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# The fate of intravenous [$^3$H]glycopyrrolate in man

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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 intravenous 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 both in bile and in urine over 80% of the radioactivity corresponded to unchanged glycopyrrolate. That appreciable amounts of glycopyrrolate were excreted into the bile suggests that the spasmolysis achieved with glycopyrrolate could be based partly on a local action on the bile ducts.

Numerous clinical trials have confirmed that 3-hydroxy-1,1-dimethylpyrrolidinium bromide α-cyclopentylmandelate, glycopyrrolate has an antisecretory effect and reduces antral motility in man (Sun, 1962; Moeller, 1962; Abbot, Sourial & others, 1962; Young & Sun, 1962). Although it has been used successfully for more than a decade to treat various gastric disorders, little is known about its pharmacokinetics in man. We have studied serum levels as well as biliary and urinary excretion of radioactivity after intravenous injection of specifically labelled [$^3$H]glycopyrrolate.

## MATERIAL AND METHODS

*Synthesis of [$^3$H]glycopyrrolate.* This was prepared at the Radiochemical Centre, Amersham, by treating inactive methylpyrrolidylcyclopentylmandelate with tritiated methyl iodide. The glycopyrrone iodide obtained was then converted into the corresponding bromide by elution through an HBr-treated Dowex 3 ion-exchange column and recrystallized to constant specific activity (7·25 mCi mmol$^{-1}$). The radiochemical purity was demonstrated by thin-layer and paper chromatography; more than 99% of the radioactivity was found at the $R_F$ value of authentic glycopyrrolate. A sterile solution of 0·2 mg ml$^{-1}$ of glycopyrrolate in saline was prepared with an activity of 3·65 μCi ml$^{-1}$ (8·1 × 10$^6$ d min$^{-1}$ ml$^{-1}$).

*Experimental procedures.* A T-drain was inserted into the common bile duct with the consent of six patients being operated for gallstones (2 males and 4 females with normal hepatic function). On the fifth post-operative day a dose of 0·2 mg diluted to a volume of 5 ml and corresponding to 3·65 μCi of [$^3$H]glycopyrrolate was injected into the cubital vein. Venous blood samples were taken from the other arm after 5, 15, 30 min, 1 and 3 h. The excreted bile was collected during the periods

0–15, 15–30, 30–60 min, 1–2, 2–6, 6–24 and 24–48 h after injection. Urine was similarly collected 0–3, 3–6, 6–12, 12–24 and 24–48 h after injection.

*Measurement of radioactivity.* Aliquots of the serum, bile and urine samples were counted in Aquasol, NEN, in a Wallac DECEM NTL 314 liquid scintillation counter. The values obtained were corrected for quenching, using internal standards. The radioactivity of the serum samples is expressed as d $min^{-1}$ $ml^{-1}$, whilst that excreted into bile and urine is presented as d $min^{-1}$ in the total amounts collected during the specified periods.

*Chromatography.* Samples of bile (15–30 min and 30–60 min) and urine (0–3 h) were subjected to descending chromatography on Whatman No. 1 paper. Two separate chromatographic systems were used: n-butanol–acetic acid–water (12:3:5) and n-butanol–pyridine–water (1:1:1). The chromatograms were cut in pieces and the radioactivity of each piece measured. Pure [³H]glycopyrrolate and its alkaline hydrolysate were used as standards. No attempts were made to identify metabolites.

## RESULTS

In all patients the radioactivity in serum was relatively low and disappeared rapidly. In the 5 min samples the mean value of radioactivity was 309 d $min^{-1}$ $ml^{-1}$. More than 90% of the given dose had disappeared from the circulation in 5 min. After 30 min almost no radioactivity could be found.

The cumulative excretion of radioactivity into bile is shown in Fig. 1. The drug or its metabolites were rapidly excreted into the bile, since the highest radioactivity was found in samples taken at 30 or 60 min (7500 or 8800 d $min^{-1}$ $ml^{-1}$, respectively), but measurable amounts of radioactivity were found after 24 h in all cases and even after 48 h in 5 cases. Most of the radioactivity (85–100%) was found in a spot having the same $R_F$ value as the glycopyrrolate standard. In three patients two additional spots were detected, one of which had the same $R_F$ value as the alkaline hydrolysate of glycopyrrolate and amounted to 5–15% of the sample chromatographed.

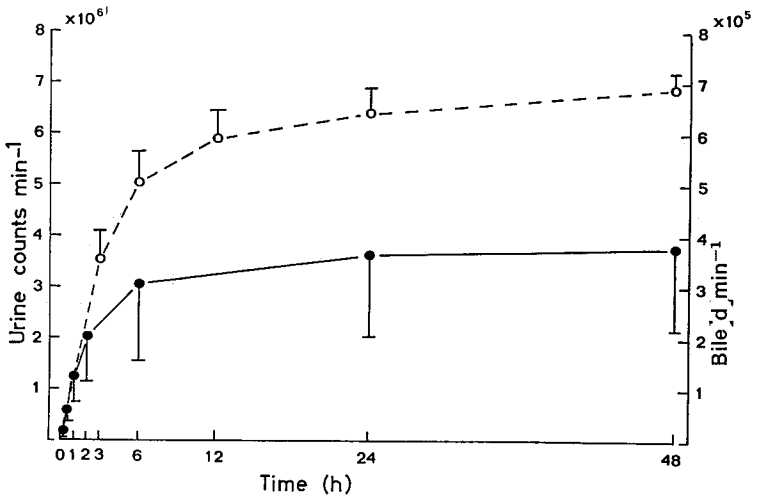


FIG. 1. Cumulative excretion of radioactivity into bile (—) and urine (- -) after intravenous injection of 0·2 mg [³H]glycopyrrolate corresponding to 8·1 × $10^6$ d $min^{-1}$. Means ± s.e. are given (n = 6).

Fig. 1 also shows the cumulative excretion of radioactivity into urine. The rapid excretion of glycopyrrolate is also evident here, since the highest radioactivity was found in the first sample, taken after only 3 h (29 000 d $min^{-1}$ $ml^{-1}$). In 5 out of 6 subjects the radioactivity of the first sample was 2–4 times higher than in the following sample. Again, over 80% of the radioactivity was located in the spot corresponding to the glycopyrrolate standard, the rest appeared in the same spots as the metabolites found in the bile. The mean urinary excretion in 48 h amounted to 85% (65–97%) of the total amount of radioactivity given.

## DISCUSSION

The rapid disappearance of glycopyrrolate from the circulation and its rapid excretion into bile and urine agrees with clinical observations concerning its duration of the effects in man. Its antisecretory action on histamine- or insulin-stimulated acid secretion is seen up to 3 h after drug administration (Abbott & others, 1962). In patients with chronic duodenal ulcer the suppression of gastric acid secretion lasted from 30 to more than 135 min (Sun, 1962). Bitsch & Kristensen (1966) found the acid secretion and the volume of gastric juice were reduced by about 90% for 4 h. The duration of glycopyrrolate action on antral motility, gastric emptying and intestinal motility was similar (Young & Sun, 1962) but Barman & Larson (1963) and Feder, Hadidi & Kahn (1963) showed that glycopyrrolate decreased the basal nocturnal gastric secretion for 8–12 h.

Glycopyrrolate has not generally been recommended in biliary spasms. To our knowledge clinical data on only 2 cases with postcholecystectomy syndrome, treated successfully with glycopyrrolate, have been described (Epstein, 1962). As glycopyrrolate is excreted to a marked degree into the bile, local effects on the gall bladder and bile ducts are a possibility. According to recent animal experiments, a local spasmolytic mechanism has also been proposed for another quaternary anti-acetylcholine drug, butylscopolamine (Pentikäinen, Penttilä & others, 1973).

We found injection of glycopyrrolate produced a spasmolytic effect on the bile ducts, but it also seemed to induce analgesia, which was expressed subjectively and was seen as a reduction in spasmolytic and analgesic drugs needed.

Our results demonstrate a rapid disappearance of intravenously administered glycopyrrolate from the circulation and excretion into bile and urine. Although this drug is mainly excreted into the urine, the amounts in the bile suggest that the spasmolytic effect on the bile ducts warrants further clinical studies.

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