

Pharmacokinetics and Drug-Alcohol Interactions

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Outline of Presentation

- Pharmacokinetic (PK) features
- PK in special populations
- PK variability
- Drug interaction with alcohol
- Summary comments

Pharmacokinetics (PK)

- Rapidly absorbed
 - T_{max} : 40 - 60 min
- Rapidly cleared
 - $T_{1/2}$: 2 - 3 hours
- Extensively metabolized
 - glucuronidation and sulfation
 - apomorphine sulfate is the major metabolite
 - apomorphine accounts for <1% total radioactivity

PK in Special Populations

- Hepatic impairment
 - 16% to 62% increase in C_{max}
 - 35% to 68% increase in AUC
- Renal impairment
 - No significant change in C_{max}
 - 52% to 67% increase in AUC

PK Variability

Dose	C_{max} (ng/mL)	AUC (ng * h/mL)
2 mg	0.19 - 1.50	0.53 - 2.22
4 mg	0.26 - 3.28	0.71 - 4.87
5 mg	0.31 - 5.19	0.71 - 6.18
6 mg	0.39 - 5.88	1.47 - 8.70

PK/PD Correlation

- No definite correlation between C_{max} , AUC and blood pressure changes
- The incidence of syncope and hypotensive adverse events occurred at T_{max} when C_{max} was relatively higher
- Safety may be difficult to predict based on dose due to variability in C_{max}

Alcohol Interaction: Overview

- Four studies were conducted

	n	Uprima™	EtOH
- Study M97-745	32	5 mg	0.60 g/kg
- Study M97-762	24	6 mg	0.15 g/kg
- Study M98-838	68	6 mg	0.30 g/kg
- Study M98-891	70	6 mg	0.60 g/kg

Uprima™ and Alcohol Dosing

- 1 oz. vodka = 0.15 g/kg
- Vodka diluted in 450 ml orange juice, ingested over 30 minute period
- Uprima™ administered one hour after start of alcohol ingestion
- Phase 3 clinical trials restricted alcohol intake to within 6 hours prior to drug administration

M97-745 (5 mg, 0.6 g/kg)

- Study terminated due to significant adverse events
- No definitive conclusions can be drawn due to premature termination of study

M97-745 (5 mg, 0.6 g/kg) Adverse Events

- One subject:
 - lost consciousness for 1 min approximately 40 min after dosing
 - no EtOH administered
 - hypotension (BP 71/37, pulse 41)
 - required IV fluids, oxygen and atropine
- Second subject:
 - experienced hypotension (BP 55/38) at 30 minutes
 - administered EtOH
 - had second highest C_{max} of Uprima™ and highest EtOH levels
- Two other subjects:
 - experienced hypotension

M98-838 (6 mg, 0.3 g/kg) Drop in Blood Pressure

	Uprima™	EtOH	Uprima™ + EtOH
Standing systolic	-19.33	-16.62	-22.27*
Standing diastolic	-12.09	-9.53	-14.21*
Supine to standing	--	--	--
Systolic	-16.65	-14.98	-18.68
Diastolic	-12.99	-9.83	-15.14*

* Statistically significant difference when compared to EtOH alone

M98-838 (6 mg, 0.3 g/kg) Incidence of Treatment Emergent AEs

	Uprima™	EtOH	Uprima™ + EtOH
Nausea	31%	1.6%	50%
Dizziness	22%	9.4%	44%
Pallor	27%	1.6%	31%
Vomiting	7.5%	0.0%	16%
Hypotension	7.5%	1.6%	13%

**M98-838 (6 mg, 0.3 g/kg)
Effects with Alcohol**

- A trend toward a greater drop in BP
- A higher incidence of abnormally low BP
- A greater sedative effect
- An increase in the incidence of adverse events

**M98-891 (6 mg, 0.6 g/kg)
Drop in Blood Pressure**

	Uprima™	EtOH	Uprima™ + EtOH
Standing systolic	-21.77	-23.23	-26.78
Standing diastolic	-12.58	-10.55	-16.87*
Supine systolic	-10.86	-14.69	-15.87*
Supine diastolic	-6.49	-8.64	-9.07

* Statistically significant difference when compared to Uprima™ or EtOH.

Statistically significant difference when compared to Uprima™

**M98-891 (6 mg, 0.6 g/kg)
Incidence of Treatment Emergent AEs**

	Uprima™	EtOH	Uprima™ + EtOH
Nausea	34%	3%	48%
Dizziness	18%	9%	34%
Pallor	15%	0%	30%
Vomiting	19%	2%	27%
Hypotension	13%	14%	37%

**M98-891 (6 mg, 0.6 g/kg)
Incidence of Abnormally Low BP Values**

	Uprima™	EtOH	Uprima™ + EtOH
Standing systolic*	1.5 %	1.6 %	20 %
Standing diastolic#	1.5 %	1.6 %	14 %

* < 80 mm Hg

< 40 mm Hg

**M98-891 (6 mg, 0.6 g/kg)
Effects with Alcohol**

- Greater drops in systolic and diastolic BPs
- A higher drop in BP at the time of peak Uprima™ and EtOH
- An increased sedative effect
- An increase in the incidence of adverse events

Summary Comments

- Bioavailability is higher in patients with renal and hepatic impairment
- Pharmacokinetic variability is too high to distinguish among doses
- There is a pharmacodynamic interaction between Uprima™ and EtOH
- Uprima™ is associated with higher incidence of adverse events when dosed with moderate and high amounts of EtOH