated. Side-effects, requiring discontinuation of medication were noted in only 2 of the 62 patients studied. Glycopyrrolate was extremely effective and well tolerated with an adequate long duration of action.

[redacted]) studied the efficacy of glycopyrrolate in 78 patients. Thereof 60 patients suffered from duodenal ulcer and irritable colon, while the remaining 18 patients suffered from hiatal hernia with esophagitis, pancreatitis, ulcerative colitis or regional enteritis. Results after treatment with glycopyrrolate and glycopyrrolate with phenobarbital were presented in Table 3. Glycopyrrolate was an effective oral therapeutic adjunct in the management of gastrointestinal disorders affected by abnormal motor and secretory function. Satisfactory results were observed in 94.9 % and significant side-effects in only 2.6 %.

Table 3: Response to glycopyrrolate and glycopyrrolate with phenobarbital ([redacted]).

Diagnosis	Number of patients	Asymptomatic	No pain occ. distress	Occ. Pain & distress	No improvement
Duodenal ulcer	40	25	7	7	1
Gastric ulcer	3	2	1	0	0
Hiatal hernia & esophagitis	6	4	1	1	0
Pancreatitis	3	1	0	2	0
Irritable colon	17	7	6	2	2
Ulcerative colitis	8	4	2	1	1
Regional enteritis	1	0	1	0	0
Totals	78	43	18	13	4
Percentages		55.1%	23.1%	26.7%	5.1%

The initial healing of chronic gastric ulcer was studied in two groups of 20 hospitalised patients. One group was treated with bed rest and antacids as required and one group was given the same therapy with addition of glycopyrrolate bromide 1 mg tablets. Glycopyrrolate was shown to accelerate the initial healing of chronic gastric ulceration in hospital inpatients. It was suggested that glycopyrrolate bromide given in maximum tolerated doses might be an effective addition to present inpatient therapy of chronic gastric ulceration. It was shown in a controlled long term study of outpatients that glycopyrrolate bromide protected against gastric

ulcer recurrence in those patients who were not salicylate users. People who regularly took salicylates gained no protection from the anticholinergic drug as regards gastric ulcer recurrence. The protective effect of the anticholinergic agent appeared within 6 months and was sustained for 1 and probably for at least 2 years ([redacted]).
In a study seventy one patients with peptic ulcer, fifty eight with duodenal, two with gastric and one with gastro-jejunal ulcer were treated with glycopyrrolate in addition to the usual dietary, antacid and sedative therapy. In 62 patients good symptomatic improvement was obtained, relief of pain being especially noted. Five patients stopped using the preparation because of a preference for other drugs and four patients required surgery for relief of symptoms ([redacted]).

2.5.4.5 Dosage

The majority of patients tolerated dosages of 4-8 mg a day. Glycopyrrolate was prescribed at dosage levels ranging from three to eight tablets (3 to 8 mg) daily. Glycopyrrolate appeared to be well tolerated in the dosage of 3 to 8 mg/day ([redacted]) .

The normal dosage range of glycopyrrolate was found to be 1-8 mg/day form various efficacy studies [redacted]

The elimination of glycopyrrolate was severely impaired in uraemic patients. Therefore, dose adjustments may be required in patients with renal impairment ([redacted]). ([redacted]).

Glycopyrrolate had marked antisecretory effects and was shown to be effective in patients with acute and chronic duodenal ulcers. Glycopyrrolate was prescribed at a dosage ranging from 3 to 8 mg daily, depending upon the severity of the condition and the therapeutic response. The dosages of 4-8 mg/day of glycopyrrolate were well tolerated in 39 ambulatory patients with uncomplicated peptic ulceration.

In placebo-controlled studies glycopyrrolate minimised the recurrences of episodes in patients with duodenal ulcers. Glycopyrrolate was also found to be more effective than propantheline in double-blind efficacy trial which was conducted in 120 peptic ulcer patients. In verum controlled studies glycopyrrolate appeared to be well tolerated in the dosage of 3 to 8 mg/day and produced fewer side-effects than atropine. In a controlled single-blind trial in patients suffering from duodenal ulcer the glycopyrrolate group reported better response as the 1-hyoscyamine group and the placebo group. In non-controlled studies, glycopyrrolate was extremely effective and well tolerated with an adequate long duration of action inpatients with gastrointestinal disorders.

2.5.5 OVERVIEW OF SAFETY

Glycopyrrolate had been found to be generally well tolerated and the safety aspects had been documented in a number of trials. The details of undesirable effects of Glycopyrrolate treatment are discussed below (Glycopyrrolate, MR, CDER, USFDA Review, 2010).

2.5.5.1 Adverse Drug Reactions

Infections and Infestations

Upper respiratory tract Infection, otitis media, urinary tract infection, influenza, pharyngitis streptococcal, pneumonia, sinusitis, gastroenteritis viral, nasopharyngitis, ear infection and cellulitis, oral herpes (SmPC, Glycopyrrolate, [redacted]).

Blood and Lymphatic system disorders

Hypokalemia, hypernatraemia and metabolic acidosis (SmPC, Glycopyrrolate, 2014)

Metabolism and Nutrition disorders

Dehydration and dysgeusia (SmPC, Glycopyrrolate, 2014)

Psychiatric Disorders

Restlessness, agitation, crying, insomnia, drowsiness, intentional self-injury, impotence, mood alteration, aggression, nervousness and confusion (SmPC, Glycopyrrolate, [redacted] .

Nervous System Disorders

Drowsiness, convulsion, somnolence, headache and disturbance in attention (SmPC, Glycopyrrolate, [redacted]).

Ear and Labyrinth disorders

Ear infection (SmPC, Glycopyrrolate, 2014).

Eye disorders

Blurred vision, pupil dilatation, cycloplegia and increased ocular tension (SmPC, Glycopyrrolate, 2014).

Cardiac Disorders

Tachycardia, dizziness, feeling faint, lightheadedness, palpitations, arrhythmias, hypotension and hypertension (SmPC, Glycopyrrolate, [redacted]).

Respiratory, Thoracic and Mediastinal Disorders

Nasal congestion, dry nose, cough, signs of an upper respiratory tract infection and respiratory arrest (SmPC, Glycopyrrolate, [redacted]).

Gastrointestinal disorders

Vomiting, diarrhoea, dry mouth, abdominal pain, constipation, chapped lips, abdominal distention, flatulence, diarrhea and experiencing incomplete intestinal obstruction (SmPC, Glycopyrrolate, [redacted]).

Hepatobiliary disorders

Alanine aminotransferase increased, blood albumin decreased, blood bilirubin increased, blood potassium decreased (SmPC, Glycopyrrolate, 2014).

Skin and Subcutaneous Tissue Disorders

Vascular disorders, flushing, dry skin, pallor, rash, urticaria, pruritus, anaphylactic and anaphylactoid reactions (SmPC, Glycopyrrolate, [redacted]).

Renal and Urinary Disorders

Dysuria and urinary retention (SmPC, Glycopyrrolate, [redacted]).

Pregnancy, puerperium and perinatal conditions

Suppression of lactation (SmPC, Glycopyrrolate, 2014).

General disorders

The study was conducted in six adult volunteers to evaluate the anticholinergic actions of glycopyrrolate bromide. Glycopyrrolate was given by three routes 0.1, 0.2 and 0.4 mg i.m., 0.1, 0.14 and 0.2 mg i.v. and 2, 4 and 8 mg p.o. In general, a significant diminution in the number of active sweat glands, while occurring less often and with less consistency, paralleled the depression in salivary secretion. The effects were less obvious with the lower dose of the drug and again came on late when the p.o. route was employed ([redacted]).

Investigations

Reduced urine output and heart rate increased (SmPC, Glycopyrrolate, 2014).

Injury, Poisoning and Procedural Complications

Feeding tube complication and fall (SmPC, Glycopyrrolate, 2014).

Social circumstances

Abnormal behaviour and irritability (SmPC, Glycopyrrolate, 2014).

[redacted]) evaluated the safety of glycopyrrolate 1 mg in comparison with atropine 0.2 mg in the patients for management of gastrointestinal disorders in a randomized, double-blind trial. Adverse effects reported during the trail are summarized in Table 4. Dryness of the mouth was noted with equal frequency with both drugs. Blurring of the vision was a complaint of only 2 patients, while 1 patient complained of lightheadedness and dryness of lung secretions each who received atropine. One patient receiving glycopyrrolate complained of hoarseness and another developed generalized pruritus which responded to antihistamine therapy within one week. In neither of the latter two cases was the complaint considered significant enough to discontinue treatment.

Table 4: Side effects of glycopyrrolate and atropine ([redacted])

Adverse Effects	Glycopyrrolate	Atropine
Dryness of mouth	5	5
Blurred vision	-	2
Lightheadedness	-	1
Pruritus	1	-
Hoarseness	1	-
Dryness of lung secretions	-	1

[redacted]) sought to evaluate the response to oral glycopyrrolate in paediatric patients. Side effects were noted in Table 5. Twenty-nine percentof the intent-to-treat patients were largely confined to dry mouth/increased thirst (26%) and dry eyes (10%, always in association with dry mouth). The dryness was dose-related and improved when the dosage was lowered (i.e. present at 3 mg daily but not at 1 mg daily), allowing partial amelioration of the hyperhidrosis while minimizing drying side effects. No patients reported increased dental caries. One patient experience blurred vision with a dosage of 5 mg daily (in two divided doses). Overall, 18% of paediatric patients with improvement experienced an adverse effect at a dose of less than or equal to 2 mg daily, whereas 57% of the 7 children who took more than 2 mg reported an adverse effect. Noneone of these discontinued the medication as a result.

Table 5: Side effects experienced when using oral glycopyrrolate ([redacted])	
Side effect	n (%)
None	22 (71)
Dry mouth	8 (26)
Dry eyes	3* (10)
Blurring of vision	1# (3)
Sensation of palpitations	1 (3)
*All children with dry eyes also experienced dry mouth # Blurring of vision occurred at dose of 5 mg/d in subject who also had dry mouth	

2.5.5.2 Warnings and Precautions

Glycopyrrolate may produce blurred vision, intestinal obstruction or decreased sweating. In patients with fever or in the presence of high temperatures or with exercise, anticholinergics may produce heat prostration ([redacted] .

As an anticholinergic drug, glycopyrrolate should be used with caution in patients with conditions that are exacerbated by such drugs, including autonomic neuropathy, renal disease, ulcerative colitis, hyperthyroidism and various heart diseases ([redacted]

2.5.5.3 Contraindications

Glycopyrrolate was contraindicated in patients with glaucoma, gastrointestinal obstruction, paralytic ileus, ulcerative colitis, obstructive uropathy, and myasthenia gravis. It should be used with caution in patients with cardiac or coronary artery disease, hyperthyroidism, autonomic neuropathy, hepatic or renal disease. It should not be used in neonates and should be used with caution in older infants [redacted]).

A case report reported of a bilateral acute angle closure glaucoma (AACG) that occurred after cervical spine surgery with the use of glycopyrolate. A 59-year-old male presented with severe bilateral bifrontal headache and eye pain that started 12 h postextubation from a cervical spine surgery. Neostigmine 0.05 mg/kg (4.5 mg) and glycopyrrolate 0.01 mg/kg (0.9 mg) had been used as muscle relaxant reversals at the end of the surgery. Ophthalmic examination revealed he had bilateral AACG with plateau iris syndrome that was treated medically along with laser iridotomies. Thorough examination of anterior chamber was recommended preoperatively on all patients undergoing surgeries in the prone position and receiving mydriatic agents under general anesthesia ([redacted]).

2.5.5.4 Pregnancy and Lactation

Pregnancy

A sensitive radioreceptor assay was used in eight caesarean section patients who received glycopyrrolate 6 µg/kg after i.m. (deltoid muscle). This dose produced a significant increase in the maternal heart rate after 10 min ($p < 0.05$) and an antisialogogue effect after 30 min ($p < 0.05$) of the drug injection ([redacted]).

The effects of i.v. glycopyrrolate on maternal and foetal heart rate, heart rate variability, and maternal electromechanical intervals and blood pressure were evaluated in 20 term parturients in labour. There were no significant changes in foetal heart rate or foetal heart rate variability. The maternal heart rate increased in all cases and the electromechanical interval decreased with the onset of maternal tachycardia. There were no significant changes in maternal blood pressure. Uterine activity increased in all cases; however, this increase does not appear to be greater than that expected as labour progresses ([redacted]). Hence, it could be concluded that glycopyrronium bromide is not recommended during pregnancy and in women of childbearing potential.

Lactation

It is unknown whether glycopyrrolate or its metabolites were excreted in human milk as no data was available in public domain. however as per SmPC of glycopyrrolate, it is excreted in human milk (SmPC, Glycopyrrolate, 2014).

2.5.5.5 Overdose

Due to the anticholinergic effects of glycopyrrolate, there could be serious adverse events with an accidental overdose. The labelling of the approved drugs with glycopyrrolate contain instructions for overdose, which includes maintaining an open airway, managing hyperthermia, administering neostigmine, or administering activated charcoal as appropriate. The labelling for this drug will carry the same instructions. In terms of potential for overdose, the pharmacology/toxicology studies reviewed results shown that 8 and 30 times the equivalent human dose when given in animals were presented without serious adverse events (Glycopyrrolate, MR, CDER, USFDA Review, 2010).

2.5.6 BENEFITS AND RISK CONCLUSION

Anticholinergic medications are been available for more than a century and have been used primarily to decrease excessive secretions, preoperatively, as an adjunctive agent for peptic ulcer disease and to diminish excessive salivation including in children with neurologic disorders.

Glycopyrrolate or glycopyrrolate bromide is an old drug that has been used for many years for its anticholinergic properties. The drug with chemical name 3 - [(cyclopentylhydroxyphenylacetyl) oxy]-1, 1-dimethylpyrrolidinium bromide is a quaternary ammonium compound in contrast to conventional anticholinergic compounds such as atropine and scopolamine which are tertiary amines. Glycopyrrolate is a long acting drug with peripheral antimuscarinic effects and competitively inhibits acetylcholine at muscarinic receptors, which are prominent in glandular tissue. Glycopyrrolate is commonly administered via p.o., i.m. and i.v. routes. Glycopyrrolate tablets in the dose of 1 mg and 2 mg tablets are indicated together with other medicines to help treat peptic ulcers (stomach) ulcers in adults.

It is used for the treatment of various gastrointestinal disorders including peptic ulcers, in anaesthesia as an antisialogogue and to prolong the effectiveness of some anticholinesterases such as physostigmine and neostigmine against neuromuscular blockade. Since it has a perspiration suppression effect, it is now used frequently in hyperhidrosis treatment. Glycopyrrolate causes a decrease in basal gastric secretion in ulcer patients with increase dosing from 1 mg to 4 mg. Also the drug produces a decrease in total acid, free acid and volume of gastric secretions as studied over a nocturnal period along with the reduction in the gastric pepsin levels. The delayed gastric emptying following glycopyrrolate treatment allows antacids to remain in the stomach for longer periods and thereby accomplish greater neutralization of gastric contents. Glycopyrrolate should not be used in patients with significant liver, kidney or unstable heart disease, patients with significant gastrointestinal disorders such as ulcerative colitis, patients with eye diseases like glaucoma and patients with a history of urinary retention. It should be used in caution in patients with prostatic obstruction, pyloric stenosis or glaucoma.

Taken orally, the drug has relatively low and variable bioavailability. Glycopyrrolate is poorly absorbed from the gastrointestinal tract. Only 10 % to 25 % is absorbed after an oral dose with an oral bioavailability of 3.3 %. Plasma concentrations produced by 2mg Glycopyrrolate are low (C_{max}: 190 - 440 pg/mL) and last up to 12 h. Food has a major effect on the absorption of glycopyrrolate with the mean C_{max} reported to be 74 % lower after high fed fat meal conditions than after fasting conditions. Glycopyrrolate is excreted primarily in urine in unchanged form (65 % - 80 %) while the remaining portion is thought to be metabolized and excreted in the bile. Mean elimination half-life of glycopyrrolate after following oral solution administration is approximately 3 h.

When a decision is made to use this drug i.e. to effectively inhibit acid secretion, it should be prescribed at an individually determined optimal effective dose. The optimum effective dose varies with each individual patient, with the type of preparation and with the time of administration. The duration of action of these drugs is greatest when taken after a meal. They are most effective if given at bedtime for reduction of nocturnal acid secretion and nighttime pain.

The recommended initial dosage is 1 mg and 2 mg tablets for adults given t.i.d (in the morning, early afternoon and at bedtime). Some patients may require two tablets at bedtime to

assure overnight control of symptoms. A maintenance dose of one tablet twice a day is frequently adequate. The recommended maximum daily dose of glycopyrrolate is 8mg.

The use of anticholinergics in the management of peptic ulcer is based on the observations that they reduce basal, nocturnal and stimulated gastric acid secretion. They also prolong the duration of antacid action by prolonging its stay in the stomach. The medical management of patients with duodenal ulcer is dependent on adequate control of gastric secretions. A large number of studies have been directed in determining the usefulness of glycopyrrolate in peptic ulcer patients.

Glycopyrrolate is used to relieve ulcer pain and to reduce symptomatic relapse in patients with duodenal ulcer. The ability of glycopyrrolate to suppress the production of gastric acid and to reduce gastric motility supports its use as a drug of value in the treatment of peptic ulcer.

The rapid action of glycopyrrolate with prompt reduction of symptoms within the first 24 to 36 h and complete remission within 36 to 48 h confirms its effectiveness in peptic ulcer. The long-acting characteristic of this drug enables the treatment of some gastrointestinal disorders with a b.i.d (twice a daily) dosage schedule which is certainly an important dose regimen factor of patient acceptance. The fact that most patients were maintained on one to two tablets /1mg) daily in clinical efficacy trials serves asevidence of its potency in patients with ulcerative diseases.

The drug is reported to be superior to placebo in the relief of peptic ulcer, ulcer recurrences and its complications. Glycopyrrolate studied in patients with upper gastrointestinal pathology showed excellent results as evidenced by complete remission of symptoms indicating glycopyrrolate tablets are a good aid in the treatment of duodenal ulcers.

Glycopyrrolate is also effective in the healing of gastric ulcers indicating that the drug deserves more attention from clinicians for follow up of patients. When combined with other measures, such as diet and antacids, glycopyrrolate is a valuable adjunct in the treatment of peptic ulcer and irritable bowel syndrome. In patients with irritable bowel syndrome, improvement following the use of glycopyrrolate is due to a suppression of exaggerated colonic contractions.

Glycopyrrolate is also reported to be effective in pediatric patients with hyperhidrosis.

Glycopyrrolate is extremely effective, well tolerated and has an adequately long duration of action. The desired antisecretory effects of anticholinergics are invariably accompanied by predictable side effects, such as dry mouth and constipation. Important potential adverse events specified in the prescribing information of glycopyrrolate include constipation, transient bradycardia, incomplete mechanical intestinal obstruction, heat prostration (in the presence of high ambient temperatures), drowsiness and blurred vision.

The most frequent adverse reactions reported in clinical trials with glycopyrrolate tablets include those that are common to anticholinergics generally including for example xerostomia, dry mouth, decreased sweating, urinary hesitancy and retention, blurred vision, tachycardia, palpitations, headaches, dizziness, nausea, vomiting and nervousness.

Side-effects are minimal and can he easily alleviated by adjustment of the dosage schedule. In a series of 62 patients, the drug was well tolerated. Side-effects requiring discontinuation of medication, were noted in only two of the 62 patients studied. Oral glycopyrrolate can be continued long-term and parents and patients are easily able to manage dosing amount and frequency to achieve the best balance between efficacy and side effects.

Adverse effects such as constipation, dry mouth, and behavioural changes occurred in >30% of patients in studies and were seen more frequently at higher doses. Not much data is available for the use of glycopyrrolate in pregnant and lactating women. Hence, as a precautionary measure, the drug should be avoided during pregnancy and breast-feeding.

Based on above discussion, glycopyrrolate was judged to be a safe, well tolerated and effective drug for the treatment of patients with peptic ulcers.

2.5.7 LITERATURE REFERENCES

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