Glycopyrrolate: pharmacokinetics and some pharmacodynamic findings

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PATTERNS AND METHODS

The study was approved by the local ethical committee and informed oral consent was obtained from the patients.

Three groups of patients were studied, each consisting of 6 subjects. Some characteristics of the three groups are shown in Table 1.

The patients were admitted to hospital for different intraocular operations to be performed under local or general anaesthesia. The patients in Group 1 were premedicated with glycopyrrolate 4 mg orally and those in Group 2 with glycopyrrolate 8 μg/kg i.m. given in the recovery room. In both groups the antiallogogue effect of the drug was subjectively estimated with a visual analogue scale (VAS) of 10 cm numbered from 0 to 10, mouth normal to extremely dry, respectively. In each group the blood pressure and the heart rate were measured with an automatic noninvasive device and the ECG was continuously observed on an oscilloscope. The pure effect of glycopyrrolate was followed in Group 1 for 2 h and in Group 2 for 1 h before the beginning of surgery, and thereafter a slight i.v. sedation was given to the patients (fentanyl 50-100 μg or diazepam 2.5 mg-5 mg i.v.). The retrobulbar block with 2% lidocaine or adrenaline was performed by the ophthalmologist.

In Group 3, the patients received a combination anaesthesia (thiopentone 3-5 mg/kg, vecuronium 0.1 mg/kg, N₂O+O₂, fentanyl 3 μg/kg and neostigmine as an antichasering agent in incremental doses up to 1.25 mg) and glycopyrrolate 6 μg/kg was injected i.v. just before the induction of anaesthesia. Glycopyrrolate was determined by using a sensitive radioreceptor assay described by Ensinger et al. (9). NMS (N-methylscopolamine) was used as a marker for cholinergic muscarinic receptors obtained from the rat brain.

The sensitivity of the assay was 100 pg/ml and the assay precision (coeffi-
Table 1

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>ASA class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>72 (59–79)</td>
<td>74 (60–85)</td>
<td>166 (158–180)</td>
<td>2: n = 4</td>
</tr>
<tr>
<td>Group 2</td>
<td>65 (60–70)</td>
<td>66 (56–87)</td>
<td>159 (135–164)</td>
<td>2: n = 3</td>
</tr>
<tr>
<td>Group 3</td>
<td>66 (60–75)</td>
<td>66 (55–89)</td>
<td>159 (150–170)</td>
<td>3: n = 3</td>
</tr>
</tbody>
</table>

Drug treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>Patient No 1</th>
<th>Patient No 2</th>
<th>Patient No 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>amiloride + hydrochlorothiazide</td>
<td>amiloride + hydrochlorothiazide, metoprolol, nitroglycerin.</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>oxazepam</td>
<td>prednisolone theophylline.</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>digoxin, triamteren + hydrochlorothiazide.</td>
<td>indomethacin, Patient No 2 = dapson.</td>
<td></td>
</tr>
</tbody>
</table>

Based on these concentrations, some pharmacokinetic parameters are shown in Tables 2 and 3.

After an intravenous injection (dose 6 µg/kg), glycopyrrolate disappeared very fast from the circulation with a mean distribution phase half-life of 2.22 ± 1.26 min and with a mean elimination phase half-life of 0.83 ± 0.27 h (Fig. 1, Table 2). There was no linear relationship between the plasma level of glycopyrrolate (Fig. 1) and the heart rate response (Fig. 3).

Following intramuscular drug administration (dose 8 µg/kg), a fast absorption rate was found with a mean time to maximum plasma concentration ($t_{max}$) of 27.48 ± 6.12 min and a mean maximum plasma concentration ($C_{max}$) of 3.47 ± 1.48 µg/l (Fig. 2, Table 3). A statistically significant increase in the
Table 2
Basic pharmacokinetic parameters based on plasma concentrations determined with a radio-receptor assay following a single intravenous injection of glycopyrrolate (6 μg/kg) in 6 elderly patients in connection with cataract operation. Mean ± s.d.

<table>
<thead>
<tr>
<th>Mean age (years)</th>
<th>N</th>
<th>t1/2d (min)</th>
<th>t1/2e (h)</th>
<th>Vdα (l/kg)</th>
<th>V∞ (l/kg)</th>
<th>Vdarea (l/kg)</th>
<th>CI (l/kg/h)</th>
<th>AUC0-8h (μg/l × h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (60-75)</td>
<td>6</td>
<td>2.22 ± 1.26</td>
<td>0.83 ± 0.27</td>
<td>0.08 ± 0.06</td>
<td>0.42 ± 0.22</td>
<td>0.64 ± 0.29</td>
<td>0.54 ± 0.14</td>
<td>8.64 ± 1.49</td>
</tr>
</tbody>
</table>

t1/2d = distribution phase half-life; t1/2e = elimination phase half-life; Vdα = distribution volume during α-phase; V∞ = distribution volume during steady state; Vdarea = distribution volume during elimination phase (area method); CI = total plasma clearance; AUC = area under curve.

heart rate was found after 60 min (P < 0.01) (Fig. 4). An antisialogogue effect could be seen, but it was not statistically significant (Fig. 5). The relationships between the plasma concentration of glycopyrrolate (Fig. 2) and the heart rate (Fig. 4) and the antisialogogue effect (Fig. 5) are shown in Table 4.

Oral drug administration (dose 4 mg) produced extremely variable and apparently incomplete drug absorption with almost no exact tmax values (Fig. 2, Table 3). Oral glycopyrrolate (4 mg) had only a minor effect on the heart rate (Fig. 4), but produced a significant antisialogogue effect (Fig. 5) after 6 h (P < 0.01). The relationship between the plasma concentration and the drug effect is shown in Table 4.

In the systolic and diastolic blood pressures no significant changes were observed following the three administration routes of glycopyrrolate.

DISCUSSION
It should be kept in mind that RRA measures all the drugs bound to the muscarinic receptors and, therefore, all the possible active metabolites of glycopyrrolate are measured as well.

The basic pharmacokinetic parameters of glycopyrrolate based on plasma levels after an intravenous injection were quite comparable to those of atropine (8, 11–15) and those of scopolamine (16). Its elimination phase half-life, however, appears to be the shortest due to its higher clearance value and the lowest volume of distribution. All these anticholinergic agents have a very short distribution phase half-life of a few minutes, and their elimination phase lasts only a few hours. This kind of pharmacokinetic profile was to be expected from the results of the early studies with a radioactive agent (17) and the preliminary studies performed with a gas chromatographic method (18).

After an intramuscular injection into the deltoid muscle, glycopyrrolate had a fast absorption rate (mean tmax = 27.48 ± 6.12 min) and a predictable clinical response. A similar fast systemic absorption after injection into the deltoid muscle has been found with scopolamine (16, 19) and atropine (20), but an injection into the gluteal muscle has produced peak serum levels of atropine approximately 1 h after drug administration (12, 19, 21, 22). The poor correlation between the plasma concentration after intramuscular glycopyrrolate and the antisialogogue effect of the drug is possibly due to the slow membrane penetration of this quaternary amine (3).

An interesting finding of the present study was the extremely variable and incomplete gastrointestinal absorption of oral glycopyrrolate followed by a late clinical response. The low plasma concentration after an oral intake did produce a distinct, statistically significant antisialogogue effect. However, the effect of the adjuvants (fentanyl and diazepam) used in connection with the retrobulbar block performed with lidocaine should be taken into consideration, too. Atropine, on
the other hand, has been shown to have a clear gastrointestinal absorption (23, 24) and dose-related CNS-effects have been reported (24). The oral dose of atropine should be at least twice as high as the intramuscular absorption (23, 24) and dose-related CNS- effects have been reported (24). The oral dose of atropine was associated with an antisialogogue effect, whereas the heart effects were only seen in connection with the orally administered dose. This and the slow onset of action of the antisialogogue effect argue against the use of oral glycopyrrolate as premedication. Surprisingly, however, 10% of Finnish anaesthetists use this kind of premedication (25).

Another finding of interest in the present study was that even very low plasma concentrations of glycopyrrolate were associated with an antisialogogue effect, whereas the heart effects were only seen in connection with the higher plasma levels.

In conclusion, based on the present kinetic data, residual clinical effects are not likely to occur after the administration of a single dose i.m. or i.v. of glycopyrrolate, especially as this anticholinergic agent is devoid of central antimuscarinic actions. Long-lasting but low plasma levels following the oral drug intake could in theory produce some undesirable effects like urinary retention during the postoperative period. Basically, however, the antisialogogue effect of orally administered glycopyrrolate, 4 mg, was far too slow to be useful in everyday clinical practice.

**REFERENCES**


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