Effect of modafinil on the pharmacokinetics **of** ethinyl estradiol **and triazolam in** healthy volunteers.

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BACKGROUND: Modafinil has been reported to produce a concentration-related induction **of** CYP3A4/5 activity **in** vitro **in** primary cultures **of human** hepatocytes. OBJECTIVE: Our objective was to determine whether the pharmacokinetics **of** steady-state ethinyl estradiol (INN, ethinylestradiol) **and single**-**dose triazolam** were altered after 4 weeks **of** modafinil treatment **in** volunteers. METHODS: This was a placebo-controlled, **single**-blind, **single**-period study **in** 41 female **subjects** who were receiving long-term treatment with an oral contraceptive that contained ethinyl estradiol (0.035 mg) **and** norgestimate (0.180-0.250 mg). Pharmacokinetic profiles for ethinyl estradiol **and** for a **single** oral **dose of triazolam** (0.125 mg) were obtained the **day** before initiation **of** treatment with modafinil (200 mg for 7 days, followed by 400 mg for 21 days) or placebo (28 days). A second **dose of triazolam** was administered with the final **dose of** modafinil, **and** pharmacokinetic profiling was repeated. RESULTS: The modafinil treatment group had a marked decrease **in** maximum observed plasma concentrations **and** areas under the plasma concentration-time curve for **triazolam** relative to placebo, with a much smaller decrease **in** these parameters for ethinyl estradiol. The half-**life of triazolam** was also decreased, but the half-**life of** ethinyl estradiol did not appear to be affected by treatment with modafinil. CONCLUSION: Modafinil induced CYP3A4/5 activity **in humans in** vivo, suggesting that there is potential for metabolic drug-drug interactions between modafinil **and** substrates **of** CYP3A4/5. However, the induction appeared to be more gastrointestinal than hepatic **in** nature. Therefore significant metabolic drug-drug interactions are most likely to occur with compounds (such as **triazolam**) that undergo significant gastrointestinal CYP3A4/5-mediated first-pass metabolism.

Major Subject Heading(s)	Minor Subject Heading(s)	CAS Registry / EC Numbers
• Benzhydryl Compounds [pharmacology] • Central Nervous System Stimulants [pharmacology] • Estrogens, Synthetic [pharmacokinetics] • Ethinyl Estradiol [pharmacokinetics] • Sedatives, Nonbarbiturate [pharmacokinetics] • **Triazolam** [pharmacokinetics]	• Adult • Area Under Curve • Benzhydryl Compounds [adverse effects] • Biological Markers • Central Nervous System Stimulants [adverse effects] • Chromatography, **High** Pressure Liquid • Cytochrome P-450 Enzyme System [metabolism] • Drug Interactions • Estrogens, Synthetic [adverse effects] • Ethinyl Estradiol [adverse effects] • Female • Half-**Life** • **Human** • Mass Fragmentography • Mixed Function Oxygenases [metabolism] • Sedatives, Nonbarbiturate [adverse effects]	• 0 (Benzhydryl Compounds) • 0 (Biological Markers) • 0 (Central Nervous System Stimulants) • 0 (Estrogens, Synthetic) • 0 (Sedatives, Nonbarbiturate) • 28911-01-5 (**Triazolam**) • 57-63-6 (Ethinyl Estradiol) • 68693-11-8 (modafinil) • 9035-51-2 (Cytochrome P-450 Enzyme System) • EC 1.- (Mixed Function Oxygenases) • EC 1.14.14.1 (CYP3A protein, **human**) • EC 1.14.14.1 (nifedipine oxidase)

	• **Single**-Blind Method • Spectrophotometry, Ultraviolet • Spectrum **Analysis**, Mass • **Triazolam** [adverse effects]	