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The Pharmacokinetics of Oxybutynin in Man

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Summary. We have studied the pharmacokinetics of oxybutynin (Ditropan) after single oral (5 mg) and intravenous administration (1 and 5 mg), and after repeated oral administration in healthy volunteers.

Oxybutynin was rapidly absorbed, maximum plasma concentrations ($8\ ng \cdot ml^{-1}$) being reached in less than 1 h. The absolute systemic availability averaged 6% and the tablet and solution forms displayed similar relative systemic availability.

Plasma concentrations of oxybutynin fell biexponentially, the elimination half-life being about 2 h. There was a large interindividual variation in oxybutynin plasma concentrations. Almost no intact drug could be recovered in the urine. During repeated oral administration steady-state was reached after eight days of treatment.

The low absolute systemic availability of oxybutynin, the large interindividual variability in its plasma concentrations, and the apparent absence of intact oxybutynin in the urine suggest that its major pathway of elimination is hepatic metabolism.

Key words: oxybutynin; pharmacokinetics, healthy volunteers, debrisoquine, genetic polymorphism

Oxybutynin (4-diethylaminobut-2-ynyl 2-cyclohexyl-2-phenyl glycolate, Ditropan) is an effective antispasmodic agent. It mainly acts as a direct smooth muscle relaxant [1] but also displays weak antimuscarinic activity [2] and is indicated for the relief of symptoms associated with both uninhibited and reflex neurogenic bladder [3].

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Although oxybutynin has been used in therapeutics for several years its pharmacokinetics in man have only been partially investigated. In one study the time-course of oxybutynin plasma concentrations was determined in an unspecified number of volunteers after an oral dose of 5 mg, and the pharmacokinetic characteristics of the drug were not calculated [4]. In another study [5] the pharmacokinetics of oxybutynin were investigated in 5 female volunteers after a single oral dose of 10 mg oxybutynin as a tablet and in solution, and after a single intravenous injection ($2.8\ \mu g \cdot kg^{-1}$). Plasma concentrations of oxybutynin were measured by a rather insensitive gas liquid chromatographic method, but the antimuscarinic activity of the parent compound and its active metabolites were assayed by a radioreceptor assay. Following intravenous administration the values of C_{max} measured by both methods were equivalent, while after oral administration the C_{max} was about 20 times higher by radioreceptor assay than by chromatography, suggesting that after oral administration oxybutynin was subject to extensive first-pass elimination.

In the present study we have further evaluated the pharmacokinetics of oxybutynin in healthy volunteers after single intravenous and oral doses and after repeated oral administration using a highly sensitive high performance liquid chromatographic method with electrochemical detection.

Materials and Methods

All the volunteers gave their written informed consent and the protocol was cleared by the ethics committee of the hospital.

Study Design

The study was divided into two parts (A and B), involving 8 and 12 healthy volunteers respectively. Two volunteers participated in both parts, so that the total number of different subjects who received 5 mg oxybutynin as a tablet was 18.

Part A: Single Oral and i.v. Administration and Multiple Dose Study. All 8 volunteers received oxybutynin orally in the form of a 5 mg tablet, and one week later intravenously either as a rapid injection of 1 mg (4 subjects) or as a slow infusion of 5 mg over 10 min (2 subjects) or 20 min (2 subjects). The order of the administration of the two drug forms was randomized, the drug being given in the morning after an overnight fast with 100 ml of water, even when the drug was given intravenously. A standardized light meal was served 8 h later. Blood was sampled at various times after drug intake up to 24 h and urine was collected during the same period of time for the determination of oxybutynin in plasma and urine respectively.

One week after the completion of the two single administrations the volunteers took oxybutynin (5 mg tablets three times daily at 5 h intervals) for one week. Blood was sampled for pharmacokinetic assessment on Days 1 and 8 of the treatment. On the assessment days standardized light meals were served 2 h after each drug administration.

Part B: Comparative Systemic Availability of the Oral Tablet and Solution Forms. All 12 volunteers took 5 mg oxybutynin both as a tablet and one week later as a 5 mg solution. The tablet form was always given first. As in Part A the drug was given in the morning after an overnight fast with 100 ml of water. Standardized light meals were served 1 and 4 h after administration. Blood was sampled at various times for up to 8 h and the urine was collected for the same period of time. In both parts of the study blood was collected from an indwelling cannula placed in the forearm into plastic tubes containing heparin. The blood sample was immediately centrifuged at $1500 \times g$ for 10 min and the plasma was separated and stored at $-20\,^{\circ}C$ until assayed. After collection the urine was immediately stored at $-20\,^{\circ}C$. During each session the volunteers remained semi-recumbent except for voiding. Heart rate, respiratory rate, and a one-lead ECG were continuously monitored. Blood pressure was measured at 30 min intervals.

Subjects

There were 10 male and 8 female volunteers aged 19–38 years (mean 33 years). Their body weights did not deviate by more than 20% from ideal [6]. None had received any medication for at least 3 months before the start of the study. None was addicted to alcohol or was a smoker and none was taking oral contraceptives. Before they entered the study the volunteers were submitted to a thorough medical examination, including history, clinical examination, 12-lead ECG, chest *X*-ray, blood chemistry, full blood count, and urinalysis.

Assay of Oxybutynin

A reverse-phase HPLC assay of oxybutynin with coulometric detection was developed based on the method of Lindeke et al. [4]. The internal standard was pipoxazine. Plasma (2 ml) was added to a Teflon-lined screw-cap test tube containing 0.2 ml of

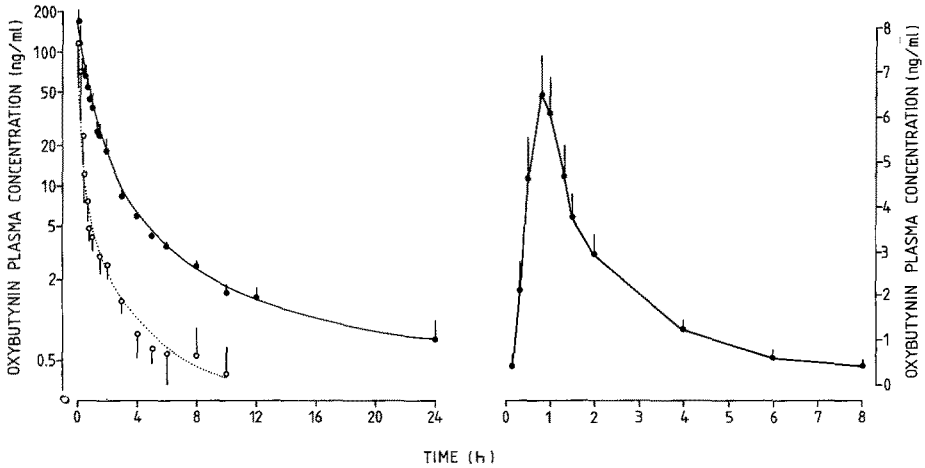

Fig. 1. Plasma profiles of oxybutynin against time after single i.v. administration of 1 and 5 mg in 8 healthy volunteers *(Part A, left panel)* and after single oral administration of a 5 mg tablet dose in 18 volunteers *(part A + Part B, right panel)*. The intravenous dose was given either as a rapid injection of 1 mg (○----○, 4 subjects) or as a slow infusion of 5 mg (●——●) over 10 min (2 subjects) or 20 min (2 subjects). Mean (SEM) plasma concentrations are expressed in $ng \cdot ml^{-1}$

1M Tris buffer (pH 9.4) and 4 ml of hexane. The mixture was extracted on a test-tube rotator (15 min) and then centrifuged at $1500 \times g$ for 10 min. The organic phase was transferred to a second glass tube and the extraction was repeated. The two extracts were combined and evaporated under reduced pressure at a temperature of 50 °C in a vortex evaporator. The residue was taken up in 0.4 ml of fresh mobile phase and 250 µl were injected into the chromatograph. Assay of plasma samples spiked with oxybutynin hydrochloride gave a mean recovery of 94%.

The chromatograph was a Varian 5060 model equipped with a column thermostatting unit and coupled to a Coulochem 5100-A electro-chemical detector equipped with a dual porous graphite electrode. A model 5020 guard cell was placed between the pump and the injector to oxidize the mobile phase and reduce background noise. The potential of the guard cell was set at +0.95 V (relative to a palladium reference electrode). The potential of the two electrodes of the detector were set at +0.70 V and +0.90 V respectively, with a time constant of 10 s. Detector attenuation was set at 10×80.

The column was pre-packed with R-Sil cyanopropyl silica (5 µm irregular particles; Alltech-Europe). The mobile phase was a 0.02 M sodium phosphate buffer, pH 6.9. Oxybutynin and the internal standard were eluted from the column within 10 min.

Calibration of the assay was performed using peak height ratio. The calibration range extended from 0.2 to 13 $ng \cdot ml^{-1}$. The minimum detectable concentration of oxybutynin hydrochloride was 0.1 ng using a 2.0 ml plasma sample. The inter-assay coefficient of variation was 3.8%

Pharmacogenetic Study and Assay of Debrisoquine and OH-Debrisoquine

In an attempt to evaluate the existence of a genetic polymorphism in oxybutynin oxidation, the AUC for oxybutynin and the metabolic ratio of debrisoquine were compared in 12 of the 18 volunteers who were previously phenotyped for debrisoquine oxidation according to Mahgoub et al. [7].

Debrisoquine and OH-debrisoquine in urine were assayed as described elsewhere [8].

Pharmacokinetic Calculations

The plasma concentrations of oxybutynin were fitted to 1 or 2 exponentials, with an absorption phase for the oral route and without an absorption phase for the i.v. route. The method of Loo and Riegelman [9] was used for the assessment of the pharmacokinetic constants after i.v. infusion.

The coefficients generated by the bi-exponential analysis were used instead of those of the mono-exponential analysis when fitting was estimated to be better (by visual inspection and by comparing the coefficients of determination of the fits obtained).

Statistical Evaluation

All data are presented as mean (SEM). Differences between mean data were assessed using two-way analysis of variance or Wilcoxon's test. The systemic equivalence of the two formulations was assessed by using the method of the symmetrical confidence interval of Westlake [10].

Results

Pharmacokinetics

Single Oral and i.v. Administration. The plasma concentration-time profiles (mean with SEM) of oxybutynin after single i.v. administration in 8 healthy volunteers (Part A) and after single oral administration in 18 volunteers (Part A + Part B) are illustrated in Fig. 1. The corresponding pharmacokinetic characteristics are given in Tables 1 and 2.

Oral Absorption and Systemic Availability. Oxybutynin was rapidly absorbed from the gastrointestinal

Table 1. Pharmacokinetics of oxybutynin after i.v. administration

Dose[a] (mg)	n	$t_{1/2}$ (h)	AUC (0-6) or AUC (0-24)[b] ($ng \cdot ml^{-1} \cdot h$)	V_Z (l)	CL ($l \cdot h^{-1}$)
1	4	1.86 (0.35)	40 (15)	89.2 (25.4)	34.1 (9.6)
5	4	5.31 (1.41)	200 (40)	192.9 (96.4)	25.7 (3.8)

[a] The dose of 1 mg was given as a bolus, the dose of 5 mg as a slow infusion over 10 or 20 min; [b] AUC was calculated over 6 h after 1 mg and over 24 h after 5 mg

Table 2. Pharmacokinetics of oxybutynin after oral administration (5 mg tablet; $n = 18$)

C_{max} ($ng \cdot ml^{-1}$)	t_{max} (h)	$t_{1/2\lambda_i}$ (h)	$t_{1/2\lambda_z}$ (h)	AUC (0-6) or AUC (0-8) ($ng \cdot ml^{-1} \cdot h$)
8.2 (1.0)	0.8 (0.06)	0.14 (0.02)	2.44 (0.38)	16 (2)

tract, the time to peak plasma concentrations ranging from 0.5 to 1.4 h. The mean half-time of absorption was 0.14 (0.02) h and the maximal plasma concentration averaged 8.2 (1.0) $ng \cdot ml^{-1}$. There was a large interindividual variation in oxybutynin plasma concentrations, as assessed by a 8 fold variation in C_{max} and a 13-fold variation in AUC. The absolute systemic availability, calculated in the 8 volunteers who received both the i.v. and the oral form of oxybutynin, was 6.2 (1.2)%

Distribution. Regardless of the route of administration oxybutynin plasma concentrations fell bi-exponentially except in two cases. The apparent volume of distribution of oxybutynin averaged 89 (25) l and 193 (96) l after the i.v. administration of 1 and 5 mg oxybutynin respectively.

Elimination. Oxybutynin was rapidly eliminated from the body, whether given orally or by rapid i.v. injection. The mean elimination half-life was about 2 h, with a wide intersubject variation (8-fold). The mean elimination half-life of oxybutynin was longer after 5 mg i.v. (5.31 (1.41) h) than after 1 mg i.v. (1.86 (0.35) h, $p<0.05$). Such a difference may only be apparent since the elimination half-life of oxybutynin after 5 mg i.v. was not significantly different from that observed after oral administration of the same dose in the same four volunteers ($p>0.4$). After rapid i.v. injection total body clearance averaged 30 (6) $l \cdot h^{-1}$ and ranged from 10 to 64 $l \cdot h^{-1}$. After i.v. infusion total body clearance was slightly but not significantly lower than after i.v. bolus injection ($p>0.4$). The fraction of unchanged oxybutynin in the urine was very small in the one subject in whom it was measured (0.017% of the dose in 12 h).

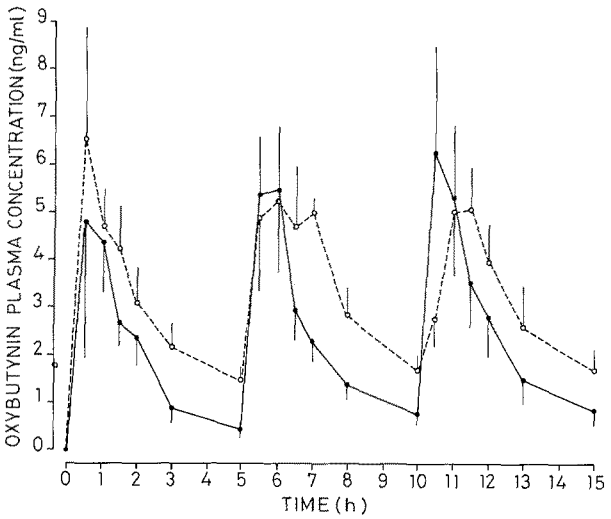

Fig. 2. Plasma concentration profiles of oxybutynin against time on the first (●—●) and eight (○----○) days of treatment with oxybutynin 5 mg t.i.d. in 8 healthy volunteers. Oxybutynin was given at times 0,5 h, and 10 h. Same presentation as in Fig. 1

Repeated Oral Administration

Figure 2 illustrates the plasma concentration time profile of oxybutynin given three times at 5 h intervals on Days 1 and 8. The corresponding values of C_{max} and AUC are given in Table 3. There was no significant difference between mean C_{max} values recorded on days 1 and 8 during the three successive periods of 5 h (0–5 h, 5–10 h, and 10–15 h). Likewise, mean C_{max} values recorded after the first, second, and third administrations of oxybutynin were not significantly different from one another on both Days 1 and 8. Mean AUC values recorded on Day 8 were higher than that recorded on Day 1 during the first (0–5 h; $p<0.025$), the second (5–10 h, $p<0.05$), and total (0–15 h, $p<0.05$) dosing intervals, but not during the third period of plasma sample collection (10–15 h, $p>0.1$). During the first day of treatment, but not the eighth, there was a progressive increase in mean AUC values ($F:3.73$, df 1/14, $p<0.05$)

Comparative Systemic Availability of the Oral Tablet and Solution Forms

Plasma concentration-time profiles of oxybutynin after a single 5 mg dose, either as a tablet or as a solution, are shown in Fig. 3. There was no significant difference between the two forms with regard to elimination half-life ($p>0.25$), the t_{max} ($p>0.05$), the absorption half-time ($p>0.10$), the C_{max} ($p>0.25$), and the AUC ($p>0.25$). The method of

Table 3. C_{max} and AUC (0–5) after the administration of oxybutynin (5 mg t.i.d.) for 1 week

Period (h)	C_{max} ($ng \cdot ml^{-1}$) Day 1	Day 8	AUC ($ng \cdot ml^{-1} \cdot h$) Day 1	Day 8	n
0– 5	6.73 (2.68)	7.59 (2.27)	9.24 (2.54)	14.82 (3.28)	8
5–10	5.74 (1.26)	7.12 (1.81)	11.71 (2.28)	16.58 (3.29)	8
10–15	7.55 (2.22)	5.97 (1.22)	13.00 (3.41)	15.85 (2.93)	8
0–15	-	-	33.70 (7.89)	47.30 (9.15)	8

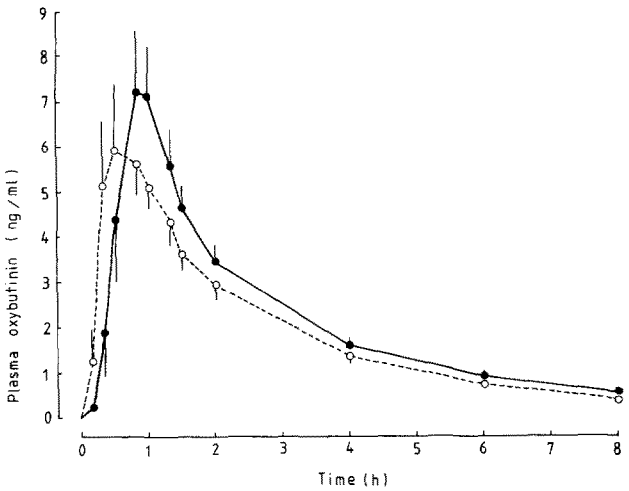

Fig. 3. Plasma concentration profiles of oxybutynin against time after the oral administration of a 5-mg tablet dose (●—●) and a 5-mg solution dose (O----O) in twelve healthy volunteers. Oxybutynin was given at time 0. Same presentation as in Fig. 1

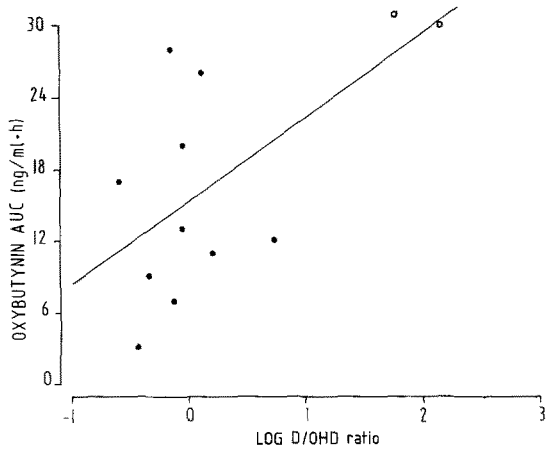

Fig. 4. The relationship between the logarithm of the urinary debrisoquine 4-hydroxy-debrisoquine ratio (D/OHD) and oxybutynin AUC (0-8) in 12 volunteers (●: extensive metabolizers; O: poor metabolizers)

the symmetrical confidence interval of Westlake [10] applied to the AUC of the two formulations showed that they were equivalent, and did not differ from one another by more than 17%, with a probability of 95%

*Oxybutynin Systemic Availability and Debrisoquine Hydroxylation.*The relationship between the systemic availability of oxybutynin (AUC 0→8) and debrisoquine hydroxylation (as expressed by the metabolic ratio of debrisoquine) in 12 volunteers is illustrated in Fig. 4.

Clinical Tolerance. Whether given orally (5 mg) or as an i.v. bolus injection (1 mg) oxybutynin was well tolerated. Only mild adverse effects were observed, mostly consisting of headache, drowsiness, or fatigue. However, when the drug was given in a higher dose (5 mg) by the i.v. route (slow infusion over 10 min) serious adverse effects were observed. Thus, one volunteer experienced generalized malaise with pronounced drowsiness and an inability to speak for 10 min. Full recovery occurred within 15 min. A second subject had a syncopal attack with a dry mouth lasting 10 min and had diarrhoea 3 h after administration. When the same dose (5 mg) was infused over 20 min no adverse effect was observed in one volunteer while marked sleepiness lasting 30 min was reported by the second.

Discussion

The aim of the present study was to further examine the pharmacokinetics of oxybutynin given orally and intravenously in young healthy volunteers.

In agreement with previous suggestions [5] oxybutynin was rapidly absorbed by the oral route, the mean t_{max} values observed in the present study being almost superimposable on the median t_{max} values measured previously [5] by radioreceptor assay after the oral administration of 10 mg. Despite rapid absorption, with maximum plasma concentrations of about 8 ng, the absolute systemic availability was low, ranging from 1.6 to 10.9%

After reaching a peak the oxybutynin plasma concentration fell rapidly, in most cases bi-exponentially. The elimination half-life was about 2 h after oral (5 mg) and bolus i.v. (1 mg) administration, slightly shorter than the antimuscarinic half-life of oxybutynin and its active metabolites (3.25 h) [5]. When the drug was given in a higher dose (5 mg) by the i.v. route its elimination half-life was probably longer than 2 h. This increase, if it exists, more probably resulted from a dose-related increase in the apparent volume of distribution than from a decrease in systemic clearance. Thus, when the intravenous dose of oxybutynin was raised from 1 to 5 mg, the volume of distribution was more than doubled while the systemic clearance was not significantly reduced. In agreement with the short half-life, there was a slight tendency towards accumulation on the first day of treatment. Such a phenomenon was no longer observed after eight days of repeated administration.

In a previous study only negligible amounts of intact oxybutynin were recovered in the urine [4]. In the present study the urinary excretion of intact oxybutynin measured in one volunteer was found to be less than 0.02% of the administered dose. This

observation is in agreement with the suggestion that after oral administration to man oxybutynin is subject to first-pass metabolism [5]. In agreement with this is the low absolute systemic availability and the large interindividual variation in plasma concentrations (see below). Oxybutynin has also been shown to be rapidly metabolized by rat liver microsomes to oxidation products, mainly N-desethyl oxybutynin and oxybutynin N-oxide [11].

In the present study there was a 13-fold interindividual variation in the AUC achieved after administration of the tablet. On the other hand, there was a good correlation between AUC and C_{max} between both oral formulations ($r=0.88$ and 0.86 respectively, $p<0.001$). This suggests that the pattern of oxybutynin elimination in each volunteer was stable with time. If hepatic oxidation represents a major pathway of oxybutynin elimination, as it does in laboratory animals, interindividual variability in oxybutynin plasma concentrations could result from genetic polymorphism in oxybutynin oxidation, similar to that described for debrisoquine [7], mephenytoin [12], carboxymethylcysteine [13], and tollbutamide [14].

The relationship between the the AUC of oxybutynin and the metabolic ratio of debrisoquine (Fig. 4) in 12 of the volunteers suggests that there may be an association between debrisoquine oxidation phenotype and the ability to metabolize oxybutynin.

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