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# Yohimbine bioavailability in humans*

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**Summary.** Pharmacokinetic profiles were determined in seven healthy young male subjects following single oral and intravenous doses of 10 mg of yohimbine hydrochloride.

The drug was rapidly eliminated ($t_{1/2\beta}$ 0.58 h orally and $t_{1/2\beta}$ 0.68 h intravenously). Following intravenous administration the data fit a two-compartment pharmacokinetic model, with a very rapid distribution phase ($t_{1/2a}$ was approximately 6 min). Both the oral and the intravenous yohimbine clearance values were high but oral clearance values were much higher (mean 9.77 $ml \cdot min^{-1} \cdot kg^{-1}$ intravenous versus 55.9 $ml \cdot min^{-1} \cdot kg^{-1}$ oral). The oral bioavailability showed great variability, ranging from 7% to 87% (mean value was 33%).

The imcomplete oral bioavailability of yohimbine may reflect either incomplete absorption from the gastrointestinal tract or an hepatic first pass effect. Although yohimbine is rapidly absorbed when given orally, the bioavailability is quite variable and considerable individualization of dosing may be necessary when the drug is used orally for clinical indications.

**Key words:** yohimbine; pharmacokinetics, bioavailability

Yohimbine is an indole alkaloid of botanical origin that has alpha$_2$ adrenoceptor blocking activity and has been extensively used for many years in folk medicine. Recently it has also been increasingly used by the medical establishment, most commonly in the treatment of male impotence, an indication where it appears to show some promise [1, 2]. Additionally, it has some efficacy in the treatment of orthostatic hypotension, both idiosyncratic and drug-induced [3, 4].

Yohimbine exhibits an interesting variety of pharmacologic and psychologic effects. Its alpha$_2$ adrenoceptor blocking action results in an interruption of the norepinephrine (NE) feedback inhibition loop resulting in a decrease in the release of NE when autoreceptors are stimulated [5, 6]. Consequently yohimbine administration may result in increases in blood pressure and heart rate as well as anxiety. The degree and type of response to yohimbine may be related to specific pathophysiology. Increments in blood pressure following yohimbine are more pronounced in patients with essential hypertension than in controls [7]. Additionally, in persons who suffer from panic disorder, or major depression with panic attacks, administration of yohimbine often results in the onset of a panic attack which is indistinguishable from a normally occurring panic attack [8, 9].

Although the physiological and psychological effects of yohimbine have been studied, little pharmacokinetic research has been conducted. Owen et al. [10] have conducted a detailed investigation of yohimbine pharmacokinetics in humans but they were not able to assess oral bioavailability due to the unavailability of an intravenous form of the drug. Oral bioavailability is an important consideration since yohimbine is most often administered orally. To determine the oral bioavailability of yohimbine we have administered a single dose of both oral and intravenous yohimbine to seven healthy male volunteers.

## Materials, methods, and subjects studied

Seven males, aged 21 to 36 y (mean 28.0 (6.7) y), were recruited by public announcement. All volunteers gave informed consent to participate. Subjects underwent a complete physical examination including blood and urine analyses, as well as an EKG. None of the subjects had any history of hypertension or other cardiovascular disease. No abnormalities were found on laboratory or EKG prescreening. None of the subjects were receiving medication and all abstained from any alcoholic beverage for 72 h prior to the study.

On the evening prior to each of the two study sessions the volunteers were admitted to the Clinical Research Center at the University of Michigan Hospitals. They fasted from the midnight preceding the procedure until three hours following the administration of yohimbine. Ten mg of yohimbine hydrochloride solution (9.07 mg free base) was administered either intravenously or orally during each of the two studies. The order in which the subject received the oral and intravenous doses was randomized and the two study sessions were separated by at least 1 week. Five ml of blood was drawn at baseline (pre-dose), and at 5, 10, 20, 45, 90, 120, 150, 180, and

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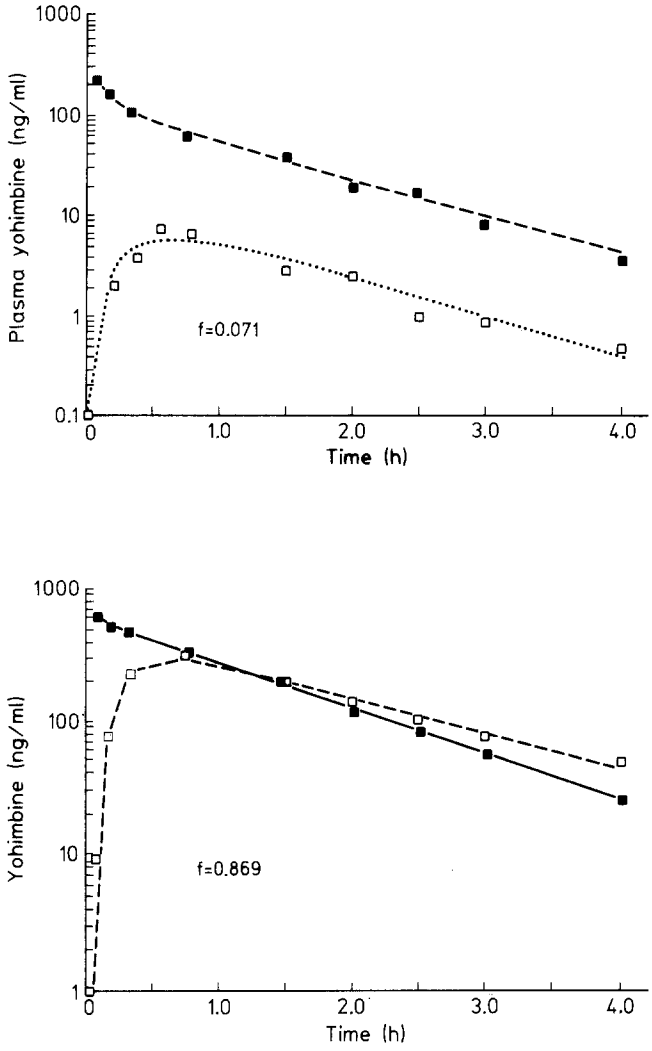


**Fig. 1.** Time versus plasma concentration curves for two subjects following both oral (□) and intravenous (■) doses of yohimbine. f = fraction of dose bioavailable when taken orally

240 min following the oral or intravenous yohimbine dose. All blood samples were centrifuged and plasma was separated and stored at −20°C until assayed. Blood pressure and heart rate were recorded in the lying position, at each blood draw time point using Air Shields (Healthdyne Co., Hatboro, PA) sphygmomanometers, which provided printed output.

Yohimbine plasma concentrations were determined using a newly developed high performance liquid chromatography coulometric electrochemical detector (Model 5100A, Environmental Assoc, Bedford, MA) method [11]. The analytical cell (Model 5010) of the detector was set at a voltage of 0.8. A 5 μm, C-8 "DB" column (25 X 0.46 cm, Supelco, Bellefonte, PA) was used. The mobile phase consisted of water and acetonitrile 65:35 (V/V) containing 1.8 g of tetraethylammonium perchlorate per liter of solution, and the flow rate was 2.0 ml · min$^{-1}$. Reserpiline was used as the internal standard. Both yohimbine and the internal standard were extracted from 1 ml of alkalinized plasma using n-butylchloride and purified by back extraction in perchloric acid. The sensitivity of the assay was 100 pg using 1 ml of plasma. The mean interassay coefficient of variation was 6%, recovery was 94% and the assay is linear from 0 to 1000 ng · ml.

The NONLIN computer program was utilized to determine the rate constants; α, β, and $k_a$, as well as the volume of distribution ($V_c$), and the constants, A and B [12]. The area under the plasma concentration versus time curve (AUC) was calculated using the trapezoidal method, the terminal portion of the area was determined using $C_n/\beta$ [13]. Both oral ($CL_{po}$) and intravenous clearances ($CL_{iv}$) were calculated using dose/AUC. Bioavailability (f) was determined by comparing the $AUC_{po}/AUC_{iv}$. Statistical analysis was performed using on an Apple Macintosh personal computer using the Statview statistical program [13].

## Results

Both the oral and intravenous data revealed a large amount of interindividual variability in yohimbine pharmacokinetic parameters (see Table 1). Fig. 1 shows representative pharmacokinetic profiles for two subjects.

Data resulting from the intravenous yohimbine dose was fit to a two-compartment open model in all seven subjects. The $\alpha_{iv}$ was high (mean 7.38 (5.91) h$^{-1}$), signifying a very rapid distribution $t_{1/2\alpha}$ of approximately 6 min. The elimination $t_{1/2\beta}$ was also very rapid, 0.68 h (mean $\beta_{iv}$, 1.02 (0.29) h$^{-1}$). The volume of distribution ($V_c$) was rather small (mean 0.26 (0.12) l · kg$^{-1}$) and the $CL_{iv}$ ranged from 2.44 to 15.8 ml · min$^{-1}$ · kg$^{-1}$ (mean 9.77 (4.46) ml · min$^{-1}$ · kg$^{-1}$).

Data resulting from the oral yohimbine dose was fit to either a one- (3 subjects) or two-compartment (4 subjects) pharmacokinetic model with a first order absorption rate constant ($k_a$). The $k_a$ varied from 5.0 to 14.3 h$^{-1}$ (mean 6.22 (4.71) h$^{-1}$), resulting in a mean absorption $t_{1/2}$ of approximately 7 min. The peak plasma concentration usually occurred within 10 to 45 min following administration. In the three subjects in which $\alpha_{po}$ could be determined, the mean was 8.87 h$^{-1}$ (ranging from 1.34 to 16.1 h$^{-1}$); these values were similar to those following the intravenous dose suggesting an extremely rapid distribution of the drug. The mean oral $t_{1/2\beta}$ was 0.58 h (mean $\beta_{po}$

**Table 1.** Intravenous and oral yohimbine pharmacokinetic values

| | Oral | | | Intravenous | | | |
|---|---|---|---|---|---|---|---|
| Subject | AUC | CL (ml · min$^{-1}$ · kg$^{-1}$) | $V_z$ (l · kg$^{-1}$) | AUC | CL (ml · min$^{-1}$ · kg$^{-1}$) | $V_c$ (l · kg$^{-1}$) | f |
| 1 | 10.7 | 200 | 10.6 | 150 | 14.2 | 0.39 | 0.071 |
| 2 | 656 | 2.82 | 0.27 | 755 | 2.44 | 0.11 | 0.869 |
| 3 | 45.1 | 42.2 | 4.32 | 121 | 15.8 | 0.31 | 0.374 |
| 4 | 54.3 | 32.4 | 0.51 | 206 | 8.53 | 0.19 | 0.263 |
| 5 | 56.7 | 37.8 | 1.43 | 202 | 10.6 | 0.23 | 0.280 |
| 6 | 52.9 | 38.1 | 3.56 | 203 | 9.93 | 0.18 | 0.261 |
| 7 | 61.8 | 37.1 | 1.89 | 331 | 6.93 | 0.43 | 0.187 |
| Mean | 134 | 55.9 | 3.22 | 281 | 9.77 | 0.26 | 0.33 |
| (SD) | (231) | (65.1) | (3.57) | (219) | (4.46) | (0.12) | (0.26) |

of 1.19 (0.42) $h^{-1}$). The $CL_{po}$ ranged from 2.81 to 200 $ml \cdot min^{-1} \cdot kg^{-1}$ (mean 55.9 $ml \cdot min^{-1} \cdot kg^{-1}$) and $V_c$ was 3.22 (3.57) $l \cdot kg^{-1}$.

The $AUC_{iv}$ ranged from 121 to 755 $ng \cdot ml^{-1} \cdot h$ (mean 281 (219) $ng \cdot ml^{-1} \cdot h$). The $AUC_{po}$ showed even greater variability, ranging from 10.7 to 657 $ng \cdot ml^{-1} \cdot h$ (mean 134 (231)). The f ranged from 0.07 to 0.87 (mean f was 0.33 (0.26)), which suggests that the average oral bioavailability of yohimbine is only about 30% of the dose administered.

Although blood pressure and heart rate both increased following yohimbine, the increment of increase was variable. None of the incremental increases were correlated with yohimbine plasma concentration, except the systolic blood pressure which correlated weakly ($r = 0.35$, $P < 0.005$) with yohimbine plasma concentration following intravenous dosing.

## Discussion and conclusions

The results of this study indicate that the oral bioavailability of yohimbine is highly variable. Although it averages approximately 30% it may vary from less than 10% to almost 90%. This may be significant since yohimbine is generally administered orally. It is possible that in some cases its lack of efficacy in the treatment of impotence or its inability to initiate a panic attack in a patient with panic disorder may be due to limited oral bioavailability.

Clearance, like bioavailability, showed a great amount of interpatient variability. One subject exhibited both an extremely slow clearance of the drug and the greatest bioavailability (89%). Unfortunately, the metabolic steps involved in the biotransformation of yohimbine in humans are currently unknown. Owen et al. [10] have shown that only a small proportion of yohimbine is eliminated unchanged in the urine, therefore the majority of the drug is probably biotransformed. Clearance values following intravenous administration are generally high and compatible with liver blood flow in many cases. This suggests that its decreased bioavailability is due to drug extraction in the liver, although decreased intestinal absorption cannot be excluded at this point.

Many of our findings are in agreement with those previously reported [10]. The $V_{z_{iv}}$ is smaller than expected for a drug that is highly lipophilic. Several of our subjects reported symptoms that were consistent with central nervous system effects, usually within about 30 min of drug administration, which would indicate that the drug quickly crosses the blood brain barrier.

Changes in diastolic blood pressure and heart rate following yohimbine did not correlate directly with plasma concentrations, although changes in general were larger following intravenous doses. Systolic blood pressure did correlate weakly with plasma yohimbine concentration following intravenous injection. Yohimbine-evoked pressor response is probably only slightly correlated with plasma yohimbine concentration because of the confounding effect of the specific adrenomedullary activity of the individual patient. The results of two yohimbine challenge studies suggest that there are subgroups of individuals that respond more robustly to a yohimbine infusion than the general population [7, 8]. Alternatively, it is possible that yohimbine has a pharmacologically active metabolite that interferes with the parent drug's pharmacodynamic activity and results in differing responses that are correlated with the concentrations of both the parent drug and the metabolite.

The results of this study indicate that the oral bioavailability of yohimbine is quite variable and it can be expected that considerable individualization of dosing may be necessary when the drug is used orally for clinical indications. Also, when yohimbine is utilized as an $\alpha_2$ adrenoceptor probe or a drug challenge, it would be preferable to administer it intravenously, since oral bioavailability is not reliable.

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