EUROPEAN JOURNAL OF DRUG METABOLISM AND PHARMACOKINETICS, 1988, Vol. 13, No 2, pp. 81-90

On the Pharmacokinetics and Metabolism of Propiverine in Man

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Received for publication: January 16, 1987

Key words: Propiverine, pharmacokinetics, metabolism, healthy volunteers

SUMMARY

The pharmacokinetics of ^{14}C-propiverine was studied in 13 volunteers and in 2 patients after a single i.v. injection of 5 mg or after oral administration of 15 mg. To each dose 1.11 MBq ^{14}C-propiverine was added. The radioactivity measured in plasma, urine (and bile fluid), and the metabolites were estimated by an extraction procedure together with TLC and radiochromatography. Propiverine was eliminated from the plasma with a half-life time ($t_{0.5}$) of 4.1 h (i.v. and per os), while the plasma radioactivity decreased with a $t_{0.5}$ of 21.2 (i.v.) or 10.4 h (per os). Within 4 days, 84.5 (i.v.) or 53.5% (per os) of the administered radioactivity was excreted in urine. The absorption of radioactivity of propiverine amounted to 84.5%, while the amount of available propiverine was only 48.9%. In two patients with cannulated ductus choledochus, 21.5 or 14.7% of the administered radioactivity was excreted within 2 days. The metabolic pattern of plasma, urine and bile fluid mainly consisted of amine oxides, substances oxidized in the propyl side chain, desalkylated metabolites, substances with a N-demethylated piperidino group or with ester cleavage, and glucuronide conjugates. Unchanged propiverine appeared in plasma, urine and bile at about 6 to 8% of the administered dose.

INTRODUCTION

For about 3 years the parasympatholytically effective agent propiverine has been used in the treatment of spasmodic vesical disturbances such as urge symptoms and other spastic uropathies. The first investigation on the pharmacokinetics of ^{3}H-propiverine was performed in rats (Franke et al., 1976). The results obtained were inconclusive because the drug was labelled by the Wilzbach technique instead of introduction of tritium by synthesis. After synthesis of a ^{14}C-labelled propiverine, we resumed our investigation of this subject and studied the kinetics and metabolism of the compound. In order to establish the kinetic parameters of propiverine it was important to determine those of the metabolites (Mohr et al., 1976) and these were evaluated by a chromatographic technique (Hüller et al., 1988). In order to characterize the pharmacokinetic behaviour of propiverine, a sensitive technique was developed for its detection in plasma.

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METHODS

Volunteers and patients

Healthy volunteers (6 females and 7 males) between the ages of 23 and 27 years and with a mean body weight of 68.9 kg (SD 9.5 kg) and 2 female patients (Medical Academy Erfurt and District Hospital Suhl) were subjects of the study. The study was carried out in accordance with current ethical practice.

The subjects were free of diseases of the heart, liver or kidneys. With the exception of two subjects, they took the drug on an empty stomach. A standardized breakfast consisting of two buttered rolls and two cups of tea was allowed 2 h post-dose. Alcohol and cigarettes were forbidden for 3 days before the start of the study.

Sampling of Materials

For investigation of the kinetics, blood, urine and bile, aliquots were taken. Blood (5 to 10 ml) was drawn by venepuncture (9 parts blood plus 1 part

sodium citrate 3.14%), and plasma was separated by centrifugation. The samples were taken before administration and 5, 15, 30, 45, 60, 90 min, 2, 3, 4, 6, 8, 24, 32 and 48 h post-dose. Post-dose, the urine fractions 0-1, 1-4, 4-8, 8-24, 24-48, 48-72 and 72-96 h were collected. The volume of every fraction was measured and aliquots were kept at −20°C. In two patients bile fluid was collected 10 to 12 days after cholecystectomy with cannulation of the ductus choledochus. Bile fluid was collected within the same time intervals as urine. Aliquots were kept at −20°C.

Measurement of Radioactivity

Radioactivity of the samples was measured by a liquid scintillation counter LSC 81000 (LKB-Wallac). To 0.2 ml plasma each 1 ml Tissue Solubilizer (Koch-Light Laboratories Ltd., England) and appropriate 10 ml scintillation cocktail was added. Quenching was corrected by external standardization. To urine samples of 0.5 ml each, 10 ml of a dioxan-based scintillator were added. One ml of a mixture containing 2 parts H_2O_2 20% and 5 parts methanol was added to 0.5 ml bile fluid each for discolouring. Thereafter, 1 ml Tissue Solubilizer and 10 ml dioxan scintillator were added. The samples of bile fluid were measured as those of urine.

Substances

As indicated by TLC, propiverine* (according to AB II of DDR, VEB Sächsisches Serumwerk Dresden) had a purity of 99.7 per cent. Additionally, [acetic acid-1,2-^{14}C]-propiverine hydrochloride was used with a specific activity of 41.3 mCi/mM (1.53 GBq/mM, or of 102 μCi/mg, corresponding to 3.77 MBq/mg), which was synthetized by Amersham International, Buckinghamshire, England, with a purity of 98% as indicating by TLC. For i.v. injection ampouls containing 5 mg ^{14}C-propiverine [30.5 μCi (1.11 MBq)] were used and for oral administration propiverine substance with a specific activity of 74.06 kBq/mg (2 μCi/mg) was used, which was dissolved in 100 to 150 ml water immediately before intake. For identification of the propiverine metabolites the substances listed in table VI were synthetized by Dr. Scheithauer (VEB Sächsisches Serumwerk Dresden) (Scheithauer, 1988).

* Propiverine is manufactured by VEB Sächsisches Serumwerk Dresden, Dresden, GDR (Mictonorm®) and by Rhöm-Pharma GmbH, D-6108 Weiterstadt, FRG (Detrunorm®).

Extraction and Separation Techniques

For extraction of propiverine and its metabolites, $CHCl_3$ was chosen because it was suitable both in acidic and alkaline medium. In an acidic medium propiverine was extracted to nearly 100% as propiverine hydrochloride. The free base was extracted from an alkaline medium in a yield of 40 to 50% (pH 8-9). Substance M-11 had analogous properties, while the metabolite M-2 could be extracted only from an alkaline medium. The acids (M-7, M-9, M-10, M-17, M-19) could be to extracted only from an acidic medium, while extraction of the amine oxides (M-5, M-6) was independent of the medium-pH. To detect additional polar metabolites, the urine was extracted by ethyl acetate and $CHCl_3$ after addition of ion pairing substances such as tetrabutylammonium hydroxide or toluenesulfonic acid. The metabolites of the plasma extracts were separated by TLC on Silufol® sheets (Kavalier, CSSR) and those of urine and bile fluid were separated by TLC plates (E. Merck, Darmstadt). For the solvent systems used cf. Table I.

Preparation of Plasma Samples

One hundred μl of an ethanolic stock solution (containing each 100 μg propiverine, M-1, M-2, M-7, M-9, M-10) were added to 1 ml plasma acidified by 1 ml HCl (1 mol.l^{-1}) and extracted twice by 4 ml $CHCl_3$ followed by a two-fold extraction after addition of 0.25 ml NaOH (5 mol.l^{-1}). The extracts were concentrated, and applied to TLC plates (20 × 20 cm) with a distance of 6 cm from the border (Silufol®). In system S the plate was developed so that the migration distance for separation was 6 cm from the starting point to the border. By this run acidic metabolites (M-7, M-9, M-10) and M-1 were separated from alkaline ones. The spots of the acids were localized by spaying bromophenol-blue. Thereafter, the spots were scraped from the plates, and the radioactivity of each spot was measured. The non-polar region of the plate between the acidic spots and the front was treated in the same manner. The remaining long distance of the plate was developed in the solvent system B separating propiverine and basic metabolites. The spots were localized by iodine vapour. They were scraped for measuring radioactivity in a cumulative manner adding the silicia gel of each spot to the scintillation vial after counting the DPM of the preceding sample. After scraping of the propiverine spot the substance was eluted by a mixture of $CHCl_3$ + HCl

Table I: Composition of the solvent systems

System (vol/vol)	B	B_1	B_2	B_4	B_5	S	S_1	S_2
Cyclohexane	50	—	—	—	—	—	—	—
Dioxane	50	50	40	30	—	45	45	—
Ethyl acetate	40	40	—	25	30	40	40	50
Ethanol (96%)	20	20	—	12	—	—	5	—
Ammonia water *(25%)*	5	5	5	3	5	—	—	—
Heptane	—	50	—	—	—	—	50	—
Acetic acid	—	—	—	—	—	1	1	1.5
Methanol	—	—	30	—	70	5	—	—
CCl_4	—	—	30	—	—	50	—	—
Diisopropyl ether	—	—	—	15	—	—	—	50
Hexane	—	—	—	15	—	—	—	—

(1 mol. l^{-1}). $CHCl_3$ was evaporated, and the residue was dissolved in 100 µl ethanol containing 40 µg diphenyloxazole as standard. To measure the recovery, 2 µl were injected into the GC (GC 18.3; VEB Chromatron Berlin; 1 m glass column, 3 mm internal diameter, filled with 3 per cent SE-superphase on Chromaton N-super 0.125–0.16 mm; temperature program: 220°C followed by heating on 260°C; FID-detector). In the remaining extract the radioactivity was measured. The plasma level of propiverine was calculated from the radioactivity by means of the recovery and of the specific activity of the used propiverine dose. To assess the propiverine N-oxide in plasma, the N-oxide area of one of three samples running in triplicate was reduced by sodium dithionite, separated by TLC in the solvent system B, and propiverine and M-2 were measured.

Preparation of Urine and Bile Samples

Fifty ml urine were taken for $CHCl_3$ extraction procedure (one time at pH = 6.0, two times each at pH = 3.0 after addition of HCl (1 mol. l^{-1}), and at pH = 10 after addition of NaOH (1 mol. l^{-1}). The $CHCl_3$-extracts were mixed. Thereafter, the urine residue was extracted with ethyl acetate (2 times each at a pH 10 and 3) and with $CHCl_3$ (one time each after addition of toluene-p-sulfonic acid, or tetrabutylammonium hydroxide).

The ratio solvent: water amounted to 1:1. After the 5 fold $CHCl_3$-extraction and after each subsequent extraction step, the radioactivity was measured in 0.5 ml urine sample to estimate the yield. With this procedure the lack of radioactivity in the solvent was demonstrated after extraction with ethyl acetate at a pH = 10 and with $CHCl_3$ plus ion pairing substances. For investigation of the metabolites, the $CHCl_3$ extract containing 50 to 80 per cent of radioactive compounds and the acidic ethyl acetate extract containing 10 to 15 per cent of radioactivity were stored. The latter extract was used for identification of glucuronides. The $CHCl_3$ extracts were applied to TLC-plates (E. Merck, Darmstadt). In a first run the system S 1 was chosen (distance of migration 14 cm). The references M-7, M-9, and M-M-10 were identified by bromocresol green, M-1 was localized by iodine vapour. The radiochromatograms were recorded by TLC scanner (model Scanner II LB 2723, Prof. Berthold, Wildbad, FRG). After registration of the radiochromatograms the starting region of the plate was scraped and silicia gel was eluted by a mixture of $CHCl_3$:H_2O (1:1; vol:vol) (twice each in acidic and alkaline medium). The loss of radioactivity amounted to 5 to 10%. The eluate was evaporated and was applied to TLC plates together with the references of propiverine, M-11, and M-2. The plates were developed in the alkaline solvent system B 1. The radiochromatograms were registered by the TLC scanner, and the reference spots were coloured by iodine vapour. Quantitative evaluation was made by measuring the area of the peaks.

Bile fluid was extracted by hexane and $CHCl_3$ at different pH. In the case of an acidic solvent system, several components of bile were precipitated and the radioactive compounds were adsorbed for the most part and was obtained resulting thus in a small yield. On the other hand, at alkaline pH-values the conjugates were split off resulting in an increase in accompanying substances of the extracts. In total, 50

to 60% of the radioactivity was extracted by hexane plus $CHCl_3$.

Identification of Metabolites

For identification of metabolites the corresponding regions of the TLC plates were eluted after chromatography (solvent system S 1 or B 1) and re-chromatographed after sampling the extracts of several subjects. Samples and references were applied to the same traces to avoid mistakes in identification due to small differences in migration between traces. The solvent system S 2 was used to separate the acidic metabolites M-7, M-9, M-25, and M-19 and the system S 3 was taken for separation of M-1 and M-10. Propiverine, the group of alkaline metabolites M-2, M-18, M-22, and M-14, and the metabolites M-4, M-15, and M-26 were separated by the system B 4. The amine oxides were separated by the solvents B 2 and B 5. After chromatography, the alkaline metabolites were converted into the corresponding acids by ester hydrolysis by NaOH (1 h at 90°C), and thereafter, the reaction products were extracted and re-chromatographed by TLC. The amine oxides were reduced to their alkaline compounds in the presence of a solution containing Na_2CO_3 plus $Na_2S_2O_4$ at 50°C for 10 min; the reaction products were extracted and identified in the same manner as propiverine and the metabolites M-2, M-18 and M-22. The metabolites M-7, M-25, M-20, and M-30 were treated with a mixture of HBr (48%) plus acetic acid (1:1) at 90°C for 1 h to split off the ether binding followed by hydrolysis with NaOH at the same temperature for 1 h. The reaction products were tested for identity with benzilic acid (M-9) by the use of solvent S 2. The lactone M-1 was split alkalinely by NaOH or ammonia water at 60°C for 30 min and was identified as the acid M-7. Vice versa, M-7 of the group of metabolites M-7, M-9, M-25, and M-30 was converted into the lactone M-1 by incubation with HCl at 60°C for 30 min. Thus, in this group the substances M-9, M-25 and M-30 had to be separated. In the case of M-8, the alkaline character was identified after esterification of the carboxyl group by diazomethane in an ethereal solution. After ester hydrolysis an acid was found whose structure was not identical with that of the metabolites M-7, M-9, M-10 or M-25. This acid must be converted to the parent substance benzilic acid by ether cleavage. The methods used for identification of the metabolites are described in detail elsewhere (Hüller et al., 1988).

Calculation of Pharmacokinetic Data

The mean curves of the propiverine plasma levels after i.v. and oral administration were seen as an open two compartment system. The kinetic constants were calculated at the computer TPA-i/OS by an iteration procedure (Spittel and Haustein, 1983). For calculation of the "individual" elimination half-life time values, a model of the apparent volume of distribution and of the AUC^{∞}-values was used in which the phase of distribution was neglected. The following data were calculated according to Wagner (1975): elimination constant ß, the initial apparent concentration c_o, the volume of distribution V_{dext}, area under curve AUC^{∞}, the total body clearance Cl_{tot}, and the elimination half-life time, $t_{1/2}$. The renal clearance Cl_{ren} was calculated by the ratio excreted radioactivity CUE^4:AUC^{∞}. The bioavailability was derived from the ratio of the corresponding AUC^{∞}-values (per os:i.v.) of the radioactivity in the plasma. Correction by dose was not necessary because of the administration of identical amounts of radioactivity in both routs of administration. The AUC^{48}-values were calculated by the trapezoidal rule. In the case of calculation of bioavailability from the propiverine data, correction by dose was necessary. The mean values, the standard deviation (SD) and the derived kinetic parameters were calculated by the calculator HP 67 (Hewlett-Packard, USA).

RESULTS

Studies in Pharmacokinetics

Immediately after i.v. injection of 5 mg ^{14}C-propiverine, a total radioactivity of 152 pmol equivalents.ml^{-1} plasma were measured (Fig. 1, Table II). The radioactivity did not decrease within 1 h post-dose, but it increased to values of about 200 pmol equivalent.ml^{-1} plasma during the following 5 h; a continuous decrease was observed 8 h post-dose (Fig. 1). The total radioactivity was eliminated from the plasma with a half-life time of 21.2 h. The mean propiverine plasma level was 125 pmol.ml^{-1} 5 min post-dose, and the drug was eliminated with a half-life of 4.1 h (SD 0.73 h) (Table III). The apparent volume of distribution amounted to 143.4 l (SD 32.4 l) or to 1.90 l.kg^{-1} (SD 0.22 l.kg^{-1}). Within the first hour after i.v. injection of propiverine, 1.4 per cent of administered radioactivity was excreted in the urine (cf. Table IV). On the first day post-dose, 31.8, and 74.5 per cent of the administered

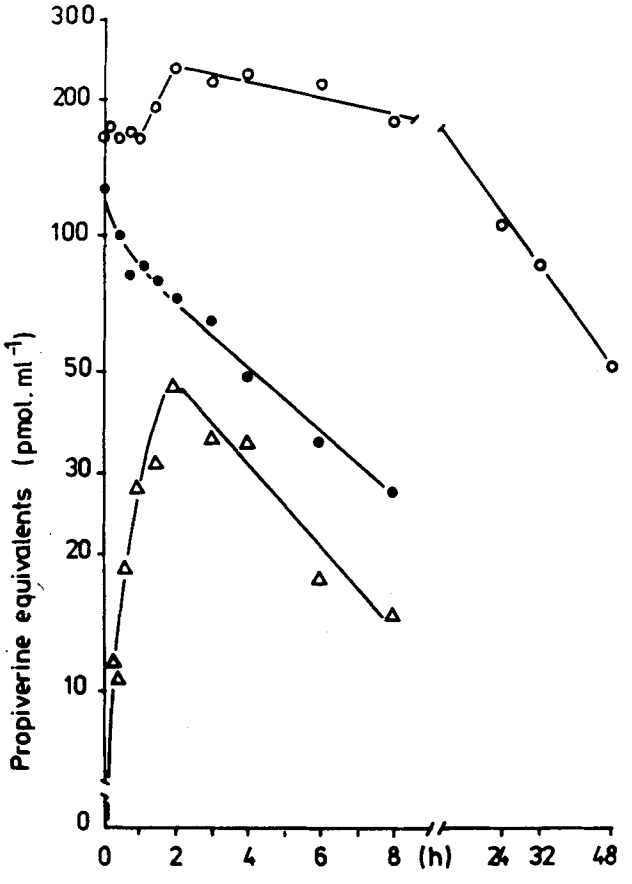


Fig. 1: Time course of the mean propiverine plasma level (●——●), of the propiverine equivalents (propiverine plus metabolites; o – o), and of the amine oxides of propiverine (Δ – Δ) after i.v. injection of 5 mg ^{14}C-propiverine (1.11 MBq) in 5 healthy volunteers.

Table II: Mean plasma level of propiverine (^{14}C-P) after i.v. injection of 5 mg (n = 5) or after oral administration of 15 mg (n = 6) in healthy subjects.

Time (min)	Propiverine equivalents Plasma Level (pmol/ml)		Propiverine Plasma Level (pmol/ml)	
	i.v.	p.o.	i.v.	p.o.
5	152	—	125	—
15	162	455	98	35
30	152	986	90	101
45	157	1,038	82	120
60	149	1,251	85	139
90	177	1,302	79	153
170	209	1,049	71	144
180	199	978	65	114
240	207	856	49	90
360	194	621	35	60
480	159	553	27	44
1440	95	161	—	—
1920	77	114	—	—
2880	47	57	—	—

dose were excreted within 4 days. From these data a mean total body clearance of 399 ml.min^{-1} and a renal clearance of 296 ml.min^{-1} were calculated. The mean concentration of radioactivity in urine exceeded that of plasma at every time of the study (cf. Tables II and IV).

After intake of 15 mg ^{14}C-propiverine in 6 subjects, the plasma radioactivity appeared already 15 min post-dose and it increased to its maximum within 45 to 90 min (cf. Table II; Fig. 2). Propiverine was absorbed with a mean constant k_a of 0.35 h^{-1} and it was eliminated with a half-life of 4.0 h (SD

Table III: Mean pharmacokinetic parameters of ^{14}C-propiverine after single i.v. injection of 5 mg (n = 5) or after single oral administration of 15 mg (n = 6). Mean value (SD).

		i.v.		per os	
B	(nmol.ml^{-1})	99	(23)	210	(111)
ß	(h^{-1})	0.17	(0.03)	0.19	(0.07)
$t_{1/2}$	(h)	4.1	(0.7)	4.0	(1.4)
V_d	(l)	143.4	(32.4)	342.1	(122.2)
	(l.kg^{-1})	1.9	(0.2)	3.9	(2.3)
AUC^{∞}	(nmol.ml^{-1}.h)	575	(74)	1079	(253)
Cl_{tot}	(ml.min^{-1})	399	(47)	666	(178)
CUE[4]	(µmol – Equiv.)	10.2	(1.4)	21.9	(5.4)
Cl_{ren}	(ml.min^{-1})	296	(49)	363	(160)

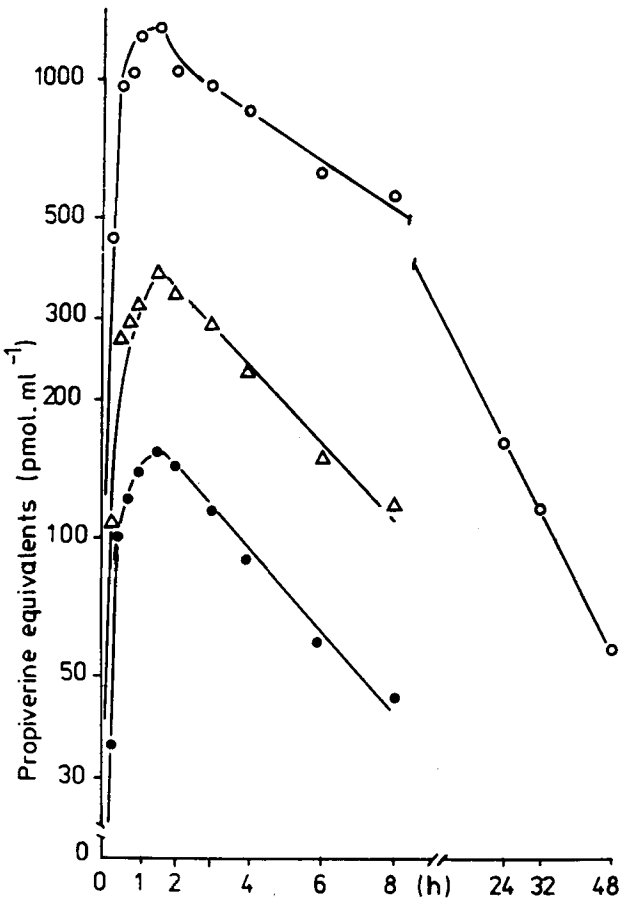


Fig. 2: Time course of the mean propiverine plasma level (o–o), of the propiverine equivalents (propiverine plus metabolites; o–o), and of the amine oxides of propiverine (Δ–Δ) after oral administration of 15 mg ^{14}C-propiverine (1.11 MBq) in 6 healthy volunteers.

1.4 h) at a mean total body clearance of 666 ml.min^{-1}. In the urine of the first fraction (0-1 h), 19 nmol-equivalents.ml^{-1} were excreted. In subsequent fractions, (8 to 24 h or 72 to 96 h) the concentration of radioactivity in urine exceeded that of the plasma level (cf. Tables II and IV). In total, 53.5% (SD 13.3%) of administered dose was excreted in urine within 4 days (Table IV). The mean renal clearance of propiverine was 363 (SD 160) ml.min^{-1}. If compared with the total clearance value, only 54.5% of the administered dose was excreted via kidneys. In 4 of 6 subjects propiverine was found in plasma 15 min. post-dose, in the other 2 subjects it occurred 45 or 60 min post-dose.

Bioavailability and Influence of Food Intake

By comparison of the AUC$^{\infty}$-values of the radioactivity or of those of propiverine after i.v. and p.o. administration a mean absorption of 84.4% was calculated. Comparison of the amounts of radioactivity excreted in urine (CUE^4-values) showed a bioavailability of 87.4%. Two subjects had a light breakfast 1 h before propiverine. Radioactivity appeared 45 min post-dose and the maximum was measured 3 h post-dose. Despite of a retarded absorption, the amount of absorbed propiverine was not affected by food intake as evaluated by the AUC-values. In the urine of both subjects 61.2% of the administered dose was excreted. Only in the first urine fraction minute amounts of radioactive compounds were found.

Table IV: Mean excretion of ^{14}C-propiverine in the urine after single i.v. injection of 5 mg (n = 5) or after oral administration of 15 mg (n = 6). Propiverine equivalents (nmol.ml^{-1} and per cent of administered dose)

Fraction (h)	i.v. Concentration (nmol/ml)	Excretion (%)	per os Concentration (nmol/ml)	Excretion (%)
0-1	19	1.4	11	1.7
1-4	40	4.7	24	6.7
4-8	40	5.5	16	7.3
8-24	32	20.2	9	13.6
24-48	24	22.0	5	11.9
48-72	12	12.6	2	8.2
72-96	8	8.1	2	4.2
Total	—	74.5	—	53.5
(SD)	—	(10.6)	—	(13.2)

Table V: Excretion of radioactivity in the urine and bile after single i.v. injection of 5 mg ^{14}C-propiverine in two cholecystectomized female patients (UR; UK). Propiverine equivalents per ml urine (nmol.ml^{-1} and per cent of administered dose)

Fraction (h)		UR Concentration (nmol/ml)	(%)	UK Concentration (nmol/ml)	(%)
Urine	0-1	1.41	0.43	1.22	0.22
	1-4	3.15	2.43	2.73	2.38
	4-8	3.25	2.38	2.82	3.31
	8-24	3.40	8.24	2.74	9.06
	24-48	2.73	13.02	2.22	12.96
	total	—	26.50	—	27.93
Bile	0-1	1.60	0.44	0.70	0.15
	1-4	2.02	2.50	1.74	0.76
	4-8	2.90	2.95	1.76	0.96
	8-24	3.51	7.67	2.54	5.91
	24-48	1.99	7.98	1.58	6.90
	total	—	21.54	—	14.68

Biliary Excretion of Propiverine

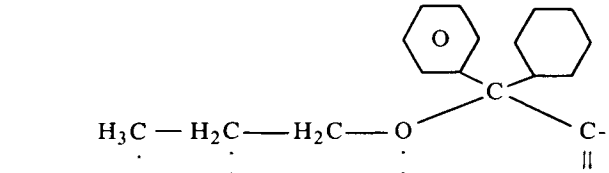
In two female patients after cholecystectomy with a cannulated ductus choledochus, 5 mg propiverine each were injected i.v. 10 to 12 days after surgical intervention. In parallel to the excretion in urine, radioactivity in the bile was measured in both patients. In one patient the urine content of radioactivity was two times higher than that of the bile fluid. Both patients excreted 48.0 or 42.6 per cent of the administered dose via urine and bile within 2 days (Table V). The pharmacokinetic parameters of absorption and elimination of either patient corresponded to those of healthy subjects, indicating that the elimination of propiverine in one cannulated patient was not reduced as compared with the elimination in healthy subjects.

Metabolism of Propiverine

The ratio of the levels of plasma radioactivity to plasma propiverine included a possible "first pass" effect and an extensive metabolism. If one compares the AUC^{∞}-values of the propiverine concentration with those of the plasma radioactivity, ratios of 0.082 in the case of i.v. injection, and of 0.069 in the case of oral administration were calculated. Both ratios indicate that less than 10% of plasma radioactivity remained in unchanged form. To study the metabolism, urine samples of various fractions (0-1, 1-4, 4-8 and 8-24 h) were used. Only 2 to 3 per cent of the radioactivity was excreted as propiverine. The main pathways of degradation were oxidation of one of the three C-atoms of the propyl moiety and oxidation of the cyclic N-atom (Table VI). Therefore, the tertiary amines M-18, M-22, and M-2, and their N-oxides M-25, M-23, and M-6 were formed. One of the main metabolites was formed by oxidation of the cyclic N-atom resulting in propiverine-N-oxide (M-5) which was extracted in urine at about 20 per cent. Oxidation of the terminal propyl-C-atom resulted not only in formation of a hydroxyl (M-18), but also in a carboxyl group (M-8). In the case of M-8, its N-oxide M-29 was found. The third pathway of propiverine degradation which was of lesser significance consisted of N-demethylation by which only 1 to 2 per cent of secondary amines such as M-14 (a demethylation product of propiverine), M-4 (of M-18), M-26 (of M-22) and M-15 (of M-2) were found. The secondary amine of M-8 was not observed.

The acidic metabolites M-10, M-25, M-7, M-9, and M-30 were seen as an additional group of substances formed by ester cleavage. It was not evident whether the ester was split off from the tertiary, secondary amino group or of the amine oxide. The acid M-7 was easily converted into the lactone M-1 which also degraded. Thus, the compounds M-7 and M-1 have to be seen as a unity. Besides the acids two additional metabolites were observed which could not be identified. Both sub-

Table VI: Metabolic pattern of propiverine in urine



Metabolic step	Metabolite	Mean Occurrence in Urine (%)
without	propiverine	2-3
NO	M-5*	≈ 20
ND	M-14*	≈ 1
EC	M-10*	< 1
G	M-10-gluc	< 10[a]
Oγ	M-18*	≈ 1
Oγ + NO	M-24	≈ 5
Oγ + ND	M-4*	< 1
Oγ + EC	M-25	≈ 1
Cγ	M-8	≈ 3
Cγ + NO	M-29	≈ 2
Oß	M-22	≈ 3
Oß + ND	M-26	< 1
Oß + EC	M-7*[b]	≈ 8[c]
EthC	M-2*	≈ 3
EthC + NO	M-6*	≈ 5
EthC + ND	M-15*	< 1
EthC + EC	M-9*	≈ 1

List of abbreviations: NO N-oxidation; ND N-demethylation; EC ester cleavage; Oγ γ-oxidation; Oß ß-oxidation; Cγ formation of the γ-carboxyl group; EC ester cleavage; EthC ether cleavage.

a) total amount of glucuronides ≈ 10%, b) formation of a lactone (M-1), c) formation of M-1 included
* reference substance

stances could not be degraded to the initial product benzilic acid (M-9). Furthermore, two conjugated products were isolated such as the glucuronides of M-10, or of a non-identified acid. Nothing points to hydroxylation of the phenyl moiety of propiverine. Only some metabolites isolated from urine were found in plasma by the TLC technique: Besides amines, the acids, and the amine oxides were isolated (cf. Table VI). The portion of propiverine-N-oxide in the group of amine oxides amounted to 88 or 91 per cent after oral intake or iv. injection. In contrast to propiverine, tertiary amines, and amine oxides, no acidic metabolites were found in the bile fluid.

General Effects

Both, i.v. injection or oral intake of propiverine was well tolerated by the volunteers and patients. Only 2 of 8 subjects reported a dry mouth for one to two hours after i.v. injection of the drug.

DISCUSSION

Propiverine can be characterized as a substance with a high absorption percentage undergoing a "first pass" effect. The rate of absorption was

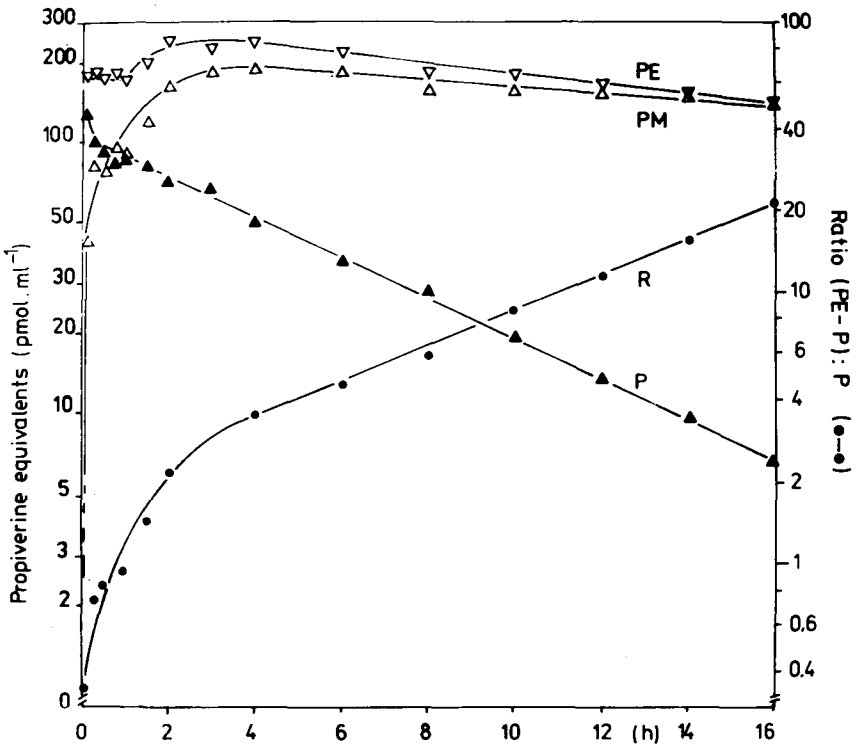


Fig. 3: Plasma level of propiverine (P), of the propiverine equivalents (PE) and of the metabolites (PM; PM = PE − P), and the ratio R between the metabolites (PM) and propiverine (P) after i.v. injection of 5 mg ^{14}C-propiverine (cf. the legend of Figure 1). The data between the 10th and 16th h were extrapolated. R follows the equation $y = 1.24 \times e^{0.19x}$ (x = time in h; r = 0.9742).

depressed by preceding food intake, while the extent of absorption was not influenced as shown by the AUC-values. Propiverine was accumulated temporarily in the liver and was excreted in bile. Furthermore, minute amounts of the unchanged drug were measured in plasma and urine, while about 92 per cent of the substances consisted of more than 15 metabolites as measured by radioactive methods.

It was evident that an initial decrease in plasma radioactivity did not occur, while two plateaus of the concentration were temporary measured. The radioactivity was eliminated by a mono-exponential process (cf. Fig. 1). The plasma concentration after i.v. injection of propiverine followed a bi-exponential function on the basis of an open two-compartment model. The plasma values of propiverine and of propiverine equivalents already differed significantly 5 min after injection indicating a rapid onset of hepatic biotransformation. The measured and extrapolated data of Figure 3 showed an immediate increase in metabolites (PM), and the ratio R (PM:R) increased exponentially. Thus, the observed plateau was considered the result of two exponential functions running in opposite directions to each other. Immediately after oral administration, propiverine was observed in plasma (Fig. 2); the predominant portion (93.1% of the administered dose as calculated by comparison of the corresponding AUC-value) appeared as metabolites. At a plasma protein binding rate of 66% (Mohr et al., 1976) the calculated volume of distribution (V_d = 143.4 l) appeared high. This high volume was mainly due to storage of propiverine in the liver and fatty tissue as evaluated in the rat. The high absorption of ^{14}C-propiverine (86%) was distinctly diminished by rapid hepatic degradation in the sense of a "first pass" effect. By comparison of the mean propiverine plasma level following both routes of administration, a bioavailability of only 48.9 per cent was calculated indicating a "first pass" of 35 to 40 per cent. The tertiary amino group of the piperidinole moiety, the propyl side-chain, and the ester grouping are metabolic points of attack. In the case of the three products hydroxylated in side-chain, the N-oxides, the N-demethylated amine and the corresponding acid occurred additionally. Thus, it was assumed that degradation was started by oxidation of the side-chain followed by oxidation of the amino

group. Ester cleavage may occur in all three products. It has not yet been clarified whether the side-chain is hydroxylated in the case of the propiverine-N-oxide (M-5), in the N-demethylated propiverine (M-14), or in the acid M-10. Thus, in the case of propiverine, metabolic pathways have been observed that were in accordance with those of substances which possess similar functional groups. It was surprising that a large portion of propiverine was N-oxidized while only a small portion was N-demethylated, N-demethylation being the main pathway of other drugs such as tertiary amines. Possibly, N-oxidation is favoured in N-atoms in ring position, while N-demethylation predominates in the case of aliphatic tertiary amines. In contrast to these parts of the drug, no metabolic degradation was observed in the phenyl moiety. Therefore, reactive intermediates such as epoxides with cancerogenic (e.g. benzene, benzpyrene) or hepatotoxic properties in the metabolic pathway are not probable.

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